Investigation of Different Shellac Grades and Improvement of Release From Air suspension Coated Pellets

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To the soul of my parents

to my wife

to my daughter Sarah

and to the rest of family

ACKNOWLEDGMENTS

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HPMC	Hydroxypropyl methylcellulose
HPC	Hydroxypropyl cellulose
CMC	Carboxymethyl cellulose
DDA	Dose-dumping in alcohol
CAP	Cellulose acetate phthalate
PVAC	Polyvinyl acetate phthalate
MC	Methyl cellulose
PEG	Polyethylene glycol,
GMP	Good manufacturing practice
FDA	Food and Drug Administration
EPA	Environmental Protection Agency
OSHA	Occupational Safety and Health Administration
AV	Acid value
Ph. Eur.	The European Pharmacopeia
Tg	Glass transition temperature
GC	Gas chromatography
MS	Mass spectrometry
MALDI-TOF-MS	Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry
FDA	Food and Drug Administration
PPO	Polyphenol oxidase
POD	Peroxidase
NKCP	Nattokinase

CP	Carbamide peroxide
PAA	Polyamidoamine
TMD	Tramadol
GIT	Gastrointestinal tract
SSB	Stroever Shellac Bremen
DSC	Differential scanning calorimetry
DLS	Dynamic Light Scattering
PCS	Photon Correlation Spectroscopy
POM	Polyoxymethylene Polyacetal Mold
MPa	Mega Pascal
USP	United States Pharmacopeia
MDT	Mean dissolution times
S D	Standard deviation
SEM	Scanning Electron Microscopy
GU	Gloss Unit
f_2	Similarity factor
MR	Modified Release
PVP	Polyvinylpyrrolidine
SGF	Simulated gastric fluids
CF	Colonic fluids
OGD	Office of Generic Drug
RLD	Reference Listed Drug
h	hour

Abstract

Shellac is the purified product of the natural polymer Lac. It is the resinous secretion of the parasite insect *Kerria lacca* on several species of trees in Asian countries such as India, Thailand and China. The physicochemical properties of shellac are variable depending on the insect strain, host trees and refining methods used for its purification. Three different processes are used for refining shellac; bleaching, melting, and solvent extraction, resulting in products with different characteristics and properties. From these methods, only shellac refined by the solvent extraction process is used for pharmaceutical applications.

Shellac types, from different origins and with different ages, all purified by the solvent extraction process were compared in this study. Their physicochemical properties acid value, glass transition temperatures, color numbers and molecular sizes were determined. Metoprolol tartrate pellets were coated by air suspension coating with these different grades of shellac. Two coating levels 20% w/w and 25% w/w were applied and then subjected to in vitro dissolution testing. Enteric resistance was achieved for all tested brands for the two coating levels. At pH 6.8, 7.2 and 7.4, significant variations were obvious between the brands. Furthermore, coated pellets produced with newer brands of the same origin showed higher release rates compared to the aged shellac products.

Despite the fact that the solvent extraction process produced shellac with similar acid values, the origin and the age of shellac are more important than the acid value for consistent product quality. Moreover the molecular size of shellac has a pronounced effect in that shellac types with larger molecular size show a higher and faster release than others, while the one with the smaller molecular size show the opposite effect on the release of metoprolol.

Formerly shellac was mainly used as an enteric coating material from alcoholic solutions and shellac films prepared from alcoholic solutions suffered from problems like esterification and polymerization or hardening after storage. Since the introduction

of aqueous ammoniacal shellac solutions, shellac regained its importance for pharmaceutical coatings. In this study commercially available ready for use aqueous shellac solutions (SSB AQUAGOLD), which are based on shellac SSB 57 (Dewaxed Orange Shellac, Bysakhi-Ber type refined in a solvent extraction process), with different manufacturing dates were used. A decrease in the pH was noticed after longer storage time. This decrease in the pH is due to evaporation of the volatile alkali from the shellac solution. Before use of the shellac solution, the pH must be readjusted to the specified range (7.3±0.2). Dissolution profiles for metoprolol tartrate pellets coated with these shellac aqueous solutions showed no significant differences in the drug released from these coated pellets

It is well known that shellac is an excellent film forming polymer and has been used for tablet coating since 1930. Shellac was noted to have a delayed intestinal release and it begins to dissolve at pH ≥7.2. The low solubility of shellac in intestinal fluids limits its use as an enteric coating material. To improve the enteric coating properties of films from aqueous shellac solutions, different aqueous polymeric solutions of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboyxmethyl cellulose (CMC), gum arabic and polysaccharides (Pullulan®) were used. These water soluble polymers will act as pore formers to enhance drug release from pellets coated with the combination of shellac and these polymers. The influence of these polymers on the gloss of the shellac films, mechanical properties of the films and drug release from metoprolol tartrate pellets were studied.

The potential of ethanol to alter the rate of drug release from shellac coated pellets was assessed by using a modified in vitro dose dumping in alcohol (DDA) method and the test concluded that shellac coated dosage forms can be co-administered with alcohol beverages containing ≤ 5% with no effect of alcohol on the shellac coat.

Pellets coated with shellac sodium salts, showed higher release rates than pellets coated with shellac as ammonium salt forms.

1 Introduction

Modern pharmaceutical coating techniques have developed over the years from the initial use of sugar to provide a pleasant taste and attractive appearance to tablets which were unpleasant to swallow due to their bitterness [1]. Generally, sugar-coated tablets are no longer developed due to the lengthy process, the high degree of operator skill required and the fact that identification of the product is difficult [2].

