Evaluation of formulation and processing factors on the disintegration and dissolution of immediate release tablets in fed state: Formulation strategy towards minimizing viscosity mediated negative food effect

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Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig verfasst und ausschließlich die angegebenen Quellen und Hilfsmittel verwendet habe.

Mainz, 19.04.2018. _____

Kamran Zaheer

He gives wisdom to whom He wills, and whoever has been given wisdom has certainly been given much good. And none will remember except those of understanding

Al-Quran (2:269).

Dedicated to

My unsung hero

My Father

Zaheer Alam (Late)
(1952-2013)

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Chapter I Introduction

Tablets represent more than 80% of all dosage forms on the market (Jivraj et al., 2000). After taken through the oral route, the tablet has to disintegrate and liberate the active pharmaceutical ingredient (API), which will be available for absorption. This free fraction of API permeates through the intestinal membrane to reach the systemic circulation in order to give its desired therapeutic effect. These general steps may be altered by some physiological factors such as gastric emptying time, gut motility, composition of intestinal fluid, changes in the pH of GI tract, bile flow stimulation, changes in luminal metabolism (Lentz, 2008; Yu et al., 2004). Simultaneous consumption of food may also cause alterations in solubility, osmolarity and distribution coefficients, in addition to the possibility of a direct interaction of the components of food with tablet excipients and/or API. Presence of food, usually influence all of the above-mentioned factors and steps, therefore altering the pharmacokinetics of the drug taken simultaneously, by decreasing or increasing the rate and extent of its absorption. Many researchers have examined the alterations in the pharmacokinetics of drug in the presence of food (Abdel-Rahman et al., 2011; Boullata & Hudson, 2012; Chan, 2002; Custodio et al., 2008; Fleisher et al., 1999; Gamsiz et al., 2010; Genser, 2008; Lentz, 2008; Rodríguez-Fragoso et al., 2011; Schmidt & Dalhoff, 2002; Singh, 1999; Welling, 1996; Won et al., 2012).

Nonetheless, the overall effect of food depends on the physicochemical properties of the drugs, the dose, excipients in the formulation, composition and quantity of food consumed and timing of ingestion (Yasuji et al., 2012). There are many more studies focusing the delayed release of API in presence of food, but main emphasis was given to the compound itself. Knowledge gained through this drug centric approach is indeed beneficial in minimizing the negative food effect for the tested drug, but it is not sufficient to devise a generalized strategy. There exist a knowledge gap regarding the effect of formulation and process variables on negative food effects.

I.1 Influence of presence of food on drug dissolution and bioavailability

I.1.1 Effect of post prandial viscosity

As early as in 1959, Abbot et al. observed that disintegration time of tablets was prolonged in pooled human gastric juice as compared to the simulated gastric juice. Authors assumed that higher viscosity of human gastric juice was responsible for the delayed disintegration (Abbott et al., 1959). Despite of this early report, the aspect of viscosity was not considered that well, by the researchers studying the food effect on drug absorption, for unknown reasons.

However, a few researchers have considered it and reported the reduced disintegration and dissolution due to food-induced viscosity. Khoury et al. have proposed that the development of a diffusion barrier may be responsible for the delayed dissolution of hydrocortisone acetate in dilute HPMC solutions (Khoury et al., 1991). Abrahamsson et al. have studied the effect of food components on tablet disintegration. They have

postulated the formation of a layer around the tablet similar to the extended release coating, which was strong enough to reduce the water penetration and possibly hindering the particles to leave the tablet. This is probably the cause of a delayed tablet disintegration (Abrahamsson et al., 2004). Anwar et al. have ascribed the significant role of viscosity when they observed the delayed disintegration of tablets in milk (Anwar et al., 2005). Poor wetting of tablet surface and hydrodynamic shear stress were also accounted for the reduced disintegration and dissolution rates of immediate release tablets in viscous solutions of HPMC (Parojčić et al., 2008). Brouwers et al. have revealed that food effects can cause an immediate release tablet to behave as if it is an enteric coated tablet, therefore presence of food have significant effect on tablet disintegration and drug absorption. They have showed impaired water uptake in nutritional drinks through magnetic resonance imaging (MRI) (Brouwers et al., 2011).

From the mechanistic point of view, in addition to the food-induced viscosity (Anwar et al., 2005; Radwan et al., 2012), development of a physical barrier around the tablet surface (Abrahamsson et al., 2004), interaction between tablet excipients and medium (Galia et al., 1998), poor hydrodynamic shear stress (Parojčić et al., 2008), are also reported in the literature which are attributed for the reduced disintegration and dissolution of immediate release tablets in fed state.

I.1.2 Effect of excipients

From the perspective of biopharmaceutics, functional excipients has the potential to enhance the rate of dissolution of the dosage form by improving the wettability. Cyclodextrins, as an example, have been found to increase the solubility of the drugs through complexation that resulted in improved bioavailability of some drugs such as glibenclamide and nifedipine in animal models (Emara et al., 2002; Savolainen et al., 1998). On the contrary, a negative effect of some excipients such as sodium lauryl sulfate (SLS) on the solubility of an API have also been observed in several studies (Buch et al., 2010; Buch et al., 2009). Some superdisintegrants have been reported to decrease the in-vitro dissolution, possibly due to some interaction with drugs thus used. Although this reduction was not found to be significant when the same formulations were evaluated in-vivo (Fransén et al., 2008; Narang et al., 2012).

Rate of dissolution is often determined through the effective surface area of excipients present in the formulation, which itself is usually dependent on the particle size. Choice of excipients usually influence the overall distribution of particle size in the formulation and thus the drug release (Vialpando et al., 2011). Some authors have studied the role of formulation factors i.e, effect of excipients on the bioavailability of different drugs under fasted and fed states (Buice et al., 1996; Hosny et al., 1994). Nevertheless, there is still a lack of related studies to formulate a strategy in order to minimize the negative food effect through optimized formulations.

The FDA database of Inactive Ingredients contains the maximum permissible levels of excipients that can be used in a particular dosage form with respect to route of administration. This database is about the safe use of commonly used excipients and does not address the concentration dependant activity of these excipients (Food and Drug Administration, 2018).

I.1.3 Effect of pharmaceutical technologies

Different pharmaceutical technologies such as particle size reduction (nanoparticles), use of amorphous formulations, solid dispersion, complexation with cyclodextrin etc. were used to improve the bioavailability of drugs having low solubility and/or dissolution in the GI tract. Some of them are found to counteract the negative food effect.

Nanoparticle formulation has minimized the food effects on the absorption of Aprepitant. Probably, larger surface area led to rapid dissolution and improved bioavailability (Wu et al., 2004). Bioavailability of Danazol which was affected by the presence of food was not reduced significantly when the formulation of Danazol containing lipid based excipients was evaluated in human volunteers (Charman et al., 1993). Similarly, a fixed-dose combination tablet of ritonavir and lopinavir, prepared with solid-dispersion technology was not found to be affected by food (Klein et al., 2007). Self-microemulsifying drug delivery system (SMEDDS) based formulation were found to successfully improve the absorption of seocalcitol, which was compromised in the presence of food (Grove et al., 2007). However product by product formulation optimization is required if SMEDDS formulations are to be employed with an objective of minimizing the negative food effects (Perlman et al., 2008).

I.2 BCS classification and food effect

It is challenging to envisage the interaction between food components and an API, merely on the basis of former's chemical structure (Adithan, 2005; Deferme & Augustijns, 2003). However, Biopharmaceutical Classification System (BCS) may somehow be useful to predict the effect of food on API. It is largely due to the consideration of drug solubility and its permeability as defined in BCS (Wu & Benet, 2005).

Some reports show that presence of food was not found to alter the oral bioavailability of BCS class I drugs (Custodio et al., 2008; Fleisher et al., 1999). These compounds have high solubility and high permeability therefore are absorbed well in the GI tract.

By virtue of their low solubility, BCS class II drugs may have a negative food effect. The amount of drug available for absorption is dependent on the rate of drug dissolution, therefore low solubility directly affects the absorption of the drug in the GI tract. Interestingly, a positive effect on the absorption of non-ionizable and weak acidic BCS class II drugs such as griseofulvin and digoxin from their immediate-release formulations was observed, when they were ingested with high-fat meals (Custodio et al., 2008; De Smidt et al., 1987; Fleisher et al., 1999; Kassem et al., 1982). Permeability of griseofulvin was found to increase with an increase in the bile micelle concentration (Yano et al., 2010). In addition to the bile pigments, lecithin and cholesterol, bile micelles in particular influences the oral absorption of low-solubility drugs by decreasing the effective diffusion coefficient and increasing drug solubility. Therefore, food effects can be estimated by an increase in the solubility of API and a change in

permeability by bile micelles when oral absorption is limited by the solubility, as is the case with BCS class II compounds (Sugano, 2009). Due to the complex nature of this interaction between food components and drugs, a product-by-product investigation will be more feasible.

For many BCS class III compounds (high solubility and low permeability), their transport across the gastrointestinal tract involves absorptive and efflux transporters. Some components of food competitively inhibit the intestinal transporter function, therefore the extent and/or rate of the membrane permeability of some class III compounds of BCS could potentially be reduced in the presence of food (Bruesewitz et al., 2006; Custodio et al., 2008; Dahan & Amidon, 2008; Marasanapalle et al., 2011; Marasanapalle et al., 2009). Increased bile secretion due to the presence of food increases the complexation of drug and bile micelle, thereby decreasing the free fraction of drug in the GI tract (Kawai et al., 2011). Bioavailability studies under fed and fasted states revealed a reduction of 86% in bioavailability of Trospium chloride (a class III compound) when taken with a high fat meal (Hotha et al., 2010).

The effects of presence of food on class IV of BCS (low solubility and low permeability) are more challenging than rest of the compounds, because compounds belonging to this class are affected by physiochemical conditions which themselves are influenced by the intake of food (Yasuji et al., 2012). A summary of the role of BCS in predicting the food effect is presented in Figure - 1.

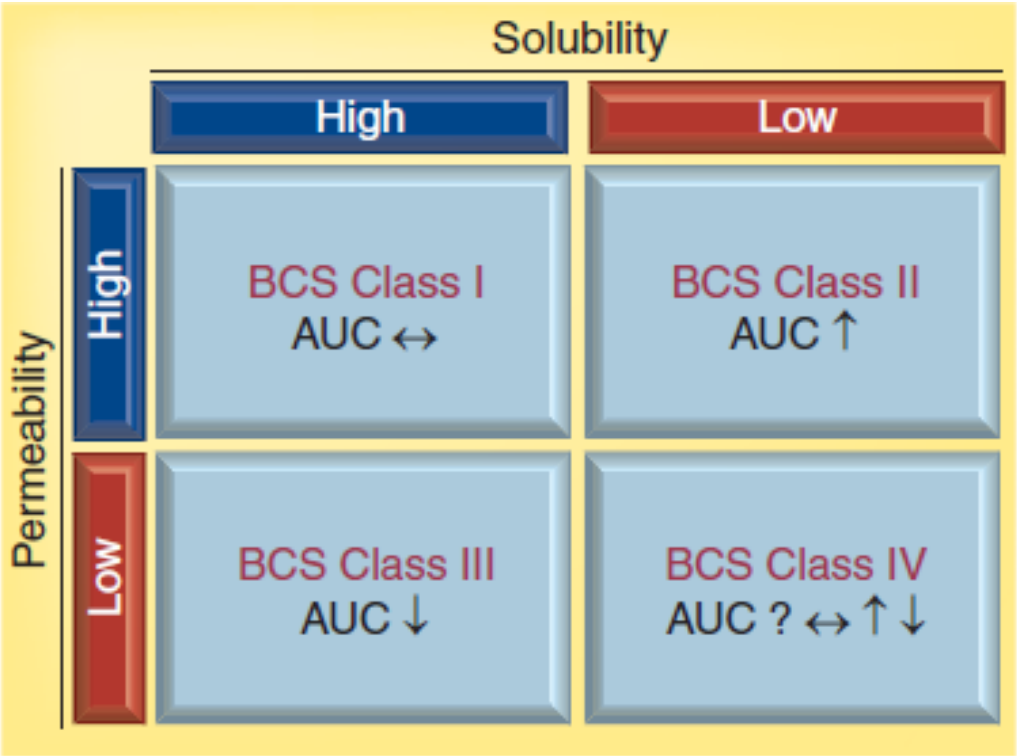

Figure - 1: Summary of prediction of food effect on extent of drug absorption (AUC) through Biopharmaceutical classification system (Yasuji et al., 2012).

I.3 Regulatory aspect

FDA provides guidance to consider the food effect in relation to the bioavailability and bioequivalence studies for new drugs and drug products during the investigational new drug applications period (Food and Drug Administration, 2002). In addition to the assessment of food effect under fed and fasted conditions, these guidelines suggested the use of high calorie (approximately 800 to 1000 kcal) and high-fat (approximately 50 percent of total caloric content of the meal) meals. Approximately 150, 250, and 500-600 kcal should come from protein, carbohydrate, and fat, respectively. Their rational is that fed conditions have a larger impact on the physiology of GIT as well as bioavailability of drugs.

European medial agency recommend to conduct a bioequivalence study under fasting condition, because they consider it the most sensitive method of detecting differences between formulations. However, for products whose intake is recommended under fed state, bioequivalence should also be assessed under fed conditions. Use of high-calorie and high-fat food similar to the food suggested by FDA is proposed. Moreover, for formulations which are aimed to improve the solubilisation such as microemulsion and solid dispersion, bioequivalence studies are required to be conducted under fasted as well as fed conditions (European Medicines Agency, 2010).

Japanese regulatory authorities instruct to conduct the bioequivalence studies under fasting conditions. Nevertheless, similar to the EMA guidelines, bioequivalence studies should be assessed under fed conditions if postprandial dose is specified, either due to low bioavailability or due to severe adverse effects under fasting conditions. Moreover, unlike FDA and EMA, low fat diet of 700 kcal or less with less than 20% calories from fats is advised. Bioequivalence studies of extended release products are recommended to be conducted under fasted as well as fed conditions. For extended release products high fat diet of 900 kcal or more with more than 35% calories coming from fats is recommended (Pharmaceutical and Food Safety Bureau Japan, 2012)

Although regulatory authorities do differ about the domain of testing under fed state and differences in the composition of recommended meal, but all of them recommend the in-vivo evaluation of food effects on drug products.

I.4 Bio relevant media for in-vitro testing

Most of the compendial methods are not appropriate for predicting the food effect on the release of drug from a dosage form. Although simulated gastric fluid represents the fasted conditions better because it has identical surface tension and pH to the natural values, but development of media simulating the natural gastric conditions after the intake of food is a challenging task. It is largely due to the varied composition of food.

Nevertheless, many researchers have used bio relevant media, such as simulated gastric fluid and simulated intestinal fluid, to predict the food effect on pharmacokinetics of drugs (Dressman et al., 1998; Nicolaides et al., 2001). It is believed that the simulated fasted and fed state gastric media are capable of providing a better correlation between in vitro and in vivo data (Jantratid et al., 2008).

In order to predict the effect of presence of food on the membrane permeability in the GI tract, the in vitro Caco-2 cell lines have been suggested (Aspenström-Fagerlund et al., 2009; Sreenivasulu et al., 2010). A combination of in vitro dissolution system and Caco-2 cell is reported to assess the bioavailability of lycopene and α-tocopherol from whole food (Déat et al., 2009).

In addition to the compendial media such as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), various bio relevant media were proposed to evaluate the effect of food on drug absorption. These media differ with respect to viscosity and surface tension therefore the medium itself has potential to influence the liquid penetration into the dosage form. (Anwar et al., 2005). Although media pH and compositions, such as bile salt, lipolytic enzymes and phospholipids contents was considered in these media but apart from very few studies the aspect of media viscosity was not considered while developing simulated fed media (Jantratid et al., 2008; Klein et al., 2004). Milk has also been suggested to simulate the postprandial gastric conditions (Galia et al., 1998), but its viscosity does not reflect the viscosity of gastric content in presence of food. Radwan et al considered the neglected aspect of viscosity by proposing a medium simulating the food induced viscosity. In this medium 1.4 % aqueous solution of HPMC was used whose viscosity was similar to the viscosity of a standard homogenized FDA meal (Radwan et al., 2012). Zaheer & Langguth have adjusted the pH of this medium to 3.0, in order to better simulate the standardised static in vitro digestion method suitable for food (Minekus et al., 2014; Zaheer & Langguth, 2018).

I.5 Disintegration

Generally, the therapeutic dose of an API is comparatively small therefore in order to compress it into an appropriately sized tablet, suitable excipients are mixed with API. In addition to address the issue of size, the admixture of such excipients is also used to improve the processing constraints like poor flow (Carstensen & Chan, 1976), difficulties in blending (Olusanmi et al., 2014) as well as sticking and/or rat-holing (Lam & Newton, 1992; Leane et al., 2015). Addition of excipients such as glidants, antiadherants, fillers, lubricants or surfactants (Davies & Gloor, 1972; Gohel & Jogani, 2005; Jivraj et al., 2000; Sohi et al., 2004) in a suitable proportion assures the product quality. However, when API particles are embedded in a matrix, it may prolong the dissolution in the case of immediate release tablets, which may have a negative influence on its bioavailability. In order to overcome it, disintegrants are added in the formulations that facilitate the breakdown of tablet into small granules/particles thereby improving the dissolution due to increased surface area. In the absence of disintegration only the API particles present at the surface of the tablet would be able to liberate, and hence the robust clinical performance of the dosage form could not be achieved. Therefore, the role of disintegrants in maximising the bioavailability of immediate release tablets in particular, cannot be avoided.

I.6 Mechanisms of disintegrant action

Disintegration refers to the breakup of a tablet into small fragments when ingested. Therefore, enough force is required to be generated during disintegration which can

overcome the interparticulate forces in the compressed tablets. Usually penetration of medium into the tablets is the first step in disintegration (Nogami et al., 1967). Liquid ingress alone is not sufficient to rupture the bonding of tablet particles, but it initiates other mechanisms of disintegration.

Various theories have been postulated to explain the mechanism of action of different disintegrants as well as that of the disintegration itself, but a comprehensive understanding however may still be lacking (El-Barghouthi et al., 2008; Zhao & Augsburger, 2005b). To date, disintegrant actions include, wicking (capillary action), swelling, interruption of particle-particle bonds and shape recover. It has also been learnt that the combination of these mechanisms may possibly provide a synergy (Sallam et al., 1998; Shah & Augsburger, 2001).

I.6.1 Wicking

Wicking is believed to be a process of liquid ingress through capillary action into the microstructure of the tablets to displace air (De Schoenmaker et al., 2011; Kissa, 1996). In addition to the penetration through pores, water can also move along a hydrophilic network of the disintegrant particles (Shotton & Leonard, 1972). The high permeability of water causes the destruction of hydrogen bonds, as well as van der Waals and electrostatic forces Although, wicking will not cause the disintegration but, it will weaken the tablet structure (Patel & Hopponent, 1966). Researchers believe that liquid penetration into the tablet is necessary for the initiation of disintegrant action as it provides the necessary water for the disintegration to happen due to other mechanisms (Moreton, 2008). Had it one of the active disintegration mechanism, tablets would disintegrate after coming in contact with water, therefore, wicking is rather considered as a prerequisite for other proposed disintegrant mechanisms (Curlin, 1955; Shangraw et al., 1980).

Higher rate of water uptake can be coupled with the better efficiency of some disintegrants (Khan & Rhodes, 1975b). Balance between capillary forces and opposite viscous forces have an impact on the penetration rate (Van Kamp et al., 1985). Volume of liquid penetration was found to reduce with an increase in packing density, therefore use of coarser particles of disintegrants was reported to improve the disintegration efficiency (Rudnic et al., 1980).

The mechanism of disintegrant action of microcrystalline cellulose is supposed to be a combination of wicking and interruption of particle-particle bonds (Peck et al., 1989). Similarly, for polacrilin potassium, wicking is reported to be the mechanism of disintegrant action (Bele & Derle, 2012c).

I.6.2 Swelling.

Swelling is undoubtedly the most reported mechanism to explain the disintegration of compressed tablets (Alebiowu & Itiola, 2003; El-Barghouthi et al., 2008; List & Muazzam, 1979b; Patel & Hopponent, 1966). It is explained as the expansion in volume of the compact particles that results in the exertion of stress on the adjacent particles. When the volume of expanding particles exceeds the volume of tablet pores where they were placed then this pressure initiates the breakup of the tablet matrix and ultimately

causes the tablet to disintegrate (Desai et al., 2016; Patel & Hopponent, 1966; Quodbach et al., 2014).

Swelling behaviour of some disintegrants is reported (Kottk & Rudnic, 2002). Various factors have an impact on the swelling tendency of the disintegrants such as chemical structure and crosslinking (Moreton, 2008). Within a tablet, binding forces are only valid for very short distances, so a higher swelling volume may not be necessary for quick disintegration. Superdisintegrants with cross linking, provide relatively rapid disintegration of the tablets due to high swelling force despite of a limited increase in volume, when compared with strongly swelling disintegrants (List & Muazzam, 1979c; Thibert & Hancock, 1996). However, not every swelling substance can be considered as disintegrant. Strongly swelling gums such a tragacanth and agar gelatinize after swelling. This gel formation will promote the adhesion between tablet particles rather disintegration (Kottk & Rudnic, 2002).

The swelling propensity of some disintegrants depend upon the pH of their surroundings. Prolonged disintegration of tablet containing Sodium starch glycolate (SSG) and Croscarmellose sodium (CCS) was observed in acidic media due to their reduced swelling at lower pH, while swelling of crospovidone (though negligible) and disintegration time of formulations containing them found unaffected when evaluated in varying pH media (Chen et al., 1997; Shangraw et al., 1980).

However, swelling may not be the main mechanism of disintegrant action because swelling time of some disintegrants is longer than the disintegration time, moreover, some polymers that do not swell well, such as crospovidone and cross-linked dextran, when incorporated in tablets, results in the rapid disintegration (Guyot-Hermann & Ringard, 1981; Hüttenrauch & Jacob, 1970; List & Muazzam, 1979b; Thibert & Hancock, 1996).

I.6.3 Interruption of particle-particle bonds.

Regarding the bonding mechanism of compressed tablets, mechanical interlocking, solid bridges and intermolecular forces are usually suggested, however, intermolecular forces are believed to be the prevailing bonding mechanism (Ferrari et al., 1996; Karehill & Nyström, 1990).

Interruption of these bonds, when a tablet comes in contact with disintegration medium or gastrointestinal liquid, is one of the proposed mechanism for tablet disintegration. For tablets containing microcrystalline cellulose this mechanism is mainly suggested, where mainly the hydrogen bonds, that develop between the cellulose fibers during the compression process, are annihilated by the imbibed water (Lowenthal, 1973). A correlation between the disintegration time and the intermolecular forces present in the tablets was found but the possibility of another supportive disintegration mechanism was postulated (Luangtana-Anan et al., 1992). In the presence of swelling disintegrants, it is difficult to distinguish the role of swelling and breakage of intermolecular force in disintegrating the tablet. There is a possibility that breakage of intermolecular forces is the consequence of swelling mechanism (Desai et al., 2016).

I.6.4 Shape recovery/ Strain recovery

Strain recovery is one of the proposed mechanism of disintegration which is less studied as compared to swelling and wicking (Patel et al., 2007). When a tablet is compacted then some polymers, then either due to interlocking of some polymer chains or spontaneous crystallization of some parts, that polymer assumes a metastable high energy state (Lendlein & Kelch, 2002; Lowenthal, 1972b; Quodbach & Kleinebudde, 2015). Upon contact with physiological fluids or disintegrating medium, hydration of polymer chains favours to assume the most energy favourable position probably through the entanglement of the polymer chains and somehow return to the original shape of polymer entity (Erdös & Bezegh, 1977; Lowenthal, 1972b; Quodbach & Kleinebudde, 2015). This mechanical activation give rise to rapid movement as well as expansion in volume, which in turn results in the generation of stress. This stress will be released through the growth of micro cracks, which enhances the easily accessible pore space in which dissolution/disintegration medium can penetrate, which not only promote further hydration of polymer chains but also causes the tablet matrix to disintegrate.

It is assumed that in shape recovery, tablets do mostly expand axially i.e, in the opposite direction of compressional force applied (Quodbach et al., 2014), therefore shape recovery is directly influenced by the compression (Desai et al., 2012). Among the popular superdisintegrants crospovidone is reported to give its disintegration action through the mechanism of shape recovery (Desai et al., 2012; Quodbach et al., 2014). Shape recovery of the croscarmellose sodium particles and starch grains is also reported, however, their swelling tendency surpasses the effect of shape recovery (Hess, 1978; Kottk & Rudnic, 2002; Lowenthal, 1972b).

I.6.5 Heat of interaction/ Heat of wetting

Some disintegrants have demonstrated exothermic interactions when interacting with aqueous media (Lowenthal, 1973). Heat thus developed, causes the air to expand, which was trapped into the pores of the powder compact. This expansion can cause localized stress, which may at least assist the breakup of interparticle bonds followed by the disintegration (Guyot-Hermann & Ringard, 1981; Kanig & Rudnic, 1984; Lowenthal, 1972a; Matsumaru, 1959).

Some researchers reported contradictory results such as slower disintegration of tablets containing materials producing high amount of heat of wetting (List & Muazzam, 1979a), insufficient generation of heat to initiate the tablet disintegration (List & Muazzam, 1979c) and the observation that increased temperature of aqueous media not always accelerate the disintegration process in tablet formulations (Caramella et al., 1989). Current literature does not have any substantial evidence(s) in the favour of this mechanism, therefore it is not considered as an active mechanism for disintegration.

I.6.6 Effervescence.

When disintegration is done through the gas generated due to the chemical reaction of tablet excipients with water, it is called effervescence. It happens when a combination of a soluble organic acid and an inorganic carbonate or bicarbonate is wetted. Despite of their hydrophilicity, disintegrants are generally water insoluble (Moreton, 2008),

however, effervescent additives are water soluble. Inorganic carbonates can also be categorized as secondary disintegrants, because they react with acid present in stomach to generate gas, thereby facilitating tablet disintegration.

I.7 Factors Affecting the Performance of Disintegrants

There are several factors reported in the literature that affect the performance of a disintegrant. Some of them are particle size, compression force, methods of disintegrant incorporation especially for wet granulation and moisture content (Bele & Derle, 2012b).

Use of lubricants in inappropriate proportions, usually prolongs the disintegration. It is believed that commonly used lubricants such as magnesium stearate add hydrophobicity in the compact (Fukami et al., 2006)

Disintegration time decreased with an increase in particle size of starch when the formulation was compressed without a lubricant. Whereas, in the presence of lubricant decrease in disintegration time was achieved with a decrease in the particle size of starch. Smaller particles increased the surface area, which in turn reduced the coverage of lubricant, thereby preventing the negative effect of lubricant on the disintegration time (Smallenbroek et al., 1981). Increased particle size of crospovidone was also reported to improve the disintegration and dissolution of tablets (Rudnic et al., 1980). However in another study no significant difference was found in the tendency of water uptake and its distribution when different particle sizes of crospovidone were evaluated through differential scanning calorimetry and dynamic vapour sorption (Saripella et al., 2014a, 2014b).

The method of disintegrant addition also has an influence, especially when tablets are prepared through a wet granulation method (Shotton & Leonard, 1976). However, another study reported that it is not the mode of incorporation of superdisintegrants, which has an impact on the tablet disintegration and dissolution. Instead nature and levels of disintegrant, as well as the granulation method may be accounting for the differences (Van Kamp et al., 1983). Both disintegration and dissolution were improved when disintegrants were added in both extra and intragranular phases, as compared to when disintegrants were added in one phase only (Bandelin, 1989; Khattab et al., 1993). In another study it was shown that intragranular incorporation of disintegrants have promoted the dissolution of poorly soluble drug (Gordon et al., 1990). Whereas, better dispersibility of poorly wettable drugs was observed with extragranular addition of disintegrants (He et al., 2008).

Performance of some disintegrants can also be influenced by the pH of dissolution medium. Sedimentation volumes of cellulose and cross-linked starch were reported to decrease in acidic pH (Shangraw et al., 1980). A strong decrease in swelling capacity of sodium starch glycolate and croscarmellose sodium in acidic medium may be ascribed to the conversion of their carboxymethyl moieties to its free acid, due to which lesser liquid holding capacity was observed as compared to its salt form. Disintegration of tablets containing sodium starch glycolate or croscarmellose sodium increased in acidic

media but disintegration of tablets containing crospovidone, a non-ionic polymer, remained unaffected (Chen et al., 1997; Zhao & Augsburger, 2005b).

It was reported that moisture increased plasticity of polacrilin potassium. Therefore, more hygroscopic brands of polacrilin potassium are more prone to the effect of moisture that result in the inferior disintegrant performance (Bele & Derle, 2012b).

Studies show that the same superdisintegrant from different vendors causes a different disintegration performance (Ferrari et al., 1996; Zhao & Augsburger, 2006)

I.8 Effect of Tablet filler/binder material on disintegration

Composition of tablet matrix especially the solubility of the filler is among the most important decisive parameters that determines the disintegration of a tablet. In general, disintegrants performed better when formulated with insoluble fillers (e.g., dicalcium phosphate) than soluble fillers (e.g., lactose and mannitol).

When liquid penetrates into the tablet pores, it can either dissolve or dislodge the particles comprising the pore wall, causing the porosity of tablet to change, which itself influences the disintegration process (Caramella et al., 1987; Kwan et al., 1957; Lowenthal, 1972a; Quodbach & Kleinebudde, 2015). This phenomenon needs to be considered when the compact contains soluble excipients, because the dissolved particles are likely to increase the local viscosity of liquid and leading to the changes in the porous system of the tablet over time. Both factors i.e, localized viscosity and changes in porous system will affect the further penetration of liquid, ultimately affecting the process of disintegration/dissolution (Radwan et al., 2012).

In a study, involving different grades of crospovidone, it was concluded that a faster disintegration was achieved for formulations where soluble fillers were used. Considering the larger proportions of fillers, matrix with sufficient dissolution rate are expected to give a faster disintegration (Shah & Augsburger, 2001).

When a poorly soluble API is to be formulated with a filler/binder which is too hydrophobic or lipophilic then the matrix needs either to have sufficient wicking capabilities or a hydrophilic network. In an early study a continuous hydrophilic network was established by incorporating starch, which resulted in the rapid disintegration (Patel & Hopponent, 1966).

Comparison of the use of potato starch and microcrystalline cellulose in a study revealed that although the use of fillers having poor cohesive properties give rise to the compression of low strength tablets but these excipients are capable of decreasing the disintegration time (Nogami et al., 1969).

Storage conditions i.e, temperature and relative humidity are reported to influence the dissolution rates of tablets having different fillers, independent of the use of disintegrant. Lactose based tablets were affected more as compared to DCP based tablets. Recrystallization of lactose was proposed as the reason for the decreased dissolution rate of lactose based tablets (Gordon, Rudraraju, Rhie, et al., 1993).

In another investigation, performance of disintegrants was found to vary with the solubility of the matrix i.e, higher dissolution rate was obtained when soluble fillers were used in the matrix (Gordon, Rudraraju, Dani, et al., 1993). Apart from the solubility, increased surface area of API, which is the result of quick dissolution/dislodging of soluble particles leaving behind the API, may be accounted for this rapid dissolution

Disintegration times of tablets are also found to vary with the variations in the solubility of the excipients of the formulation. However, quick disintegration was observed with in tablets with insoluble fillers (Ferrari et al., 1995). Increase in localized viscosity/ formation of a viscous barrier due to dissolved material is probably the reason behind impeded water penetration and delayed disintegration of tablet matrices with high solubility.

I.9 Disintegrants used in Pharmaceutical tablets

Disintegrants are hydrophilic but insoluble in water or gastrointestinal juices. (Moreton, 2008).In literature, disintegrants are further classified as disintegrants and superdisintegrants.

Normal disintegrants include starch- and cellulose-based excipients e.g., maize or corn starch, partially pregelatinized starch and microcrystalline cellulose. Some clays (e.g., Veegum HV), gums (e.g., agar, guar, tragacanth, alginate), resins (e.g., polacrilin potassium), and finely divided solids (e.g., colloidal silicon dioxide, magnesium aluminum silicate) also give disintegrant action.

Superdisintegrants provide better disintegration action at lower concentrations. They are usually developed through chemical modification of cellulose, povidone and starch. They include croscarmellose sodium (CCS), crospovidone (CPD) and sodium starch glycolate (SSG) (El-Barghouthi et al., 2008; Shah & Augsburger, 2001).

I.9.1 Starch and Its Derivatives

Starch and its derivatives are among the earliest tablet disintegrant used (Bandelin, 1989; Moreton, 2008). Starch is a carbohydrate consisting mainly of soluble amylose and insoluble amylopectin. Amylose is a linear α1- 4 linked polymer chain of glucose subunits while amylopectin is composed of larger, branched polymer chains of α - glucose units with α 1-4 and α 1-6 linkages (Hausler, 2012). Swelling is the primary mechanism of action for starch-based disintegrants. Researchers postulated that considering the starch grain as a 3-dimensional molecular network, hydration at the junction points could expand the whole structure. Extent of hydration would determine the extent of swelling.

Although starch and its derivatives are probably the most versatile excipients used in the formulation of tablets. Although, they can be used as disintegrants, binders, diluents, glidants, and thickening agents in tablet formulations, but, unless modified, larger amounts are usually required to give some of its reported functions such as, 10 – 15% starch is required to act as an effective disintegrant.

I.9.2 Cellulose and Its Derivatives

β1-4-linked glucose subunits comprises celluloses which are further consist of alternating portions of compact microcrystalline and amorphous regions. Microcrystalline cellulose is prepared through acid hydrolysis of cellulose which break down the amorphous region but keep the microcrystalline portion intact (Sun, 2012). For its disintegrant action, it is believed that cylindrical shaped microcrystalline particles draw water into the tablets by providing the capillarity. This water annihilates the hydrogen bonds that were formed between the microcrystalline particles during the process of compression (Peck et al., 1989). However, literature suggest that concentration up to 20% may be required to cause an effective tablet disintegration.

I.9.3 Resin and Its Derivatives

Polacrilin potassium is highly hydrophilic with good swelling property and is probably the most common ion exchange resin used as a disintegrant (Moreton, 2008; Palmieri, 2012). Wicking and strain recovery are reported as potential mechanisms for this cation exchange resin (Bele & Derle, 2012c; Quodbach & Kleinebudde, 2014b). It is effective in the concentration range of 2-10% (Palmieri, 2012). It is also proposed that bioavailability of anionic drugs can be improved by a cation exchange resin through the Donnan membrane phenomenon, where drug is gradually exchanged for cations (Bele & Derle, 2012a). Similarly, some anion exchange resins were found better disintegrant in case of basic drugs (Akkaramongkolporn et al., 2014).

I.9.4 Superdisintegrants

I.9.4.1 Sodium starch glycolate (Primojel)

Sodium starch glycolate is the sodium salt of cross-linked carboxymethylated starch, which shows improved moisture absorption, resulting in massive volumetric increase (Augsburger et al., 2007; Bolhuis et al., 1994; Young et al., 2005). Concentrations of sodium starch glycolate used in tablet formulations may range from 2% to 8% (Li, 2012).

I.9.4.2 Croscarmellose Sodium

Croscarmellose sodium, is a crosslinked carboxymethyl cellulose sodium (Augsburger et al., 2007; Guest, 2012) Its particles are long and narrow (fibrous) with curves and twists. Swelling, wicking, and shape recovery mechanisms are proposed for this superdisintegrant (Moreton, 2008). In a tablet formulation its effective concentration as a disintegrant ranges from 2% to 5%.

I.9.5 Crospovidone

Crospovidone is a water insoluble synthetic cross-linked polyvinylpyrrolidone (Kibbe, 2012). Crospovidone is generally reported as an effective disintegrant in tablet formulation when used in the range of 2%-5% (Kibbe, 2012), while coarser grades are reported for faster disintegration (Shah & Augsburger, 2001). Some researchers proposed wicking followed by secondary swelling as its mechanism of disintegrant

action (Kalasz & Antal, 2006; Kornblum & Stoopak, 1973; Shiyani et al., 2008), whereas, recently, shape recovery is proposed and validated as the mechanism of disintegrant action of crospovidone (Desai et al., 2012; Moreton, 2008; Quodbach et al., 2014).