A film coating is a thin polymer-based coat applied to a solid dosage form such as a tablet, granule, pellet or other particle. The thickness of such a coating is usually between 20 and 100 μm [1]. It is a very important unit operation in the pharmaceutical industry [3-4]. Film coatings are used for many reasons including improvement of mechanical stability, reduction of the dosage form abrasion during manufacturing, shipping and storage [5-7], masking of unpleasant taste or odor [8], protection from light or humidity [9], easing digestion [10], imparting enteric properties and modulating release of active ingredients [3, 11-13].

Since its inception, film coating of pharmaceutical dosage forms has shown significant increases in popularity, owing to the many advantages it has to offer[14]. The first reference to tablet film coating appeared in 1930 but it was not until 1954 that Abbott Laboratories produced the first commercially available film-coated tablet [15-16]. Coating of particles is also an important unit operation in the pharmaceutical industry. There are numerous applications of coating, including drug layering, modified release coating, physical and chemical protection, aesthetic purposes, taste-masking and better identification of drug products [17-20]. Film-coating formulations also encompass those that are expected to allow a drug to be rapidly released from the dosage form. In such cases they are used for taste masking or moisture protection.

These coatings should maintain their barrier function during storage as well as during intake of the dosage form[7, 16]. Once the formulation reaches the stomach the coating should dissolve rapidly and release the drug. This type of coating is usually prepared with water soluble polymers [21] and in some cases with water insoluble, basic

polymers that dissolve in the acidic milieu of the stomach [7]. Enteric coatings are applied to solid oral dosage forms to improve the chemical stability of acid-sensitive drugs [22-23], to decrease gastric irritation [24-25] and to target the drug to the colon [15, 26]. The film remains intact as long as the pH is below the release pH, above which the drug is released [16, 27].

For the application of sustained release coatings, water insoluble polymers are used. After swelling of the coating film or dissolution of incorporated pore formers, the coating film becomes permeable and/or the drug release occurs by slow diffusion through the coating layer [24, 28].

As such, these coating formulations are exemplified by:

- Organic solvent–based solutions of polymers [18, 23]
- Aqueous solutions or dispersions of polymers [18, 23]
- Hot-melt systems [29]
- Powder coatings [29]

Despite the apparent variety expressed by these options, aqueous systems hold a dominant position in the pharmaceutical industry at this time [24]. As a consequence, serious constraints are often imposed on the products being coated, the coating formulations used and the coating processes that are adopted, with the result that scaling the coating process up can present serious challenges [30].

1.1. Film coating formation mechanisms

Film formation from aqueous polymers, can be either from aqueous solutions or aqueous dispersions of polymers.

1.1.1. Film-formation from aqueous polymeric solution

Polymeric solutions form films through a series of phases. When the polymer solution is cast on a surface, cohesion forces form a bond between the polymer molecules [31-32]. When the cohesive strength of the polymer molecules is relatively high, continuous surfaces of the polymer material coalesce. Coalescence of an adjacent polymer

molecule layer occurs through diffusion. Upon evaporation of water, gelation progresses and allows the polymer chains to align in close proximity to each other and to be deposited over a previous polymer layer [33]. When there is adequate cohesive attraction between the molecules, sufficient diffusion and complete evaporation of water, polymer chains align themselves to form films [7, 31, 33].

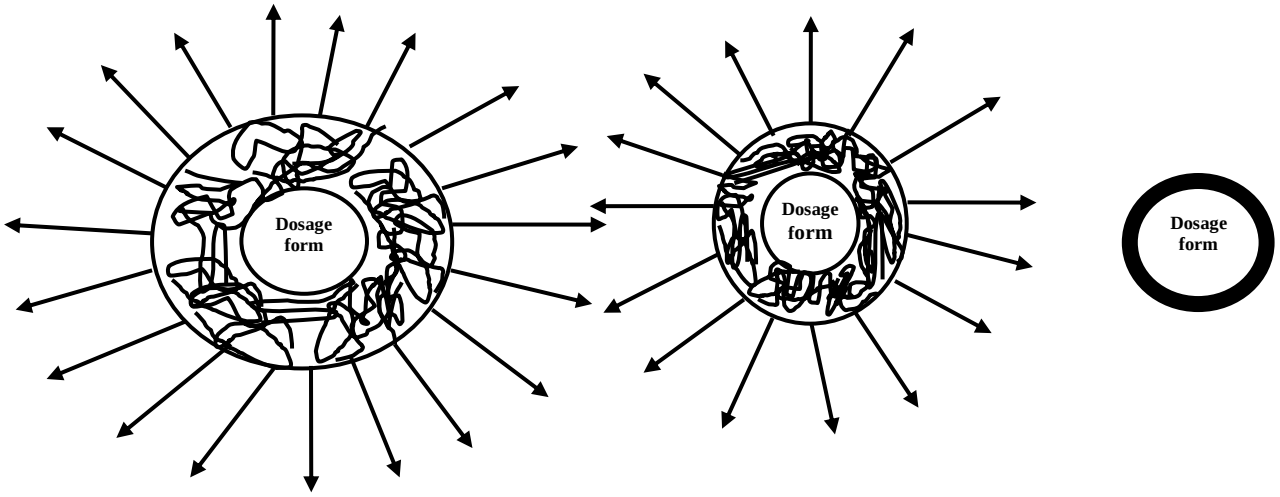
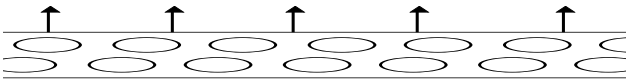


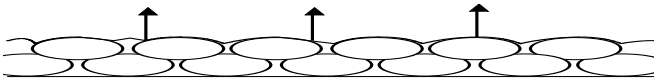
Figure 1: Film-forming mechanism of aqueous polymeric solution.

1.1.2. Film-formation from aqueous polymeric dispersion

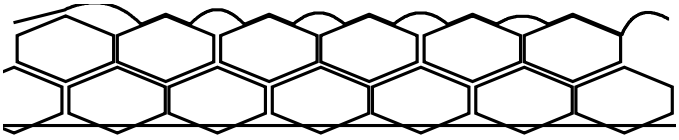
Film formation from an aqueous polymeric dispersion is a complex matter and has been examined by several authors [16, 34]. In the wet state the polymer is present as a number of discrete particles. These must come together in close contact, deform, coalesce and ultimately fuse together to form a discrete film. During processing, the substrate surface will be wetted with the diluted dispersion. Under the prevailing processing conditions water will be lost as water vapor and the polymer particles will increase in proximity to each other, a process which is greatly aided by the capillary action of the film of water surrounding the particles [16]. Complete coalescence occurs when the adjacent particles are able to mutually diffuse into one another [7], as shown in Fig. 2.



Phase i. Water evaporation



Phase ii. Polymer particles approaching each other



Phase iii. Deformation of polymer particles

Phase iv. Inter-diffusion of polymer chains and film formation

Figure 2: Film-forming mechanism of aqueous polymeric dispersion.

1.2. Film coating formulations

Usually the film contains polymer, plasticizer, colorants/ opacifiers and solvent/ vehicle.

1.2.1. Polymers

Amongst the vast majority of the polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers [16, 35-36]. They can be classified as:

1.2.1.1. Enteric coating polymers

These includes cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAC), methacrylate ester copolymers, ethyl cellulose and shellac which is the first enteric coating polymer used for enteric coatings [37].

1.2.1.2. Non-enteric coating polymers

The majority of the cellulose derivatives used in film coating are ethers of cellulose. Broadly they are manufactured by reacting cellulose in alkaline solution with, for example, methyl chloride, to obtain methylcellulose. Examples include methyl cellulose (MC), hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC). Also included are the acrylic polymers which comprise a group of synthetic polymers with diverse functionalities.

1.2.2. Plasticizers

Plasticizers are relatively low molecular weight materials which have the capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film-coating material [2, 35, 38].

It is generally considered that the mechanism of action of plasticizer molecules is to interpose themselves between individual polymer strands thus breaking down to a large extent polymer-polymer interactions. Hence, the polymer strands now have a greater opportunity to move past each other [2]. Thus polymer is converted into more pliable materials. Experimentally, the effect of a plasticizer on a polymeric system can be demonstrated in many ways; for instance, isolated film work using tensile or indentation

methods will reveal significant changes in mechanical properties between the plasticized and unplasticized states [2]. Mainly the glass transition temperature is lowered by the plasticizer [16]. Plasticizers are classified into three groups:

1. Polyols: such as Glycerol, propylene glycol, PEG (Polyethylene glycol).

2. Organic esters: such as phthalate esters, dibutyl sebacete, citrate esters, triacetin.

3. Oils/glycerides: such as castor oil, monoglycerides and fractionated coconut oil.

With the predominance today of aqueous-based film coating there is a concentration on those plasticizers with appreciable water miscibility. This includes the polyols and, to a lesser extent, triacetin and triethylcitrate. Glycerol has the added advantage of its regulatory acceptance for food supplement products [2, 16].

1.2.3. Colorants / opacifiers

These materials are generally used as ingredients in film-coating formula to contribute to the visual appeal of the product. They also improve the product in other ways [16, 35] such as its identification by the manufacturer. Therefore they act as an aid for existing good manufacturing practice (GMP) procedures, also for identification of the product by patients by using colorants.

Colorants for film coating also act to some extent as an opacifier. So they would give protection to active ingredients in presence of light. Colorants are mainly classified into three types [2]:

i- Organic dyes and their lakes (Sunset, Yellow Tartrazine, Erythrosine).

ii- Inorganic colors (Titanium dioxide, Iron oxide yellow, red and black, Talc).

iii- Natural colors (Riboflavine, Carmine, Anthocyanins).

Some natural polymers are colored (shellac), in this case there is no need for using colorants.

1.2.4. Solvents / vehicles

The function of the solvent system is to dissolve or disperse the polymers and other additives. These materials perform a necessary function in that they provide the means of conveying the coating materials to the surface of the tablet or particle [2].

The major classes of solvents capable of being used are water, alcohols, ketones, esters and chlorinated hydrocarbons.

A prerequisite for the solvent is that it must interact well with the chosen polymer because the solvent-polymer interaction determines the film properties such as adhesion and mechanical strength [16]. Thus the solubility parameters should be evaluated and modified if needed [16, 36, 39-41].

Currently, the most common technology for coating solid dosage forms is the liquid coating technology. In liquid coating, a mixture of polymers and excipients are dissolved in an organic solvent (for water insoluble polymers) or water (for water soluble polymers) to form a solution, or dispersed in water to form a dispersion and then used for coating the dosage forms [13, 30, 42].

Organic solvent based coating provides a variety of useful polymer alternatives, as most of the polymers are soluble in a wide range of organic solvents. There are several disadvantages associated with their use [13, 30, 42].

1. They are flammable and toxic

2. Their vapor causes hazards to the coating equipment operator

3. High cost of solvent

4. Solvent residue in formulation

5. Strict environmental regulations by United States Food and Drug Administration (USFDA), Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) [30].