I.10 Disintegration force

With a view to understand and explain the physical phenomenon of tablet disintegration and dissolution, many researchers have studied the development of disintegration force and related parameters in tablets. This disintegration force is not limited to the swelling of disintegrant particles incorporated in the tablet. Most of the researchers have recorded the swelling force of the tablet exerted against a fixed barrier during the process of disintegration, followed by the development and evaluation of the disintegration force-time curves (Joshi et al., 2014; Massimo et al., 2000; Massimo et al., 2003; Quodbach & Kleinebudde, 2014b). Measurement of disintegration force allows a "dynamic" evaluation of the tablet structure which further provides deep insight into the disintegration process and subsequent release of the active ingredient (Colombo et al., 1984). Based on the measurement of disintegration force development, a mathematical model was proposed for the phenomena of disintegration. Two mechanisms for the process of tablet disintegration, i.e, interface-controlled mechanism and diffusion-controlled mechanism may be characterized from this model. Interface-controlled phenomenon involves tablet particles, breaking apart from the interface of the tablet while, diffusion-controlled phenomenon involves particles diffusing away from the tablet (Caramella et al., 1987; Caramella et al., 1988; Colombo et al., 1988; Peppas et al., 1989).

$$\frac{F}{F_\infty} = 1 - \exp(-kt^n)$$

Where,

F is the disintegration force measured as a function of time,
F_∞ is the maximum developed force,
k is an expansion rate constant,
n indicates the mechanism of disintegration.

Values of n greater than 1, signifies that the disintegration process is interface-controlled., while values of n smaller than 1, are indicative of diffusion-controlled phenomenon (See Figure - 2).

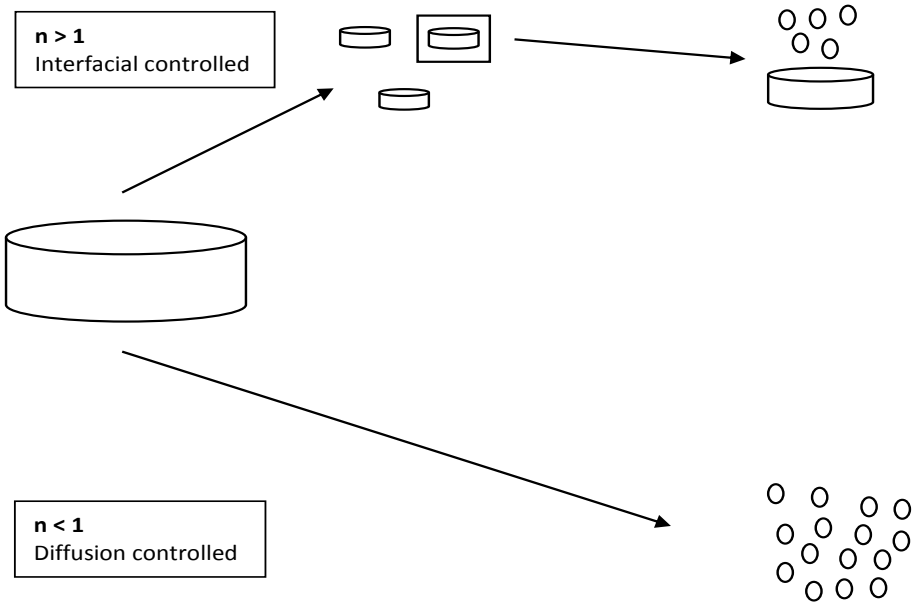

Figure - 2: Schematic representation of interfacial-controlled and diffusion-controlled mechanisms of tablet disintegration. In the interfacial-controlled mechanism, aggregates detach from the surface and disintegrate/dissolve further. In the diffusion-controlled situations, the whole dosage form disintegrates into smaller particles, which further disintegrate/dissolve. The main difference between both scenarios is that in the former case aggregates detach from the surface only, whereas, in the latter case, the drug will be liberated directly.

Tablets with a soluble matrix usually follow the diffusion-controlled mechanism where matrix solubilizes first and water acts as a plasticizer, thereby reducing the generation of disintegration force. In case of insoluble matrix, interface-controlled mechanism is dominant therefore, resulting in the rapid disintegration. That is why presence of disintegrants appeared to be more effective in insoluble fillers. (Augsburger et al., 2007).

In 1991, it was highlighted to develop a database for each disintegrant containing the effects of formulation and processing parameters on their performance (Marshall et al., 1991). In our project, we are studying the performance of individual disintegrants against the food-induced viscosity by varying different formulation and processing parameters. These results could be beneficial for the formulation scientists in order to optimize the performance of any formulation in fed state.

I.11 Aims and Objective

It is widely reported in the literature that presence of food interferes with the bioavailability of a drug, if taken simultaneously. Delayed disintegration and dissolution are believed to be the major reasons behind this delay which themselves are affected by some physicochemical factors like pH, osmolarity etc. Interestingly, in several studies where delayed release of API in presence of food was discussed, the main emphasis has been given to the compound itself and not to its formulation. To the extent of our knowledge based on the literature search it is unresolved that whether or not the formulation and process variables can be optimized to improved robustness of disintegration performance of tablets in fasted and/or fed state conditions.

The current study was designed to improve our current understanding on the role of formulation and processing factors in the presence of food. The aspect of food induced viscosity was considered in this regard which was surprisingly not given the due importance.

A screening phase was designed to figure out the important formulation and processing factors, which can be further optimized to minimize the negative food effect. After the identification of significant disintegrants and lubricants, if any, are subjected to further evaluation for their performance with respect to the presence of fillers having different functionality. Just like the aspect of viscosity, combination of disintegrants is not emphasized much during formulation development. Therefore, in search of some synergistic action combination of disintegrants at different levels are also included to this study.

Disintegration and dissolution test and media used thereof mentioned in pharmacopeias are more concerned with the quality of the product than to understand the underlying mechanism. Therefore, viscous media based on the viscosity of homogenized FDA standard meal is selected for the better reflection of the food effect. Similarly, texture analysis is incorporated in the study protocol to have a better insight into the physical process of disintegration.

The overall objective is to devise a formulation strategy for the development of formulations which will be least affected by the food induced viscosity.

Chapter II Effect of nature of single disintegrants on tablet disintegration in fed viscosity media: Lactose as a model soluble filler.

II.1 Introduction

The presence of food generally reduces the bioavailability of BCS class III drugs. In part, this negative food effect can be ascribed to slow tablet disintegration and dissolution imparted by food induced viscosity (Cvijić et al., 2014). In order to get rapid disintegration and dissolution of tablets superdisintegrants are used. Role of superdisintegrants is well studied under fasted conditions, but there is a scarcity in literature regarding their role under fed conditions. During current study, role of different superdisintegrants was studied in the presence of a soluble matrix. Lactose was selected by virtue of it aqueous solubility.

Lactose is widely used as a filler or diluent in tablets and several grades are commercially available with differing physical properties. Spray dried lactose and agglomerated lactose, produced by fluid bed drying, possess best fluidity among all the direct compression fillers. It has high dilution potential, but is not effective in diluting high-dose drugs having crystalline nature. Several grades of directly compressible lactose have borderline compressibility. Therefore, formulations containing lactose as a major portion of filler require high compression pressures to produce hard tablets.

II.2 Materials and Methods

II.2.1 Materials

Dr. R. Pfleger GmbH, Germany, gifted Trospium chloride (purity – 99.9%). Mean particle size was 276.7 ± 229.3 µm. Methyl hydroxypropyl cellulose E4M for preparation of viscous disintegration/dissolution medium was obtained from Synopharm (Germany). Primellose (Croscarmellose Sodium, DFE Pharma, Germany, 59.96 ± 38.68 µm), Primojel (Sodium Starch glycolate, DFE Pharma, Germany, 44.94 ± 19.37 µm) and Kollidone CL-SF (Crospovidone, BASF, Germany, 31.30 ± 36.90 µm) were used as superdisintegrants. Tablettose 80 (Lactose, Meggle, Germany, 142.1 ± 145.8 µm), PVP K-30 (Polyvinylpyrrolidone, Carl Roth GmbH, Germany, 267.2 ± 213.9 µm) and magnesium stearate (Fagron GmbH, Germany, 10.18 ± 10.75 µm) were used as filler, binder and lubricant, respectively in the direct compression tablet formulations.

II.2.2 Tablet preparation

Batches of 100 tablets each were prepared by dry blending the ingredients followed by direct compression. CCS, CPD and SSG were used at 4% of compression weight. Each blend of all formulations also contained Trospium Chloride as model drug (40 mg/tablet), Magnesium stearate as lubricant (0.5% w/w) and Polyvinylpyrollidone (K – 30) as binder (2.5%, w/w). All constituents of each formulation, except magnesium stearate, were blended in a mixer (Turbula T2F type, Switzerland) for 15 minutes. Magnesium stearate, which was screened through a 60-mesh sieve, was added and mixed for additional 2 minutes. Round shaped tablets with a constant weight of 250 mg, were compressed on a manual hydraulic press (Specac, USA – 25 tons), by filling the exactly weighed quantity of powder mixture, using a 9 mm die and a flat-faced with bevelled edge punch assembly. Each formulation was compressed at 10 KN and 30 KN with a dwell time of 10s.

II.2.3 Media composition

Fasted state was simulated by preparing simulated gastric fluid without enzymes (SGF, USP), whereas, food viscosity was simulated by 1.4% aqueous solution of Hydroxypropylmethyl Cellulose (HPMC E4M) at a pH value of 3.0 (Minekus et al., 2014; Radwan et al., 2012). Simulated fed state medium was prepared by dispersing 14 g of HPMC E4M in 250 ml distilled water, pre heated to 80 ^{o}C, while stirring it with a mechanical stirrer. Once it is dispersed, approx. 50 ml of distilled water, containing 6.84 g of Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_2O$) and 0.40 ml of 85% aqueous solution of Phosphoric acid was added. Finally, volume was made up to 1000 ml with distilled water and stirring was continued until a translucent dispersion was achieved.

II.2.4 Disintegration studies

In compliance with USP, disintegration tests were conducted in a tablet disintegration tester (Pharma Test, Type PTZ 2EH, Germany) without disks in 800 ml of simulated fasted and fed media at 37 ^{o}C. Use of disks during the disintegration test make the test less bio-relevant by virtue of additional shear imparted by the disks. Therefore, disks were not used during disintegration studies. Six tablets, one per vessel, were used for each test. The disintegration process was considered complete when no residue remained on the mesh. Disintegration times for individual tablets were noted.

II.2.5 Dissolution studies

Dissolution studies in viscous and non-viscous media were performed in USP apparatus II (Erweka DT 7R, Germany) using 500 ml of media at 50 rpm. All experiments were conducted at 37±0.5^{o}C. Five ml samples were withdrawn at predetermined time intervals of 5, 10, 15, 30, 45, and 60 minutes and 5, 10, 15, 30, 45, 60, 90 and 120 minutes in simulated fasted condition and in simulated fed conditions, respectively, and replaced by an equal volume of medium. Their absorbance was recorded UV-photometrically (Lambda 35 UV/Vis Spectrophotometer, Perkin Elmer, USA) at 210 nm after filtration and proper dilution (Radwan et al., 2012). Following measurements,

cumulative dissolution versus time profiles were constructed. The mean dissolution time (MDT) was calculated by the following equation:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t} \,.\, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

where j is the sample number, n is the number of dissolution sample times, $\hat{t}$ is the time at midpoint between tj and tj-1 (calculated with the expression ((tj + tj-1)/2)) and ΔM is the additional amount of drug dissolved between tj and tj-1.

The following formula was used to calculate the f2 similarity factor.

$$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1} n\,(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. Only one data point after the 85% of drug release was considered. f_2 value above 50, suggests similarity of dissolution profiles.

II.2.6 Determination of viscosity imparted by disintegrants

Viscosity measurements were performed in duplicate on Haake, RheoStress 1, Thermo Scientific, Germany by using Platte P 35 TiL. Three dispersions containing CPD, CCS and SSG in amounts equal to 4% of the compressional weight of a tablet i.e, 250 mg were prepared in 4ml of water and 1.4% aqueous solution of HPMC, respectively. Four ml was used in accordance with the volume used to submerge the tablet, while performing texture analysis. In addition to these three dispersions, the viscosity of water and 1.4% aq. solution of HPMC was measured at 1, 5 and 10 min intervals.

II.2.7 Disintegration force determination

Disintegration force development was measured by texture analysis (TA. XT plus, Stable microsystems, UK). A tablet was attached axially to the flat bottom of the probe (A/TDR) by using a double sided tape; the probe shaft was then screwed into the load cell carrier. It is obvious that a disintegration force was also generated in radial direction, but the emphasis was to observe the more realistic disintegration behavior when the tablet is submerged in the dissolution medium. Measurements of disintegration force by gluing the tablet diametrically were not successful. The vessel was then centralized on the base of the texture analyzer with respect to the probe. The perforated platform was placed at the bottom of the vessel. In order to obtain a dynamic evaluation, 4 ml of dissolution medium was transferred to the vessel, which was enough to submerge the tablet. The force-time profiles were obtained by moving the tablet glued probe towards the bottom of the vessel with a predetermined pre-test speed of 1.0 mm/s, until the tablet touches the perforated platform in the vessel and the trigger force of 0.049 N is reached.

At this point, the tablet after coming in contact with the dissolution medium exerts a force (disintegration force) which is recorded at a predetermined data acquisition rate of 10 data points per second. Using the software (Exponent, TA. XT plus stable microsystems, UK) the data was initially analyzed and exported to MS Excel for further interpretation.

n – exponent value was calculated from the slope of the plot between the term *In*[-*ln*(l - F/F_∞)] versus *ln* t according to the following equation (Caramella et al., 1988)

$$ln\left\{-ln\left[1-\frac{F}{F_\infty}\right]\right\} = \ln k + n \ln t$$

II.3 Results

II.3.1 Disintegration studies

Figure - 3A shows the disintegration times (DT) of all formulations tested in simulated fasted state. In formulations containing no disintegrant, apparently due to lack of any active mechanism for disintegration, DT was much longer than the formulations containing disintegrants. Formulations containing CCS and CPD, showed reductions in DT with an increase in compressional force. Conversely, formulations containing SSG, showed an increase in DT with an increase in compressional force.

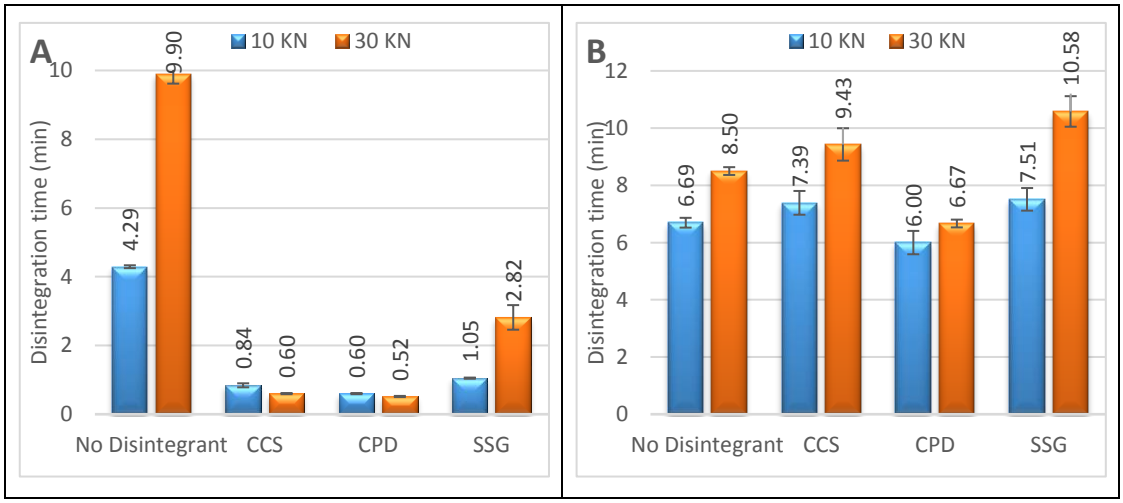

Figure - 3: Effect of compressional force and nature of disintegrants on the disintegration time of Lactose based Trospium chloride formulations (n = 6) A – Formulations tested in fasted state, B – Formulations tested in fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

In simulated fed state, a direct relationship between compressional force and DT of formulations containing disintegrants is obvious (Figure - 3B). Formulations containing CPD gave the shortest DT, irrespective of the compressional force, among all formulations tested. The DTs of all formulations complied with compendial limits (i.e, <15 min for uncoated tablets). Interestingly, DTs of formulations containing no disintegrant were not much different from the formulations containing disintegrants (Figure - 3B). One way to explain this phenomenon is the existence of a boundary layer

around the surface of the tablet, which may hinder the de-aggregation and subsequent disintegration of tablets in viscous medium. However, within the domain of our project there is no experimental proof for this suggestion. Due to reduced mobility of water in viscous medium, disintegrant particles took longer time for activation; therefore, a large difference was observed in formulations containing disintegrants, when their DTs were determined in simulated fed and fasted state. However, due to the fact that lactose particles dissolve relatively quickly, this insufficiency of water did not influence the dissolution of lactose particles that much. Comparable disintegration times of formulation containing no disintegrants in simulated fasted and fed state provides the basis for this postulate of boundary layer.

II.3.2 Viscosity Determination

All dispersions of the disintegrants exhibited newtonian flow behaviour in non-viscous medium, whereas, in viscous medium pseudoplastic flow behavior was observed with all dispersions of disintegrants.

In non-viscous medium, all disintegrants show an increment in viscosity with time (Table - 1). At 1 min, higher viscosity than water was observed for dispersions containing SSG and CCS, which continue to increase with time thus indicating gelling tendency associated with both disintegrants. On the other hand, viscosity of CPD was in line with the viscosity of water even after 10 minutes suggesting the absence of gel formation. A similar trend of time-dependent increase in viscosity was also observed in viscous medium, however with greater magnitude as compared to non-viscous medium. This could possibly explain the relatively rapid disintegration and dissolution associated with formulations containing CPD as single disintegrant in respective simulated states. The order of gelling can be presented as SSG > CCS > CPD.

Table - 1 Viscosity of different dispersions containing disintegrants. (Shear rate = 4.0 s^{-1}) CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium Starch Glycolate. Mean ±SD, n=2

	Viscosity η (cp)					
	Non viscous medium (Distilled water)			Viscous medium (1.4% aqueous sol. of HPMC)		
	1 min	5 min	10 min	1 min	5 min	10 min
No disintegrant	0.87 ± 0.020	0.88 ± 0.024	0.87 ± 0.022	236 ± 4.261	237 ± 3.754	237 ± 4.253
CPD	0.67 ± 0.051	0.78 ± 0.020	0.90 ± 0.010	237 ± 7.103	238 ± 2.797	238 ± 3.503
CCS	0.88 ± 0.036	1.00 ± 0.025	1.03 ± 0.017	245 ± 3.130	253 ± 6.517	252 ± 6.256
SSG	0.93 ± 0.015	0.98 ± 0.045	1.07 ± 0.025	231 ± 6.508	254 ± 3.950	260 ± 4.551

II.3.3 Dissolution studies

In simulated fasted state, all formulations – irrespective of compressional force and nature of disintegrant used– overwhelmingly complied with the criterion for "very rapid dissolution" i. e. more than 85 % dissolved in 15 min (Yu et al., 2002)(Figure - 4). On the contrary, the release of drug was found to be much slower when the same formulations were tested under simulated fed conditions. Therefore, no formulation complied neither with "very rapid" nor "rapid" dissolution criteria in fed state (Figure - 5)

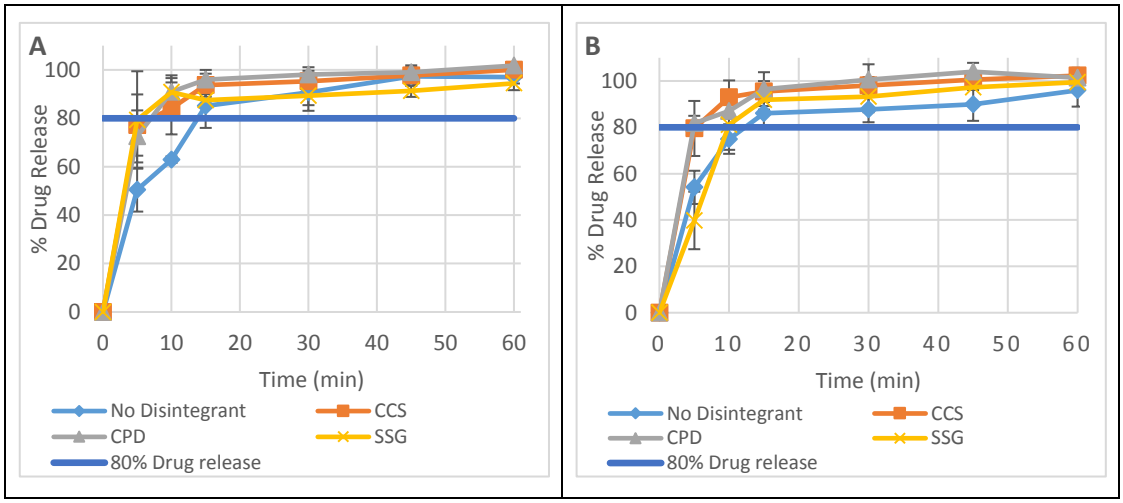

Figure - 4: Effect of compressional force and nature of disintegrants on % drug release of Lactose based Trospium chloride formulations, in simulated fasted state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

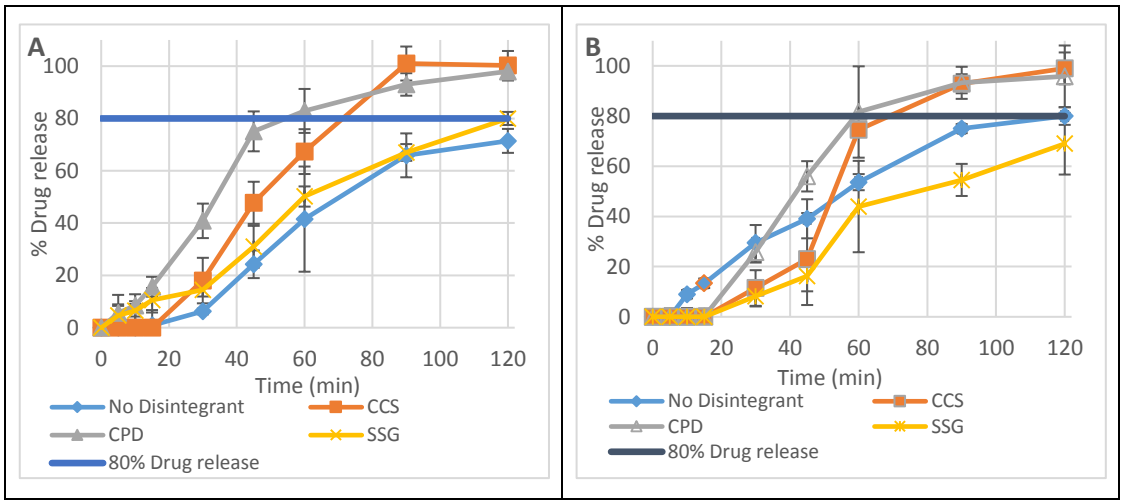

Figure - 5: Effect of compressional force and nature of disintegrants on % drug release of Lactose based Trospium chloride formulations, in simulated fed state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

When tested in simulated fasted state, the presence of disintegrants generally was found to reduce MDT values as compared to formulations containing no disintegrant. Changes in compressional force were found to influence MDT, though the magnitude was modest. MDT of formulations containing CCS and CPD as single disintegrants, was found to decrease with an increase in compressional force, whereas MDT of formulations containing SSG as single disintegrant and those containing no disintegrant was found to increase with an increase in the compressional force. Yet, because formulations comply with very rapid dissolution criteria these differences become irrelevant (Table - 2).

Table - 2: Effect of media viscosity, compressional force and nature of disintegrants on Mean dissolution time (MDT) and f_2 statistic. (Mean ± SD; n=4). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate.

Disintegrant	Fasted state			Fed state		
	*MDT (min)		f_2^+	*MDT (min)		f_2^+
	10 KN	30 KN		10 KN	30 KN	
No Disintegrant	8.81	9.05	60.48	71.72	55.32	44.67
CCS	6.13	4.57	67.98	50.60	54.93	48.81
CPD	5.19	3.75	66.05	34.80	45.04	48.15
SSG	5.54	8.46	38.34	64.47	86.75	49.53

* Calculated on the averaged values.
+ - 10 KN vs 30 KN

In simulated fed state, all formulations containing disintegrants hold a direct relationship between mean dissolution time (MDT) and compressional force. Interestingly, the formulation containing no disintegrant showed improved MDT with increasing compressional force. Among single disintegrants, CCS was relatively insensitive to changes in compressional force, whereas, SSG and CPD gave comparatively higher MDT with an increasing compressional force. F_2 statistic values revealed dissimilarity in dissolution profiles of formulations in fed state when compressed at different compressional forces (Table - 2)

II.3.4 Texture analysis

A typical disintegration force versus time curve obtained from texture analysis is presented in Figure - 6. Initially, swelling and shape recovery of compacted particles dominate over the rate of particles leaving the compact. This phase suggests minimal disintegration. At T_{max}, (time required to reach maximum disintegration force i.e, F_{max}) structural integrity is presumed to be distorted. Beyond this time point, a fall in disintegration force represents an increase in the rate of disintegration and dissolution. In the terminal phase of the curve, disintegration force decreasing rate (DFdR) is higher than the disintegration force development rate (DFDR) due to the weakening of the stimuli for force development. In this phase water is mainly drawn into the pores of the tablet mass through much slower capillary activity (Quodbach & Kleinebudde, 2014b).

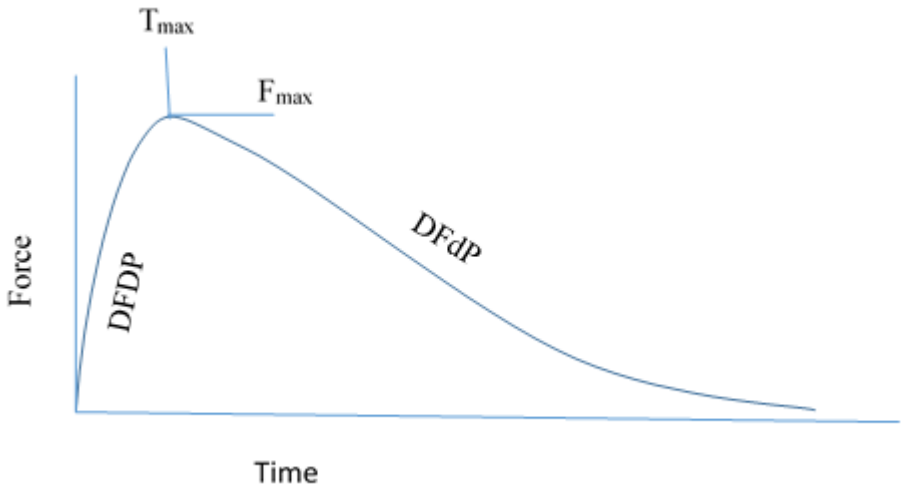

Figure - 6: Typical Disintegration Force Time Curve. F_{max} – Maximum disintegration force, T_{max} – Time required to reach the maximum disintegration force, DFDP – Disintegration force development phase, DFdR – Disintegration force decreasing phase.

Disintegration force development rate (DFDR) and time required to reach maximum disintegration force (T_{max}) of tested formulations containing disintegrants, compressed at different compressional forces, showed large differences when measured under simulated fasted and fed states. DFDR reduced from a range of (6.82×10^{-3} N/s – 63.81×10^{-3} N/s (fasted)) to (0.29×10^{-3} N/s – 2.34×10^{-3} N/s (fed)), whereas, T_{max} values were largely increased from 9 – 43s (fasted) to 910 – 2150s (fed) (Table - 3 & Table - 4).

Table - 3: Parameters from disintegration force – time curves of lactose based tablets in simulated fasted state. F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate; Mean ±SD, n=3.

Disintegrant in formulation	F_{max} (N)		T_{max} (s)		Disintegration force development rate (DFDR) N/s $x10^{-3}$		Disintegration force decreasing rate (DFdR) N/s $x10^{-3}$	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No disintegrant	0.66 ± 0.070	0.39 ± 0.023	90 ±8	1350 ± 106.6	4.89 ± 0.368	0.13 ± 0.009	0.035 ± 0.003	0.026 ± 0.001
CPD	0.30 ± 0.024	0.96 ± 0.034	16 ± 1.78	29 ± 1.4	13.26 ± 0.98	25.84 ± 1.42	4.624 ± 0.362	4.651 ± 0.068
CCS	0.60 ± 0.042	1.90 ± 0.089	9 ± 0.70	25 ± 0.90	59.46 ± 3.864	63.81 ± 1.56	7.142 ± 0.470	11.143 ± 0.32
SSG	0.51 ± 0.038	0.79 ± 0.029	43 ± 3.2	40 ± 1.42	6.82 ± 0.39	14.18 ± 0.28	1.243 ± 0.078	0.878 ± 0.036

Table - 4: Parameters from disintegration force – time curves of lactose based tablets in simulated fed state. F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate; Mean ±SD, n=3.

Disintegrant in formulation	F_{max} (N)		T_{max} (s)		Disintegration force development rate (DFDR) N/s x10^{-3}		Disintegration force decreasing rate (DFdR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No disintegrant	0.13 ± 0.016	0.28 ± 0.03	2130 ± 247.84	3270 ± 545.13	0.02 ± 0.0001	0.07 ± 0.008	0.010 ± 0.0003	0.014 ± 0.0005
CPD	2.44 ± 0.229	1.46 ± 0.232	910 ± 48.08	1230 ± 133.03	2.34 ± 0.284	0.97 ± 0.308	0.851 ± 0.062	0.410 ± 0.026
CCS	1.81 ± 0.173	1.26 ± 0.156	1170 ± 108.16	1730 ± 282.35	1.20 ± 0.132	0.55 ± 0.068	0.562 ± 0.049	0.195 ± 0.016
SSG	1.25 ± 0.086	0.84 ± 0.106	1750 ± 67.47	2150 ± 168.68	0.63 ± 0.046	0.29 ± 0.0535	0.182 ± 0.018	0.100 ± 0.008

The sensitivity of the disintegration force – time curve to reflect the changes in process variables and understanding of tablet disintegration and dissolution beyond PhEur type disintegration and dissolution experiments has been reported (Massimo et al., 2003). It should be kept in mind though that the test conditions in the current experiments were static whereas dynamic conditions are reflected in PhEur disintegration and dissolution apparati. Therefore, due to other processes involved in disintegration and dissolution testing (e.g., hydrodynamic factors) weak but significant relationships were established among parameters of disintegration force curve, DT and MDT, in fed and fasted state. (Figure - 7)

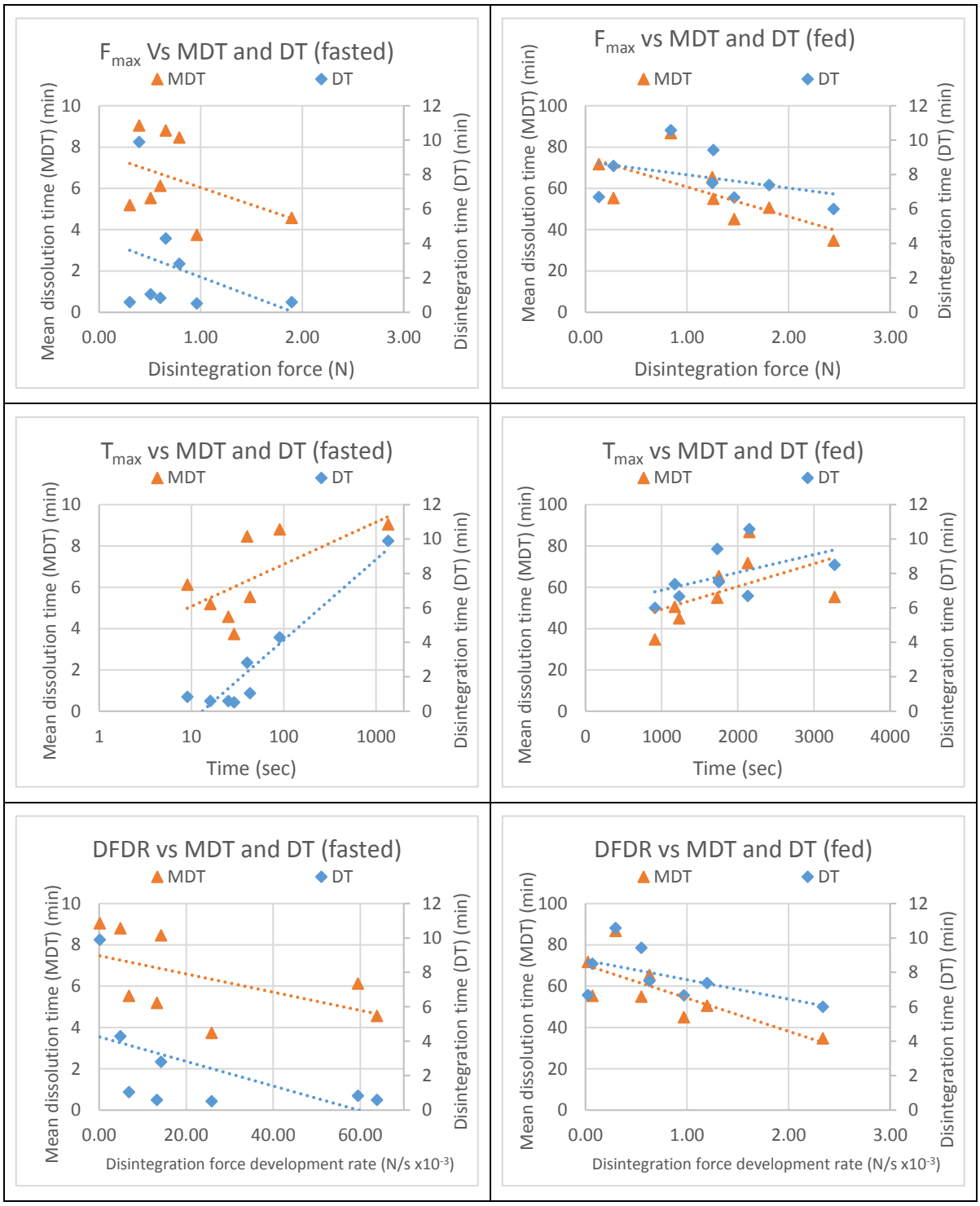

Figure - 7: Relationship of F_{max}, T_{max} and DFDR with disintegration time (DT) and mean dissolution time (MDT).

II.4 Discussion

Upon contact with aqueous medium, water ingress causes disturbances in the internal structure of the tablet due to shape/strain recovery and swelling of disintegrant particles in the compact. Shape recovery may be elucidated as return of deformed particles during the tableting phase to the original shape upon contact with water (Quodbach & Kleinebudde, 2015). Thus, tablet particles will continue to exert stress on adjacent particles until they leave the compact.

Highly soluble diluent particles, e.g. lactose, dissolve as soon as they are exposed to the dissolution medium resulting in a local change in viscosity of the dissolution medium within the pore where the lactose particle was situated. In order to further improve the rate of disintegration and release of API, disintegrants may be incorporated in the tablet formulation, which drag more dissolution medium (through wicking) into the tablet thereby leading to a rapid distortion of the compact structure. Consequently, low magnitudes of T_{max} and F_{max} with high DFDR are typical features of rapidly disintegrating formulations in fasted state i.e, low viscous media (Figure - 8A & Figure - 9A).