All of the above problems with organic solvents have resulted in a shift to the use of water as the preferred coating solvent. Aqueous-based coatings have been increasingly used compared with organic-based coatings. However, water-based coatings also suffer from problems:

1. Heat and water involved in coating process can degrade the drug

2. Validation of coating dispersion for controlling microbial presence is necessary

3. Solvent removal process is time consuming and extremely energy consumptive [30]

1.2.5. Other coating solution components

To provide a dosage form with a single characteristic, special materials may be incorporated into a solution [16].

i - Flavours and sweeteners

These are added to mask unpleasant odors or to develop the desired taste. For example, aspartame, various fruit spirits (organic solvent), water-soluble pineapple-flavor (aqueous solvent) etc. [2].

ii - Surfactants

These are supplementary materials used to solubilize immiscible or insoluble ingredients in the coating solution. For example, Spans, Tweens etc. [2].

iii -Antioxidants

They are incorporated to stabilize a dye system against oxidation and color change, for example, oximes and phenols.

iv - Antimicrobials

They are added to put off microbial growth in the coating composition. Some aqueous cellulosic coating solutions are mainly prone to microbial growth and long-lasting

storage of the coating composition should be avoided [2]. Examples are carbamates and benzothiazoles.

1.3. Film coating process

Film coating is a multivariate process, with many different factors, such as coating equipment, coating liquid, and process parameters which affect the quality of the final product [43-46].

1.3.1. Coating equipment

Formerly different types of coating pans were used for coatings. These include conventional coating pans, manesty accelacota, driam (driacoater), butterfly coater etc. Later the side-vented, perforated pan-coater used for coating of tablets [1-2, 47] and wurster coaters, which are bottom spray fluid bed coaters, were extensively used in the pharmaceutical industry for coating of small particulates, especially pellets [17, 47]. They produce uniform coats, [18] however, their use has been limited by the propensity of the particles to agglomerate during the coating process [48]. Thus various modifications to conventional Wurster coaters have been made to improve the coating process [47].

1.3.2. Coating liquid

The coating liquid affects the final quality of the film. Viscosity may affect the spreading of coating liquid across the surface of substrate. Surface tension may affect the wetting of surface. The % solid content generally affects the solid dosage surface and coating efficiency [2, 49].

1.3.3. Process parameters

1.3.3.1. Spray rate

A low coating liquid spray rate causes incomplete coalescence of polymer due to insufficient wetting, which could affect the mechanical properties of the film, leading to brittle films [50]. High coating liquid spray rates result in over-wetting and subsequent problems such as picking and sticking [2, 50-51].

1.3.3.2. Atomizing air pressure

In general, increasing the spraying air pressure decreases the surface roughness of the coated dosage form and produces denser and thinner films [14, 44, 52]. If spraying air pressure is excessive the spray loss is great and the formed droplets are very fine and could spray-dry before reaching the substrate bed, resulting in inadequate droplet spreading and coalescence [44]. If spraying air pressure is inadequate, the film thickness and thickness variation are greater, possibly due to change in the film density and smaller spray loss [2].

1.3.3.3. Inlet air temperature

High inlet air temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water penetration into the coated dosage form core, tensile strength and residual moisture content of coated dosage form [52-53]. If the air temperature is too high, the premature drying of the spray during application is increased which decreases the coating efficiency [2, 54-55].

Farag and Leopold found that even though coating was performed with aqueous shellac solutions, a minimum inlet air temperature had to be exceeded to obtain a continuous coating film. Below that temperature, cracks in the coating film appeared, resulting in changes in the release profiles and especially loss of gastric resistance [7].

1.4. Origin and method of manufacture of shellac as film coating material

Shellac is the general term for the refined form of lac, a natural polymer resin secreted by insects [35, 56-57]. It is produced by different types of insects from different host trees. The tiny insects *Kerria Lacca* (Kerr) Lindiger (Coccideae), are parasitic on certain trees in India, Thailand and southeast Asia, they are the most important species, that they produce the major percentage of the commercial lac [35, 58]. Other species like, Kushmi strain are related to the Kusum tree (*Schleichera oleosa*), whereas insects of the Rangeeni strain (Bysakhi) live on the Palas (*Butea monosperma*) and Ber (*Zizyphus mauritiana*) trees. Species of Laccifer chinensis (Madihassan) [57, 59] relate to another type of tree, Raintree (*Samanea saman*), are found in Thailand and South China. Each insect strain is related to one type of tree only [7, 35, 57].

The insects pierce through the bark of the tree and suck the sap from the host tree. They transform it internally to a natural polyester resin, which is then secreted through the surface of the body. It is a by-product of the insects [7, 35, 57].

The resin forms thick encrustations on the twigs. The life cycle of the insects is approximately 6 months, so there are two generations of lac insects, thus two crops per year [7, 35]. After the swarming of the young insects, the crop is collected either by scraping the resin of the twigs [India] or by cutting down the lac-bearing twigs [Thailand]. At this stage the resin is called stick lac.

The stick lac is then ground and further processed and washed with water to remove the water soluble coloring agent laccaic acid. In this stage it is called seedlac. Seedlac is then refined by three different methods to become shellac [35]. The chemical composition, properties and the color of shellac depend on the insect species or insect strain and thus the host tree, as well as the process used for refining [57].

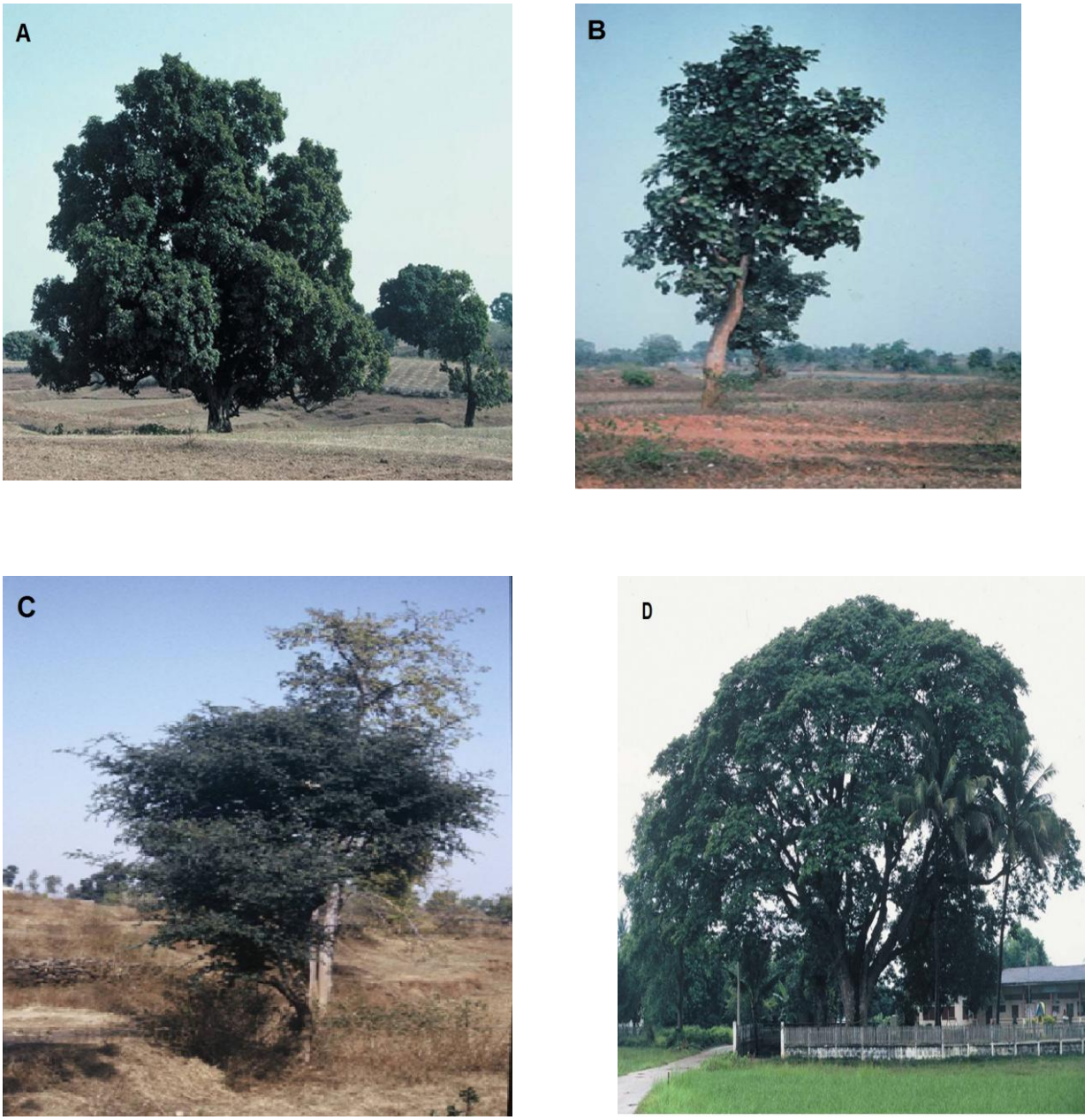


Figure 3: Shellac host trees: (A) Kusum tree, India (*Schleichera oleosa*); (B) Palas tree, India (*Butea monosperma*); (C) Ber tree, India (*Zizyphus mauritiana*); and (D) Raintree, Thailand & China (*Samanea saman*).

(Pictures kindly provided by Manfred Penning)