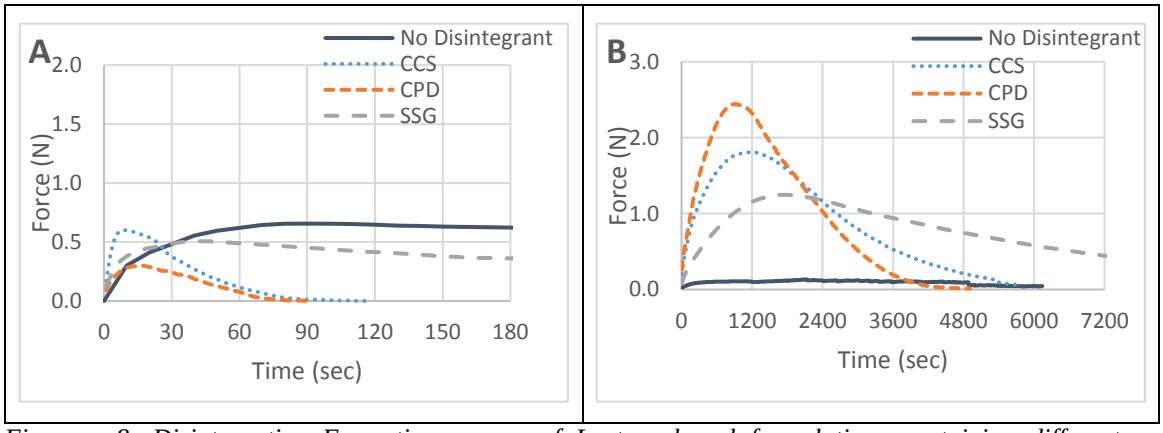

Figure - 8: Disintegration Force-time curves of Lactose based formulations containing different disintegrants, compressed at 10 KN (n = 3) A – simulated fasted state, B – simulated fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

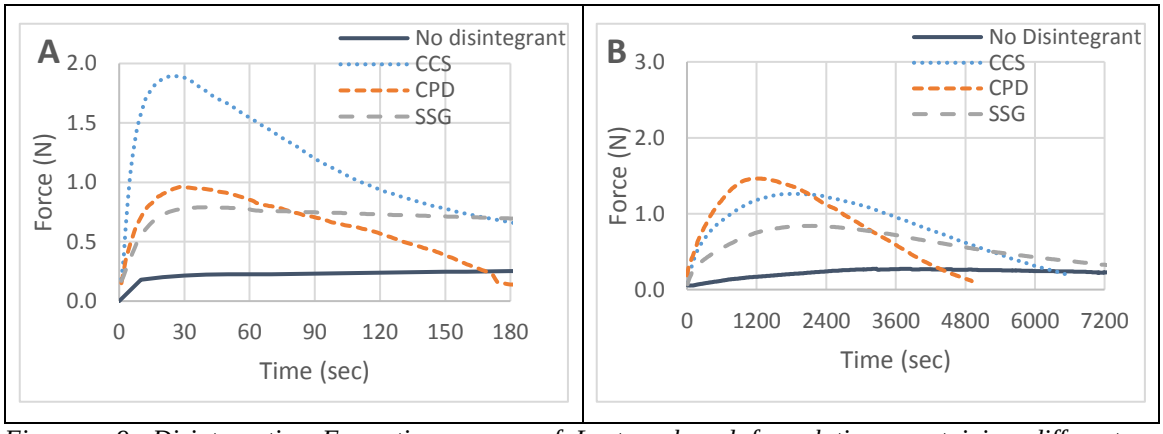

Figure - 9: Disintegration Force-time curves of Lactose based formulations containing different disintegrants, compressed at 30 KN (n = 3) A – simulated fasted state, B – simulated fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

In viscous fed state media, the wicking process is severely impaired. The wicking process is well known to be governed by the fluid viscosity, its surface tension, wetting angle as well as the properties of the porous matrix (which are kept constant in our experiments). It is hence not surprising that the T_{max} is higher, given the slower liquid ingress into the tablet matrix. A similar observation has been described earlier (Abbott et al., 1959). In the viscous fed state media, a boundary layer is likely to develop on the surface of the tablet, which may limit the inward penetration of medium and outward movement of compact particles, commensurate with a slow DFDR. Earlier the reduced penetration of water into tablets when placed in viscous medium was reported (Radwan et al., 2012; Radwan et al., 2013). In the absence of a boundary layer, on the other hand, more rapid uptake of water into the tablets is enabling the formation of a sufficient disintegration force (Caramella et al., 1986; Quodbach & Kleinebudde, 2014b).

Therefore, under viscous conditions, rapid disintegration is associated with high magnitudes of F_{max} and DFDR along with low values of T_{max} (see curves of CPD in Figure - 8B & Figure - 9B). In addition, low magnitudes of DFDR and high T_{max} may partially also be linked to the strength of the internal matrix structure, thereby indicating strong binding of the compact or resistance to disintegrate. Figure - 7, shows the relationships of T_{max} and DFDR with DT and MDT.

II.4.1 Effect of nature of disintegrants

At either compressional force, DT in fed state ranged from 6 min to 10.58 min whereas, that in fasted state has a range of 0.52 min to 2.82 min. Similarly, MDT ranged from 34.80 min to 86.75 min and 3.75 min to 8.46 min, in simulated fed and fasted state, respectively, irrespective of the compressional force.

In fasted state, disintegration and dissolution rates of tablet formulations containing single disintegrants were too rapid to draw any meaningful inference (Figure - 3A & Table - 2). The high DFDR and short T_{max} values of these formulations are indicative of rapid water uptake thereby facilitating the disintegration and dissolution (Table - 3). The absence of a viscous layer around the tablet as well as its detached particles also enables rapid water penetration into the tablet thus avoiding gelling or increase in localized viscosity due to dissolution of lactose, which could clog up the pores of tablets.

In fed state, the crospovidone containing formulation gave a relatively short DT (i.e, 6 min and 6.6 min at 10 KN and 30 KN respectively), among all other formulations. It may be due to the mechanism of CPD action which is reported to be through shape recovery (Desai et al., 2012) or by wicking and swelling in water, without gelling (Khairnar et al., 2014). It is interesting to note that DTs given by SSG and CCS containing formulations in the fed state were almost identical, especially at lower compressional force (Figure - 3B). Commensurate, low values of DFDR in formulations containing CCS and SSG point to a reduction in water penetration. Rapid solubility of lactose, and gelling tendencies of both disintegrants, exaggerated by reduced water uptake may account for the longer DT in simulated fed state medium. CCS, forms a weak gel upon swelling, due to hydration (Bi et al., 1999; Camargo, 2011) whereas, SSG acts through rapid absorption of water followed by a strong increase in particle

volume (Rowe et al., 2009). Due to hydration and gelling of disintegrant particles, the medium surrounding the disintegrant particles may increase in viscosity (El-Barghouthi et al., 2008). Such rise in the viscosity values of SSG and CCS in viscous medium is presented in Table - 1. It provides an indirect evidence for the existence of gel formation within the tablet. This gelling is more likely to hinder the passage of water inside deep layers thereby resulting in longer disintegration as well as mean dissolution times.

In simulated fed state, dissolution of Trospium from formulations containing CPD as single disintegrant was faster (MDTs of 34.80 min and 45.04 min at 10 & 30 KN respectively) than the other formulations tested. However, MDT is found to be affected by the changes in compressional force, though its DT was relatively insensitive to such changes. Comparatively rapid dissolution of formulations containing CPD might be linked to its non-gelling activity. Table 1 also shows that CPD did not increase the viscosity of viscous medium further. While, dissolution from formulations containing CCS was a bit slower (MDTs of 50.60 min and 54.93 min at 10 & 30 KN respectively) than formulations containing CPD, the former was least affected by compressional force (Table - 2). In case of SSG containing formulations MDT values greater than 65 min are discouraging its consideration as single disintegrant in any formulation strategy that considers the food induced viscosity. Low values of DFDR and longer T_{max} in formulations containing CCS and SSG, advocates the reduced water uptake and presence of viscous barriers in deep layers of tablets, respectively; thus resulting in relatively slower disintegration and dissolution. (Table - 4). Undesirably slow dissolution in SSG containing formulations may be linked to the decreased availability of free water, within the gel layer, which may lead to decreased drug diffusion across the gel layer (El-Barghouthi et al., 2008). Figure - 8B & Figure - 9B suggest that a high F_{max} is required to reduce DT, due to the viscous layer around the tablet. The same figures also contains the curve of formulation with no disintegrant. An almost flat curve with very low DFDR and DFdR was found due to the absence of any stimuli for disintegration except dissolution of lactose itself (Table - 4). High solubility of lactose may itself is responsible for localized viscosity in deep layers of tablets which may also be reason for longer MDT of formulations containing no disintegrant.

II.4.2 Effect of compressional force

Tablets containing lactose as a major filler require higher compressional force in order to produce tablets with sufficient hardness (Jivraj et al., 2000). Therefore, influence of compressional force need to be examined carefully.

MDT values tend to decrease with the increasing compressional force when tested in fasted state. Nonetheless, most of the formulations were found to possess similar profiles (i.e, $f_2 > 50$) when formulations compressed at 10 and 30 KN were compared. Formulations containing SSG alone, deviated the trend, and reflected dissimilarity in this regard ($f_2 < 50$; Table - 2). This slight delay in SSG containing formulations may be due to the increased localized viscosity associated with the immediate dissolution of lactose particles in water. Comparatively smaller curves presented in Figure - 8A & Figure - 9A, provide an insight about the changes in the microstructure of the tablet which give a hint that tablet's internal structure might have ruptured quickly thus allowing API to release rapidly in fasted state. DFDR was found to increase with an increase in compressional force. At 10 KN, an immediate clogging of pores followed

by rapid rupture of tablet's microstructure could probably explain a slight delay in release of API when it is compared with the formulations compressed at 30 KN, where clogging may have not been that rapid. Higher magnitude of F_{max}, at higher compressional force, may be indicative of relatively strong internal structure of tablet as well as better performance of swelling disintegrants simultaneously. It may be ascribed to the popular notion that disintegrant particles perform better when particles of compact are closer to them.

In fed state, rate of dissolution decreased noticeably when formulations were compressed at higher compressional force, in formulations containing SSG and CPD, (Table - 2). Torturous diffusion pathway and low porosity are associated with higher compressional force. Therefore, F_{max}, DFDR and DFdR were reduced while T_{max} was increased with an increase in compressional force. Limited water penetration due to gel formation and lack of any active mechanism of disintegration besides wicking could be accounted for retarded release of API from formulations containing SSG and CPD respectively at higher compressional force. Inadequate penetration of water at higher compressional force potentiated the gelling tendency of SSG and CCS.

Differences in parameters obtained from disintegration force – time curve in fed and fasted state parameters encourage to consider the testing of formulations in fed state as well while optimizing formulations, where the presence of food may be the reason of reduced bioavailability.

Chapter III Effect of combination of disintegrants and their levels on tablet disintegration in fed viscosity media: Lactose as a model soluble filler.

III.1 Introduction

Formulation and process variables are not that well studied in fed state, as they are evaluated in fasted state. Various studies pointed out delayed absorption followed by reduced bioavailability when tablets were taken with food (Galia et al., 1998; Hotha et al., 2010). Delayed disintegration and dissolution in this regard emphasize the use of disintegrants in order to reduce as much as possible, if not prevent, the negative effect of food viscosity. It is worth mentioning that majority of studies pertaining performance of disintegrants focused the use of single disintegrant whereas, importance of disintegrant combinations was not that much highlighted. Current study is an attempt to understand the role of combination of superdisintegrants in the presence of a soluble matrix. Lactose was selected by virtue of it aqueous solubility. Identification of disintegrant combinations which are least affected by the negative food effect will be beneficial for the formulators.

III.2 Materials and Methods

III.2.1 Materials

See II.2.1

III.2.2 Tablet preparation

Different combinations of CCS, CPD and SSG i.e, CPD+CCS, SSG+CCS and SSG+CPD were used in a 1:1 ratio at low level (4% of total tablet weight) and at a high level (8% of total tablet weight) according to the scheme presented in Table - 5. Each blend of the formulations contained Trospium chloride as model drug (40 mg), Polyvinylpyrrolidone (K – 30) as binder (2.5%, w/w) and magnesium stearate as lubricant (0.5% w/w). All constituents of each formulation, except the lubricant, were blended in a mixer (Turbula T2F type, Switzerland) for 15 minutes. Magnesium stearate, which was screened through a 60-mesh sieve, was then added and mixed for further 2 minutes. Round shaped tablets with a compressional weight of 250 mg, were compressed on a manual hydraulic press (Specac, USA – 25 tons), by filling the exactly weighed quantity of powder mixture. Each formulation was compressed at 10 KN and 30 KN with a dwell time of 10s by using a 9 mm die and a flat-faced with beveled edge punch assembly.

Table - 5: Composition of formulations showing the varying levels of disintegrant combinations.

Disintegrant combination	Sodium Starch Glycolate (SSG)	Crospovidone (CPD)	Croscarmellose Sodium (CCS)
	%	%	%
CPD+CCS (Low level)	0	2	2
SSG +CCS (Low level)	2	0	2
SSG +CPD (Low level)	2	2	0
CPD+CCS (High level)	0	4	4
SSG +CCS (High level)	4	0	4
SSG +CPD (High level)	4	4	0

III.2.3 Media composition

See II.2.3

III.2.4 Disintegration studies

See II.2.4

III.2.5 Dissolution studies

See II.2.5

III.2.6 Determination of viscosity imparted by disintegrants

Viscosity measurements were performed in duplicate on Haake, RheoStress 1, Thermo Scientific, Germany by using Platte P 35 TiL. Six dispersions of different combinations of disintegrants and their levels according to the scheme presented in Table - 5, were prepared in viscous and non-viscous media Four ml was used in accordance with the volume used to submerge the tablet, while performing texture analysis. Viscosities of these dispersions were recorded at 1, 5, and 10 min intervals.

III.2.7 Disintegration force determination

See II.2.7

III.3 Results

III.3.1 Disintegration studies

In simulated fasted state, disintegration times were found to be influenced by the levels of disintegrant combinations. DT was found to be in inverse relation with the level of disintegrant combination, i.e, increased level of disintegrants reduced DT and vice versa (Figure - 10A). In addition, the effect of compressional force was also found to be governed by the levels of disintegrant combinations. Compressional force was found to be in direct relationship with DT when combinations of disintegrants were used at low

levels, whereas, an inverse relationship was observed when the same combinations were used at high levels. A combination of SSG + CCS revealed a relatively longer DT, at either level of disintegration combination.

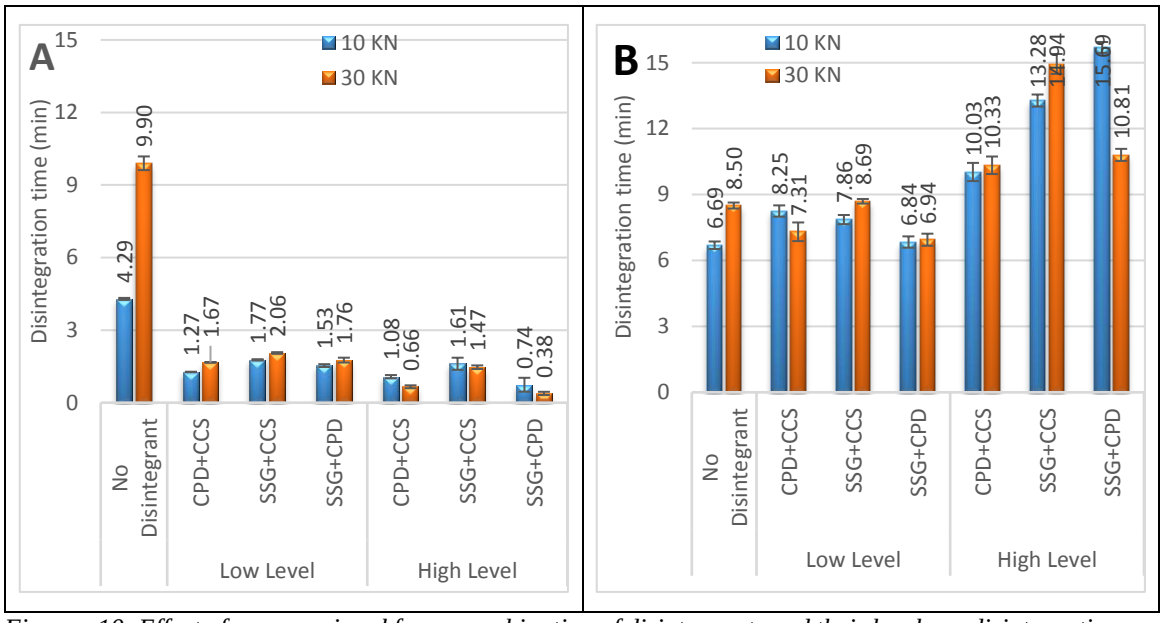

Figure - 10: Effect of compressional force, combination of disintegrants and their levels on disintegration time of Lactose based Trospium chloride formulations (n = 6) A – Formulations tested in fasted state, B – Formulations tested in fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

On the contrary, when tested in simulated fed state, DTs of tablets was found to be in direct relation with the level of disintegrant combination used, i.e, DT increased when disintegrant combination was used at a higher level (Figure - 10B). Although, an increase in compressional force generally delayed the disintegration, but the presence of CPD in the disintegrant combination appeared to minimize the influence of compressional force on DT. However, at the high level of SSG+CPD and low level of CPD+CCS, increased compressional force improved the disintegration.

III.3.2 Viscosity Determination

In non-viscous medium, an increase in viscosity was found with an increase in the level of disintegrant combination at all recorded time points (Table - 6). Beyond the time point of 5 minutes, the disintegrant combination of SSG + CCS showed an increment in viscosity, whereas, no noticeable change in viscosity was observed in disintegrant combinations containing CPD. It suggests a possible role of CPD in limiting the gelling tendencies of CCS and SSG. Interestingly, at 5 min time point, a considerable increase in viscosity was observed for combinations of CPD + CCS. This means that if formulations containing a combination of CPD + CCS do not disintegrate rapidly then a slight delay in disintegration may be observed.

In viscous medium, increasing the levels of disintegrant combination also increases the viscosity of the medium further. Probably, due to higher gelling tendency, a significant rise in viscosity was observed in disintegrant combinations involving SSG at high level. Viscosity of combination of CCS + CPD were found to be least influenced by the changes in levels as well as over the period of time.

The order of gelling can be presented as SSG +CCS (high) > SSG + CPD (high) > SSG + CCS (Low) > SSG +CPD (low) ~ CPD + CCS (high) ~ CPD + CCS (Low) in viscous medium, whereas for non-viscous medium it would be SSG + CCS (high) > SSG + CPD (high) > CPD + CCS (High) > CCS +SSG (Low) > CCS + CPD (Low) > SSG + CPD (Low).

Table - 6: Influence of the nature and level of disintegrant combinations on the viscosity of simulated fasted and fed media. (Shear rate = 4.0 s^{-1}). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium Starch Glycolate Mean ±SD, n=2.

	Viscosity (η) cp					
	Non viscous medium			Viscous medium		
	1 min	5 min	10 min	1 min	5 min	10 min
No disintegrant	0.87 ± 0.020	0.88 ± 0.024	0.87 ± 0.022	236 ± 4.261	237 ± 3.754	237 ± 4.253
CPD+CCS (Low level)	0.80 ± 0.020	0.98 ± 0.040	0.95 ± 0.009	240 ± 5.978	247 ± 5.396	247 ± 7.001
SSG +CCS (Low level)	0.82 ± 0.025	0.86 ± 0.045	0.97 ± 0.004	238 ± 4.072	245 ± 2.554	254 ± 1.515
SSG +CPD (Low level)	0.89 ± 0.020	0.88 ± 0.055	0.85 ± 0.025	238 ± 2.011	246 ± 4.500	247 ± 6.001
CPD+CCS (High level)	0.81 ± 0.020	1.02 ± 0.013	1.01 ± 0.025	251 ± 7.855	251 ± 4.530	247 ± 5.701
SSG +CCS (High level)	0.90 ± 0.015	0.87 ± 0.020	1.07 ± 0.010	255 ± 2.769	255 ± 3.582	286 ± 4.801
SSG +CPD (High level)	0.98 ± 0.060	1.02 ± 0.020	1.03 ± 0.070	262 ± 5.047	266 ± 3.286	263 ± 2.723

III.3.3 Dissolution studies

When tested under simulated fasted conditions, most of the formulations showed very rapid dissolution i. e. more than 85 % of API was released within 15 min (Yu et al., 2002), except the high level of CPD+CCS compressed at 10 KN and low level of the same combination compressed at 30 KN (Figure - 11). However both of these formulations complied with the criterion for rapid dissolution i. e. more than 80 % of API was released within 30 min (Yu et al., 2002).

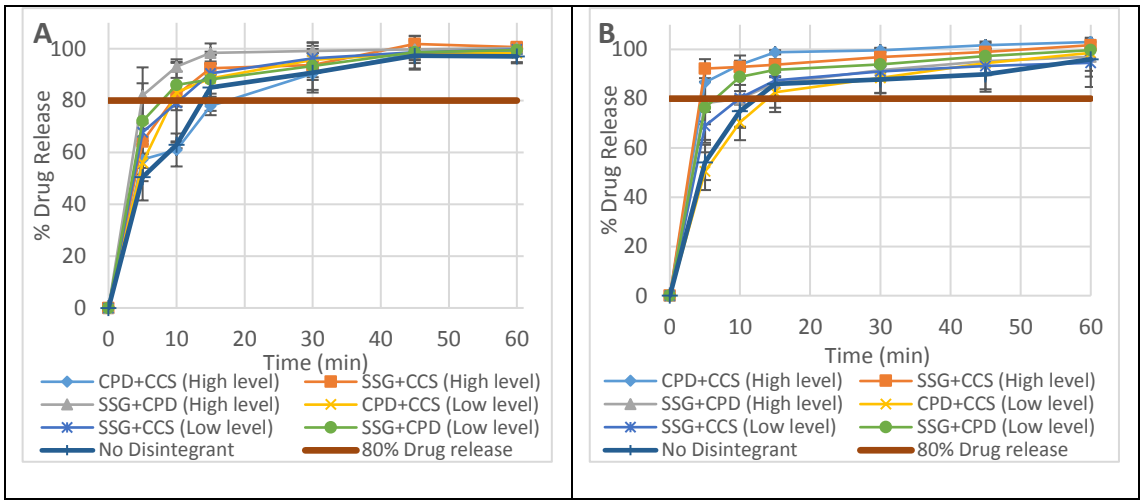

Figure - 11: Effect of compressional force, combination of disintegrants and their levels on % drug release from Lactose based Trospium chloride formulations, in simulated fasted state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Release of drug was found to be slower when the formulations were tested under simulated fed conditions. Less than 60% of drug was released within 30 minutes. Therefore, no formulation complied with "very rapid dissolution" nor "rapid dissolution" criteria in fed state (Figure - 12). However, except for the formulation containing high level of SSG+CPD, all formulations release more than 80% of API during the test duration i.e, 120 minutes.

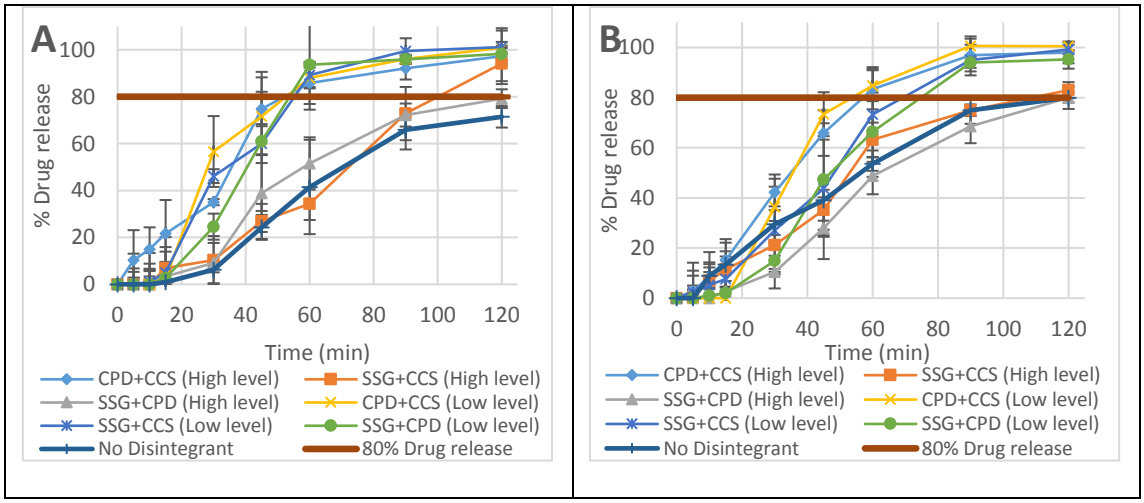

Figure - 12: Effect of compressional force, combination of disintegrants and their levels on % drug release from Lactose based Trospium chloride formulations, in simulated fed state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Under simulated fasted conditions, very rapid dissolution and lower magnitude of MDT makes it difficult to draw some meaningful inference. Despite of low MDT, formulations having a high level of disintegrant combination showed dissimilarity i.e, f_2 values lower than 50, which indicates the effect of compressional force. However, a decrease in MDTs with an increase in compressional force as well as the level of disintegrant combination was observed in most of the formulations. Effect of compressional force was more pronounced in combinations of CPD+CCS, where at 10

KN increasing the level of disintegrant combination increased the MDT of formulation, but at 30 KN, increasing the level of disintegrant combination reduced the MDT (Table - 7). Therefore, it would be safe to say that the effect of compressional force and level of disintegrant will be governed by the nature of disintegrants used in the combination.

Table - 7: Effect of media viscosity, compressional force and level of disintegrant combinations on Mean dissolution time (MDT) and f_2 statistic of Lactose based formulations. (Mean ± SD; n=4). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate.

Disintegrant combinations	Fasted state			Fed state		
	MDT (min)		f_2^+	MDT (min)		f_2^+
	10 KN	30 KN		10 KN	30 KN	
No Disintegrant	8.81	9.05	60.48	71.72	55.32	44.67
CPD+CCS (Low level)	6.82	10.16	57.44	37.66	40.17	56.07
SSG +CCS (Low level)	6.72	6.13	69.28	39.62	47.78	48.20
SSG +CPD (Low level)	6.73	6.25	77.60	41.30	49.75	47.19
CPD+CCS (High level)	10.16	3.44	34.53	36.61	36.28	57.56
SSG +CCS (High level)	6.61	4.50	45.28	70.40	53.29	45.33
SSG +CPD (High level)	4.07	6.59	53.60	69.50	67.78	68.04

* Calculated on the averaged values
+ - 10 KN Vs 30 KN

When tested in simulated fed state, similar to the trend seen with disintegration time, MDT was found to be in a direct relation with the level of disintegrant combination used. i.e, higher MDT was observed with higher level of disintegrant combination. However, at lower levels of disintegrant combinations MDT was in a relatively narrow range of 37.66 - 49.75 min, while at higher level MDT was in a relatively broader range of 36.61 to 70.40 min. (Table - 7). In addition, the effect of compressional force was also found to be governed by the levels of disintegrant combinations used. Compressional force was found to be in direct relationship with MDT when combination of disintegrants were used in low levels, whereas, an inverse relationship with MDT was observed when disintegrant combinations were used in high levels. However, combinations of CPD + CCS appeared to be least influenced by the variations in compressional force, as well as variations in levels of disintegrant combination used.

III.3.4 Texture analysis

Parameters from Disintegration Force time curve were found helpful in better understanding of the mechanism of disintegration and dissolution, which was difficult with the compendial disintegration and dissolution tests. Development of sufficient disintegration force is required to overcome the internal bonding as well as resistance offered by the boundary layer around the tablet. Time required to reach maximum disintegration force (T_{max}) is the time after which disintegration force started to weaken; therefore, shorter T_{max} is associated with the rapid degeneration of disintegration force. Disintegration force development rate (DFDR) is the result of a complex interplay of

formulation variables e.g., disintegrants, binders and filler. Rapid DFDR generally favours short T_{max}.

In fasted state, disintegration force curves of formulations containing high level of disintegrant combinations, and compressed at 10 and 30 KN are relatively close with each other. However, these curves of formulations containing low levels of disintegrant combinations were quite distinct (Figure - 13A to Figure - 15A). Whereas in fed state, disintegration force curves were found to be in a close proximity with each other with respect to the level of disintegration combination used. It signifies that the effect of compressional force was not that strong as was seen in fasted state (Figure - 13B to Figure - 15B). Moreover, high level of disintegrant combination had higher magnitude of F_{max} and bigger area under the disintegration force curves as compared to the curves obtained with formulations having low levels of disintegrant combination.

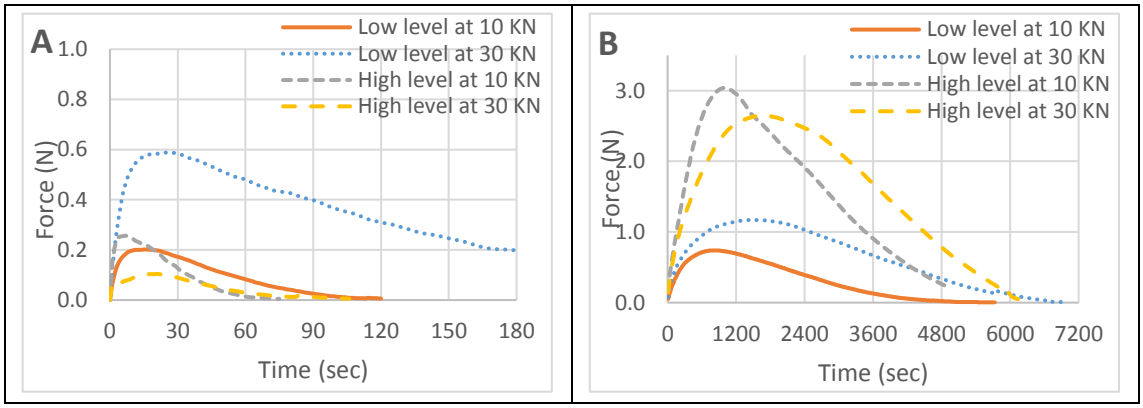

Figure - 13: Disintegration Force-time curves of Lactose based formulations containing the combination of Crospovidone and Croscarmellose Sodium at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

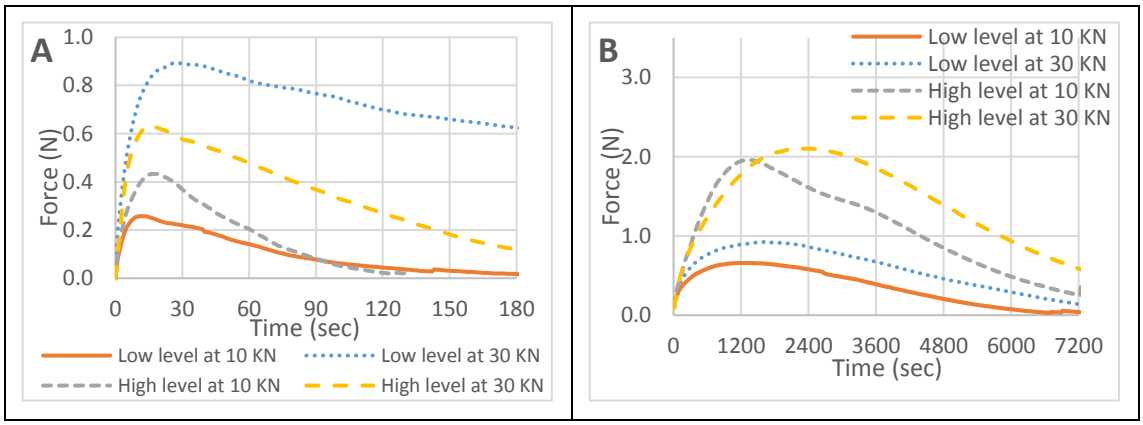

Figure - 14: Disintegration Force-time curves of Lactose based formulations containing the combination of Sodium Starch Glycolate and Croscarmellose sodium at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

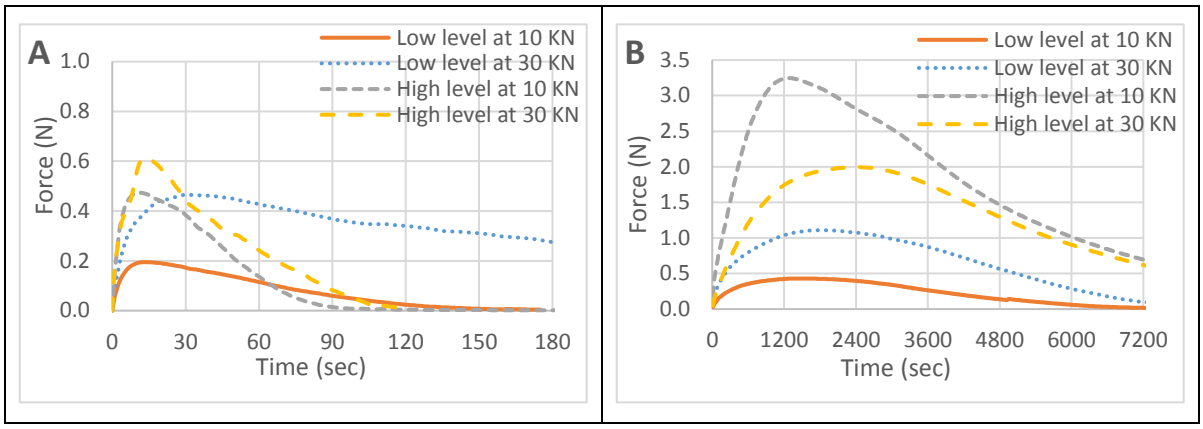

Figure - 15: Disintegration Force-time curves of Lactose based formulations containing the combination of Sodium Starch Glycolate and Crospovidone at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

In fasted state, values of F_{max} and T_{max} increased with an increase in compressional force, as expected, because at higher compressional internal structure of tablet become stronger. In the same connection, DFDR is expected to be reduced accordingly, but surprisingly DFDR gave a mixed response when compressional force was changed. It is to be noted that at higher level of disintegrant combinations the effect of compressional force on DFDR was more pronounced. However, the influence of the compressional force on F_{max} and T_{max} was more visible when disintegrant combinations were used in low levels (Table - 8).

Table - 8: Parameters from disintegration force – time curve of lactose based tablets in simulated fasted state (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No Disintegrant	0.66 ± 0.070	0.39 ± 0.023	90 ±8	1350 ± 106.6	1.04	0.50	4.89 ± 0.368	0.13 ± 0.009
CPD+CCS (Low level)	0.20 ± 0.023	0.59 ± 0.06	15 ± 2.49	27 ± 4.2	1.02	1.05	8.84 ± 0.796	14.04 ± 0.980
SSG +CCS (Low level)	0.26 ± 0.041	0.89 ± 0.107	11 ± 1.23	27 ± 3.4	1.12	0.99	18.90 ± 2.130	23.93 ± 0. 53
SSG +CPD (Low level)	0.20 ± 0.009	0.46 ± 0.062	13 ± 2.42	32 ± 2.307	1.09	0.99	11.39 ± 0.267	9.86 ± 1.38
CPD+CCS (High level)	0.26 ± 0.034	0.10 ± 0.004	7 ± 0.212	21 ± 3.2	1.02	0.65	19.56 ± 0.890	2.46 ± 0.49
SSG +CCS (High level)	0.43 ± 0.074	0.64 ± 0.087	17 ± 3.406	16 ± 2.38	1.11	1.25	20.95 ± 4.38	34.89 ± 6.89
SSG +CPD (High level)	0.47 ± 0.104	0.61 ± 0.020	10 ± 0.361	13 ± 2.95	1.11	0.92	36.90 ± 2.29	36.36 ± 1.17

In fed state, a general increase in values of maximum disintegration force (F_{max}) and $T_{max,}$ whereas, a decrease in the values of DFDR was observed with an increase in level of disintegrant combinations as well as compressional force. It is apparently due to more torturous microstructure of tablet (Table - 9).

Table - 9: Parameters from disintegration force – time curves of lactose based tablets in simulated fed state (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No Disintegrant	0.13 ± 0.016	0.28 ± 0.03	2130 ± 247.84	3270 ± 545.13	0.45	0.75	0.02 ± 0.0001	0.07 ± 0.008
CPD+CCS (Low level)	0.74 ± 0.120	1.17 ± 0.186	800 ± 68.98	1490 ± 170.45	1.07	0.93	0.77 ± 0.031	0.57 ± 0.048
SSG +CCS (Low level)	0.66 ± 0.105	0.92 ± 0.145	1280 ± 186.58	1600 ± 206.49	0.82	0.77	0.32 ± 0.051	0.36 ± 0.035
SSG +CPD (Low level)	0.43 ± 0.077	1.11 ± 0.148	1510 ± 129.40	1780 ± 130.79	0.94	0.88	0.21 ± 0.028	0.46 ± 0.053
CPD+CCS (High level)	3.04 ± 0.425	2.65 ± 0.481	990 ± 83.65	1670 ± 68.42	1.13	1.03	2.91 ± 0.480	1.35 ± 0.179
SSG +CCS (High level)	1.96 ± 0.423	2.10 ± 0.405	1310 ± 83.08	2250 ± 149.05	1.06	0.99	1.38 ± 0.193	0.78 ± 0.143
SSG +CPD (High level)	3.25 ± 0.061	1.99 ± 0.331	1290 ± 175.26	2370 ± 105.71	1.10	1.10	2.32 ± 0.086	0.72 ± 0.143

It is equally interesting that though F_{max}, DFDR and T_{max} differ significantly in low levels of disintegrant combinations, dissolution remained unaffected as MDT values were confined to a close range of 6.13 to 6.82 min (Table - 7) except for combinations of CPD + CCS compressed at 30 KN.

III.4 Discussion

III.4.1 Effect of combination of disintegrants and their levels

In simulated fasted state, irrespective of compressional force and levels of disintegrant combinations used, MDT and DT values were found to be in a narrow range of 3.44 to 10.16 and 0.38 min to 2.06 min respectively. Increase in the level of disintegrant combination was found to generally decrease the values of DT and MDT, though with low magnitude. Higher DFDR values at higher levels of disintegrant combination is evident of minimum hindrance in water uptake by the tablets in fasted state (Table - 8).

Although slightly higher disintegration time of the combination of SSG + CCS, among all combinations, may be ascribed to the potential gelling tendency of both disintegrants (Figure - 10A), but reduction in DT and MDT at high level of SSG+CCS i.e, gel forming disintegrants is interesting. Table - 6, reveals that at initial time point, viscosity of most of the disintegrant combinations in fasted state was either identical to or lower than the test medium i.e, water. Probably, a large number of disintegrant particles caused quick development of disintegration force that enabled disintegrants to disintegrate the tablets rapidly before gelling associated with higher level of disintegrants could influence disintegration. Similarly, significantly rapid DT of higher level of SSG + CPD combination may be ascribed to the DFDR values of approx. 36 x 10-3 N/s, at either compressional force. The curve of high level of CPD + CCS combination compressed at 10 KN (Figure - 13A) showed a rapid dissipation of disintegration force. This quick return of the curve towards x-axis might be due to the instant breakdown of internal structure of tablet, which further caused the delay in the release of API due to more torturous diffusion pathways, thereby resulting in a MDT value of 10.16, despite of T_{max} value of 7s and DFDR of 19.56 x 10-3 N/s.

Evaluation of formulations containing combinations of CPD + CCS, SSG + CCS and SSG + CPD, under simulated fed conditions, revealed that with an increase in levels of disintegrant combinations from low to high, both disintegration and dissolution times were also prolonged (Figure - 10B & Table - 7). Increase in MDT and DT values with a rise in levels was more pronounced in combinations involving SSG i.e, SSG + CCS and SSG + CPD, however under simulated fasted conditions, more rapid dissolution and disintegration was observed when disintegrant combinations of SSG+CCS and SSG+CPD were used in higher levels (Table - 7). Combination of CPD + CCS was found to be least affected to the changes in the levels of disintegrant combination.

In order to understand the less significant impact of the levels of combination of CPD + CCS on dissolution and disintegration of tablets in fed state their mechanism of disintegrant action may be considered. Swelling of CCS with moderate gelling and presumed shape recovery mechanism of CPD without gelling may be accounted in this regard (Bi et al., 1999; Camargo, 2011; Desai et al., 2012; Khairnar et al., 2014). Shape recovery of CPD appeared to curtail the weak gelling of CCS, which is evident by the viscosity of the respective combination, presented in Table - 6. Albeit, initial viscosity of this combination was increased comparatively at higher level of disintegrant combination, the viscosity associated with both higher and lower level of combination become identical at 10 min. Among all the disintegrant combinations tested, this combination possesses shortest T_{max} and highest magnitude of F_{max} and DFDR at either level, (Table - 9). Whereas, relatively steeper curves in Figure - 13B are suggestive of rapid development and subsequent degeneracy of disintegration force. It can comprehensively explain the rapid disintegration and dissolution associated with this combination of disintegrants. Rapid DT, at low level of the combination of CPD+CCS as compared to the high level of its combination, may be associated with the presence of only 2% CCS. This low level of CCS is sufficient to give its wicking action but may not be enough to impart a weak viscous barrier in deep pores of the tablets.

SSG gives its disintegrant action through a strong increase in volume of its particles (Rowe et al., 2009). Hydration of SSG particles coupled with high swelling rate results in an increase in the viscosity of medium surrounding the disintegrant particles, which

could form a gel layer (El-Barghouthi et al., 2008). Therefore, in disintegrant combinations, where SSG was used in higher proportion (4%), the presence of gelling was supposed to induce viscous barriers in the internal structure of the tablets. This notion is supported by considering the viscosity data presented in Table - 6. At 1 min., the viscosity of the higher levels of SSG + CCS and SSG+CPD was found to be 255 and 262 cp respectively, which is noticeably higher than the viscosity of the medium i.e, 236 cp. At 10 min., the viscosity of the combination of SSG + CCS has risen to 286 cp, whereas that of SSG + CPD was consolidated at 263 cp. The role of CPD in limiting the gelling induced by SSG has been exhibited. On the contrary, the viscosity of the same combinations when used in low levels was almost identical except at 10 min. However, the magnitude of viscosity was comparatively lower. SSG induced gelling at higher levels was further translated into longer T_{max} and higher F_{max} i.e, it took longer to dissipate disintegration force, which resulted in a longer range of DT (10.81 – 15.69 min) (see Table - 9). In Figure - 14 & Figure - 15 short and flat curves of low levels of disintegrant combinations containing SSG as well as relatively low F_{max} and shorter T_{max} suggest that the amount of SSG was not sufficient to impart enough gelling to hinder the disintegration; therefore, DT was reduced (i.e, 6.84 – 8.69 min.).

Interfacial controlled mechanism ($n > 1$) was found to be dominant when combinations were used in higher levels (Table - 9). Interfacial controlled mechanism suggests detachment of particles from the compact. Further disintegration of detached particles depend upon the nature of disintegrants used (Quodbach & Kleinebudde, 2014a). In addition to the boundary layer, these detached particles may still have weak gel structure inside, therefore, liberation of API from particles may further be retarded. On the contrary, diffusion controlled mechanism ($n < 1$) was observed at low levels of these combinations. At low levels of SSG and CCS, widespread blockade in the porous system of the tablet was reduced due to lesser number of disintegrant particles available. Therefore, comparatively more free water was supposed to be available thereby facilitating the movement of API across the presumed viscous barrier. Therefore, despite of higher T_{max}, lower F_{max} due to less detachment of particles and lower DFDR values, MDT values were reduced to the range of 39.62 min – 49.75 min when both combinations were used in lower combination as compared to the range of 53.29 min – 70.40 min when higher level of these combinations was used.

When lactose is used as a filler, we have suggested the use of CPD or CCS as single disintegrant in the formulations in order to minimize the negative effect of food induced viscosity (Zaheer & Langguth, 2018). However, the result of our studies regarding the combination of disintegrants indicates the potential of the combination of CPD + CCS to outperform the use of either CPD or CCS as single disintegrant at 4% total concentration in formulations. Therefore, while optimizing the formulations, which will be least affected by food-induced viscosity, formulators may consider the suitable proportions of this combination.

III.4.2 Effect of compressional force

MDTs tend to decrease generally, with an increase in compressional force when tested in fasted state. Increased values of F_{max} and T_{max} at 30 KN, are indicative of delayed rupture of a tablet's micro structure, thereby allowing the significant release of API before the clogging of deep pores occur. It could be a possible explanation for this

trend. However, the magnitude of change was low and most of the formulations found to possess similar profiles (f_2 > 50) when drug release profiles of formulations compressed at 10 and 30 KN were compared (Table - 7). Formulations containing high level of disintegrant combination of SSG + CCS and CPD +CCS deviated the trend. Slightly delayed disintegration and elevated viscosity of the dispersion of SSG+CPD combinations in the early time points, while change of disintegration mechanism from interfacial controlled to diffusion controlled with an increased compressional force in CPD+CCS combination could possibly explain this nominal deviation. Consideration of localized viscosity associated with rapid dissolution of lactose in water, could be a better explanation of generally broader disintegration force time curve of disintegrant combinations when compressed at 30 KN, in fasted state, as depicted in Figure - 13A to Figure - 15A.

A lesser number of disintegrant particles at the low level of disintegrant combination may take longer to overcome the bonding of tablets. This is evident from the higher values of F_{max} and T_{max} of respective formulations (Table - 8). It might explain the relatively higher DT with low level of disintegrants and vice versa, when tested in simulated fasted state.

In simulated fed state, a direct relationship, though with low magnitude, was observed between disintegration time and compressional force. Interestingly, the combination of SSG + CPD at the higher level was an exception, where DT was reduced with an increase in compressional force. At higher compressional force, particles are packed in a close proximity; therefore, swelling disintegrants like SSG are expected to give their immediate effect on adjacent particles, providing that water penetration is adequate. CPD present in the combination, due to its wicking action, apparently helped to maintain the adequate water penetration despite of gelling potential of SSG. At low level of the same combination, DT was almost the same, probably due to low concentration of SSG.

In formulations containing low levels of disintegrant combination, disintegration was relatively rapid but MDT values were found to increase with an increase in compressional force, when tested under simulated fed conditions. Relatively higher F_{max} and longer T_{max} values of the respective formulations (Table - 9), at 30 KN, are indicative of resistance of internal structure of the tablet that increases the MDT when compared with the same formulations compressed at 10 KN.

Changes in compressional force did not appear to have any impact on MDT when high levels of disintegrant combinations were used. However, the combination of SSG+CCS is an exception where MDT was found to reduce with a rise in compressional force. It may be attributed to the better performance of swelling disintegrants when compressed at higher compressional force. Combination of CCS + CPD either at low or higher level, was least affected by the changes in compressional force. Similarity of their dissolution profiles at either compressional force is evident by the f_2 statistic value (f_2> 50) ((Table - 7)). F_2 statistic value of combination of SSG + CPD at higher level, also advocates its insensitivity to changes in compressional force, but high MDT values i.e, beyond 67, rules out its further consideration; though, its DT was significantly reduced with an increase in compressional force.

Torturous diffusion pathways and low porosity associated with higher compressional force generally restrict penetration of dissolution medium inside the tablet. Inadequate

penetration of medium at higher compressional force, when viscous layer surrounds the tablet, potentiates the gelling tendency of SSG. It resulted in comparatively higher MDT values in formulations containing SSG. Weak capillary forces keep water drawn into the tablet mass as long as the particles are in close proximity. Wicking ability of disintegrants are expected to maintain effective fluid uptake, therefore, a reduction in DFDR was seen in disintegrant combinations containing SSG, which has a modest wicking ability.

In fed state, penetration of medium and subsequent release of API is already compromised due to the viscous barrier surrounding the tablet and its detached particles. Therefore, while devising a strategy for formulations, which are to be least affected by food-induced viscosity, anything contributing to potentiate viscous barrier need to be avoided or at least be limited. If we consider the inclusion of SSG in mixture of disintegrants, then formulation optimization may result in too low concentration of SSG to give sufficient results besides increasing the level of other disintegrant. Therefore, formulators may skip the inclusion of SSG in formulations with above mentioned objective and having lactose as a major filler.

Chapter IV Effect of nature of single disintegrants on tablet disintegration in fed viscosity media: Dibasic Calcium Phosphate as a model insoluble and non-swellable filler.

IV.1 Introduction

Bioavailability of tablets containing BCS class III drugs is reduced when taken with food. This negative food effect can be ascribed partly to slow tablet disintegration and dissolution imparted by food induced viscosity (Cvijić et al., 2014). Role of superdisintegrants in reducing the disintegration and dissolution times is studied thoroughly under fasted conditions. However, data regarding the role of superdisintegrants under fed conditions is insufficient to develop a formulation strategy. During current study, role of different superdisintegrants having different mechanisms was studied in the presence of an insoluble matrix. Dibasic calcium phosphate was selected by virtue of its aqueous insolubility.

Dibasic calcium phosphate (dihydrate) is a commonly used filler. It is predominantly used in vitamin and mineral supplements because of the high calcium and phosphorus content. The addition of a lubricant is necessary to facilitate the ejection of dibasic calcium phosphate based tablets from dies, during the compression process. Alkaline lubricants such as magnesium stearate have practically no effect on the binding properties if dibasic calcium phosphate is used as a filler (Bolhuis et al., 1975). This insensitivity to magnesium stearate has been attributed to the fact that clean, lubricated surfaces are created by crystal fragmentation during the process of consolidation and compaction.

When placed in water, dibasic calcium phosphate tablets are rapidly and completely penetrated by the liquid (Van Kamp et al., 1985). This rapid penetration is caused by the hydrophilic nature of the material and the high porosity of the tablets (Lerk et al., 1976). Despite the fast and complete water penetration, dibasic calcium phosphate tablets do not disintegrate because the excipient is relatively insoluble in water and no disintegration force is developed (Caramella C. et al., 1986). Therefore, it is important to include a disintegrant with an active mechanism such as swelling, for example, starch, povidone and sodium starch glycolate, to develop the disintegration forces necessary to disintegrate the tablet.

IV.2 Materials and Methods

IV.2.1 Materials

Calcium Hydrogen Phosphate dihydrate (Dibasic Calcium Phosphate), Merck, Germany was used as a filler. For remaining materials, see II.2.1.

IV.2.2 Tablet preparation

See II.2.2

IV.2.3 Media composition

See II.2.3

IV.2.4 Disintegration studies

See II.2.4

IV.2.5 Dissolution studies

See II.2.5

IV.2.6 Disintegration force determination

See II.2.7

IV.3 Results.

IV.3.1 Disintegration studies

Tablets devoid of disintegrants did not disintegrate, until 30 minutes, when tested in simulated fasted state. It is in line with earlier reports that DCP tablets either did not disintegrate or take quite long to disintegrate (Caramella et al., 1986). However, the presence of disintegrants caused the DCP based tablets to disintegrate rapidly (Figure - 16A). Disintegration of tablets was too quick, except in case of SSG containing formulations compressed at 30KN, to draw any meaningful conclusion about the role of the nature of disintegrants. Nevertheless, an obvious direct relationship between disintegration time (DT) and compressional force applied was observed.

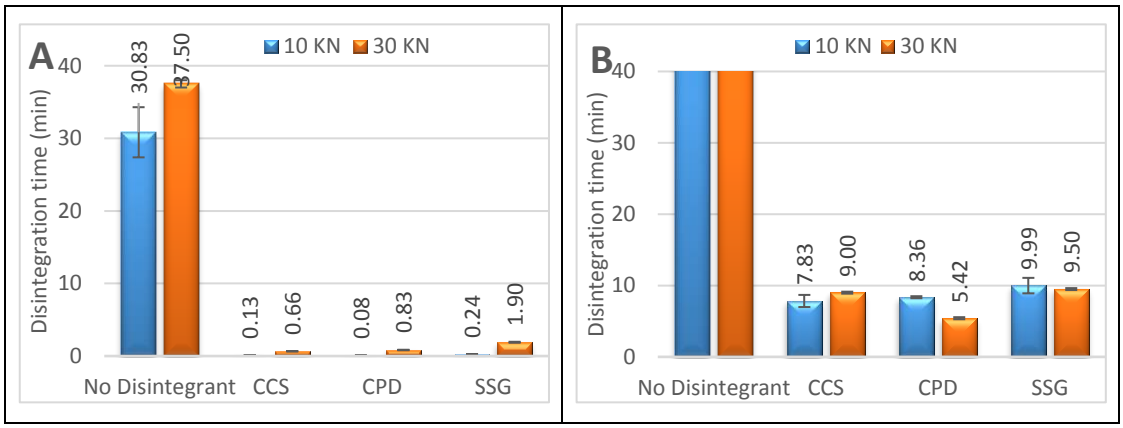

Figure - 16: Effect of compressional force and nature of disintegrants on disintegration time of Dibasic Calcium Phosphate based Trospium chloride formulations (n = 6) A – Formulations tested in fasted state, B – Formulations tested in fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

In fed state, formulations having no disintegrants did not disintegrate within 45 minutes. However, the inclusion of disintegrants caused a noticeable reduction in DT which was sufficient for the compliance of existing compendial limits (i.e, <15 min for uncoated tablets). Compressional force did obviously influence the disintegration of tablets but it was found to be dependent on the nature of disintegrant used. For example, a direct relationship of DT with compressional force was found in formulations containing CCS as disintegrant, whereas the same relationship was inverse in formulations containing CPD or SSG as disintegrant (Figure - 16B). Khan and Rhodes coined that in contrast to the general notion increased compressional force does not necessarily increase the DT of DCP based tablets (Khan & Rhodes, 1975a). Based on our results, the disintegration behaviour of DCP based tablets, in viscous state, was more dependent on the nature of disintegrant than the compressional force.

IV.3.2 Dissolution studies

When tested in simulated fasted state, formulations containing disintegrants were found to release the drug rapidly and complied the criterion for "very rapid dissolution" (i. e. more than 85 % drug dissolved in 15 min)(Yu et al., 2002). On the other hand, less than 80% drug was released in 30 min from the formulation devoid of any disintegrant; therefore even the criterion for "rapid dissolution" (i. e. more than 80 % dissolved in 30 min) was not met at either compressional force (Figure - 17).

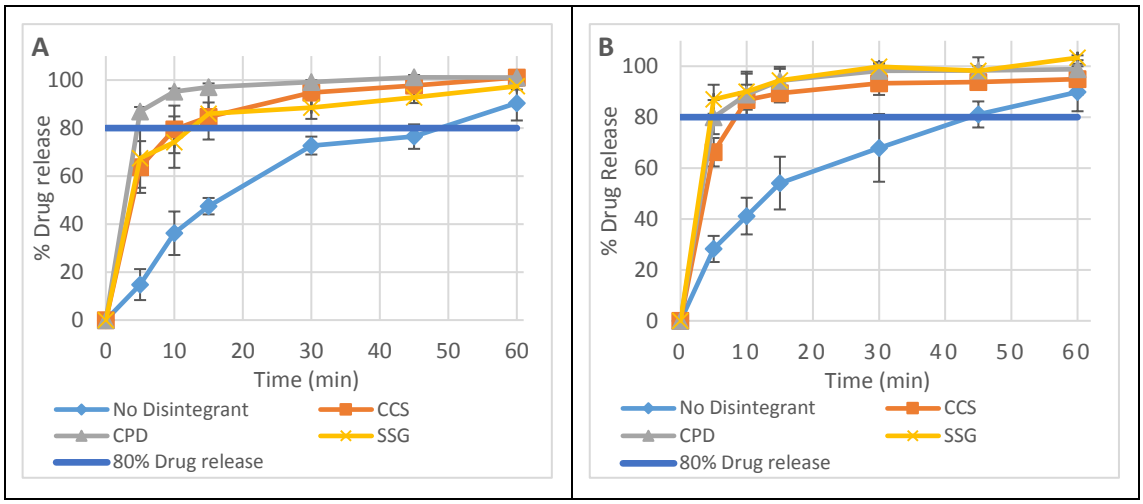

Figure - 17: Effect of compressional force and nature of disintegrants on % drug release from Dibasic Calcium Phosphate based Trospium chloride formulations, in simulated fasted state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

However, no tested formulation complied with neither "very rapid dissolution" nor "rapid dissolution" criteria when tested under viscous conditions (Figure - 18). Formulations containing CCS and SSG showed very similar drug release profiles, especially at lower compressional weight, whereas formulations having CPD and formulations devoid of any disintegrant showed similar release profiles at either compressional force (Figure - 18). This may be suggestive of a common mechanism of drug release.

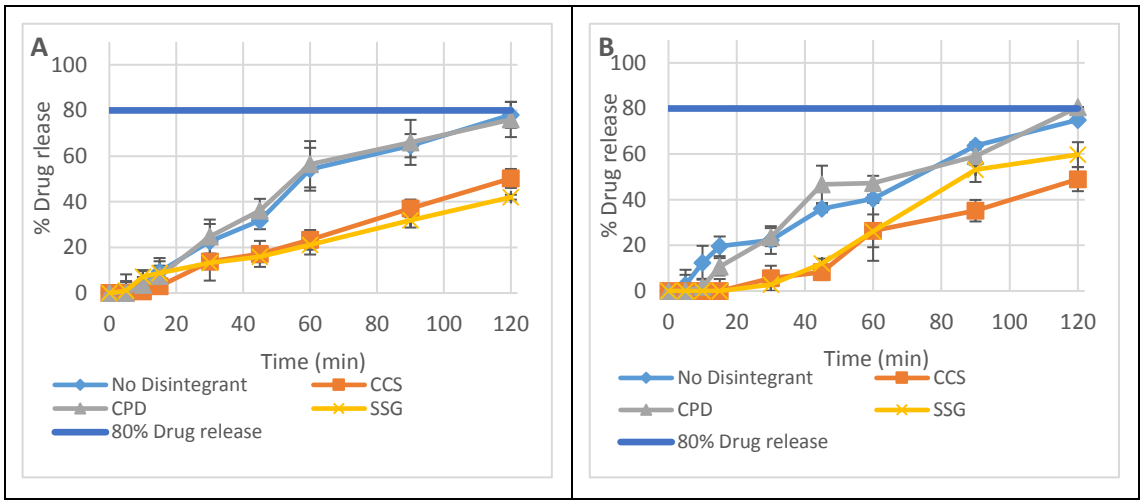

Figure - 18: Effect of compressional force and nature of disintegrants on % drug release from Dibasic Calcium Phosphate based Trospium chloride formulations, in simulated fed state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Contrary to the direct relationship of DT with compressional force (see IV.3.1), mean dissolution time (MDT) of formulations containing disintegrants were found to have an inverse relationship with compressional force, under non-viscous conditions. However, very rapid dissolution and f_2 statistic values of above 50, for these formulations, this

inverse relationship become insignificant. Exception is the formulations having SSG as single disintegrant, where f_2 value reflects the dissimilarity in drug release profile (Table - 10).

Table - 10: Effect of media viscosity, compressional force and nature of disintegrants on Mean dissolution time (MDT) and f_2 statistic on Dibasic Calcium Phosphate based tablet formulations. (Mean ± SD; n=4). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate.

Disintegrant	Fasted state			Fed state		
	*MDT (min)		f_2 (10 KN Vs 30 KN)	*MDT (min)		f_2 (10 KN Vs 30 KN)
	10 KN	30 KN		10 KN	30 KN	
No Disintegrant	19.70	22.06	57.54	69.91	70.59	57.01
CCS	7.98	5.47	65.46	120	120.37	66.17
CPD	3.65	4.56	68.09	63.32	70.09	61.15
SSG	8.48	4.53	45.54	144.57	100.44	47.00

* Calculated on the averaged values

Under viscous conditions, formulations having no disintegrant did not disintegrate within 45 minutes, but surprisingly at either compressional force, their MDTs were approx. 70 in fed state, which is lower than the MDT of formulations containing gel forming disintegrants i.e, CCS and SSG (Table - 10). Similar to DTs, a mixed response of MDT with compressional force was seen. MDT of formulations devoid of any disintegrant and those containing CCS was not found to be influenced by changes in compressional force. In formulations containing CPD, MDT was increased with an increase in compressional force, whereas, MDT of SSG containing formulations was decreased with an increase in compressional force. However, f_2 value suggests that dissimilarity, due to the influence of compressional force, was found only in SSG containing formulation (Table - 10).

IV.3.3 Texture analysis

Both in fed and fasted state, a general trend of increased magnitudes of maximum disintegration force (F_{max}) and time to reach maximum disintegration force (T_{max}) was observed when formulations containing disintegrants were compressed at higher compressional force. In Figure - 19 & Figure - 20, it is reflected as the broadening of disintegration force curves at higher compressional force i.e, 30KN.

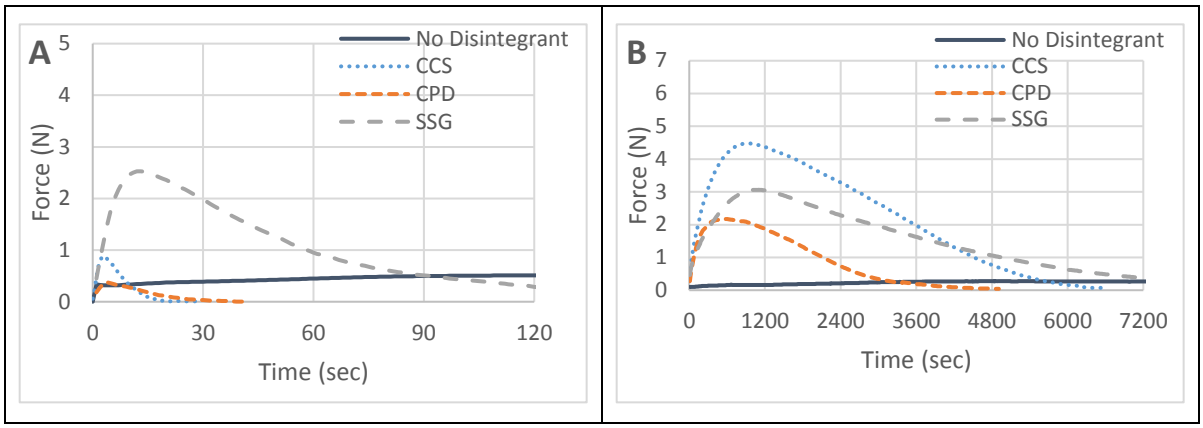

Figure - 19: Disintegration Force-time curves of Dibasic Calcium Phosphate based formulations containing different disintegrants, compressed at 10 KN (n = 3) A – simulated fasted state, B – simulated fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

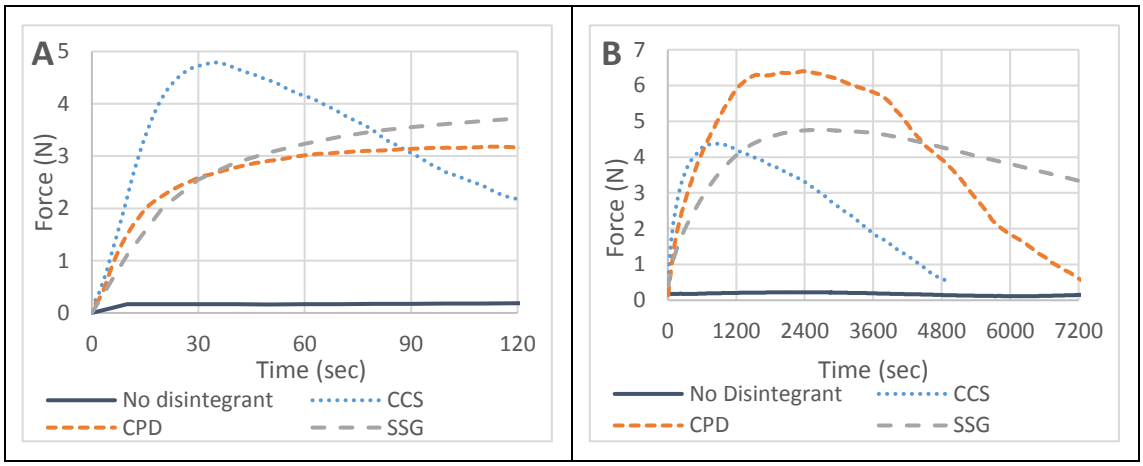

Figure - 20: Disintegration Force-time curves of Dibasic Calcium Phosphate based formulations containing different disintegrants, compressed at 30 KN (n = 3) A – simulated fasted state, B – simulated fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

In fasted state, F_{max} and T_{max} were increased, while DFDR decreased with an increase in compressional force (Table - 11). In case of CPD and SSG, T_{max} and DFDR were affected more by the changes in compressional force. Interfacial-controlled mechanism was changed to diffusion-controlled at higher compressional force in these formulations. In case of CCS, disintegration force and related parameters were least affected by the compressional force.

Table - 11: Parameters from disintegration force – time curves of dibasic calcium phosphate based tablets in simulated fasted state (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

Disintegrant in formulation	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s $x10^{-3}$	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No disintegrant	0.60 ± 0.05	0.23 ± 0.02	325 ± 34.9	460 ± 59.4	0.51	0.45	0.76 ± 0.12	0.16 ± 0.03
CCS	0.88 ± 0.04	4.79 ± 0.48	03 ± 0.25	35 ± 1.35	1.31	1.57	330.52 ± 78.50	146.52 ± 16.84
CPD	0.37 ± 0.03	3.18 ± 0.24	04 ± 0.52	113 ± 16	1.31	0.94	66.66 ± 9.70	17.22 ± 3.20
SSG	2.53 ± 0.09	4.46 ± 0.05	13 ± 2.35	450 ± 79.56	1.51	0.67	185.52 ± 45.50	4.41 ± 0.35

In fed state, F_{max} and T_{max} were increased, while DFDR decreased with an increase in compressional force, except in case of CCS where F_{max} and T_{max} remained almost intact (Table - 12). Disintegration force and related parameters were greatly influenced by the changes in compressional force, in case of formulations containing CPD. It is the only disintegrant where interfacial controlled mechanism was found to be dominant in fed state. In SSG containing formulations, despite of its strong swelling, T_{max}, F_{max} and DFDR were less influenced by the compressional force when compared with CPD containing formulations (Table - 12). Under viscous conditions, the disintegrants may be arranged in the following order with respect to their sensitivity to the changes in compressional force: CPD> SSG> CCS.

Table - 12: Parameters from disintegration force – time curves of dibasic calcium phosphate based tablets in simulated fed state. (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

Disintegrant in formulation	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s $x10^{-3}$	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No disintegrant	0.27 ± 0.047	0.22 ± 0.586	4890 ± 880	2160 ± 268	0.60	0.29	0.035 ± 0.002	0.025 ± 0.003
CCS	4.48 ± 0.213	4.37 ± 0.571	920 ± 124	880 ± 168	0.99	0.94	3.90 ± 0.319	3.32 ± 0.368
CPD	2.18 ± 0.380	6.40 ± 0.034	530 ± 102	2360 ± 390	1.03	1.05	3.05 ± 0.250	2.15 ± 0.195
SSG	3.06 ± 0.361	4.76 ± 0.280	1100 ± 86	2660 ± 176	0.90	0.93	2.17 ± 0.185	1.36 ± 0.118

IV.4 Discussion

If we compare the disintegration force and related parameters of DCP based tablets with lactose based tablets, then relatively lower F_{max} and DFDR values were observed in lactose based tablets when evaluated in fed state. It may be due to the simultaneous dissipation of disintegration force because of evacuating lactose particles. However relatively higher values of F_{max} and DFDR may be attributed to the insolubility and hydrophilicity of DCP respectively. Therefore, nature of disintegrant and type of disintegration mechanism are worth to consider in formulations having insoluble and non swellable fillers.

IV.4.1 Effect of nature of disintegrants

IV.4.1.1 Fasted state

Short disintegration times and compliance of criterion for very rapid dissolution of disintegrant containing DCP based formulations in fasted state make it difficult to draw any meaningful inference about the role of disintegrants. Hydrophilicity of DCP and higher DFDR values are indicative of rapid water uptake (Quodbach & Kleinebudde, 2014b) thereby facilitating the disintegrant molecules to give their disintegrant action while short T_{max} values give a hint about quick loss of structural integrity (Table - 11). Both result into a prompt destruction of tablet microstructure and rapid bursting of the compact, which is reflected as quick DTs. Although CCS containing tablets disintegrated quickly, relatively slower dissolution was observed when compared with CPD containing formulations (Table - 10). A weak gelling tendency of CCS may be attributed to the slightly higher MDT value. Nevertheless, in CPD containing formulations, despite the dominancy of interfacial-controlled mechanism of disintegration, the MDT value was relatively low, probably due to non-gelling shape recovery mechanism of CPD. Despite relatively slow disintegration and dissolution among tested formulations, development of strong disintegration force because of strong swelling potential of SSG, with noticeable DFDR caused the tablet to disintegrate before the gelling could take place. Nevertheless, clogging of pores of de-aggregated particles due to gelling tendency of SSG may be one of the reason of relatively slow drug release observed in SSG containing formulation, as interfacial controlled mechanism was dominant at lower compressional force (Table - 11). Viscosity determinations of dispersion of disintegrants suggest that if tablets containing these 3 disintegrants disintegrate within 1 minute then associated gelling is not expected to influence the disintegration (Zaheer & Langguth, 2018). However, it may influence the drug dissolution depending upon the dominant mechanism of tablet disintegration. Overall, DCP based tablets showed relatively rapid disintegration as compared to lactose based tablets, under non-viscous conditions (see Figure - 3 & Figure - 16).

IV.4.1.2 Fed state

When evaluated in fed state, dissolution profiles of formulations containing CCS and SSG were found quite similar, especially when compressed at 10KN (Figure - 18). MDT values of more than 100 min and percent drug release of less than 60% in 120 minutes from both formulations, may be ascribed to the hydration and subsequent swelling of

CCS and SSG followed by weak gel formation, in addition to the limited mobility of solvent molecules in viscous medium (Bi et al., 1999; Camargo, 2011; Rowe et al., 2009). Differences in the gelling tendencies of the two disintegrants may be one of the reason for differences in MDT values of their formulations, although DT of these formulations was within a narrow range of 7.83 – 9.99 minutes. Earlier, we have evaluated the gelling tendencies of different disintegrants in simulated fed state, which showed that the gelling tendency of SSG was higher than that of CCS. CPD did not show any noticeable gelling (Zaheer & Langguth, 2018).

Although tablets containing no disintegrant did not disintegrate within 45 min, while those containing CPD, disintegrated in less than 8.5 minutes, dissolution profiles and MDT values of both formulations are found to be similar. Lower MDT values associated with these formulations suggests relatively rapid release of API as compared to the formulations containing gel-forming disintegrants such as CCS and SSG (Figure - 18 & Table - 10). It may be attributed to the fact that there is no gel formation upon contact with water, due to insolubility of DCP and shape recovery mechanism of CPD (Desai et al., 2012; Quodbach et al., 2014). It may be postulated that due to the hydrophilic nature of DCP (Jivraj et al., 2000), pores of tablets were filled with the medium. Nevertheless, the porous system didn't collapse rapidly due to the insolubility of DCP, as evident by disintegration time, allowing the API to release through these water-filled pores, though at lower pace mainly due to lack of any active mechanism. Shape recovery mechanism of CPD is believed to be in search for a more energy favourable position of polymer chains through their entanglement, when they are hydrated after coming in contact with the dissolution/disintegration medium. Mechanical activation of these chains results in the expansion of volume without gelling, which further enhances the accessible pores filled with medium (Desai et al., 2012; Quodbach et al., 2014). Volume expansion causes the tablet to disintegrate and medium filled pores facilitate the release of API with high solubility. Therefore, not only in the current study with DCP based tablets, but in our previous study with lactose based tablets, CPD appeared to be the effective disintegrant under viscous conditions (Zaheer & Langguth, 2018).

Zhao & Augsburger have observed that in non-viscous medium, both CCS and SSG containing tablets disintegrated into primary particles, though tablets having CCS disintegrated relatively rapidly. Whereas, CPD containing tablets also disintegrated rapidly but into larger aggregated particles (Zhao & Augsburger, 2005a). Table - 12, suggests that under viscous conditions, diffusion-controlled mechanism (i.e, n-exponent value less than 1) was found to be dominant in all tested formulations except in formulations containing CPD, where interfacial controlled mechanism (i.e, n-exponent value > 1) appeared to be the dominant mechanism of disintegration. Despite of the fact that the detached aggregates of particles from CPD containing formulations were surrounded by presumed boundary layer in viscous medium but a comparatively rapid release of drug was observed than the formulations containing gel forming disintegrants i.,e CCS and SSG. Apparently, the absence of weak gel in deep pores of tablets containing CPD as disintegrants and increased surface area could be the underlying factors in this regard.

Generally, high values of F_{max} and DFDR with lower values of T_{max} are indicative of relatively rapid disintegration/dissolution of tablets in viscous state (Zaheer & Langguth, 2018). However, despite having the lower value of F_{max} and DFDR as

compared to CCS containing formulations (Table - 12), relatively rapid drug release from CPD containing formulations was observed. High F_{max} in CCS is supposed to be due to the swelling of disintegrant and subsequent blockade of pores that lead to slow release of API. Therefore, it is more underperformance of CCS than the improved effect of CPD.

Although, the inclusion of a disintegrant is necessary in DCP based compacts, the better drug release from the DCP based tablets without any disintegrant, as compared to those containing gel-forming disintegrants in viscous medium is interesting. Researchers have suggested the addition of highly hydrophilic and strongly swelling disintegrants in tablets with insoluble filler. While, in tablets with soluble fillers, disintegrants having limited swelling but with water wicking ability are advised (Caramella et al., 1986; Rojas et al., 2012). Slow release evident by larger MDT values provides a basis to preclude the use of CCS and SSG as disintegrants in compacts having DCP as filler. However, based on our results, we suggest to consider a non-gelling disintegrant as a part of formulation strategy while developing a tablet formulation in order to minimize the negative food effect.

IV.4.2 Effect of compressional force

IV.4.2.1 Fasted state

Parameters from disintegration force – time curves provide a better understanding of the rapid dissolution at higher compressional force in DCP based formulations. Increased T_{max} at 30 KN indicates that tablet particles took longer to detach from the compact. Whereas, high F_{max} means more particles of tablets has exerted the stress on the sensing probe of texture analyzer, either due to swelling of disintegrants and/or dislocation of particles leaving behind the pores. Stress thus induced due to swelling of disintegrants in narrow pores may have contributed to the dislocation of particles and subsequent creation of new pores/ widening of existing pores thereby allows the API to leave the compact by virtue of more availability of water in newly formed pores. In this regard, high F_{max} of 4.46 N and T_{max} of 450s in SSG containing formulations may explain the reduction of MDT at high compressional force. In formulations compressed at 10 KN due to relatively larger pores, swelling disintegrants may not have induced sufficient stress on the adjacent particles in order to create new pores, thus blocking the pores, because of gel formation, in which they are located. That is why relatively low F_{max} and T_{max} was observed in formulation compressed at low compressional force (Table - 11).

Due to insolubility and non-swellability of DCP, the effect of compressional force was largely dependent on the nature of the disintegrant present in the formulation. Under non-viscous conditions, DT increased with an increase in compressional force in all tested formulations. It is more probably due to relatively strong compact and lesser pore structure associated with higher compressional force, as reflected by reduced DFDR and increased F_{max} in formulations compressed at higher compressional force. MDT values of formulations containing disintegrants having more swelling yet gelling tendency i.e, CCS and SSG were decreased, while MDT of formulations devoid of any disintegrant and those containing CPD increased slightly with an increase in compressional force. Nonetheless, the magnitude of change was low and most of the formulation, except those containing SSG, were found to possess similar release profiles i.e, $f_2 > 50$, when

similar formulation compressed at 10 and 30 KN was compared (Table - 10). This dissimilarity may be attributed to the availability of more water due to the hydrophilic nature of DCP, which facilitated SSG to give its strong swelling action in harder tablets.