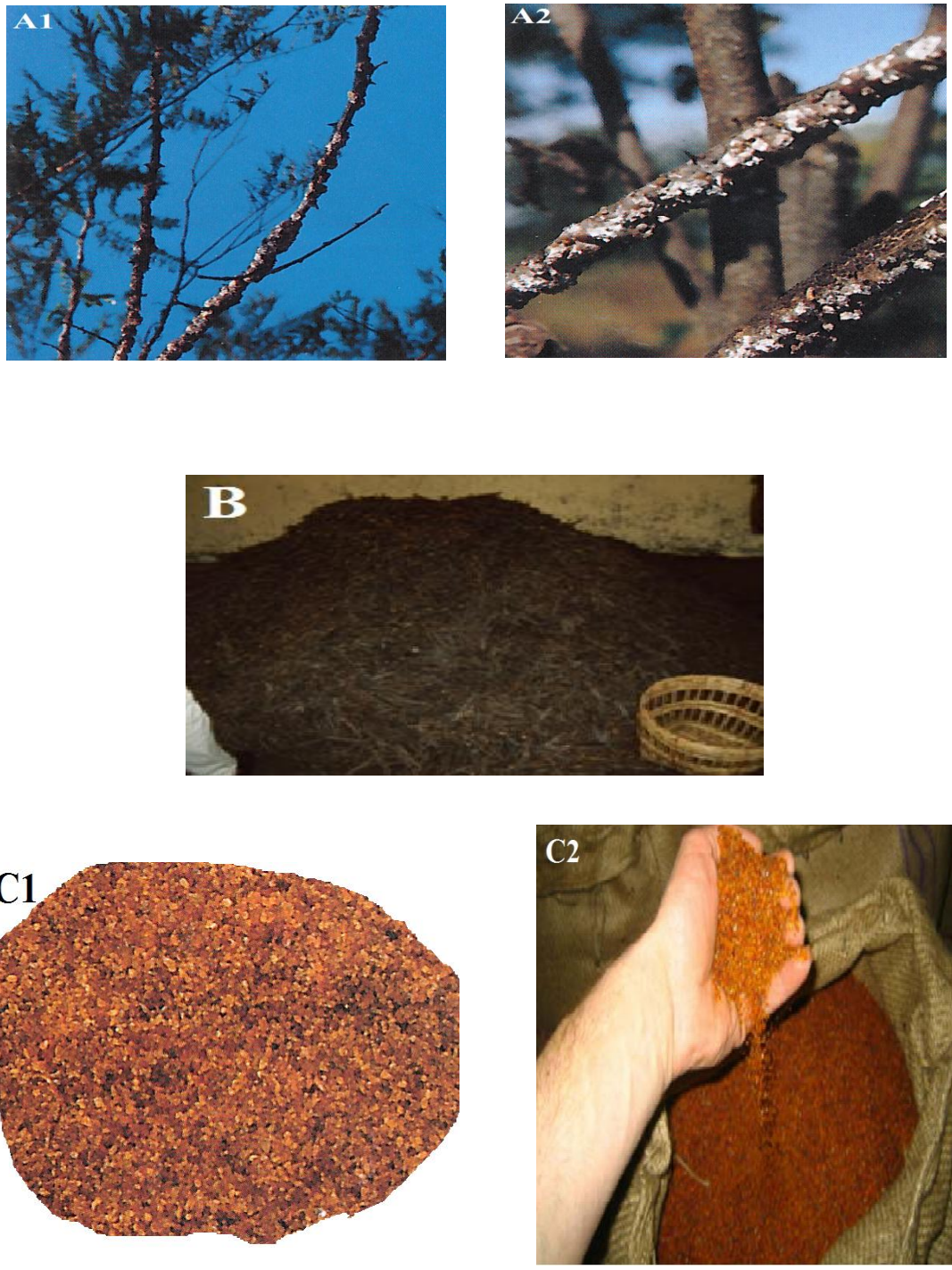


Figure 4: Lac steps from the host tree; Lac covered twigs (A1&A2), Stick lac (B), Seedlac while drying in the air (C1) and final dried Seedlac (C2).

(Pictures kindly provided by Manfred Penning and Stroever Schellack Bremen)

1.5. Refining processes

There are three different processes (Figure 6) used for refining seedlac to shellac [59-60], resulting in products with different chemical compositions, properties, colors and release characteristics [35, 57, 61].

1.5.1. Melting process

A traditional melting filtration process; in it, the molten seedlac is pressed through a filter, drawn and cast into a thin film on a roller band. After film cooling, it breaks into small flakes. Using this process, the shellac wax cannot be removed and the color of shellac depends on the seedlac used [7, 35, 62]. Products from this method are mainly used for technical applications [35].

1.5.2. Bleaching process

Here the seedlac is dissolved in an aqueous alkaline solution, followed by addition of sodium hypochlorite to destroy and removal of the coloring materials in the lac, which is mainly due to the water insoluble erythrolaccin [63]. Shellac is then precipitated by addition of sulphuric acid.

Solutions of bleached shellac are almost colorless, which is an advantage for many technical applications. The use of alkaline solutions and sodium hypochlorite leads to changes in the molecular structure of shellac, such as addition of chlorine groups; this can lead to cross linking and polymerization and thus reduce stability and shelf life.

Due to variations in the raw materials, batch to batch variations can be expected. Bleached shellac is used for technical applications such as wood coatings, coating of citrus fruits and apples as well as for confectionery and pharmaceutical glazes [35].

1.5.3. Solvent extraction process

The solvent extraction process is a gentle process for refining shellac. The seedlac is dissolved in ethanol first, then impurities and shellac wax are removed by filtration. For production of light-colored grades, activated carbon is used followed by another filtration step to remove the activated carbon. After that, the solvent is removed by evaporation in a thin film evaporator and recovered. The resin is then drawn to a thin film, which breaks into flakes after cooling. The properties of the final product are influenced by the processing parameters, the type of seedlac used and the grade of activated carbon [7, 35, 57]. The molecular structure of shellac is not affected by this method.

Shellac for pharmaceutical applications is usually refined by this method, because it allows production within narrow specifications and uniform batch to batch quality [7, 35, 57, 64].

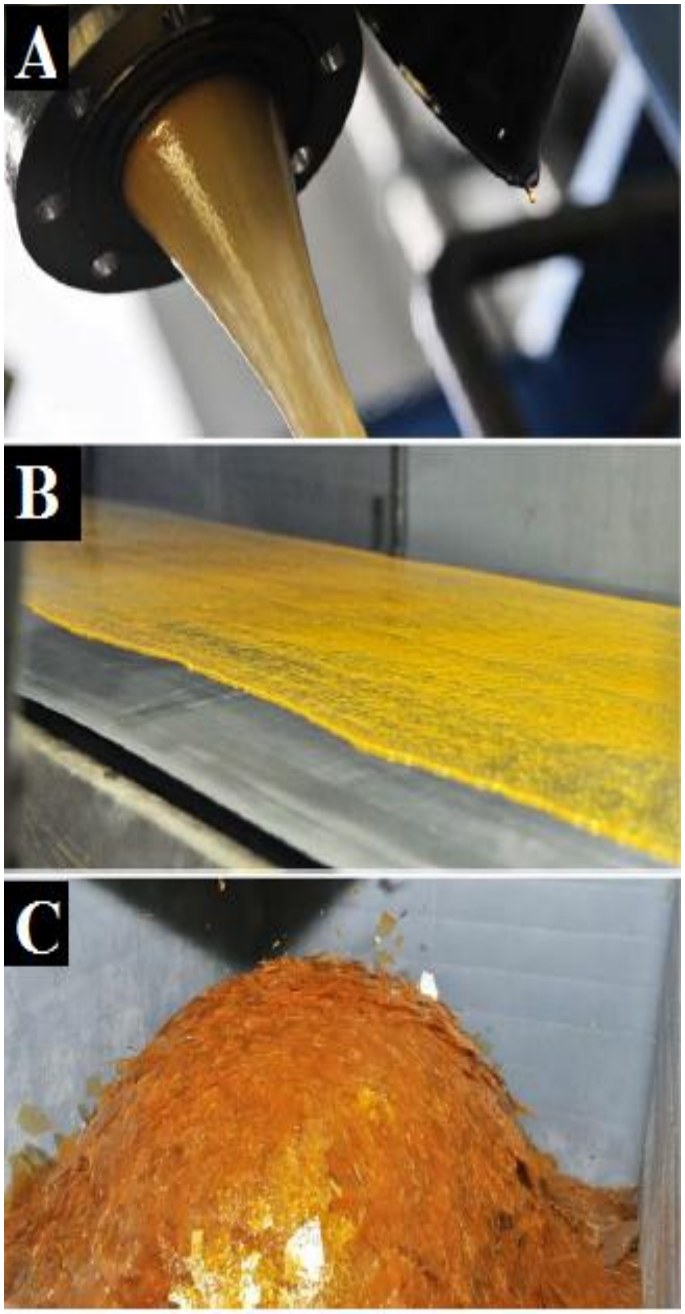


Figure 5: Solvent extraction process: (A) discharge of molten shellac from a thin film evaporator; (B) cooling of cast shellac film and (C) shellac flakes.

(Pictures kindly provided by Stroever Schellack Bremen)

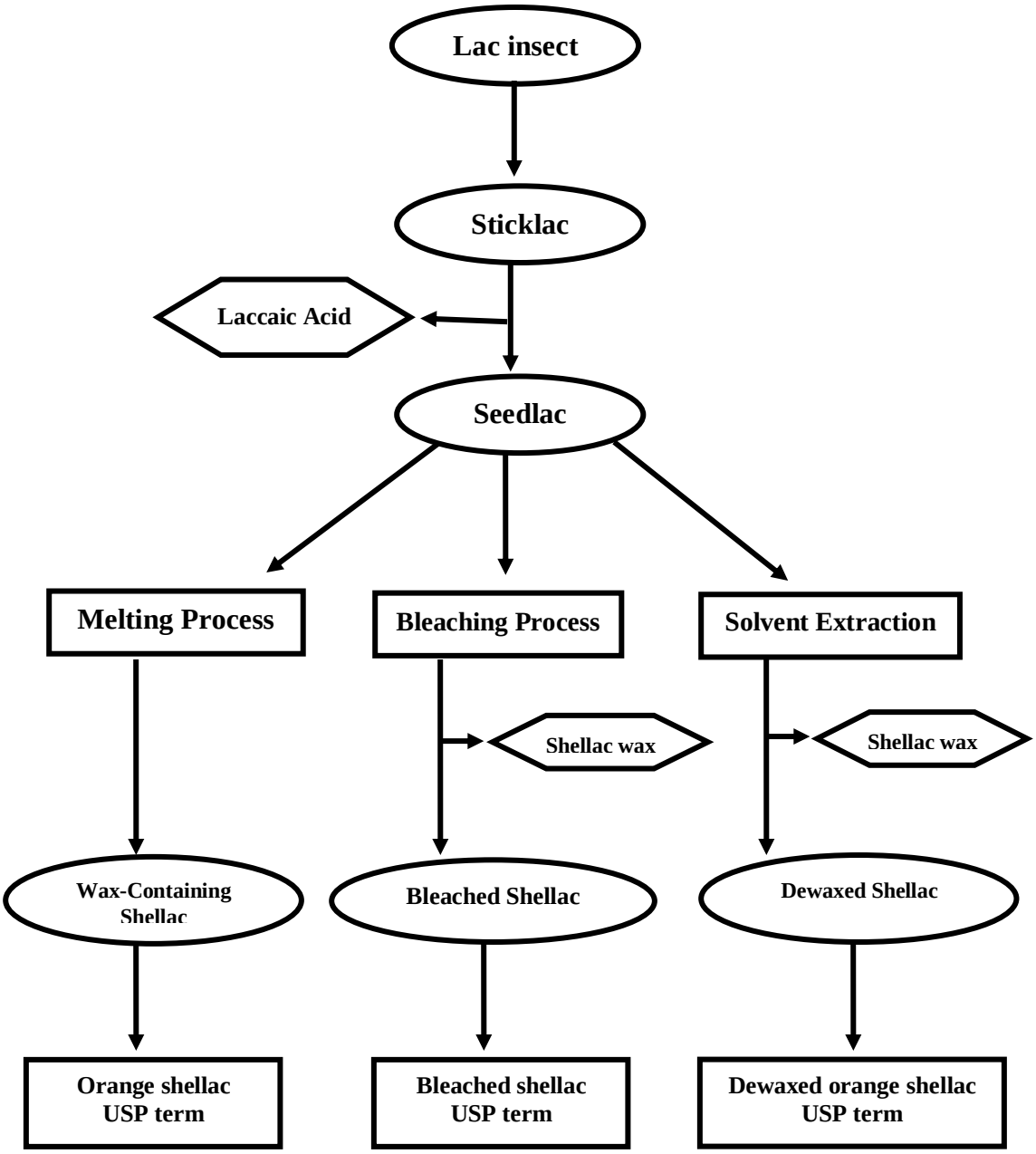


Figure 6: Flow chart for the refining processes of shellac

(Modified from Manfred Penning shellac refining process flow chart)

1.6. Properties of shellac

Shellac is obtained in the form of hard, brittle flakes with or without wax, depending on the refining process used and it is found in a variety of colors, these colors ranging from light yellow to dark red. Its color is usually characterized by Lovibond scale [65], the Gardener [66], or Iodine color [57].