IV.4.2.2 Fed state

Testing under viscous conditions revealed that formulations containing CCS was not influenced by the changes in compressional force as related parameters of disintegration force and MDT almost remained constant. Whereas, other swelling disintegrant i.e, SSG gave reduced MDT values with an increase in compressional force while DT remained unaltered. The effect of compressional force is also reflected as $f_2 < 50$ (Table - 10 & Table - 12). High F_{max} at 30 KN suggests that due to the hydrophilicity of DCP, SSG particles may have taken up some water to swell noticeably before the interior of the compact become relatively inaccessible to water due to gelling associated with SSG particles. This limited swelling may have created new pores due to dislocation of compact particles but due to subsequent gelling tendency of SSG because of inadequate penetration of water in viscous medium and the surrounding boundary layer, tablet pores may not be sufficient to enhance the drug release better than CPD containing formulations.

Disintegration times of formulations containing CPD were noticeably influenced by compressional force. The hydrophilic nature of DCP apparently synergized the wicking and shape recovery action of CPD, which is evident from the high magnitude of F_{max} and dominancy of interfacial controlled mechanism (Table - 12). The same interfacial controlled mechanism may explain why commensurate reduction in MDT of the same formulations was not observed. However, despite impeded liberation of API at high compressional force, MDT values were still shorter than MDT values of CCS and SSG containing formulations.

Figure - 19B & Figure - 20B, offer additional information in-situ about the changes in microstructure of tablets during the process of disintegration under viscous and non-viscous conditions. For example, generation of more disintegration force in formulations containing CPD when compressed at higher compressional force in non-viscous medium. It would have not been detected through conventional disintegration test. Similarly testing in viscous conditions provide a substantial evidence to limit the use of swelling disintegrants with gelling tendency in formulations containing APIs whose bioavailability is compromised in the presence of food. However, evaluation of proper combination of disintegrants in fed state may be beneficial in improving the development of formulation strategy to minimize the API independent negative food effect.

Chapter V Effect of combination of disintegrants and their levels on tablet disintegration in fed viscosity media: Dibasic Calcium Phosphate as a model insoluble and non-swellable filler.

V.1 Introduction

Delayed disintegration and dissolution of tablets when taken with food, emphasize the inclusion of disintegrants in tablet formulations. This addition of disintegrants aims to reduce the negative effect of food as much as possible. Interestingly, majority of studies pertaining performance of disintegrants focused the use of single disintegrant whereas, importance of disintegrant combinations was not that much highlighted. Current study is an attempt to understand the role of combination of superdisintegrants in the presence of an insoluble matrix. Dibasic calcium phosphate (DCP) was selected by virtue of it aqueous insolubility. Tablets containing this filler requires the addition of disintegrants because tablets containing DCP do not disintegrate rapidly. Moreover, non-disintegrating nature of DCP based tablets provide a better platform to improve the current understanding of the effect of disintegrants under fed conditions. Identification of any synergism or antagonism between disintegrants under fed conditions will be beneficial for the formulators who are working to develop formulations in order to minimize the negative food effect.

V.2 Materials and Methods

V.2.1 Materials

See II.2.1.

V.2.2 Tablet preparation

See III.2.2

V.2.3 Media composition

See II.2.3

V.2.4 Disintegration studies

See II.2.4

V.2.5 Dissolution studies

See II.2.5

V.2.6 Disintegration force determination

See II.2.7

V.3 Results

V.3.1 Disintegration studies

In simulated fasted state, the use of disintegrant combinations caused a rapid disintegration of DCP based tablets within 1 minute, just like CCS and CPD as single disintegrants (see Chapter IV). The effect of level of disintegrant combination was found to be dependent on the compressional force. In tablets compressed at higher compressional force (30 KN), DT was reduced with a reduction in the level of disintegrant combination, whereas, in tablets compressed at lower compressional force (10 KN) DT was increased with a reduction in the level of disintegrant combination. The combination of SSG+CCS was found to be least affected by the changes in compressional force. Generally, DT increased slightly with an increase in the compressional force (Figure - 21A).

It is interesting to note the influence of the filler. In case of DCP as a filler, the effect of level of disintegrant combination is dependent on the compressional force. While, in case of Lactose as a filler, the effect of compressional force was dependent on the level of disintegrant combination, i.e, DT of formulation containing lower levels of disintegrant combinations increased with an increase in compressional force, whereas, DT of formulations containing higher levels of disintegrant combinations decreased with an increase in compressional force (see III.3.1).

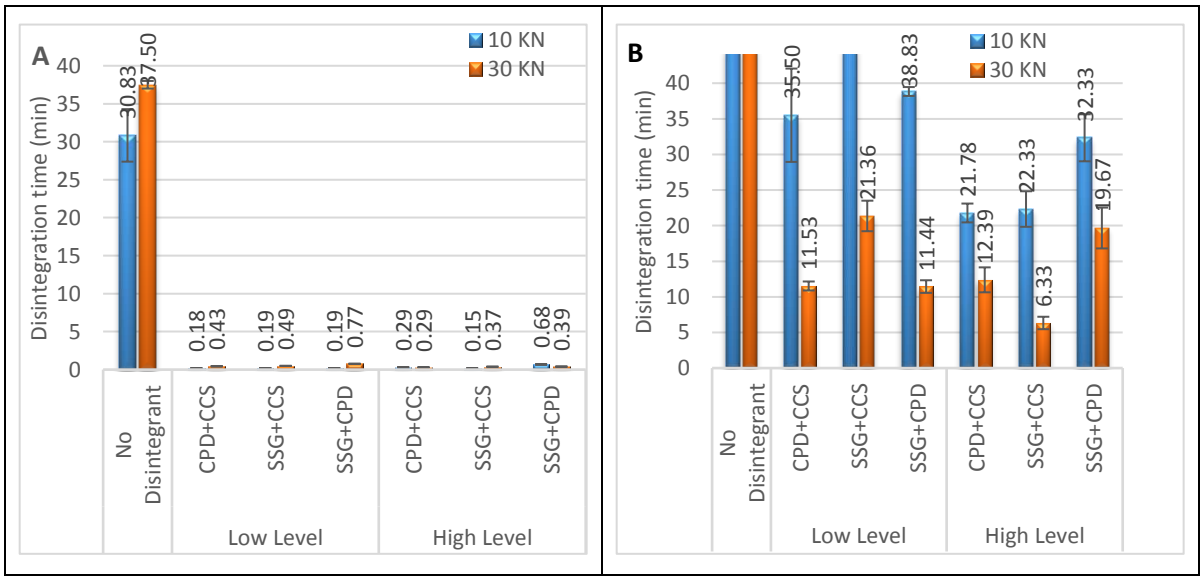

Figure - 21: Effect of compressional force, combination of disintegrants and their levels on disintegration time of Dibasic Calcium Phosphate based Trospium chloride formulations (n = 6) A – Formulations tested in fasted state, B – Formulations tested in fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

Unlike in fasted state, the DT of tablets showed an inverse relationship with the compressional force, i.e, an increase in compressional force resulted in reduced DT, when tested in simulated fed state (Figure - 21B). Similar to the fasted state, the effect of level of disintegrant combination was found to be dependent on the compressional force. In tablets compressed at higher compressional force (30 KN), no clear trend was identified, whereas, in tablets compressed at lower compressional force (10 KN) DT was reduced with a reduction in the level of disintegrant combination, which is opposite to the observations seen in fasted state. In fasted state, a combination of SSG+CCS was found to be least affected by the changes in compressional force, but in fed state this combination was found to be most affected by the changes in the compressional force as well as its level. However, tablets containing the high level of SSG+CCS, compressed at 30 KN disintegrated in 6.33, which is most rapid among all disintegrant combinations tested in fed state.

V.3.2 Dissolution studies

When tested under simulated fasted conditions, most of the formulations compressed at 10 KN showed very rapid dissolution behavior, and some formulations, compressed at 30 KN showed the same behaviour. Generally, all of the formulations complied with the criterion for rapid dissolution i. e. more than 80 % of API was released within 30 min. (Figure - 22).

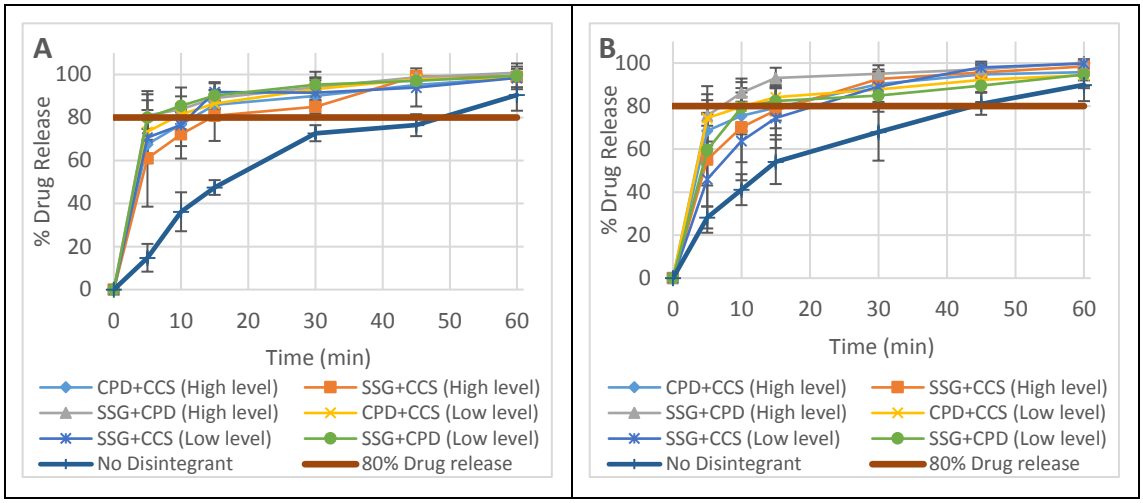

Figure - 22: Effect of compressional force, combination of disintegrants and their levels on % drug release from Dibasic Calcium Phosphate based Trospium chloride formulations, in simulated fasted state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Release of drug was found to be slower when the formulations were tested under simulated fed conditions. Less than 60% of drug was released within 30 minutes. Therefore, no formulation complied either with "very rapid dissolution" or with "rapid dissolution" criteria in fed state (Figure - 23). Generally, formulations containing low levels of disintegrant were found to release more drug within the test duration of 120 minutes.

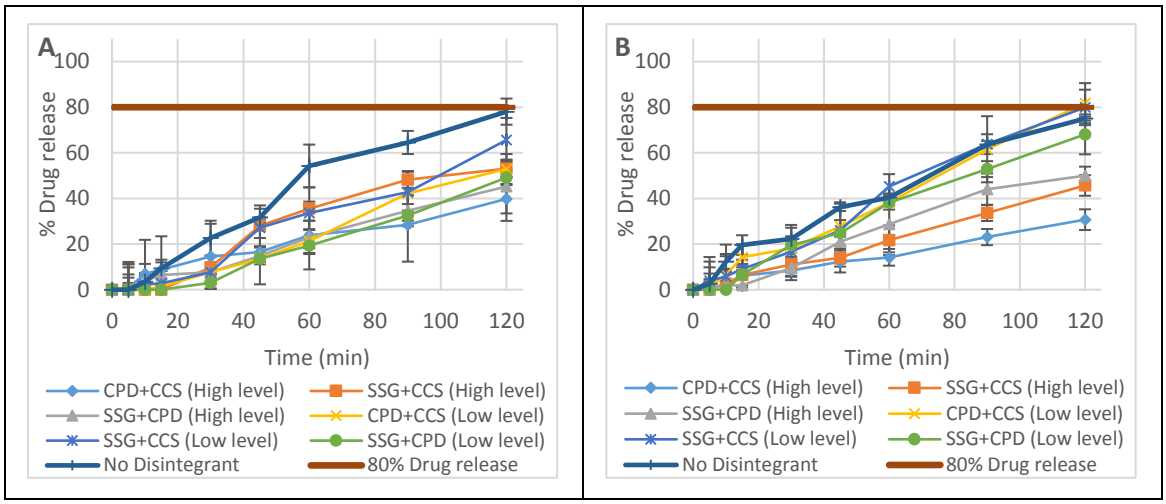

Figure - 23: Effect of compressional force, combination of disintegrants and their levels on % drug release from Dibasic Calcium Phosphate based Trospium chloride formulations, in simulated fed state (Mean ± SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Under simulated fasted conditions, MDT was found to have a direct relationship with compressional force at low level of disintegrant combination. However, in formulations having high level of disintegrant combination MDT revealed an inverse relationship with compressional force (Table - 13). Moreover, MDT was found to increase with an increase in the level of disintegrant combination, except for the formulation having SSG in the high level of disintegrant combination. It is concluded that lower level of disintegrant combinations compressed at lower compressional force favours reduction in MDT, under non-viscous test conditions.

Table - 13: Effect of media viscosity, compressional force and level of disintegrant combinations on Mean dissolution time (MDT) and f2 statistic on Dibasic Calcium Phosphate based formulations. (Mean ± SD; n=4). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate.

Disintegrant	Fasted state			Fed state		
	MDT (min)		f_2 (10 KN vs 30 KN)	MDT (min)		f_2 (10 KN vs 30 KN)
	10 KN	30 KN		10 KN	30 KN	
No Disintegrant	19.70	22.06	57.54	69.91	70.59	57.01
CPD+CCS (Low level)	6.70	6.84	70.11	98.18	62.01	39.92
SSG +CCS (Low level)	7.41	11.41	43.33	77.32	69.12	48.24
SSG +CPD (Low level)	6.13	8.81	48.30	109.41	81.12	42.65
CPD+CCS (High level)	8.26	7.73	75.17	151.38	197.64	60.91
SSG +CCS (High level)	9.70	9.52	67.04	100.51	130.66	51.25
SSG +CPD (High level)	6.45	6.29	74.81	131.78	100.91	64.00

* Calculated on the averaged values

When tested under viscous conditions, MDT was found to have an inverse relationship with compressional force when a low level of disintegrant combination was used. F_2 statistic values lower than 50 also endorsed that pattern. Whereas in formulations having a high level of disintegrant combination MDT revealed a direct relationship with compressional force (Table - 13). This trend is completely opposite to the trend obtained under non-viscous conditions. Moreover, level of disintegrant combination were found to have a direct relationship with MDT. Therefore, in order to get a relatively rapid dissolution, formulation need to be compressed at higher compression force, while maintaining the lower level of disintegrant combination.

V.3.3 Texture analysis

In fasted state, disintegration force curves of formulations containing high levels of disintegrant combinations, and compressed at 10 and 30 KN were found to be distinct. Although similar curves of formulations containing low levels of disintegrant combination were also distinct with each other but their spread was comparatively smaller (Figure - 24A to Figure - 26A). This appeared to be due to the presence of DCP, because when lactose was used as a filler, disintegration force curves of formulations containing high levels of disintegrant combination were relatively closer (see III.3.4).

In fed state, high levels of disintegrant combination showed higher magnitude of F_{max} and larger area under the disintegration force curves as compared to the curves obtained with formulations having low levels of disintegrant combination (Figure - 24B to Figure - 26B).

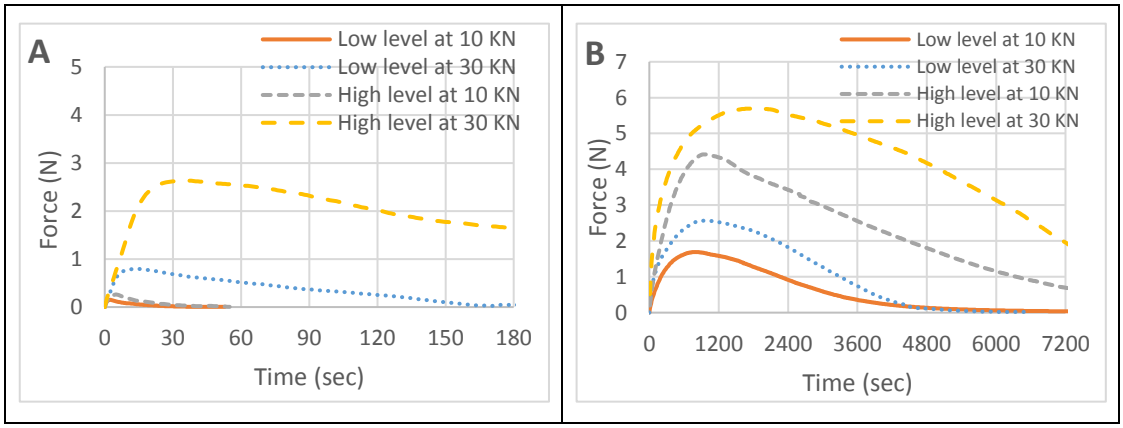

Figure - 24: Disintegration Force-time curves of Dibasic Calcium Phosphate based formulations containing the combination of Crospovidone and Croscarmellose Sodium at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

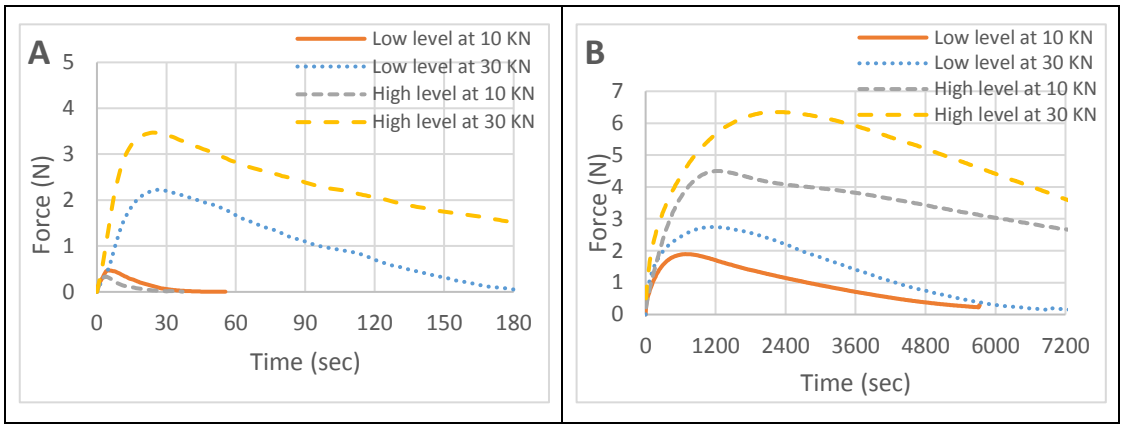

Figure - 25: Disintegration Force-time curves of Dibasic Calcium Phosphate based formulations containing the combination of Sodium Starch Glycolate and Croscarmellose sodium at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

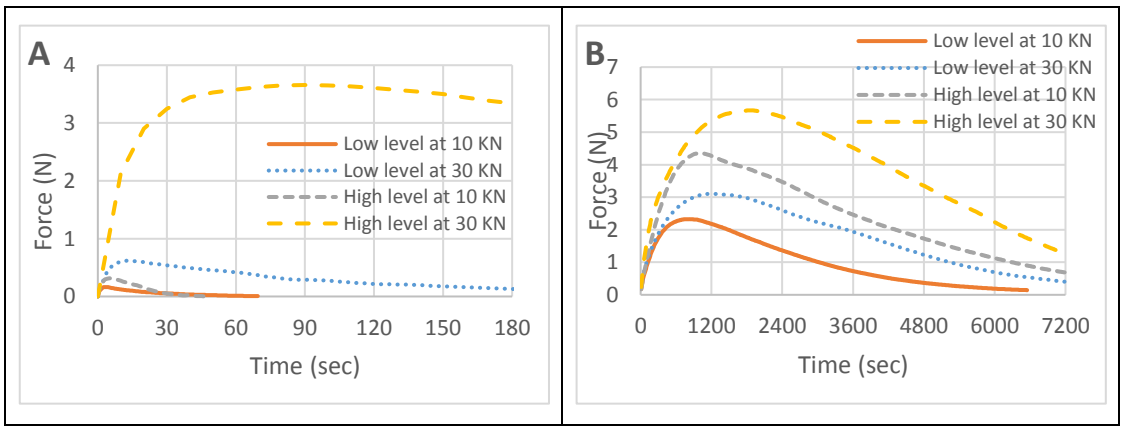

Figure - 26: Disintegration Force-time curves of Dibasic Calcium Phosphate based formulations containing the combination of Sodium Starch Glycolate and Crospovidone at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

In fasted state, values of F_{max} and T_{max} increased with an increase in compressional force, while the magnitude of increase was higher with high level of disintegrant combination. In the case of DFDR, a mixed response depending upon the nature of disintegrant combination was found. Inverse relation of DFDR with compressional force at low level changed to the direct relation at higher level of disintegrant combination (Table - 15). Here, level of disintegrant combination appeared to define the role of compressional force. Interface-controlled mechanism of disintegration was found in almost every formulation.

Table - 14: Parameters from disintegration force – time curves of dibasic calcium phosphate based tablets in simulated fasted state. (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No Disintegrant	0.60 ± 0.05	0.23 ± 0.02	325 ± 34.9	460 ± 59.4	0.51	0.45	0.76 ± 0.12	0.16 ± 0.03
CPD+CCS (Low level)	0.15 ± 0.02	0.79 ± 0.04	2 ± 0.28	15 ± 2.75	1.13	1.39	59.44 ± 8.48	45.75 ± 9.19
SSG +CCS (Low level)	0.47 ± 0.05	2.22 ± 0.35	5 ± 1.13	26 ± 6.06	1.19	1.49	88.55 ± 13.68	94.65 ± 16.78
SSG +CPD (Low level)	0.16 ± 0.03	0.62 ± 0.02	4 ± 0.64	14 ± 1.98	1.19	1.25	33.27 ± 5.82	36.29 ± 4.24
CPD+CCS (High level)	0.26 ± 0.01	2.64 ± 0.16	5 ± 0.98	36 ± 16	1.01	1.35	39.04 ± 5.87	70.67 ± 11.84
SSG +CCS (High level)	0.34 ± 0.13	3.47 ± 0.66	4 ± 0.07	25 ± 5.94	1.40	1.47	81.79 ± 7.37	137.33 ± 16.04
SSG +CPD (High level)	0.31 ± 0.12	3.66 ± 0.85	5 ± 1.56	90 ± 16.55	1.20	0.89	48.13 ± 4.84	18.18 ± 2.29

In fed state, a general increase of maximum disintegration force (F_{max}) and T_{max} was observed, along with a decrease in DFDR was observed with an increase in the level of disintegrant combinations as well as compressional force. It is apparently due to more torturous microstructures of tablets (Table - 15). Similarly, an increase in compressional force appeared to favour the dominance of diffusion-controlled mechanism of disintegration (n – exponent value < 1)

Table - 15: Parameters from disintegration force – time curves of dibasic calcium phosphate based tablets in simulated fed state. (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No Disintegrant	0.27 ± 0.05	0.22 ± 0.59	4890 ± 880	2160 ± 268	0.60	0.29	0.035 ± 0.002	0.025 ± 0.003
CPD+CCS (Low level)	1.69 ± 0.15	2.57 ± 0.24	790 ± 8	890 ± 110	1.06	0.85	1.80 ± 0.18	2.13 ± 0.57
SSG +CCS (Low level)	1.90 ± 0.20	2.74 ± 0.14	680 ± 37	1150 ± 154	0.93	0.84	2.10 ± 0.31	1.52 ± 0.29
SSG +CPD (Low level)	2.32 ± 0.26	3.10 ± 0.33	830 ± 165	1230 ± 120	1.09	1.02	2.32 ± 0.53	2.01 ± 0.47
CPD+CCS (High level)	4.42 ± 0.52	5.70 ± 0.01	940 ± 139	1810 ± 356	1.11	0.84	4.30 ± 1.1	1.88 ± 0.98
SSG +CCS (High level)	4.50 ± 0.80	6.35 ± 0.45	1240 ± 60	2190 ± 239	1.13	0.86	3.26 ± 0.48	2.05 ± 0.22
SSG +CPD (High level)	4.35 ± 0.65	5.67 ± 0.33	970 ± 102	1890 ± 68	1.15	0.97	4.22 ± 0.38	2.23 ± 0.43

V.4 Discussion

V.4.1 Effect of combination of disintegrants and their levels

Due to lack of any active mechanism of disintegration, DCP, as a filler, is beneficial in understanding the behavior of different combination of disintegrants without confounding factor. When tested in fasted state, a higher magnitude of F_{max} was observed in formulations containing a high level of disintegrant combination especially those containing gel forming disintegrants (Table - 14). This was not observed in formulations where lactose was used as a filler, probably due to simultaneous dissolution of lactose.

Among all tested formulations in fasted state, those formulations containing disintegrant combinations at low level, containing CPD gave the shortest MDT. Interestingly, in disintegrant combinations at low level, containing CPD, relatively lower magnitude of F_{max} was observed (Table - 14). It may be due to the fact that CPD works through shape recovery and it is assumed that in shape recovery, tablets do mostly expand axially i.e, in the opposite direction of compressional force applied (Quodbach et al., 2014), therefore due to less number of CPD particles, disintegration force was not sufficiently generated. However, in the same formulations, T_{max} values were the shortest, which

itself reflects rapid disruption of internal tablet structure. Due to insoluble nature of DCP, the deep pores of the tablet may not have clogged and provided some channels through which API continued to release.

Due to the insolubility of DCP matrix and lack of any intrinsic property which can be beneficial in the disintegration of the matrix, disintegrants with swelling property need to be considered. That is the reason why the n-exponent value was found to be higher in SSG containing combinations. However, Interfacial-controlled mechanism was dominant in almost every formulation tested in fasted state,

Under simulated fed conditions, evaluation of formulations containing combinations of CPD + CCS, SSG + CCS and SSG + CPD, , revealed that a reduction in the levels of disintegrant combinations from high to low, have resulted in the reduction of disintegration as well as dissolution times (Figure - 21B & Table - 13). This trend was probably due to lesser number of disintegrant particles at lower level, which themselves were not enough to cause the generalized blockade of the deep pores of tablets due to gelling of CCS and SSG. This effect of level of disintegrants was more pronounced in disintegrant combination of SSG + CCS. Despite of the notion that higher magnitudes of F_{max} is desirable to overcome the boundary layer in fed state an obvious reduction in F_{max} values was seen with the reduction in level of disintegrant. Interestingly, despite reduced F_{max} values, a reduction in disintegration and dissolution times was observed. DFDR values were also reduced with a reduction in disintegrant levels, reduced penetration of dissolution medium inside the tablet pointing to this reduction was lesser in magnitude than the reduction of F_{max}. T_{max} on the other hand, was reduced surprisingly (Table - 15). It gives an idea that possibly the low level of disintegrant combination was sufficient to overcome the internal bonding of the tablet. Use of high level of disintegrant, especially gel-forming ones may have contributed to increase the strength of tablet further by filling the deep pores of tablets with their weak gels forming ability. Gel formation is promoted with an inadequate supply of water to the disintegrant particles. This is the case in fed state, where a boundary layer around the tablet impedes the water penetration into the tablets.

Therefore, while optimizing the formulations of tablets with an objective of minimizing the negative food effect, lower levels of disintegrant combinations having CPD should be used, when DCP is used as a filler or comprises the major proportion of filler combination. Proportion of SSG, if used in the combination due to its swelling tendency, should be kept as low as possible.

V.4.2 Effect of compressional force

In fasted state, the effect of the level of disintegrant combination seems to be influenced by the changes in compressional force. A generalized increase in DT was observed with an increase in compressional force. Nevertheless, a closer look reveals that at 10 KN, DT decreased but MDT increased with an increase in the level of disintegrant combination, while at 30 KN, DT increased, but MDT decreased with an increase in level of disintegrant combination.

It may be due to the higher porosity in tablets compressed at low compressional force, where lesser number of disintegrant particle at low level took longer to overcome the

tablet bonding, however more gel will be formed at higher level of combinations containing gel forming disintegrants, but due to larger pores it may not be enough to block the pores. In tablets compressed at higher compressional force, pores are small, therefore, even lesser number of disintegrant particles will be sufficient to cause the disintegration. However, due to small pores, disintegrant particles with swelling tendency are expected to perform better. On the other hand, disintegrant particles especially with gel forming tendency will also cause the disintegration but even the smaller gelling might be sufficient to block the small pores where these disintegrant particles lie. The trend of MDT may be understandable by considering the values of n-exponent (Table - 14). Higher MDT value were found to be associated with the higher n-exponent value i.e, more pronounced interfacial phenomenon. Dominance of interfacial-controlled mechanism means that the process of disintegration will be rapid and yield more fragments of tablets detached from the surface of the tablet. These fragments could have API inside, which has to liberate further, thus causing a slightly longer MDT.

In fed state, higher DT at lower compressional force was found. DCP is hydrophilic in nature; therefore, DCP tablets draw water quickly through capillary forces. In addition to the boundary layer surrounding the tablets larger pores of tablets compressed at 10 KN, may have filled with the viscous medium. The disintegrants have to overcome this viscous medium in addition to the bonding of tablet and surrounding boundary layer. At higher level of gel forming disintegrant combinations, they themselves, though slightly, contribute to the localized viscosity. In addition to all of these factors, lack of any active mechanism of disintegration of DCP, results in larger DT and MDT values at lower compressional force.

In case of high compressional force, due to torturous and smaller pores viscous medium did not penetrate the tablet as it happened in tablets compressed at low compressional force (see DFDR values in Table - 15), and due to close proximity of particles disintegrants were more effective, as reflected by the increased values of F_{max}. Therefore, a generalized reduction in DT and MDT was observed in tablets compressed at higher compressional force. However, at high level of disintegrant combination, higher number of disintegrant particles did contribute to the slight elevation of localized viscosity that resulted in a slight prolongation of DT and MDT.

In fed state, dominance of diffusion-controlled mechanism of disintegration seems to improve the dissolution, because most of the API will diffuse from the compact through the boundary layer (Table - 15).

Chapter VI Effect of nature of single disintegrants on tablet disintegration in fed viscosity media: Microcrystalline Cellulose as a model insoluble but swellable filler.

VI.1 Introduction

This negative food effect can be ascribed partly to slow tablet disintegration and dissolution imparted by food induced viscosity (Cvijić et al., 2014). When taken with food, bioavailability of tablets containing BCS class III drugs is reduced. Scientific literature pertaining the role of formulation and processing under fed conditions is insufficient to develop a formulation strategy. During current study, role of different superdisintegrants having different mechanisms as well as and compressional force was studied in the presence of a swellable matrix. Microcrystalline cellulose was selected by virtue of its swelling abilities.

Formulation scientists ranked microcrystalline cellulose as the most useful filler for direct compression. Its popularity can be ascribed to its excellent compactibility at low pressures, high dilution potential and superior disintegration properties. Microcrystalline cellulose can be compressed both with and without magnesium stearate and still produced hard compacts. A microcrystalline cellulose tablet may be visualized as a special form of cellulose fibril in which the crystals are compacted close enough together so that hydrogen bonding between them can occur (Reier & Shangraw, 1966). Hydrogen bonds between hydrogen groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness of compacts. Microcrystalline cellulose is regarded as being chemically inert and compatible with most drugs

VI.2 Materials and Methods

VI.2.1 Materials

VIVAPUR, Type 102 (Microcrystalline cellulose) JRS Pharma, Germany was used as a filler. For remaining materials, see II.2.1.

VI.2.2 Tablet preparation

See II.2.2

VI.2.3 Media composition

See II.2.3

VI.2.4 Disintegration studies

See II.2.4

VI.2.5 Dissolution studies

See II.2.5

VI.2.6 Disintegration force determination

See II.2.7

VI.3 Results

VI.3.1 Disintegration studies

Except for the formulations containing CCS and CPD as single disintegrant and compressed at 10 KN, no other formulation complied the USP criterion for tablet disintegration test for uncoated immediate release tablets i.e, disintegration in less than 15 minutes. DT of the same formulations was found to be identical therefore; no meaningful inference could be drawn. Moreover, DT was found to be in direct relation with compressional force, i.e, DT increased with an increase in compressional force (Figure - 27A).

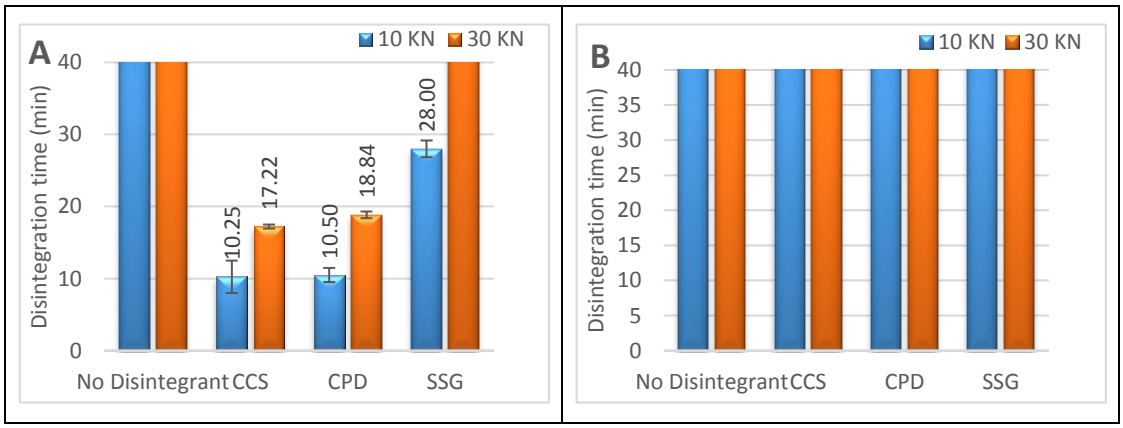

Figure - 27: Effect of compressional force and nature of disintegrants on ***disintegration time*** *of Microcrystalline Cellulose based Trospium chloride formulations (n = 6) A – Formulations tested in fasted state, B – Formulations tested in fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.*

In fed state, no formulations disintegrated during the test period of 45 minutes, therefore, the effect of nature of disintegrants in the presence of MCC was not determined (Figure - 27B).

VI.3.2 Dissolution studies

When tested in simulated fasted state, only the formulation containing CCS as disintegrant, at either compressional force, was found to comply with the criterion for "rapid dissolution" (i. e. more than 80 % dissolved in 30 min) (Yu et al., 2002). In addition to this formulation, only the tablets containing SSG as disintegrant and compressed at 10 KN were able to release more than 80% of API in 60 minutes (Figure - 28).

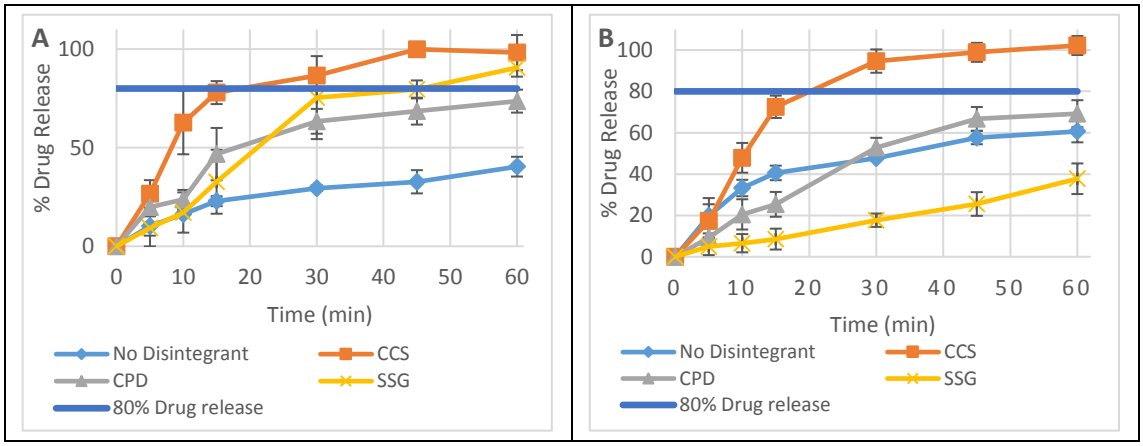

Figure - 28: Effect of compressional force and nature of disintegrants on % drug release from Microcrystalline cellulose based Trospium chloride formulations, in simulated fasted state (Mean ±SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

When tested under viscous conditions, no formulation complied either "very rapid dissolution" or "rapid dissolution" criteria. Similar to the non-viscous conditions, only the formulation containing CCS was found to release approx. 80% of API in 120 minutes, at either compressional force (Figure - 29).

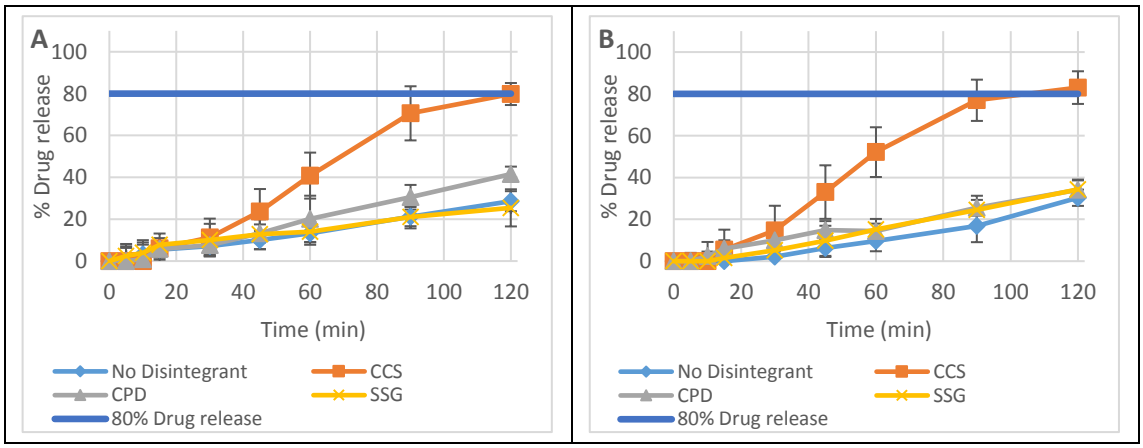

Figure - 29: Effect of compressional force and nature of disintegrants on % drug release from Microcrystalline cellulose based Trospium chloride formulations, in simulated fed state (Mean ±SD; n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Similar to the direct relationship of DT with compressional force (see VI.3.1) in non-viscous state, MDTs of formulations containing disintegrants showed a direct relationship with compressional force. However, not only the magnitude of difference but also the f_2 statistic value of more than 50 are suggestive of minimum effect of compressional force in formulations containing CCS. For the remaining formulations, f_2 statistic values lower than 50, indicate a noticeable effect of compressional force on MDT. Interestingly, MDT was rather improved in formulations where no disintegrant was used (Table - 16).

Table - 16: Effect of media viscosity, compressional force and nature of disintegrants on Mean dissolution time (MDT) and f_2 statistic on Dibasic Calcium Phosphate based tablet formulations. (Mean ± SD; n=5). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate.

Disintegrant	Fasted state			Fed state		
	*MDT (min)		f_2 (10 KN vs 30 KN)	*MDT (min)		f_2 (10 KN vs 30 KN)
	10 KN	30 KN		10 KN	30 KN	
No Disintegrant	72.92	40.07	36.57	208.18^{+}	199.60^{+}	70.52
CCS	11.52	12.93	53.80	74.25^{+}	61.89^{+}	65.40
CPD	29.60	35.52	48.04	142.42^{+}	178.84^{+}	69.65
SSG	21.77	82.55	19.72	248.94^{+}	167.69^{+}	65.40

* Calculated on the averaged values
$^{+}$ Extrapolated values

Under viscous conditions, MDT of tested formulations was found to be reduced with an increase in compressional force, except for the formulation containing CPD. This trend is in disagreement with the trend observed in fasted state, where MDT was increased with an increase in compressional force. However, in the light of magnitudes of MDTs only the formulation containing CCS could be of some practical consideration (Table - 16).

VI.3.3 Texture analysis

When MCC was used as filler, no big difference in the shape of disintegration force curve of formulations containing different disintegrants was observed (Figure - 30 & Figure - 31). This is in contrast to lactose and DCP based tablets where, a significant difference in the shape of the curves and related parameters was observed. This may be ascribed to the swelling tendency of MCC itself, which was not affected by the changes in viscosity of the test medium. In case of MCC based formulations, only those formulations containing CCS as disintegrant showed a decline of disintegration force within the test period of 4 hours.

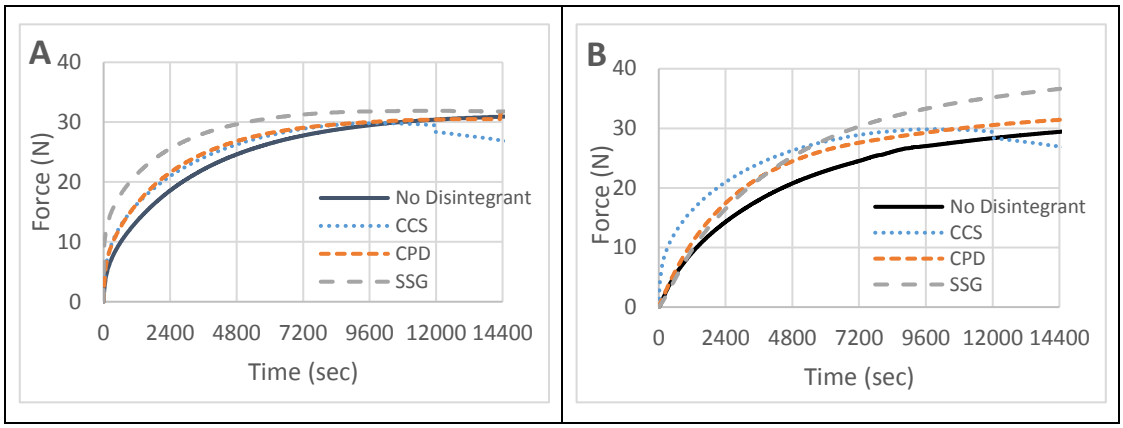

Figure - 30: Disintegration Force-time curves of Microcrystalline cellulose (Avicel PH 102) based formulations containing different disintegrants, compressed at 10 KN (n = 3) A – simulated fasted state, B – simulated fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

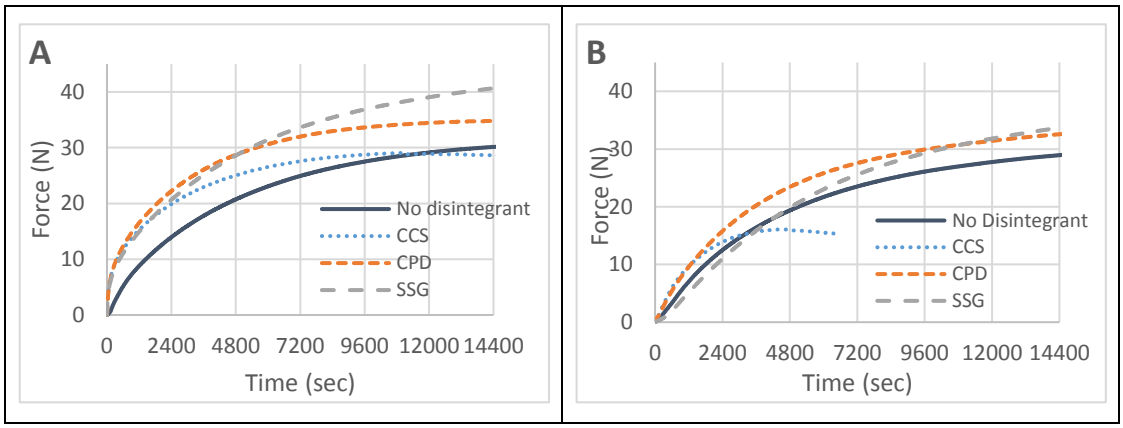

Figure - 31: Disintegration Force-time curves of Microcrystalline cellulose (Avicel PH 102) based formulations containing different disintegrants, compressed at 30 KN (n = 3) A – simulated fasted state, B – simulated fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

In case of formulations containing CPD and SSG, F_{max} was found to increase, while DFDR decreased with an increase in compressional force when evaluated under non-viscous conditions. However, compressional force does not seem to influence the formulations containing CCS (Table - 17). Diffusion-controlled mechanism of disintegration was found to be dominant in all formulations containing disintegrants.

Table - 17: Parameters from disintegration force – time curves of microcrystalline cellulose (Avicel 102) based tablets in simulated fasted state. (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

Disintegrant in formulation	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s $x10^{-3}$	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No disintegrant	31.18* ± 0.97	30.65* ± 1.25	16270* ± 0.00	16270* ± 0.00	0.79	1.03	1.18* ± 0.02	1.49* ± 0.08
CCS	29.85 ± 1.11	29.04 ± 0.92	9900 ± 781	10940 ± 1142	0.77	0.75	1.89 ± 0.26	1.64 ± 0.36
CPD	31.63 ± 1.41	34.82* ± 2.05	14740 ± 2700	16040* ± 0.00	0.64	0.83	1.10 ± 0.09	1.30* ± 0.14
SSG	31.89 ± 0.78	41.63* ± 1.26	12090 ± 0.00	16270* ± 0.00	0.69	0.77	1.13 ± 0.04	1.81* ± 0.05

*. – Disintegration force continued to develop until the end of the experiment.

In fed state, an increase in compressional force was found to decrease the F_{max} in all formulations, except for those containing CPD. T_{max} was only observed in formulations containing CCS, while in rest of the formulations disintegration force continued to rise until the end of experiment duration. An increase in compressional force was found to increase the DFDR in all formulations, except those containing CCS as disintegrant. Unlike in fasted state, interfacial-controlled mechanism of disintegration was observed in fed state, especially in formulations compressed at higher compressional force. Formulations containing CPD, however, are an exception in this regard (Table - 18).

Table - 18: Parameters from disintegration force – time curves of microcrystalline cellulose (Avicel 102) based tablets in simulated fed state. (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

Disintegrant in formulation	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No disintegrant	30.13 ± 2.76	29.65 ± 1.95	16270* ± 0.00	16270* ± 0.00	0.95	1.08	1.35 ± 0.09	1.50 ± 0.12
CCS	17.26 ± 2.60	16.06 ± 1.80	3720 ± 178	4510 ± 632	1.14	1.18	3.94 ± 0.62	3.11 ± 0.23
CPD	31.86* ± 1.58	33.19* ± 2.05	16270* ± 0.00	16270* ± 0.00	0.94	0.98	1.36* ± 0.12	1.55* ± 0.16
SSG	37.52* ± 2.48	34.78* ± 2.13	16270* ± 0.00	16270* ± 0.00	1.05	1.24	1.85* ± 0.09	1.98* ± 0.06

*. – Disintegration force continued to develop until the end of the experiment.

VI.4 Discussion

If we compare the development of disintegration force under viscous conditions in formulations where lactose, DCP and MCC were used as a filler then relatively lower F_{max} values were observed in lactose based tablets (II.3.4). It may be due to the simultaneous dissipation of disintegration force because of evacuating lactose particles. However relatively higher values of F_{max} and DFDR values were observed in DCP based tablets, which may be attributed to the insolubility and hydrophilicity of DCP respectively (IV.3.3). However, the highest values of F_{max} were observed with MCC based tablets, which was expected due to the swelling tendency of MCC (VI.3.3) Therefore, the nature of disintegrant and type of fillers used need to be studied carefully.

VI.4.1 Effect of nature of disintegrants

Liquid penetration is a most important step in the process of tablet disintegration, because the penetration of dissolution medium not only disrupts the particle bonding of tablets, responsible for the integrity of its structure, but it also activates the disintegrant particles to allow their disintegrant activity. This wicking process is believed to be driven by capillary forces that facilitate the inward movement of fluid while viscous forces impede the fluid movement (Curlin, 1955). Subsequent retention of penetrated fluid in the tablet pores filled with both fluid and water is thus the interplay of cohesion among liquid molecules and adhesion of liquid molecules and the particle surface (Szymkiewicz, 2012).

Under fed and fasted conditions, CCS is the only disintegrant where a drop in F_{max}, from the formulation devoid of any disintegrant, was observed. This reduction in F_{max} coupled

with reduced T_{max}, which is also the least among all formulations tested, is an indication of weakening of the internal tablet structure, which may cause the creation of new pores, or the widening of existing pores, ultimately leading to tablet disintegration. In addition to the relatively shorter T_{max}, an increased DFDR is characteristic of shorter MDT (see Table - 17 & Table - 18). It may be attributed to the mechanism of disintegrant action of CCS which is reported to be a mixture of swelling, wicking and shape recovery (Moreton, 2008).

Cylindrical-shaped particles of MCC provides the capillarity to draw liquid into compacts for the separation of bonded particles through annihilation of hydrogen bonding created between adjacent particles when compacted (Al-Khattawi et al., 2014; Peck et al., 1989). In the absence of any disintegrant, destruction of these hydrogen bonds results in an impermeable structure that leads to longer disintegration times, as was seen in formulations devoid of any disintegrant (Figure - 27A&B). In case of CPD, DT was identical with CCS containing formulations in fasted state, but MDT was quite higher, while DT and MDT of SSG containing formulations were longer. In CPD although wicking and shape recovery are dominant mechanisms but swelling is not much effective, while in case of SSG swelling is dominant. In fed state, MDT of CPD and SSG containing formulations was very high as compared to CCS containing formulations.

Water uptake causes the polymeric chains of disintegrant particles to move and expand to create some space between them, which results in the formation of a three dimensional network where water is retained. In case of CPD due to negligible particle expansion, a minor disruption is observed in the tablet structure. On the other hand, carboxylic moieties present in the structure of SSG, hydrate quickly leading to the development of gels upon water uptake(Camargo, 2011). Moreover, these carboxylic moieties are also present in CCS but a weaker gel is formed.

VI.4.2 Effect of compressional force

Both in fasted and fed state, DT and MDT of almost all tested formulations has increased with an increase in compressional force.

The permeability of a tablet is dependent on its pore structure, which itself depends greatly on the compressional force (Adolfsson & Nyström, 1996; Nogami et al., 1967; Ruegger & Çelick, 2000; Sinka et al., 2009; Tye et al., 2005; Wu et al., 2005). Reduced penetration of dissolution/disintegration medium into the tablet with low porosity is generally observed, which is translated into prolonged disintegration and dissolution times, because wicking is the prerequisite for the disintegrant action. On the other hand, high porosity, associated with large void space, usually lowers the impact of disintegrant force induced by the swelling excipients. Therefore, a lower swelling force increases the time to break up inter-particle bonds and thus increase the disintegration time (Berry & Ridout, 1950; Lowenthal, 1972a).

Chapter VII Effect of combination of disintegrants and their levels on tablet disintegration in fed viscosity media: Microcrystalline Cellulose as a model insoluble but swellable filler.

VII.1 Introduction

The ongoing study is an attempt to enrich our understanding about the role of combination of superdisintegrants in the presence of a filler, which is swellable i.e, possesses an active mechanism of disintegration. Microcrystalline cellulose (MCC) was selected in this regard because despite of it swelling ability, it can easily be compressed into hard compacts. Combination of disintegrants are expected to reduce the disintegration time, better than the single disintegrants, if there exist a synergism between them. Identification of any synergism or antagonism between disintegrants under fed conditions will be beneficial for the formulators who are working to develop formulations in order to minimize the negative food effect.

VII.2 Materials and Methods

VII.2.1 Materials

See II.2.1.

VII.2.2 Tablet preparation

See III.2.2

VII.2.3 Media composition

See II.2.3

VII.2.4 Disintegration studies

See II.2.4

VII.2.5 Dissolution studies

See II.2.5

VII.2.6 Disintegration force determination

See II.2.7

VII.3 Results

VII.3.1 Disintegration studies

In simulated fasted state, the compressional force was found to be directly related to the DT, whereas, the level of disintegrant combinations was found to be inversely related with the disintegration time. All formulations compressed at 10 KN, disintegrated in less than 15 min. However, among formulations compressed at 30 KN only high level of disintegrant combination containing CCS complied with that pharmacopeial criterion (Figure - 32A). Although DT of formulations containing CCS and CPD as single disintegrants were identical (see VI.3.1), shorter DT of formulations having CCS in the disintegrant combination suggests better performance of CCS.

It is worth mentioning that, in case of DCP as a filler, the effect of level of disintegrant combination on DT was dependent on the compressional force, while the effect of compressional force was independent of the level of disintegrant combinations (Figure - 32). In case of Lactose as a filler, the effect of compressional force on DT was dependent on the level of disintegrant combination, while the effect of level of disintegrant combination was independent (see III.3.1). However, in case of MCC as a filler, effect of compressional force and level of disintegrant combination on DT, was found to be independent of each other.

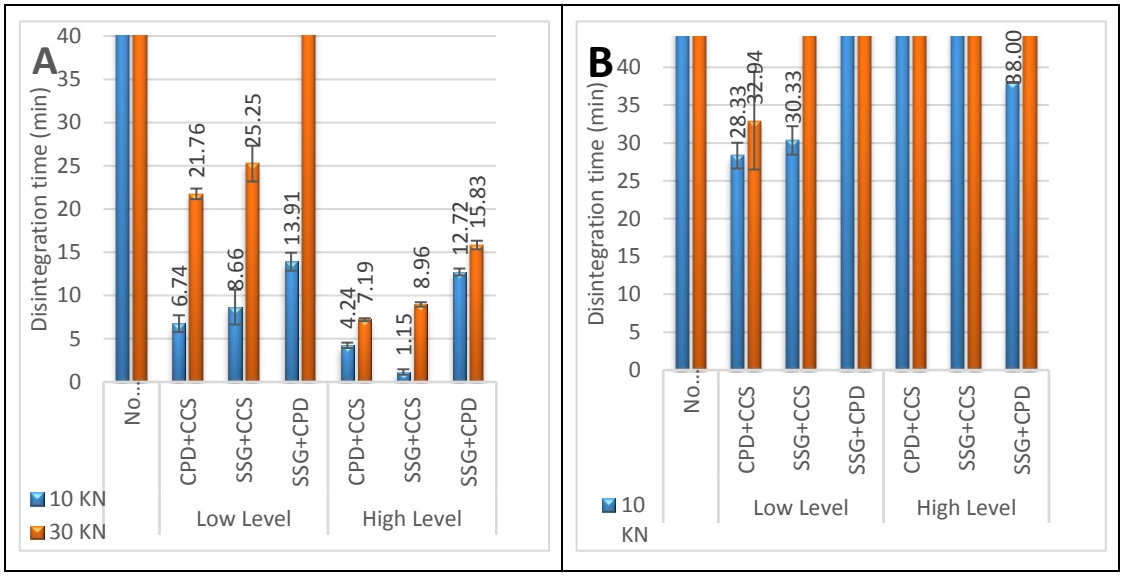

*Figure - 32: Effect of compressional force, combination of disintegrants and their levels on **disintegration time** of Microcrystalline cellulose based Trospium chloride formulations (n = 6) A – Formulations tested in fasted state, B – Formulations tested in fed state. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.*

When tested in fed state, no formulation disintegrated within 15 minutes, therefore, failed to comply the USP criterion for tablet disintegration. Most of them also failed to disintegrate within the test duration i.e, 45 minutes (Figure - 32B). Moreover, lower levels of disintegrant combinations are found to be more effective as compared to higher levels, which was not the case in simulated fasted state.

VII.3.2 Dissolution studies

When tested under simulated fasted conditions, only 2 formulations i.e, low levels of disintegrant combination of CPD+CCS and SSG+CCS compressed at 10 KN showed "very rapid dissolution". Interestingly, no other formulation complied even the "rapid dissolution' criterion. Moreover, when compressed at 30 KN, all formulations except two (low level of SSG+CPD and high level of SSG+CCS) meet the criterion for "rapid dissolution. (Figure - 33).

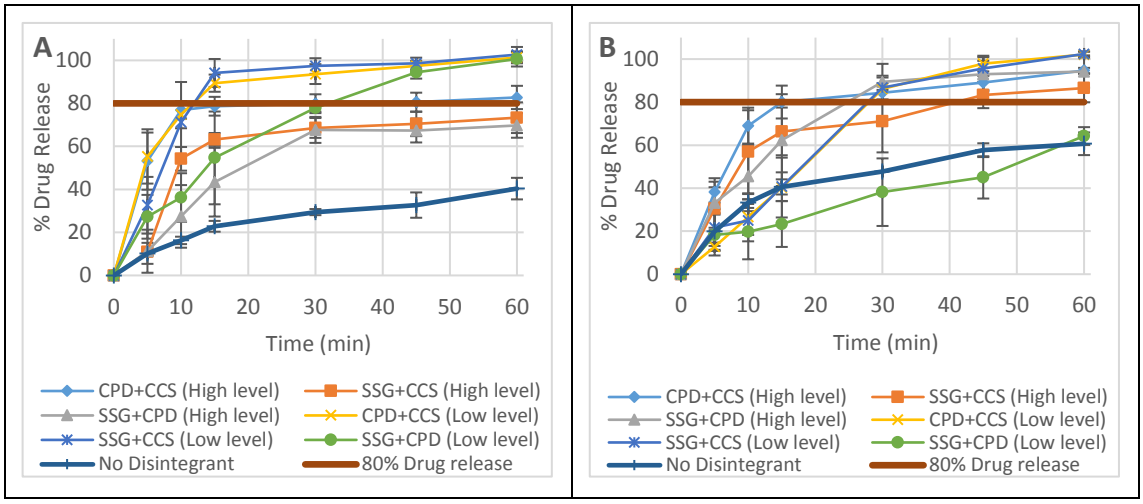

Figure - 33: Effect of compressional force, combination of disintegrants and their levels on % drug release from Microcrystalline cellulose based Trospium chloride formulations, in simulated fasted state (n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Release of drug was found to be slower when the formulations were tested under simulated fed conditions. Less than 20% of drug was released within 30 minutes. Therefore, no formulation complied neither "very rapid dissolution" nor "rapid dissolution" criteria in fed state (Figure - 34). Generally, formulations containing low level of disintegrant were found to release more drug within the test duration of 120 minutes. Figure - 34B, also reveals that higher compressional force noticeably impeded the release of API at earlier time points.

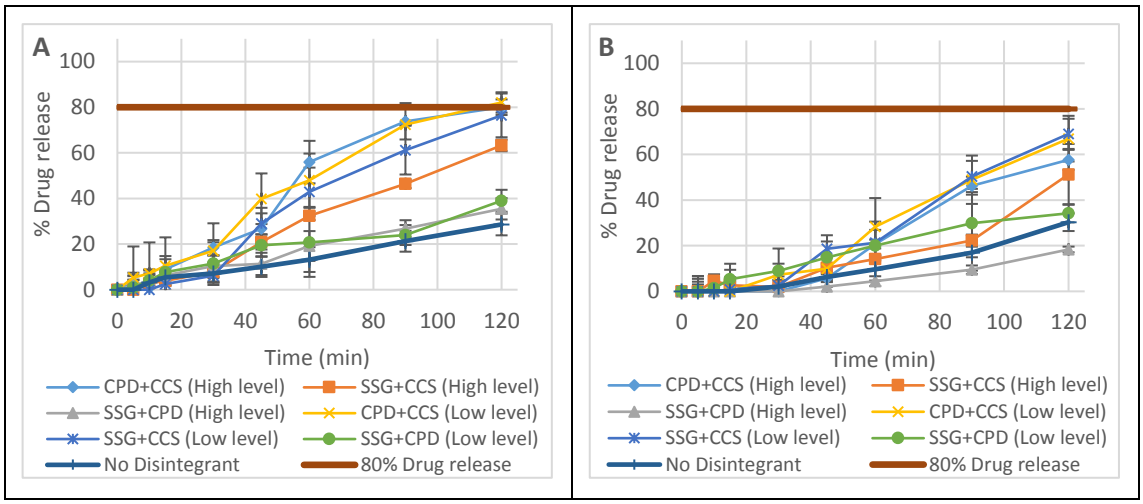

Figure - 34: Effect of compressional force, combination of disintegrants and their levels on % drug release from Microcrystalline cellulose based Trospium chloride formulations, in simulated fed state (n = 4) A – Formulations compressed at 10 KN, B – Formulations compressed at 30 KN . CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate

Under simulated fasted conditions, MDT was found to have a direct relationship with compressional force when low levels of disintegrant combinations were used. However, in formulations having high level of disintegrant combination MDT revealed an inverse relationship with compressional force (Table - 19). Moreover, MDT was found to increase with an increase in the level of disintegrant combination. It is concluded that lower levels of disintegrant combinations compressed at lower compressional force favours reduction in MDT, under non-viscous test conditions.

Table - 19: Effect of media viscosity, compressional force and level of disintegrant combinations on Mean dissolution time (MDT) and f2 statistic on Microcrystalline cellulose (Avicel PH 102) based formulations. (Mean ± SD; n=5). CPD – Crospovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate.

Disintegrant	Fasted state			Fed state		
	MDT (min)		f_2	MDT (min)		f_2
	10 KN	30 KN		10 KN	30 KN	
No Disintegrant	72.92	40.07	36.57	208.18^{+}	199.60^{+}	70.52
CPD+CCS (Low level)	8.40	18.84	23.94	49.55^{+}	91.80^{+}	38.29
SSG +CCS (Low level)	8.50	18.67	26.45	61.35^{+}	87.51^{+}	50.46
SSG +CPD (Low level)	17.98	45.63	23.80	148.95^{+}	159.10^{+}	71.66
CPD+CCS (High level)	15.79	10.91	51.39	61.20^{+}	109.26^{+}	34.38
SSG +CCS (High level)	25.71	19.40	47.56	95.33^{+}	136.95^{+}	45.44
SSG +CPD (High level)	30.42	12.66	32.90	168.73^{+}	322.10^{+}	46.89

* Calculated on the averaged values
$^{+}$ Extrapolated values

When tested under viscous conditions, MDT was found to have a direct relationship with compressional force at either level of disintegrant combination. This relationship resulted in the dissimilarity of the respective dissolution profiles. F_2 statistic values lower than 50 also endorsed that pattern (Table - 19). This trend is in contrast with the

trend observed under non-viscous conditions, where the level of disintegrant combination was governing the effect of compressional force on MDT. In addition to the relationship of MDT and compressional force, the level of disintegrant combination is in an obvious direct relation with MDT i.e, increasing the level of disintegrant combination resulted in increased MDT. Therefore, in order to obtain a relatively rapid dissolution, formulations need to be compressed at lower compression force, while having the lower level of disintegrant combination. It is worth mentioning that, under section V.3.2, where use of DCP as filler was discussed, higher compressional force was suggested to obtain short MDT. It however reflects the importance of the appropriate filler. Using both filler in the same formulation will be interesting, as the apparent interaction may result is some beneficial results.

VII.3.3 Texture analysis

In fasted state, except for the disintegration force curve of low level of disintegrant combination compressed at 10 KN, all other curves were overlapping each other (Figure - 35A to Figure - 37A). Most probably, it is due to the swelling behavior of microcrystalline cellulose that the peculiar effect of disintegrant combination was not identified clearly, as it was observed in formulations where either lactose or DCP were used as filler.

In fed state, similar to the fasted state pre-peak portions of the disintegration force curve was highly overlapped to draw any conclusion (Figure - 35B to Figure - 37B). However, it was found that irrespective of the nature of disintegrant combination, a high level of disintegrant combination compressed at 30 KN, gave the smaller AUC with comparatively low F_{max}, which is in contrast to the findings in fasted state, where the same formulations gave the relatively larger curve with high F_{max}. Moreover, post-peak portion of curves appeared early when tested under viscous conditions as compared to non-viscous conditions.

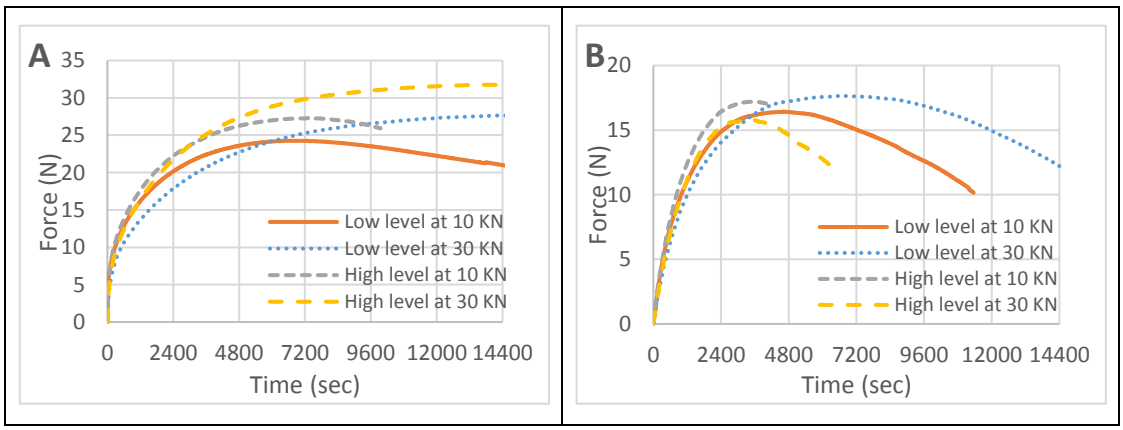

Figure - 35: Disintegration Force-time curves of Microcrystalline cellulose (Avicel PH 102) based formulations containing the combination of Crospovidone and Croscarmellose Sodium at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

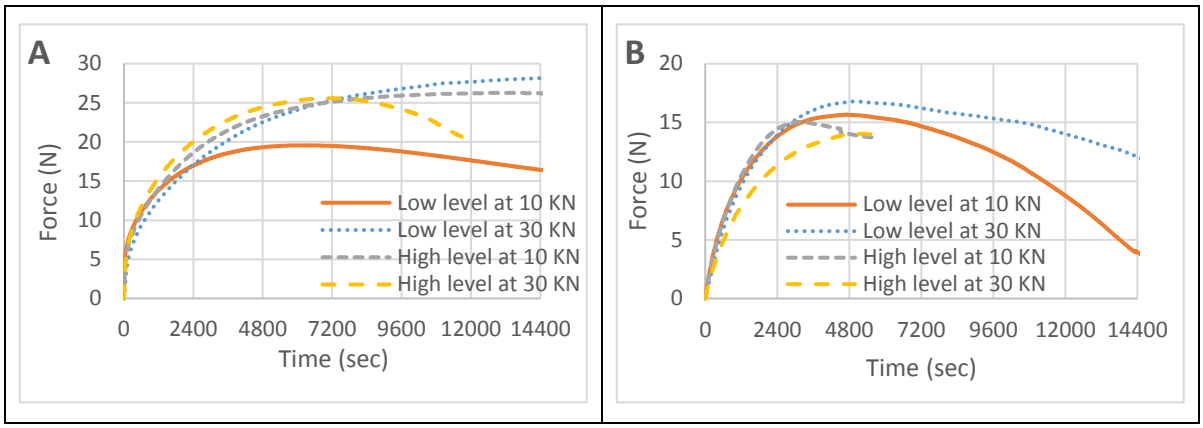

Figure - 36: Disintegration Force-time curves of Microcrystalline cellulose (Avicel PH 102) based formulations containing the combination of Sodium Starch Glycolate and Croscarmellose sodium at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

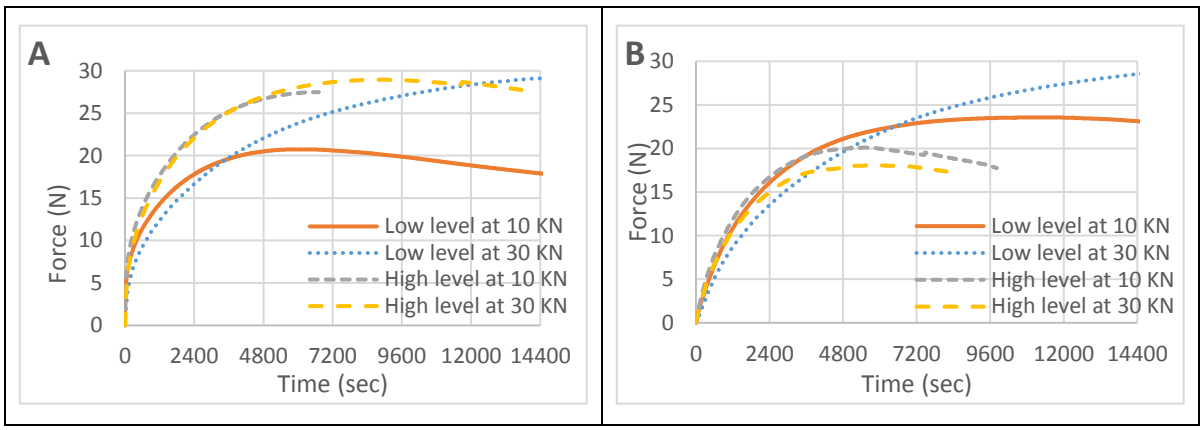

Figure - 37: Disintegration Force-time curves of Microcrystalline cellulose (Avicel PH 102) based formulations containing the combination of Sodium Starch Glycolate and Crospovidone at low (2% each) and high (4% each) levels (n = 3) A – simulated fasted state, B – simulated fed state.

In fasted state, there was a general rise in the values of F_{max} and T_{max} with an increase in compressional force. The same was observed with an increase in the level of disintegrant combination except for the formulations containing the combination of SSG+CCS compressed at 30KN. The magnitude of increase was higher with low level of disintegrant combination. Interestingly, when DCP was used as filler, the same magnitude was observed with high level of disintegrant combination. Increase in the level of disintegrant combination increased the DFDR, while an increase in compressional force decreased the DFDR except for the combination of SSG+CCS (Table - 20). Moreover, the dominance of diffusion-controlled mechanism of disintegration was observed i.e, n – exponent value < 1.

Table - 20: Parameters from disintegration force – time curve of Microcrystalline cellulose (Avicel PH 102) based tablets in simulated fasted state (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate.

	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No Disintegrant	31.18* ± 0.97	30.65* ± 1.25	16270* ± 0.00	16270* ± 0.00	0.79	1.03	1.18* ± 0.02	1.49* ± 0.08
CPD+CCS (Low level)	24.26 ± 0.37	27.73* ± 1.87	6850 ± 470	16230* ± 0.00	0.74	0.77	2.01 ± 0.01	0.96*± 0.08
SSG +CCS (Low level)	19.57 ± 0.81	28.31* ± 1.25	6270 ± 208	16220* ± 0.00	0.72	0.81	1.68 ± 0.05	1.01*± 0.13
SSG +CPD (Low level)	20.75 ± 0.07	29.14* ± 1.37	6070 ± 108	16270* ± 0.00	0.74	0.96	1.95 ± 0.12	1.39*± 0.21
CPD+CCS (High level)	27.27 ± 0.43	31.74 ± 0.94	7320 ± 1339	13860 ± 198	0.76	0.78	2.17 ± 0.05	1.30 ± 0.16
SSG +CCS (High level)	26.89 ± 0.86	25.57 ± 1.26	14710 ± 1877	7280 ± 2250	0.64	0.81	1.14 ± 0.06	2.25 ± 0.21
SSG +CPD (High level)	27.47 ± 1.86	28.95 ± 0.65	6640 ± 1088	8910 ± 180	0.75	0.81	2.50 ± 0.34	1.97 ± 0.19
*. – Disintegration force continued to develop until the end of experiment.								

In fed state, F_{max} was found to be in direct relationship with compressional force at low level of disintegrant combination, while this relationship become inverse at high level of disintegrant combination. DFDR increased markedly with an increase in the level of disintegrant combination, while it decreased with an increase in compressional force, except with the formulation containing the combination of SSG+CCS (Table - 21). However, in contrast to fasted state, dominance of interfacial-controlled mechanism of disintegration was observed i.e, n – exponent value > 1.

Table - 21: Parameters from disintegration force – time curve of Microcrystalline cellulose (Avicel PH 102) based tablets in simulated fed state (Mean ±SD; n=3). F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

	F_{max} (N)		T_{max} (s)		n-exponent value		Disintegration force development rate (DFDR) N/s x10^{-3}	
	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN	10 KN	30 KN
No Disintegrant	30.13± 1.39	29.65 ± 1.95	16270 ± 0.00	16270 ± 0.00	0.95	1.08	1.35± 0.09	1.50 ± 0.12
CPD+CCS (Low level)	16.42 ± 1.17	17.66 ± 1.03	4660 ± 1264	6700 ± 869	1.09	1.03	2.73 ± 0.42	2.01 ± 0.20
SSG +CCS (Low level)	15.65 ± 0.84	16.79 ± 0.17	4710 ± 211	5030 ± 1093	1.05	1.11	2.62 ± 0.03	2.86 ± 0.29
SSG +CPD (Low level)	23.57 ± 1.57	29.14* ± 1.98	11290 ± 897	16270* ± 0.00	1.02	0.96	1.46 ± 0.25	1.39* ± 0.11
CPD+CCS (High level)	17.20 ± 0.37	15.82 ± 0.28	3560 ± 94	3430 ± 106	1.10	1.17	4.06 ± 0.36	4.10 ± 0.45
SSG +CCS (High level)	15.03 ± 0.52	14.03 ± 0.31	3170 ± 138	5150 ± 272	1.14	1.07	4.28 ± 0.09	2.31 ± 0.35
SSG +CPD (High level)	20.10 ± 1.56	18.08 ± 0.64	5520 ± 1088	5840 ± 913	1.05	1.05	2.91 ± 0.53	2.44 ± 0.13
*. – Disintegration force continued to develop until the end of experiment.								

VII.4 Discussion

VII.4.1 Effect of combination of disintegrants and their levels

In simulated fasted state, an increase in the level of disintegrant combination resulted in rapid disintegration (Figure - 32A). The same trend was also seen in the formulations containing lactose and in formulations containing DCP compressed at lower compressional force. The most likely reason would be the higher concentration of disintegration particles that synergize with the swelling behavior of MCC. It is important to note that combinations containing CCS gave rapid disintegration, especially when used at higher levels. This might be due to their weak gelling with swelling that did not interfere with the DT as much as SSG did. With respect to MDT, role of CCS containing combinations in reducing the MDT was found to be dependent on compressional force (see VII.4.2). However, higher values of DT and MDT, in fasted state, advocate precluding the use of MCC as a single filler in tablet formulations.

When evaluated in fed state, most of the tablets did not disintegrate within the test duration of 45 minutes, however, few have disintegrated with a disintegration time of

more than 25 minutes. (Figure - 32B). Considering the DT and MDT values there is no practical reason to consider the use of MCC as major filler.

Texture analysis of the combination of CPD+CCS revealed that it is the only combination where steeper curves are observed in fed state (Figure - 35B). Despite these, disintegration force was large beyond the T_{max}, which may be indicative of strong internal bonding of tablet.

From the perspective of a formulator, reduced MDT of lower level of CPD+CCS combination in formulations compressed at lower compressional force merits consideration. It is reconfirmation of the potential of this combination in minimizing the impact of viscous medium on the release of API. The same combination performed better than single disintegrants in lactose as well as DCP based tablets in reducing duration of disintegration and dissolution.

Our results suggests that MCC should not be used as major fraction of filler in formulations because despite strong swelling it is more prone to negative food effect due to its ability to produce harder compact at lower compressional force. However considering its swelling tendency that results in high disintegration force (F_{max}) it is suggested to be used as a minor fraction of filler combination. Formulations containing lactose or DCP as a single filler, usually result in a weaker tablets, though compressed at higher compressional force, therefore, MCC may be considered as a part of filler combination because it has an ability to give sufficiently harder compact with minimum compressional force. When MCC is included as a filler mix, presence of CCS as disintegrant or in combination with CPD is expected to minimize the negative effects of food-induced viscosity

VII.4.2 Effect of compressional force

In fasted state, an increase in compressional force prolonged the DT of all tablets and MDT of tablets with low level of disintegrant combination. However, similar to the tablets where lactose or DCP was used as a filler, formulations having high level of disintegrant combination gave reduced MDT when compressed at higher compressional force. At higher compressional pressure, overall effect of disintegrants was not sufficient to cause faster disintegration as compared to formulations compressed at lower compressional force due to more bonding of tablet particles. However, disintegrant actions are sufficient to create some pores through which API can diffuse out of the tablets.

Under viscous conditions, increased MDT and DT with an increase in compressional force has already been explained in earlier sections, where torturous pathways of tablet structure and limited mobility of water molecules under viscous conditions were discussed. Table - 19, shows that in most of the formulations, f_2 statistic value was less than 50, which reflects the dissimilarity in dissolution profiles of same formulations compressed at different compressional force.

Chapter VIII Statistical evaluation of the role of disintegrants and fillers using Design of Experiment (DoE).

VIII.1 Introduction

VIII.1.1 Design of experiment (DoE)

With the introduction of ICH Q8 guidelines on Pharmaceutical development, regulatory authorities of the European Union, Japan and USA, recognized the importance of Quality by Design (QbD) i.e, "quality should be built in by design". It is defined by ICH as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"(International Conference on Harmonization, 2009). In order to develop a quality product or process, which will be able to deliver its intended outcomes consistently, an enhanced knowledge of product performance over a range of material attributes and process parameters, critical to product quality is required. ICH Q8 (R2) guidelines recommend using formal experimental designs, process analytical technology (PAT), besides prior knowledge to gain such understanding.

"Design of Experiments" (DoE) is an effective tool of achieving process knowledge, through the establishment of mathematical relationships between process inputs and its outputs, when working with a large number of parameters. Inputs are intentionally varied in order to determine their effects on the outputs (Montgomery, 2017). DoE is utilized to do the process characterization followed by optimization and robustness tests.

The objective of process characterization is to exclude the non-significant factors. Screening designs are mainly used in this phase. It is followed by the optimization phase, in which the optimum levels of the significant factors, which were identified in the earlier phase, are studied to improve the product quality. Response Surface Methodology (RSM) techniques are the primary tool used in the optimization phase. Full factorial and D-optimal designs are generally used in this phase (Politis et al., 2017).

Mixture and factorial designs are the two important categories of experimental designs commonly used in pharmaceuticals. When dealing with formulation factors, where the total amount is defined e.g. compressional weight of a tablet, mixture designs are used for characterizing and rationalizing the presence of each constituent and its level in the formulation. However for factors which can be adjusted independently of each other e.g. compressional force, factorial designs are used (Bolton & Bon, 2009).

VIII.2 Materials and Methods

In order to identify the formulation and processing factors, a screening step was conducted. Based on the results of the screening phase, 3 separate factorial designs, with respect to filler used, with an objective of identifying the interaction between the factors were created.

VIII.2.1 Screening Phase

VIII.2.2 Design of Experiment

The DoE initial screening phase was designed by using the MODDE 9.0 software (Umetrics). Based on the prior knowledge and literature search, 12 factors i.e, independent variables, including 3 disintegrants, 3 lubricants, 4 fillers with varying properties, API and compressional force as a processing factor were selected for evaluation (Table - 22). Disintegration time in SGF (simulating fasted condition) and Mean dissolution time in SGF as well as in 1.4% aqueous solution of HPMC at varying pH of 1.2, 4.5 and 6.8 were the responses i.e, dependent variables. D-optimal design with linear model was selected.

Table - 22: Factors and their levels used in the screening phase.

	Name of Factors	Abbr.	Levels	Units
Disintegrants	Croscarmellose Sodium	CCS	0, 2, 4	%
	Crospovidone	CPD	0, 2, 4	%
	Sodium Starch Glycolate	SSG	0, 2, 4	%
Lubricants	Magnesium Stearate	MgS	0, 1, 2	%
	Talcum	Talc	0, 1, 2	%
	Polyethylene glycol 6000	PEG	0, 1, 2	%
Fillers	Lactose	Lacto	0 to 1	Fraction
	Microcrystalline Cellulose pH 102	MCC	0 to 1	Fraction
	Calcium Phosphate dibasic dihydrate	DCP	0 to 1	Fraction
	Calcium Carbonate	$CaCO_3$	0 to 1	Fraction
	Compressional Force	CF	10, 20, 30, 40	KN
	Drug (Trospium Chloride)	API	20 to 40	mg

VIII.2.2.1 Preparation of tablets

Tablets were compressed with a dwell time of 10s on a manual hydraulic press (Specac, USA – 25 tons), by filling the exactly weighed quantity of powder mixture i.e,400 mg , using a 13 mm die and a flat-faced punch assembly. Each formulation was prepared in the batches of 100 tablets following the worksheet presented in Table - 23.

Table - 23: Worksheet for screening phase

Experiment Number	Croscarmellose Sodium	Crospovidone	Sodium Starch Glycolate	Magnesium Stearate	Talcum	Polyethylene glycol 6000	Lactose	Microcrystalline Cellulose pH 102	Calcium Phosphate dibasic dihydrate	Calcium Carbonate	Compressional Force	Drug (Trospium Chloride)
N1	0	0	0	0	0	0	1	0	0	0	10	40
N2	0	0	4	0	0	0	0	1	0	0	40	20
N3	4	4	4	0	0	0	1	0	0	0	40	40
N4	0	4	4	2	0	0	0	0	0	1	10	40
N5	4	0	0	2	0	0	0	0	1	0	40	20
N6	0	0	4	0	2	0	0	0	1	0	40	40
N7	4	4	0	0	2	0	0	0	0	1	10	20
N8	0	4	4	2	2	0	1	0	0	0	10	20
N9	0	4	0	2	2	0	0	1	0	0	40	40
N10	4	0	4	2	2	0	0	1	0	0	10	40
N11	0	4	0	0	0	2	0	0	1	0	40	20
N12	4	0	4	0	0	2	0	0	1	0	10	20
N13	4	0	0	0	0	2	0	0	0	1	40	40
N14	0	0	4	2	0	2	1	0	0	0	40	40
N15	4	4	0	2	0	2	0	1	0	0	10	20
N16	0	4	4	0	2	2	0	1	0	0	10	40
N17	4	0	0	0	2	2	1	0	0	0	40	20
N18	0	0	0	2	2	2	0	0	0	1	10	20
N19	4	4	0	2	2	2	0	0	1	0	10	40
N20	4	4	4	2	2	2	0	0	0	1	40	20
N21	4	4	4	2	2	2	0.5	0.5	0.5	0.5	25	30

VIII.2.3 Lactose based tablets

VIII.2.3.1 Design of Experiment

In the light of results obtained in the screening phase, a full factorial 2 levels design with interactions was created by using the MODDE 9.0 software (Umetrics). Factors i.e, independent variables, including 3 disintegrants and compressional force as a processing factor were selected for evaluation, while lactose was used as a filler (Table - 24). Disintegration time and Mean dissolution time in simulated fasted and fed state (see II.2.3) were the responses i.e, dependent variables.

Table - 24: Factors and their levels used in experimental design of lactose based tablets.

Name of factors	Abbr.	Units	Type	Levels
Compressional Force	CF		Quantitative	10 to 30
Croscarmellose Sodium	CCS	Fraction	Formulation	0 to 0.04
Crospovidone	CPD	Fraction	Formulation	0 to 0.04
Sodium Starch Glycolate	SSG	Fraction	Formulation	0 to 0.04
Lactose	Lac	Fraction	Filler	

VIII.2.3.2 Preparation of tablets

Batches of 100 tablets were prepared and compressed following the procedure mentioned in II.2.2. The composition of the formulations is presented in Table - 25.

Table - 25: Worksheet for the DoE of lactose based tablets. Given are the fractions of components.

Experiment No	Compressional Force (KN)	Croscarmellose Sodium	Crospovidone	Sodium Starch Glycolate	Lactose
1	10	0	0	0	1
2	10	0.04	0	0	0.96
3	10	0	0.04	0	0.96
4	10	0.04	0.04	0	0.92
5	10	0	0	0.04	0.96
6	10	0.04	0	0.04	0.92
7	10	0	0.04	0.04	0.92
8	10	0.02	0.02	0	0.96
9	10	0.02	0	0.02	0.96
10	10	0	0.02	0.02	0.96
11	30	0	0	0	1
12	30	0.04	0	0	0.96
13	30	0	0.04	0	0.96
14	30	0.04	0.04	0	0.92
15	30	0	0	0.04	0.96
16	30	0.04	0	0.04	0.92
17	30	0	0.04	0.04	0.92
18	30	0.02	0.02	0	0.96
19	30	0.02	0	0.02	0.96
20	30	0	0.02	0.02	0.96

VIII.2.4 Dibasic Calcium Phosphate based tablets

VIII.2.4.1 Design of Experiment

In the light of results obtained in the screening phase, a full factorial 2 levels design with interactions was created (MODDE 9.0). Factors i.e, independent variables, including 3 disintegrants and compressional force as a processing factor were selected for evaluation, while dibasic calcium phosphate was used as a filler (Table - 26). Disintegration time and Mean dissolution time in simulated fasted and fed state (see II.2.3) were the responses i.e, dependent variables.

Table - 26: Factors and their levels used in experimental design of dibasic calcium phosphate based tablets.

Name of factors	Abbr.	Units	Type	Levels
Compressional Force	CF		Quantitative	10 to 30
Croscarmellose Sodium	CCS	Fraction	Formulation	0 to 0.04
Crospovidone	CPD	Fraction	Formulation	0 to 0.04
Sodium Starch Glycolate	SSG	Fraction	Formulation	0 to 0.04
Dibasic Calcium Phosphate	Lac	Fraction	Filler	

VIII.2.4.2 Preparation of tablets

Batches of 100 tablets were prepared and compressed following the procedure mentioned in II.2.2. The composition of the formulations is presented in Table - 27.

Table - 27: Worksheet for the DoE of dibasic calcium phosphate based tablets. Given are the fractions of components.

Experiment No	Compressional Force (KN)	Croscarmellose Sodium	Crospovidone	Sodium Starch Glycolate	Dibasic Calcium Phosphate
1	10	0	0	0	1
2	10	0.04	0	0	0.96
3	10	0	0.04	0	0.96
4	10	0.04	0.04	0	0.92
5	10	0	0	0.04	0.96
6	10	0.04	0	0.04	0.92
7	10	0	0.04	0.04	0.92
8	10	0.02	0.02	0	0.96
9	10	0.02	0	0.02	0.96
10	10	0	0.02	0.02	0.96
11	30	0	0	0	1
12	30	0.04	0	0	0.96
13	30	0	0.04	0	0.96
14	30	0.04	0.04	0	0.92
15	30	0	0	0.04	0.96
16	30	0.04	0	0.04	0.92
17	30	0	0.04	0.04	0.92
18	30	0.02	0.02	0	0.96
19	30	0.02	0	0.02	0.96
20	30	0	0.02	0.02	0.96

VIII.2.5 Microcrystalline cellulose based tablets

VIII.2.5.1 Design of Experiment

In the light of results obtained in the screening phase, a full factorial 2 levels design with interactions was created (MODDE 9.0). Factors i.e, independent variables, including 3 disintegrants and compressional force as a processing factor were selected for evaluation, while microcrystalline cellulose PH 102 was used as a filler (Table - 28). Disintegration time and Mean dissolution time in simulated fasted and fed state (see II.2.3) were the responses i.e, dependent variables.

Table - 28: Factors and their levels used in experimental design of Microcrystalline cellulose PH 102 based tablets.

Name of factors	Abbr.	Units	Type	Levels
Compressional Force	CF		Quantitative	10 to 30
Croscarmellose Sodium	CCS	Fraction	Formulation	0 to 0.04
Crospovidone	CPD	Fraction	Formulation	0 to 0.04
Sodium Starch Glycolate	SSG	Fraction	Formulation	0 to 0.04
Microcrystalline cellulose PH 102	Lac	Fraction	Filler	

VIII.2.5.2 Preparation of tablets

Batches of 100 tablets were prepared and compressed following the procedure mentioned in II.2.2. The composition of the formulations is presented in Table - 29.

Table - 29: Worksheet for the DoE of Microcrystalline cellulose PH 102 based tablets. Given are the fractions of components.

Experiment No	Compressional Force (KN)	Croscarmellose Sodium	Crospovidone	Sodium Starch Glycolate	Microcrystalline cellulose PH 102
1	10	0	0	0	1
2	10	0.04	0	0	0.96
3	10	0	0.04	0	0.96
4	10	0.04	0.04	0	0.92
5	10	0	0	0.04	0.96
6	10	0.04	0	0.04	0.92
7	10	0	0.04	0.04	0.92
8	10	0.02	0.02	0	0.96
9	10	0.02	0	0.02	0.96
10	10	0	0.02	0.02	0.96
11	30	0	0	0	1
12	30	0.04	0	0	0.96
13	30	0	0.04	0	0.96
14	30	0.04	0.04	0	0.92
15	30	0	0	0.04	0.96
16	30	0.04	0	0.04	0.92
17	30	0	0.04	0.04	0.92
18	30	0.02	0.02	0	0.96
19	30	0.02	0	0.02	0.96
20	30	0	0.02	0.02	0.96

VIII.3 Results

VIII.3.1 Screening Phase

The unrefined model revealed that all lubricants were insignificant (i.e, $p > 0.05$) in all responses, while the remaining factors were significant in different responses. However, exclusion of any factor, whose p value is just greater than 0.05 e.g., 0.08, may result in unexpected outcomes. Therefore, not only the *p* value but also the respective role of that excipient in the formulation should be given a due consideration. Figure - 38 depicts the effects of meaningful factors, sorted ascending in their absolute value. Effects are described as the change in response, when a factor is varied from its lower level to higher level, while keeping all other factors constant at their average levels. For the purpose of graphical presentation of the effect plot, effect bars, which have been traversed by the error bars, are considered non-significant in statistical terms.

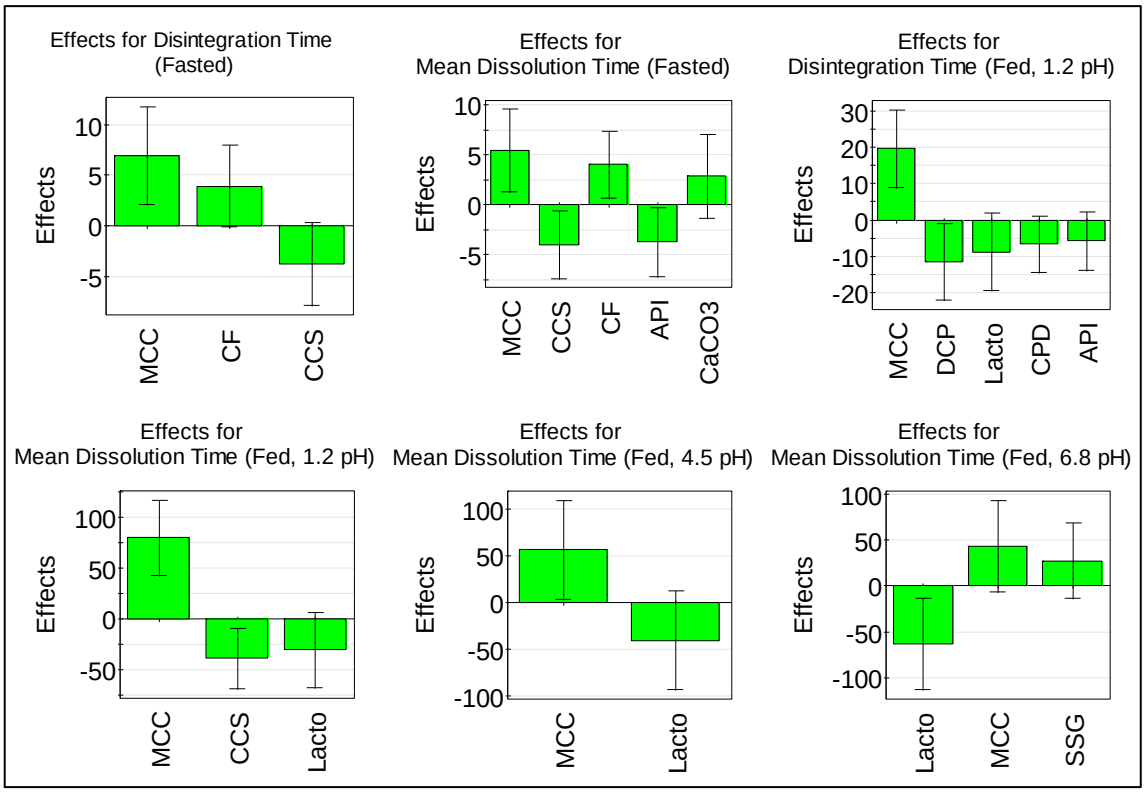

Figure - 38: Effects plots for the Dissolution time (DT) and Mean Dissolution time (MDT), with a confidence interval of 95%, in fasted and fed state at different pH levels. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force, MCC – Microcrystalline cellulose (PH102), CaCO3 – Calcium carbonate, DCP – Di calcium phosphate, Lacto – Lactose, API – Active Pharmaceutical ingredient.

Based on these results, it was decided to create separate experimental designs based on the solubility of the filler. In the objective of DoE we have also incorporated the interactions among factors (if any). Despite the non-significance of SSG and compressional force, we have kept it in the design to have a better insight both from the academic and formulator point of view.

VIII.3.2 Lactose based tablets

Effect plots are presented in Figure - 39, where a positive effect is downward and negative effect is upward. Effects are statistically significant at the level of 0.05, when the error bar did not include the value of zero for effects. In the objective of design, interaction between factors was also included. In statistics, lack of additivity is termed as interaction. Bolton defined the term interaction as "an interaction between two factors A and B means that the effect of factor A on the response is different at the various levels of factor B" (Bolton & Bon, 2009). In the following figures, interaction will be depicted as "factor*factor".

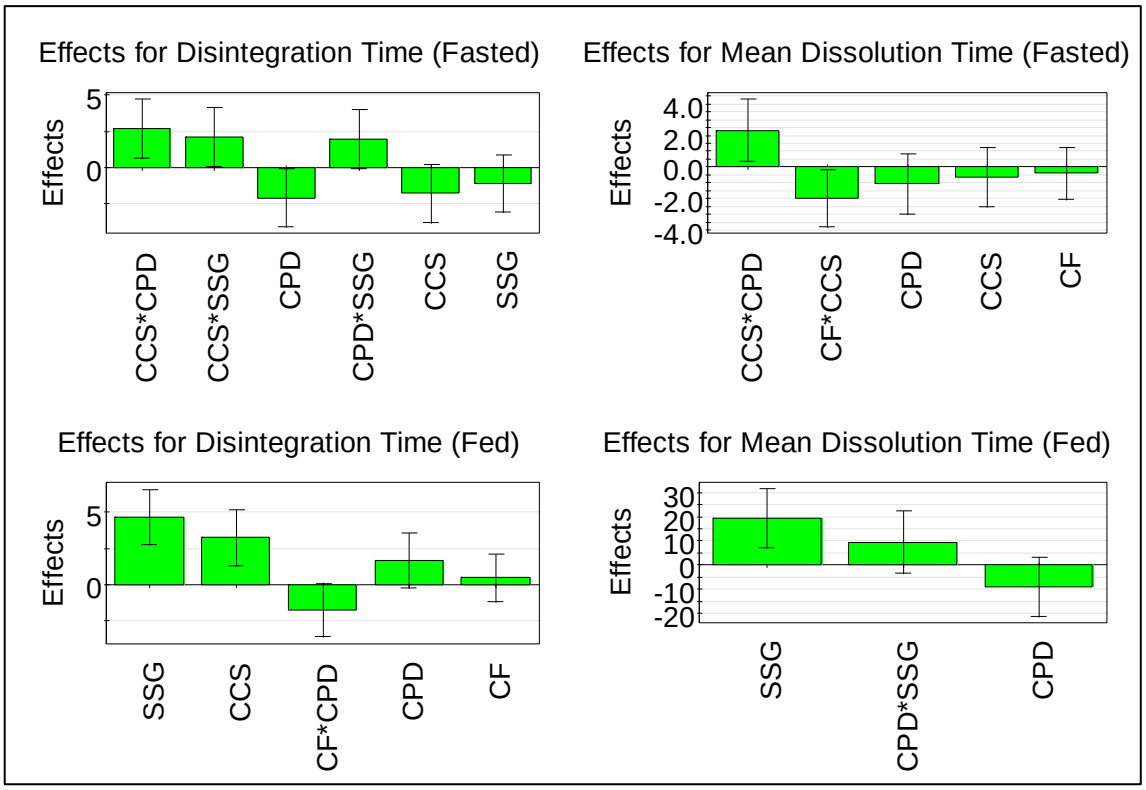

Figure - 39: Effect plots of lactose based formulations for the Disintegration time (DT) and Mean Dissolution time (MDT), with confidence intervals (error bars). CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force.

Because the primary objective is to understand the role of excipients in minimizing the negative aspect of food induced viscosity therefore, the effects, which were observed after testing in fed state, will be discussed. In order to establish a mathematical model, a list of coefficients is presented in Table - 30

Table - 30: Coefficients of a multiple regression linear (MLR) model, (Lactose based formulations). CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force.

Disintegration Time (Fasted)		
	Coefficient	*p* value
Constant	2.30688	0.000160447
CCS	-0.793043	0.107533
CPD	-0.931828	0.0632049
SSG	-0.490917	0.304048
CCS*CPD	1.07569	0.0398033
CCS*SSG	0.854499	0.0927262
CPD*SSG	0.789125	0.117661
Mean Dissolution Time (Fasted)		
	Coefficient	*p* value
Constant	6.64739	1.39314e-010
CF	-0.19953	0.607775
CCS	-0.281118	0.534506
CPD	-0.480548	0.294707
CF*CCS	-0.90334	0.0517715
CCS*CPD	0.93367	0.0627065
Disintegration Time (Fed)		
	Coefficient	*p* value
Constant	9.187	2.62207e-012
CF	0.256983	0.509859
CCS	1.45267	0.00554013
CPD	0.747792	0.114055
SSG	2.08613	0.000339969
CF*CPD	-0.803991	0.0792825
Mean Dissolution Time (Fed)		
	Coefficient	*p* value
Constant	53.4	7.56096e-013
CPD	-4.04216	0.180616
SSG	8.65641	0.0085136
CPD*SSG	3.77707	0.229052

VIII.3.3 Dibasic calcium phosphate based tablets

Effect plots are presented in Figure - 40, where a positive effect is downward and negative effect is upward. Some insignificant factors are kept in the effect plot because their interaction with another factor was significant. It is the limitation of the software (MODDE 9.0) that if we remove the insignificant factors then all the interactions involving that factor will also be removed.

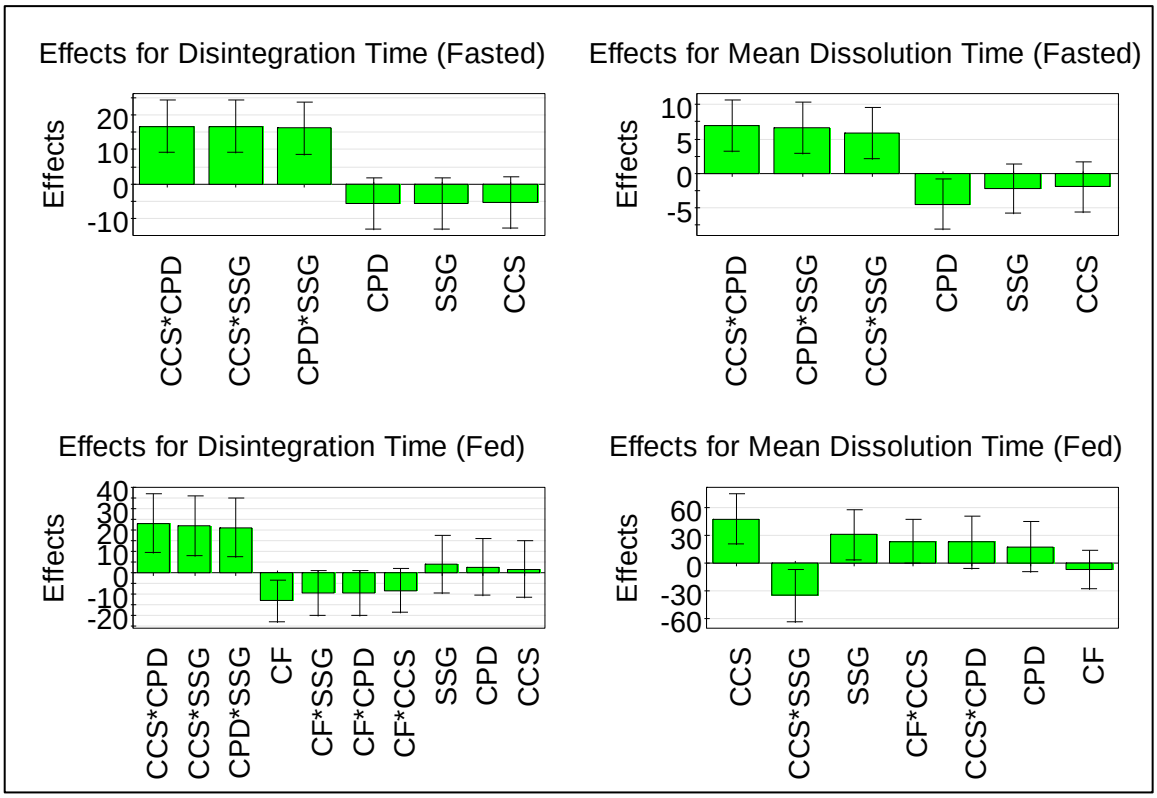

Figure - 40: Effect plots for DCP based formulations. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force.

In order to establish a mathematical model, a list of coefficients is presented in Table - 31.

Table - 31: Coefficients of a multiple regression linear (MLR) model, (DCP based formulations). CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force.

Disintegration Time (Fasted)		
	Coefficients	*p* value
Constant	7.30616	0.000661639
CCS	-2.42231	0.180638
CPD	-2.52963	0.163367
SSG	-2.48993	0.169586
CCS*CPD	6.69817	0.0021608
CCS*SSG	6.65822	0.00225615
CPD*SSG	6.51023	0.00264834
Mean Dissolution Time (Fasted)		
	Coefficients	*p* value
Constant	9.94197	1.39841e-008
CCS	-0.861646	0.320654
CPD	-1.98107	0.0336871
SSG	-0.97992	0.261356
CCS*CPD	2.77701	0.00642769
CCS*SSG	2.34577	0.0169066
CPD*SSG	2.63704	0.00880379
Disintegration Time (Fed)		
	Coefficients	*p* value
Constant	25.8636	2.07394e-006
CF	-7.05587	0.00508355
CCS	0.8625	0.790725
CPD	1.40025	0.667371
SSG	1.85761	0.569747
CCS*CPD	9.89527	0.0104093
CCS*SSG	9.28596	0.0147264
CPD*SSG	9.01386	0.0171898
Mean Dissolution Time (Fed)		
	Coefficients	***p* value**
Constant	102.614	7.56524e-010
CF	-3.58119	0.476292
CCS	21.2748	0.005368
CPD	7.86324	0.234087
SSG	13.6907	0.049758
CF*CCS	10.6269	0.0747267
CCS*CPD	9.15894	0.184218
CCS*SSG	-14.0298	0.0518665

VIII.3.4 Microcrystalline cellulose PH 102 based tablets

Effect plots are presented in Figure - 41. Response of disintegration time (DT) in fed state was not included because most of the tablets failed to disintegrate within the test duration of 45 minutes.

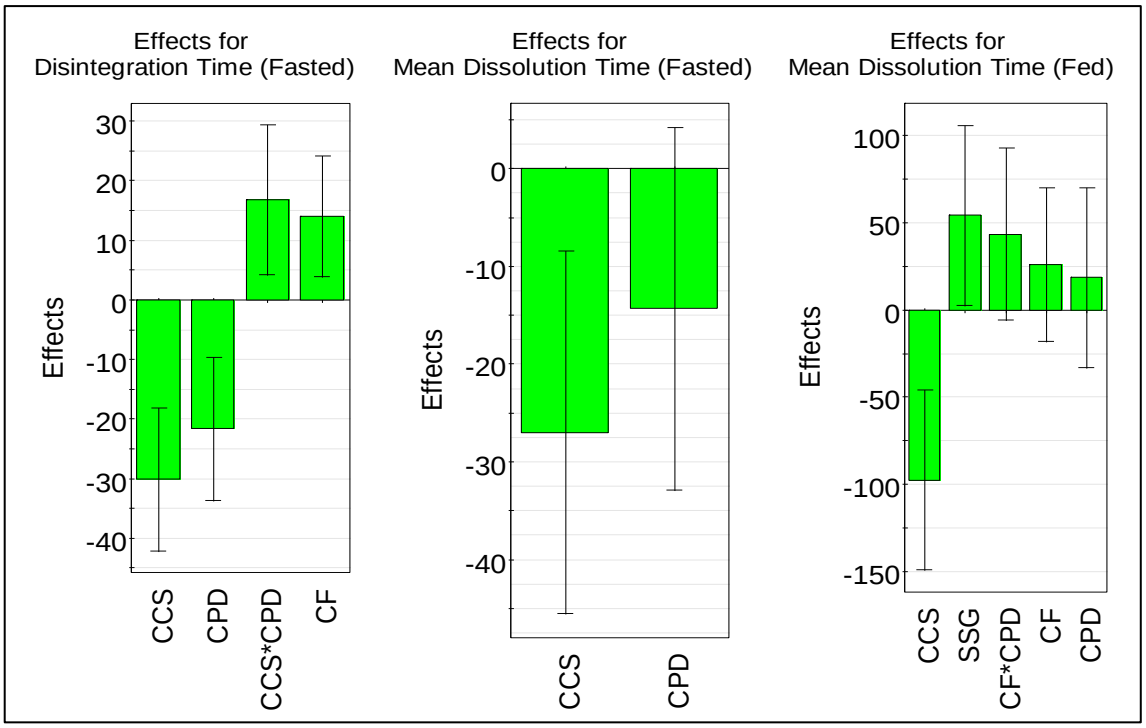

Figure - 41: Effect plots for MCC based formulations. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force.

Although it was revealed in VIII.3.1 that MCC is not suitable as a single filler for fed state conditions, however it is commonly used as a part of combination of fillers. Therefore, evaluation of different disintegrants in fed state is worthwhile in order to understand the behaviour of disintegrants in the formulations where MCC is present. In order to establish a mathematical model, a list of coefficients is presented in Table - 32.

Table - 32: Coefficients of a multiple regression linear (MLR) model, (MCC based formulations). CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, CF – Compressional force.

Disintegration Time (Fasted)		
	Coefficient	*p* value
Constant	23.7381	1.41352e-007
CF	7.21388	0.00818388
CCS	-13.4728	0.000246983
CPD	-9.66416	0.00377407
CCS*CPD	6.72633	0.0378126
Mean Dissolution Time (Fasted)		
	Coefficient	*p* value
Constant	26.9895	3.42159e-006
CCS	-12.0612	0.0138162
CPD	-6.41043	0.162832
Mean Dissolution Time (Fed)		
	Coefficient	*p* value
Constant	138.682	6.24555e-009
CF	13.3472	0.215041
CCS	-43.623	0.00270397
CPD	8.29069	0.500956
SSG	24.2582	0.0627869
CF*CPD	19.8579	0.105941

VIII.4 Discussion

In the screening phase, effect of lubricants was non-significant, within the scope of their levels tested i.e, 0 to 2 % (Figure - 38). It means that if they are used within these levels they will not affect the disintegration or dissolution of formulation in fasted or fed state. Therefore, we have selected magnesium stearate as lubricant, in experiments were we have evaluated the role of disintegrants in the presence of different fillers. Differences in the effects and their absolute values of factors were observed when evaluated in fed and fasted state. In fasted state, compressional force was a significant factor for both DT and MDT, but in fed state, it was not significant. Calcium carbonate was not significant which depicts that effervescence is not an effective mechanism of disintegrant action in fed state. MCC has significantly increased, while lactose decreased, both the DT and MDT in fasted as well as at all pH levels in fed state. DCP decreased the MDT when tested in fed state at pH 1.2. These effects highlight the solubility aspect of fillers, which become more important by considering the fact that fillers comprises the major proportion of the tablet. Disintegrants were also found to have significant effects in fed state. CPD was significant in reducing the DT in fed state. CCS decreased the MDT

while SSG increased the MDT when evaluated at pH 1.2 and pH 6.8 respectively in fed state. Therefore, outcomes of screening phase suggest the use of lactose as filler while CCS and CPD as disintegrant in fed state.

Evaluation of DoE for lactose based tablets revealed contrasting effects of disintegrants on DT in fasted and fed conditions (Figure - 39). Disintegrants have decreased the DT in fasted state while contributed to increase in the fed state. It yet again highlights the importance of testing the formulations considering the aspect of viscosity when testing the food effects. Although CPD and compressional force increased the DT in fed state, their interaction resulted in a decrease of DT. Moreover, CPD has an important role in reducing the MDT in fed state. It also has interacted with SSG to lower the negative effect of SSG. Therefore, this statistical evaluation suggests that CPD and compressional force can be further optimized in the presence of lactose, to obtain a formulation which will be least affected by viscous conditions.

In case of DCP based tablets, when evaluated in fed sate, almost all interactions of disintegrants with each other lead to an increase in DT and MDT, except the interaction of CCS with SSG, which caused the reduction in MDT (Figure - 40). Compressional force itself has reduced the DT and MDT (though not significant in case of MDT). It has also interacted will all disintegrants to reduce the DT. Therefore, statistical evaluation suggests exclude the combination of disintegrants as well as optimizing the compressional force and single disintegrants in the formulations where dibasic calcium phosphate is used as a filler, while developing a formulation which will be least affected by viscous conditions.

In MCC based formulations, CCS as a single disintegrant is found to significantly reduce the MDT (Figure - 41). Therefore, statistical evaluations suggest optimizing the levels of CCS in order to get a formulation, containing MCC, which will be least affected by viscous conditions.

Overall discussion

The aim of this study is to devise a formulation strategy, which can minimize the viscosity mediated negative food effects. Various formulation and processing factors were evaluated under fed conditions. In the screening phase, statistical evaluation of disintegration and dissolution times, under fed conditions, was conducted through MODDE 9.0 (Umetrics). It revealed that the effect of lubricants i.e, Talcum, Magnesium stearate and Polyethylene glycol 6000 and calcium carbonate as filler is insignificant under fed conditions. However, all disintegrants i.e, CCS, CPD and SSG and fillers i.e, lactose, DCP and MCC showed significant effect on the disintegration and dissolution times, under fed conditions, at different pH levels (See VIII.3.1. Therefore, the significant factors were further evaluated to obtain a better insight.

Formulations containing single disintegrants, when evaluated under fed conditions, revealed a direct relationship of DT with compressional force, in lactose based formulations. Although, the magnitude of change was not more than 3 minutes (Figure - 3).Whereas, an inverse relationship was dominant in DCP based formulations, containing single disintegrants. For MCC based tablets, most of the tablets failed to disintegrate within the test duration of 45 min, therefore no relationship between DT and compressional force could be established (Figure - 42). With respect to the combination of disintegrants, the relationship of DT with compressional force was dependant on the level of disintegrant combination use, in lactose based formulations i.e, the nature of the relationship was changed from direct to inverse and vice versa with a change in levels of disintegrant combinations. However, in DCP based tablets, an inverse relationship between DT and compressional force was found, irrespective of the level of disintegrant combination used (Table - 33).

Generally, single disintegrants were more beneficial in reducing the disintegration time as compared to their respective combinations, under fed conditions, in both lactose and DCP based formulations. The combination of disintegrants, however were found to be more effective in lactose based tablets as compared to DCP based tablets. Moreover, DCP based tablets, compressed at higher compressional force provided relatively rapid disintegration (Figure - 42). It may be attributed to the aqueous solubility of lactose, because lactose based formulations devoid of any disintegrant were disintegrated quicker than those containing combinations of disintegrants.

Table - 33 : Relationship of compressional force with different parameters tested. F_{max} – Maximum Disintegration Force, T_{max} – Time to achieve F_{max}, DT - Disintegration time, MDT - Mean dissolution time, CPD – Crospovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate, ND – Not disintegrated within the test duration of 45 minutes, Direct – direct relationship with compressional force, Inverse – inverse relationship with compressional force.

		F_{max}	T_{max}	DFDR	DT	MDT
Lactose	No Disintegrant	Direct	Direct	Direct	Direct	Inverse
	CCS	Inverse	Direct	Inverse	Direct	Direct
	CPD	Inverse	Direct	Inverse	Direct	Direct
	SSG	Inverse	Direct	Inverse	Direct	Direct
	CPD+CCS (Low level)	Inverse	Direct	Inverse	Direct	Inverse
	SSG+CCS (Low level)	Direct	Direct	Inverse	Direct	Inverse
	SSG+CPD (Low level)	Inverse	Direct	Inverse	Inverse	Inverse
	CPD+CCS (High level)	Direct	Direct	Inverse	Inverse	Direct
	SSG+CCS (High level)	Direct	Direct	Direct	Direct	Direct
	SSG+CPD (High level)	Direct	Direct	Direct	Direct	Direct
Dibasic Calcium Phosphate	No Disintegrant	Inverse	Inverse	Inverse	Inverse	Direct
	CCS	Inverse	Inverse	Inverse	Direct	Direct
	CPD	Direct	Direct	Inverse	Inverse	Direct
	SSG	Direct	Direct	Inverse	Inverse	Inverse
	CPD+CCS (Low level)	Direct	Direct	Inverse	Inverse	Direct
	SSG+CCS (Low level)	Direct	Direct	Inverse	Inverse	Direct
	SSG+CPD (Low level)	Direct	Direct	Inverse	Inverse	Inverse
	CPD+CCS (High level)	Direct	Direct	Direct	Inverse	Inverse
	SSG+CCS (High level)	Direct	Direct	Inverse	Inverse	Inverse
	SSG+CPD (High level)	Direct	Direct	Inverse	Inverse	Inverse
Microcrystalline Cellulose	No Disintegrant	Inverse	ND	Direct	ND	Inverse
	CCS	Inverse	Direct	Inverse	ND	Inverse
	CPD	Direct	ND	Direct	ND	Direct
	SSG	Inverse	ND	Direct	ND	Inverse
	CPD+CCS (Low level)	Inverse	Inverse	Direct	ND	Direct
	SSG+CCS (Low level)	Inverse	Direct	Inverse	ND	Direct
	SSG+CPD (Low level)	Inverse	Direct	Inverse	Inverse	Direct
	CPD+CCS (High level)	Direct	Direct	Inverse	Direct	Direct
	SSG+CCS (High level)	Direct	Direct	Direct	Inverse	Direct
	SSG+CPD (High level)	Direct	Direct	Inverse	ND	Direct

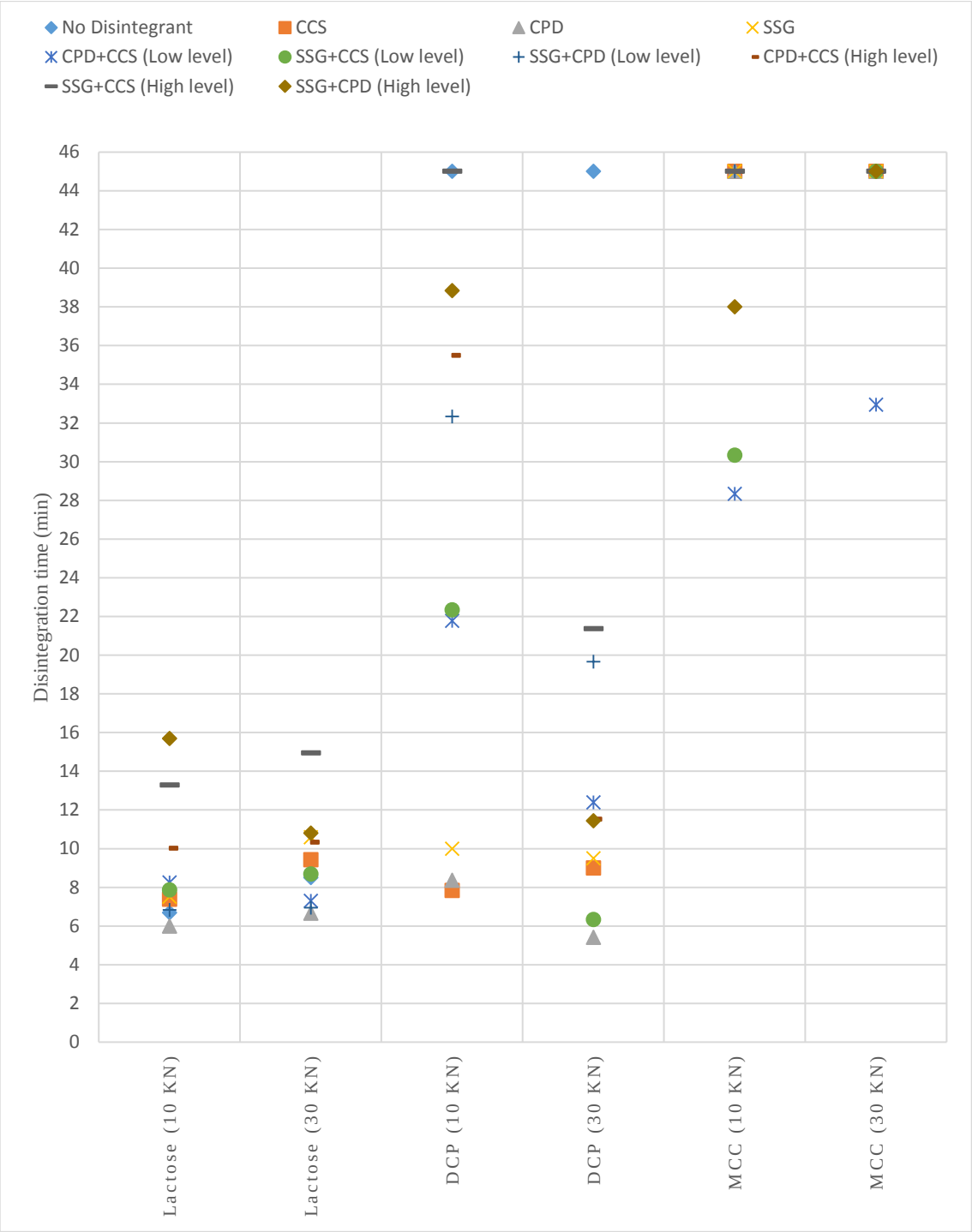

Figure - 42: Summary of disintegration times in fed state. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, DCP – Dibasic Calcium Phosphate, MCC – Microcrystalline cellulose.

In order to develop a formulation that can disintegrate within 10 minutes, under fed conditions, use of CCS or CPD as single disintegrant, or the combination of CPD with CCS or SSG at low level is suggested. Both lactose and DCP can be used as major filler, however, in case of DCP, a formulation needs to be compressed at higher compressional force.

Summary of mean dissolution times (MDT) of all tested formulation, under fed condition, is presented in Figure - 43. It is obvious that MDT was dependent on the filler used. Lactose based formulations provide rapid dissolution followed by DCP and MCC based formulations. In lactose based tablets, low levels of disintegrant combinations gave rapid dissolution as compared to single disintegrants. DCP based tablets provides an interesting scenario, where an increase in compressional force decreased the MDT values in formulations containing low levels of disintegrant combination, while increased the MDT in formulations containing high levels of disintegrant combination. Although, a general decrease in DT was observed in DCP based tablets when compressed at higher compressional force. Moreover, DTs of lactose and DCP based tablets, containing single disintegrants were comparable, but their MDT values are distinct. It may be attributed to the aqueous solubility of fillers. In case of lactose, its rapid dissolution allowed the particles to leave the compact, leaving behind the pores. This dislocation of dissolved lactose particles not only has created new pores, which were subsequently filled with dissolution medium, but also increased the effective surface area for the API. While, DCP based tablets although, disintegrated under the influence of disintegrants, but detached particles did not disintegrate further due to the insolubility of DCP. Therefore, new pores were not developed thereby slowing down the overall dissolution. However, in case of MCC based formulations the combination of CPD+CCS only, at either level, provides a comparable rate of dissolution with lactose or DCP based formulations. Overall, the rate of dissolution was found to be more rapid in formulations containing low levels of disintegrant combinations as compared to those containing high levels respectively. It is apparently due to the gelling tendency of SSG and CCS. Therefore, use of SSG as a single disintegrant is not recommended in formulations whose dissolution is affected in the presence of food. However, considering our results, CCS can be used in this regard. Gelling tendency of CCS is weaker than SSG under fed conditions (Table - 1).

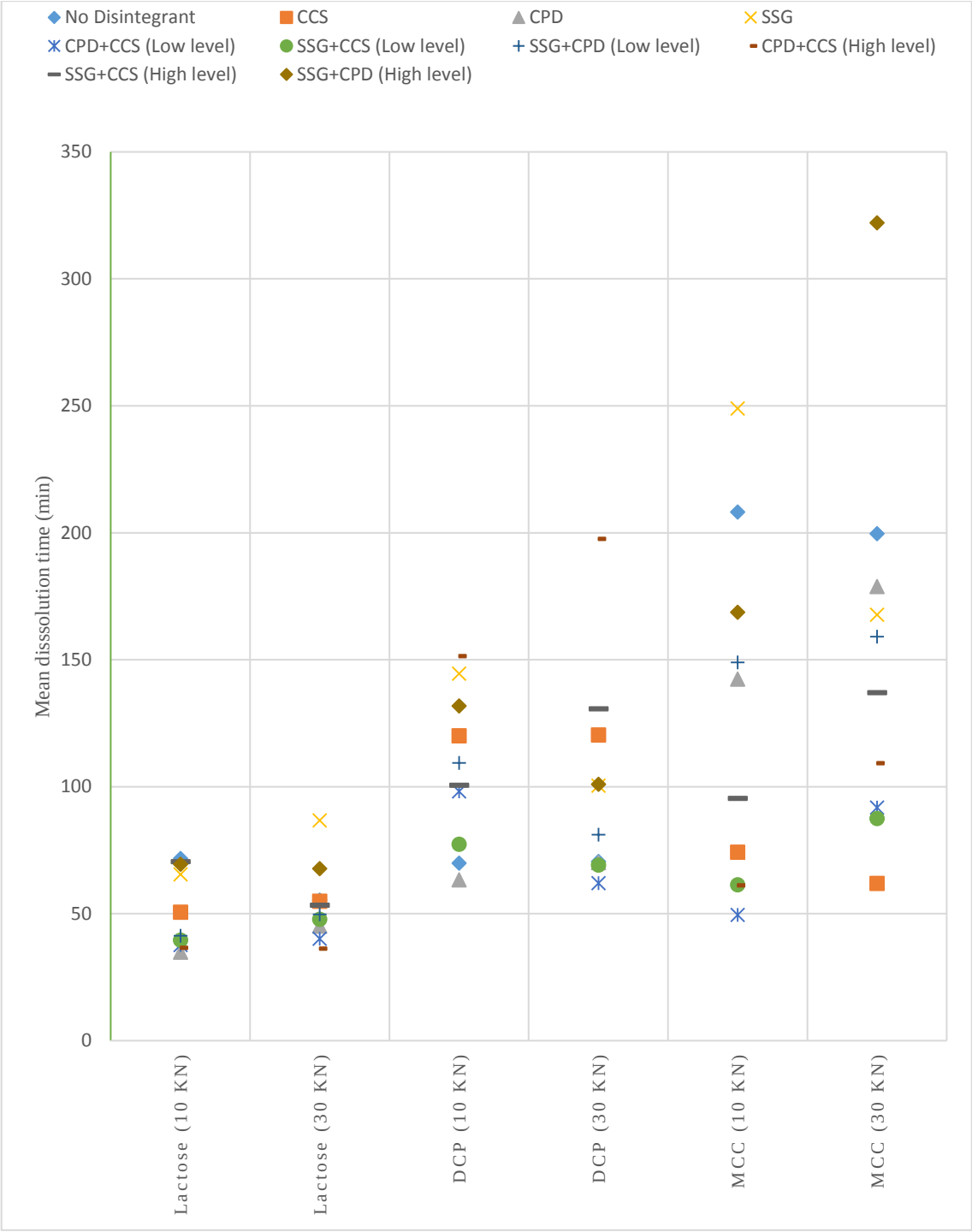

Figure - 43: Summary of mean dissolution times in fed state. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, DCP – Dibasic Calcium Phosphate, MCC – Microcrystalline cellulose.

For both, lactose based and MCC based tablets, disintegrant combination of CPD+CCS is suggested to improve the dissolution. While, for DCP based tablets, CPD as single disintegrant will be beneficial in reducing the mean dissolution time.

Disintegration force – time curves also provided valuable information to understand the mechanism of disintegration under fed conditions. When the disintegration force and related parameters of lactose based tablets containing single disintegrant were compared with DCP based tablets, then relatively lower F_{max} and DFDR values were observed in lactose based tablets when evaluated in fed state (Table - 4). It may be due to the simultaneous dissipation of disintegration force because of evacuating lactose particles. However relatively higher values of F_{max} and DFDR may be attributed to the insolubility and hydrophilicity of DCP respectively. Similarly, higher values of F_{max} and lower values of DFDR, considering the high magnitude of F_{max}, may also be attributed to the insolubility and swellability of MCC, in MCC based tablets. Interestingly, in all MCC based tablets, F_{max} values evaluated under fasted conditions were not much different from F_{max} values evaluated under fed conditions (Table - 17 - 21). Surprisingly, in some formulations especially those containing the combination of disintegrants, F_{max} values under fed conditions were lower than the F_{max} values evaluated under fasted conditions. However, DT and MDT of these formulations are too high to consider the MCC as single filler, but it gives an opportunity to consider the inclusion of MCC as adjunct filler with either lactose or DCP. Generally, under fed conditions, higher T_{max} is associated with slow dissolution in lactose based tablets, but no clear trend was identified in DCP and MCC based formulations. Therefore, the nature of disintegrant and type of disintegration mechanism are to be considered in formulations having insoluble and non swellable fillers.

In the light of our results, formulations having lactose as a filler and either CPD as a single disintegrant or its combination with CCS are expected to be least affected by the negative food effect. Nevertheless, tablets containing lactose as a major filler require higher compressional force to obtain a sufficient hardness. Therefore, a combination of fillers, where lactose comprises a major fraction and either MCC or DCP are used as a minor fraction, may not require higher compressional force. These combinations may further be optimized with either CCS or CPD, as single disintegrant, or their combinations, in order to develop a formulation strategy to minimize the negative effect of food induced viscosity.

Future outlook

1. As an extension of this work, we suggest to study the combination of different fillers, e.g., DCP and MCC with lactose. Optimized combination of filler is expected to reduce the magnitude of compressional force required to compress the tablet. Formulations will further be optimized with either CCS or CPD, as single disintegrant, or their combinations, in order to reduce the disintegration and dissolution times, under fed conditions. Outcome of this proposed study may enrich the formulation strategy towards minimizing the negative food effect.

2. Optimized combination of fillers and disintegrants may further be optimized with at least two BCS class III compounds to validate the outcome of point 1. The optimized blend may be a breakthrough in minimizing negative food effects.

3. Formulation scientists may consider using texture analysis in parallel with disintegration and dissolution tests, in order to get more insight about the physical phenomenon of tablet disintegration.

Zusammenfassung

Die Bioverfügbarkeit von Tabletten wird im Allgemeinen verringert, wenn sie mit Nahrungsmitteln verabreicht werden. Insbesondere, wenn Sie BCS-Klasse-III-Arzneistoffe enthalten. Ein Grund für die Beeinträchtigung der Bioverfügbarkeit ist ein verzögerter Zerfall und verzögerte Auflösung von Tabletten im postprandialen Zustand. Einer der wichtigsten Faktoren in dieser Hinsicht ist, abgesehen von verschiedenen physikochemischen Faktoren, die nahrungsmittelinduzierte Viskosität. Solche Tablettenformulierungen müssen im Hinblick auf diesen postprandialen Viskositätsfaktor optimiert werden. Über den Effekt der nahrungsmittelinduzierten Viskosität auf Formulierungs- und Prozessvariablen ist jedoch noch vieles unbekannt. Um das derzeitige Verständnis über das Verhalten verschiedener Hilfsstoffe unter verschiedenen Zufuhrbedingungen zu verbessern, wurden vier verschiedene Füllstoffe, drei verschiedene Sprengmittel, sowie drei Schmiermittel mit unterschiedlichen Funktionalitäten untersucht. Zu den untersuchten Füllstoffen zählen Lactose (löslich), dibasisches Calciumphosphat (unlöslich und nicht quellbar), mikrokristalline Cellulose (unlöslich aber quellbar) und Calciumcarbonat (aufbrausend im sauren Magenmedium). Außerdem wurden die Sprengmittel Croscarmellose-Natrium (Quellung und Dochtwirkung), Crospovidon (Quellung) und Natriumstärkeglycolat (Quellung) sowie die Schmiermittel Magnesiumstearat (unlöslich), Talkum (unlöslich) und Polyethylenglykol 6000 (löslich) untersucht. Zusätzlich wurde der Effekt der Änderung der Kompressionskraft auf die Bioverfügbarkeit als Verarbeitungsfaktor bewertet.

Die statistische Auswertung der Zerfalls- und Auflösungszeiten im simulierten postprandialen und nüchternen Zustand erfolgte durch D-optimales Design, erzeugt durch die Software MODDE 9.0. Alle Sprengmittel und Füllstoffe außer Calciumcarbonat zeigten einen signifikanten Effekt auf die Zerfalls- und Auflösungszeiten bei unterschiedlichen pH-Werten. Für alle Schmiermittel und Calciumcarbonat zeigte sich ein nicht signifikanter Einfluss im postprandialen Zustand.

Um einen besseren Einblick zu erhalten, wurden drei unabhängige Studien auf Basis eines einzelnen Füllstoffs entwickelt, mit dem Ziel, die Verwendung von drei Sprengmitteln zu untersuchen - Croscarmellose-Natrium (CCS), quervernetztes Polyvinylpolypyrrolidon (CPD) und Natriumstärkeglycolat (SSG). Diese wurden, alleine oder in Kombination, bei unterschiedlicher Druckkraft getestet. Zusätzlich zu den Zerfalls- und Auflösungszeiten wurde die Kraftentwicklung während des Zerfalls gemessen.

In Gegenwart von Lactose als Füllstoff ergaben Formulierungen, die CPD enthielten, den kürzesten Zerfall. Die mittleren Auflösungszeiten im postprandialen Zustand, wurden jedoch durch die Änderungen der Kompressionskraft beeinflusst. CCS enthaltende Formulierungen ergaben geringfügig höhere Zersetzungs- und Auflösungszeiten, wurden allerdings durch die Änderungen der Kompressionskraft nicht beeinflusst. Im Falle von Zerfallskombinationen wurde ein auffallender Unterschied zwischen den Ergebnissen der postprandialen und nüchternen Zustände beobachtet. Im nüchternen Zustand wurde ein schnellerer Zerfall und Auflösung der

Arzneiformulierung beobachtet, wenn höhere Mengen an Sprengmittelkombinationen verwendet wurden. Wohingegen im postprandialen Zustand niedrige Konzentrationen an Sprengmittelkombinationen benötigt wurden. Die Kombination von CPD + CCS, war dabei die effektivste aller Kombinationen.

In Gegenwart von dibasischem Calciumphosphat (DCP) als Füllstoff spielte die Kompressionskraft eine signifikante Rolle und war vorteilhaft bei der Verbesserung der Wirkstofffreisetzung. Obwohl CPD-haltige Formulierungen einen langsameren Zerfall als die auf Lactose basierenden Formulierungen zeigten, verbesserten sie die Wirkstofffreisetzung im postprandialen Zustand. Die Zersetzungs- und Auflösungsgeschwindigkeit in DCP-basierten Formulierungen waren jedoch vergleichsweise schneller, wenn sie im nüchternen Zustand bewertet wurden. Im postprandialen Zustand wurde zudem festgestellt, dass verringerte Konzentrationen an Sprengmittelkombinationen und erhöhte Kompressionskraft den Zerfall und die Auflösung verbessern. Im nüchternen Zustand war die Wirkung des Gehalts an Sprengmittelkombination abhängig von der Kompressionskraft, d. h. bei niedriger Kompressionskraft, verbesserte sich die Wirkstofffreisetzung mit einer Verringerung des Gehalts an Sprengmittelkombination und umgekehrt. Die Kombination von CPD + CCS in niedrigen Konzentrationen war unter höherer Kompressionskraft am wirksamsten.

In Gegenwart von mikrokristalliner Cellulose als Füllstoff überstiegen die Zerfallszeiten die Grenzen des Kompendiums und die Wirkstofffreisetzung war im postprandialem Zustand stark beeinträchtigt. CCS-haltige Formulierungen ergaben eine bessere Wirkstofffreisetzung. Die vielversprechendste Formulierung für MCC basierte Tabletten ergab eine Kombination der Sprengmittel von CCS und CPD bei jeweils 2% die bei 10 kN komprimiert wurde.

Unterschiede in den Ergebnissen zwischen nüchternen und postprandialen Zuständen, erfordern die Entwicklung eines standardisierten Protokolls, um die Formulierungen im postprandialen Zustand während der Entwicklungsphase zu testen. Diese Arbeit soll hierfür von Formulierungsentwicklem und Regulierungsbehörden in Betracht gezogen werden.

Relativ schnelle Zerfalls- und Auflösungszeiten wurden bei auf Lactose basierenden Formulierungen beobachtet. In ähnlicher Weise wurde herausgefunden, dass CPD, CCS und ihre Kombinationen im postprandialen Zustand wirksam sind. Daher können Formulierungen von Tabletten durch den Anteil von CPD und CCS, entweder allein oder in Kombination, in Bezug auf die Dosis und die Art der verwendeten Arzneistoffe im Hinblick auf die Nahrungsmittelbeeinflussung optimiert werden.

Als eine Erweiterung dieser Arbeit schlagen wir vor, dass das Potential der Kombination verschiedener Füllstoffe mit Lactose untersucht wird. Eine optimale Kombination von Füllstoffen könnte nützlich sein, um die Zerfallszeit sowie die umgebende Grenzschicht um die Tabletten im postprandialen Zustand zu reduzieren, wodurch die Formulierungsstrategie zur Minimierung des negativen Nahrungsmitteleinflusses optimiert wird.

Summary

Bioavailability of tablets, particularly those containing BCS class III compounds, is generally reduced when administered with food. Delayed disintegration and dissolution of tablets observed in fed state is believed to be a reason for the impaired bioavailability. In addition to various physicochemical factors, food induced viscosity is one of the important factors in this regard. Formulations of such tablets need to be optimized in view of this postprandial viscosity factor. Unfortunately, there exists a knowledge gap about the effect of food induced viscosity on formulation and process variables. In order to enhance the current understanding about the behavior of various excipients under fed conditions, 4 fillers with different functionalities i.e, Lactose (soluble), Dibasic calcium phosphate (insoluble and non swellable), Microcrystalline cellulose (insoluble but swellable) and Calcium carbonate (give effervescence in gastric medium); 3 disintegrants, i.e, Croscarmellose sodium (swelling and wicking), Crospovidone (shape recovery) and Sodium starch glycolate (swelling); 3 lubricants i.e, Magnesium stearate (insoluble), Talc (insoluble) and Polyethylene glycol 6000 (soluble) as well as compressional force as a processing factor were assessed at different levels.

Statistical evaluation of disintegration and dissolution times, in simulated fed and fasted state through D-optimal design, generated through MODDE 9.0 software revealed the insignificance of lubricants and calcium carbonate in fed state. However, all disintegrants and fillers except calcium carbonate, showed significant effect on the disintegration and dissolution times, at different pH levels.

To obtain a better insight, three independent studies, based on a single filler were designed, with an objective to study the use of three disintegrants i.e, Croscarmellose sodium (CCS), cross-linked polyvinylpyrrolidone (CPD) and sodium starch glycolate (SSG), alone and different levels of their combination at varying compressional force. In addition to the compendial tests of disintegration and dissolution, disintegration force development was also measured.

In the presence of lactose as a filler, formulations containing CPD gave the shortest disintegration and mean dissolution times in fed state. However, these formulations were affected by the changes in compressional force. CCS containing formulations gave slightly higher disintegration and dissolution times, but were not affected by the changes in compressional force. In case of disintegrant combinations, a striking difference between the results of fed and fasted states was observed. Rapid disintegration and dissolution of drug was seen in fasted state, when higher levels of disintegrant combinations were used, while it was achieved in fed state when disintegrant combinations were used in low levels. Combination of CPD+CCS, was more effective among all combinations at either level and compressional force.

In the presence of dibasic calcium phosphate (DCP) as a filler, compressional force showed a significant role and was beneficial in improving the drug release. Though slower than the lactose based formulations, CPD containing formulations improved the drug release in fed state, however the disintegration and dissolution was comparatively

faster in DCP based formulations when evaluated in fasted state. In fed state, decreased levels of disintegrant combinations and increased compressional force were found to improve the disintegration and dissolution. While in fasted state, the effect of level of disintegrant combination was dependent on the compressional force i.e, at low compressional force drug release improved with a reduction in level of disintegrant combination and vice versa. Combination of CPD+CCS in low levels was effective under higher compressional force.

In the presence of microcrystalline cellulose as a filler, disintegration times exceeded the compendial limits and drug release was greatly impaired in fed state. However, CCS containing formulations gave considerable better rate of drug release. Formulation containing combination of CCS and CPD at 2% each and compressed at 10 KN is interesting from a formulator's perspective.

Differences in the results obtained in fasted and fed states advocates the development of a standardized protocol to test the formulations in fed state during development phase. Concerned formulators and regulatory authorities may consider our work.

Relatively rapid disintegration and dissolution times were observed with lactose based formulations. Similarly, CPD, CCS and their combinations were found to be effective in fed state. Therefore, formulators can optimize the proportion of CPD and CCS either alone or in combination with respect to the dose and nature of API used, in formulations of tablets, which are affected by the presence of food.

As an extension of this work, we suggest to study the potential of combination of different fillers with lactose. An optimum combination of fillers could be beneficial in reducing the disintegration time as well as the surrounding boundary layer around the tablets in fed state thereby enriching the formulation strategy towards minimizing the negative food effect.

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Zaheer, K., & Langguth, P. (2018). Formulation strategy towards minimizing viscosity mediated negative food effect on disintegration and dissolution of immediate release tablets. *Drug Development and Industrial Pharmacy, 44*(3), 444-451.

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Zhao, N., & Augsburger, L. L. (2005b). The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS PharmSciTech, 6*(1), E120-E126.

Appendix 1: List of Publications

1. Zaheer, K., & Langguth, P. (2018). Formulation strategy towards minimizing viscosity mediated negative food effect on disintegration and dissolution of immediate release tablets. *Drug Development and Industrial Pharmacy, 44*(3), 444-451.

2. Asghar, M., Mumtaz, N., Niaz, S., Zaheer, K., & Raza, M. (2017). Prescribing behaviour of practitioners in public and private hospitals in Pakistan evaluated using the World Health Organization (WHO) indicators: A comparative approach. *Le Pharmacien Hospitalier et Clinicien*, *52*(3), 299-305.

3. Usmani, M. T., Shoaib, M. H., Nasiri, M. I., Yousuf, R. I., Zaheer, K., & Ahmed, K. (2015). Development and Evaluation of Orally Disintegrating Tablets of Montelukast Sodium by Direct Compression Method. *Tropical Journal of Pharmaceutical Research*, *14*(1), 1-6.

Appendix 2: Curriculum Vitae

Germany: Am Taubertsberg 4, 55122 Mainz Germany *Pakistan: C-39, Hoor Palace, block 11 Gulshan-e-Iqbal, Karachi. 75300*	Germany: +49 15211621729 Pakistan:+92 3452220504 E-mail: kamranzaheer63@hotmail.com kazaheer@uni-mainz.de, kamran.zaheer@hamdard.edu.pk

KAMRAN ZAHEER

Born on August 20, 1978 in Karachi Pakistan

Objective	To acquire a distinctive and novel position in my pharmaceutical career especially regarding formulation and dosage form development.
Experience To date: **(17 y 1 m)** As on April 1, 2018	❖ Oct. 2014 – Apr 2018 ***Research Associate*** Institute of Pharmacy Johannes Gutenberg-Universität Mainz, Germany ❖ Aug. 2013 – May 2014 (on study leave) ***Deputy Director (Acting)*** Faculty of Pharmacy Hamdard University, Karachi, Pakistan Activities ➢ Conducted visit of CIEC in February 2014. ➢ Improvised the system as Incharge Examination Cell. ➢ Implemented rules and regulations laid down by PCP in letter and spirit. ➢ Restructured and conducted BoF and BoS for all departments. ➢ Successfully implemented new curriculum for Pharm. D. and grading system. ❖ Mar. 2006 – May 2014 (on study leave) ***Assistant Professor (Pharmaceutics)*** Faculty of Pharmacy Hamdard University, Karachi, Pakistan.

Activities

- Designed curriculum for semester system of FOP.
- Designed the system to record the attendance record of students on daily basis.
- Organized 3 Industrial visits for Pharm. D and B.Pharm. Final year.
- Set up and managed class time tables and examination schedules until 2010.
- Looks after the cases of migration from other institutions to Faculty of Pharmacy, Hamdard University

❖ Dec. 2003 – Mar. 2006

LECTURER (Pharmaceutics)

Faculty of Pharmacy

Hamdard University.

Activities

- Established Industrial Pharmacy Lab.
- Re-structured course contents for B.Pharm. (annual system)
- Incahrge time table for classes.and examination schedule for the year 2005.

❖ Feb. 2001 – Nov. 2003

Production Pharmacist

TABROS PHARMA Karachi, Pakistan

Activities

- Successfully supervised the Granulation, Compression, and Coating sections.
- Supervised the capsule filling area for 1 year.
- Wrote up-to-date SOPs for the areas under my supervision
- Served as dispensing officer/Asst. R/M store incahrge for 2 month.
- Involved in the formulation development especially those of tablets
- Supervised the liquid filling area for 2 months.

Education	**Ph.D. fellow** *JGU, Mainz Germany* 2014 to date (Pharmaceutical Technology) **M.Phil. (Pharmaceutics)** *Karachi University* C.G.P.R = 3.33 2005 **B.Pharm.** *Karachi University* C.G.P.R = 3.49 2000
Research Publications Impact Factor : 4.049	1. Zaheer, K., & Langguth, P. (2018). Formulation strategy towards minimizing viscosity mediated negative food effect on disintegration and dissolution of immediate release tablets. *Drug Development and Industrial Pharmacy*, *44*(3), 444-451. (IF=2.295) 2. Asghar, M., Mumtaz, N., Niaz, S., Zaheer, K., & Raza, M. (2017). Prescribing behaviour of practitioners in public and private hospitals in Pakistan evaluated using the World Health Organization (WHO) indicators: A comparative approach. *Le Pharmacien Hospitalier et Clinicien*, *52*(3), 299-305. 3. Usmani, M. T., Shoaib, M. H., Nasiri, M. I., Yousuf, R. I., Zaheer, K., & Ahmed, K. (2015). Development and Evaluation of Orally Disintegrating Tablets of Montelukast Sodium by Direct Compression Method. *Tropical Journal of Pharmaceutical Research*, *14*(1), 1-6. (IF=0.543) 4. Shoaib, M. H., Siddiqi, S. A. S., Yousuf, R. I., Zaheer, K., Hanif, M., Rehana, S., & Jabeen, S. (2010). Development and evaluation of hydrophilic colloid matrix of famotidine tablets. *AAPS PharmSciTech*, *11*(2), 708-718. (IF=1.211)
Achievements	✓ **HEC Overseas Scholarship 90%(Batch V) 2014** ✓ **GAT – Subject (Pharmacy) 2011 – I** Score **: 68** Percentile **: 90.30** ✓ **GAT – General 2011 – II** Score **: 70** Percentile **: 98.30**
Courses	• ***Training on Hitachi HPLC system and Chromeleon Chromatography Software*** **Merck** (1st February – 10th February 2010) • ***Arabic Language Course Level – I*** **NUML** (November 2008 – January 2009) Karachi Campus

	• ***Arabic Language Course Level – II*** (February 2009 – May 2009)	**NUML** Karachi Campus
	• ***Arabic Language Course Level – III*** (June 2009 – October 2009)	**NUML** Karachi Campus
	• ***Certified Quality Professional*** (May – September 2007)	**CCEE, NED University, Karachi** In collaboration with, **PIQC Institute of Quality**
	• ***Medical Transcription Training*** (April – July 2001)	**COMSATS** Govt. of Pakistan, Ministry of Science and Technology
	• ***E- Commerce*** (February – April 2001)	**PC Horizon Computer Center**
Languages	• Can understand and communicate well in **URDU** & **ENGLISH** • Little Proficient in **Arabic** and **German.**	
Professional Affiliation	• Registered Pharmacist by Pharmacy Council of Sindh (Reg No. **2337**)	
Other Skills	Can understand and expertly work on the following computer packages.	
	▪ MS – Word ▪ MS – Excel ▪ MS – Power Point	▪ In Page (Urdu Software) ▪ Macromedia Freehand ▪ Macromedia Flash

Workshops	▪ "**National <u>workshop</u> to educate the stakeholders about the implication of WTO / TRIPS agreement and patent laws on traditional medicine trade**" Organized by Ministry of Health, NIH, WHO and WIPO Geneva on 21st - 22nd Feb. 2005. at Board Room Hamdard Foundation Karachi ▪ "**A <u>workshop</u> on Introduction to digital library resources & their effective usage**" Organized by HEC on October 12, 2005, at FEST Auditorium Hamdard University Karachi. ▪ "**A <u>workshop</u> on Research Methodology**" Organized by Dept of Community Health Sciences HCM&D on November 23 – 25 2010; at Board Room Hamdard University Karachi ▪ "**2 Day <u>workshop</u> on Stability Testing/ cGMP Compliance: Strategies for establishing complaint and effective stability and cGMP Programs**" Organized by **Pakistan Pharmaceutical Educational Foundation** held on January 12 – 13 2007, at Pearl Continental Karachi.
Presentations	▪ Gave <u>presentation</u> about "**Admissions in Pharm. D. at Faculty of Pharmacy, Hamdard University Karachi**" during Admission Campaign – 2005; July 10, 2005 at Hotel Sheraton Karachi. ▪ Gave <u>presentation</u> about "**Admissions in Pharm. D. at Faculty of Pharmacy, Hamdard University Karachi**" during Admission Campaign – 2006 June 25, 2006. at Hotel Sheraton Karachi. ▪ Gave 3 <u>presentations</u> about "**Admissions in Pharm. D. at Faculty of Pharmacy, Hamdard University Karachi**" during Admission Campaign – 2006 July 10, 2006. Open House at Hamdard University. ▪ Gave <u>Presentation</u> on "**Application of MS-Excel**" in a workshop on "**Basic applications of computer**" on February 3rd 2011, held at Faculty of Pharmacy, Hamdard University Karachi.
Others	➢ **Internal Quality Auditor** in Tabros Pharma in a Quality Audit conducted by Delta Consultants. November 11th 2003. ➢ On **Panel of Examiners** for *M.Pharm*. Faculty of Pharmacy, University of Karachi, Karachi ➢ On **Panel of Examiners** for *Pharm.D*. Faculty of Pharmacy, Dow University of Health Sciences Karachi.

	➢ Has evaluated 3 thesis of M.Pharm. ➢ Conducted viva voce of 2 students of M.Pharm. in **2006 – 2007**. ➢ **Member,** Un Fair Means Committee, Hamdard University Karachi. ➢ **Member,** Prospectus Committee, Hamdard University Karachi for the year 2006. ➢ **Member**, Faculty selection committee for sports week 2000 at Faculty of Pharmacy, University of Karachi. ➢ **Captain** of Runner's up Pharmacy cricket team in Inter departmental cricket tournament 1999.
References	• **Prof. Dr. Iqbal Azhar,** Dean, Faculty of Pharmacy, University of Karachi, Karachi. • **Prof. Dr. Muhammad Harris Shoaib,** Chairman, Depart. of Pharmaceutics Faculty of Pharmacy, University of Karachi. Karachi