Shellac is tasteless and the odor of it is a result of a complex fragrance system [67]. The major component of shellac, aleuritic acid is used as the starting material for the synthesis of fragrances [68-70]. In general, the properties of shellac depend on the insect strain, the host tree and the method used for refining.

Shellac is water insoluble. It is soluble in ethanol, methanol and partially soluble in ether, ethyl acetate and chloroform [71].

Shellac is characterized in the pharmacopoeias by the acid value (AV). In the European Pharmacopeia (Ph. Eur.) the range of it is between 65 and 80. For dewaxed shellac, it is about 70-74. For bleached shellac it is considerably higher [35, 71].The acid value of aged shellac may be significantly lower [72].

The glass transition temperature (Tg) of shellac varies between 35 and 52 °C for the acid form depending on the shellac type [57, 73], while for the ammonium salts form of shellac it may be significantly higher [72].

After long storage times shellac undergoes aging, as a result of self esterification of the material [74]. This esterification is associated with decrease in the acid value, loss of solubility and an increase in Tg [71-72, 75]. It has been reported that storing shellac at low temperatures below 20°C and protection from light [35], or addition of antioxidants [75] can prolong stability by prevention of aging; also it can greatly be improved by salt formation with ammonia [76].

Shellac is used in oral pharmaceutical formulations, food products and neutraceutical supplement formulations and the material is generally regarded as nontoxic at the level

employed as an excipient, it is physiologically harmless and it is approved as food additive in the United States, Europe (E904) and Japan [7, 35, 77-78].

For topical applications, in the cosmetic industry, very few allergic reactions of skin; contact dermatitis, contact cheilitis, [77, 79-84] and respiratory tract allergy [85] are reported for shellac-containing products, these reactions reported from alcoholic shellac solutions used in mascara and shellac may be an under-recognized allergic cause of these reactions and it can be included in cosmetics [81].

1.7. Lac composition

From elementary analysis, shellac contains carbon, oxygen, hydrogen, and a negligible amount of ash. Orange shellac contains approx. 68% carbon, 23% oxygen and 9% hydrogen. The molecular weight of orange shellac is 1006, while for bleached shellac is 949. The empirical formula for the average shellac molecule is $C_{60}H_{90}O_{15}$ [35].

Lac is a complex mixture of aliphatic and alicyclic acids. The major components are aleuritic, jalaric and shellolic acids, as well as butolic and kerrolic acids. Seedlac and orange shellac contain approximately 5–6% wax and two coloring components, the water soluble laccaic acid and the water insoluble erythrolaccin [35].

1.7.1. Lac resin

The first systematic analysis of lac composition was performed by Tschirch et al. in 1899 after fractionation of the material in different solvents. Variations of this method have been used up to the present for separation of the shellac components [86-89].

Various acids can be obtained through basic hydrolysis of lac resin. Three chain aliphatic acids (aleuritic acid, kerrolic acid and butolic acid) and eight cyclical terpenic acids (shellolic acid, jalaric acid, epishellolic acid, laksholic acid, epilaksholic acid, laccishellolic acid, epilaccishellolic acid and laccijalaric acid) had been separated [90-95].

Among the various component acids isolated from lac resin, there is growing demand for aleuritic acid, which is isolated from shellac by saponification, as it is a starting material for the synthesis of various bioactive and perfumery chemicals [71, 96-97], also for the synthesis of macrocyclic musk compounds for fragrances and pheromones [35, 69] and it represents about 30%–40% of the lac resin [96, 98-99].

Several modern analytical techniques have been so far employed for the identification of resins and the characterization of their degradation pathway. In particular, gas chromatography (GC) and mass spectrometry (MS) can provide specific information on molecular composition, biological source and degradation effects [100-104], combined Pyrolysis-GC/MS has been widely employed for the characterization of natural resins [98, 100, 105-109] This technique is actually less time consuming than GC/MS because no sample pretreatment is required [110].

MALDI-TOF-MS has proven to be a powerful technique to provide detailed information about the molecular structure of shellac components. It shows presence of a wide range of shellac components with groups of single acids and polyesters. Buch et al suggested that the use of MALDI-TOF-MS further allows distinguishing unbleached from bleached shellac grades and also between the various grades of shellac refined by solvent extraction [57, 111]

1.7.2. Lac pigment

Laccaic acid or lac dye is a natural water soluble food additive extracted from the sticklac. The red color of the lac is derived from a water soluble pigment which including a mixture of laccaic acids (A, B, C, D and E), all of them are hydroxy anthraquinone derivatives; they are the main components of lac dye [112-120]. Laccaic acid B is used in Japan for food coloring [116]. Shellac also contains water insoluble dye, mainly erythrolaccin, deoxyerythrolaccin and isoerythrolaccin [121].

Chemical structure of shellac

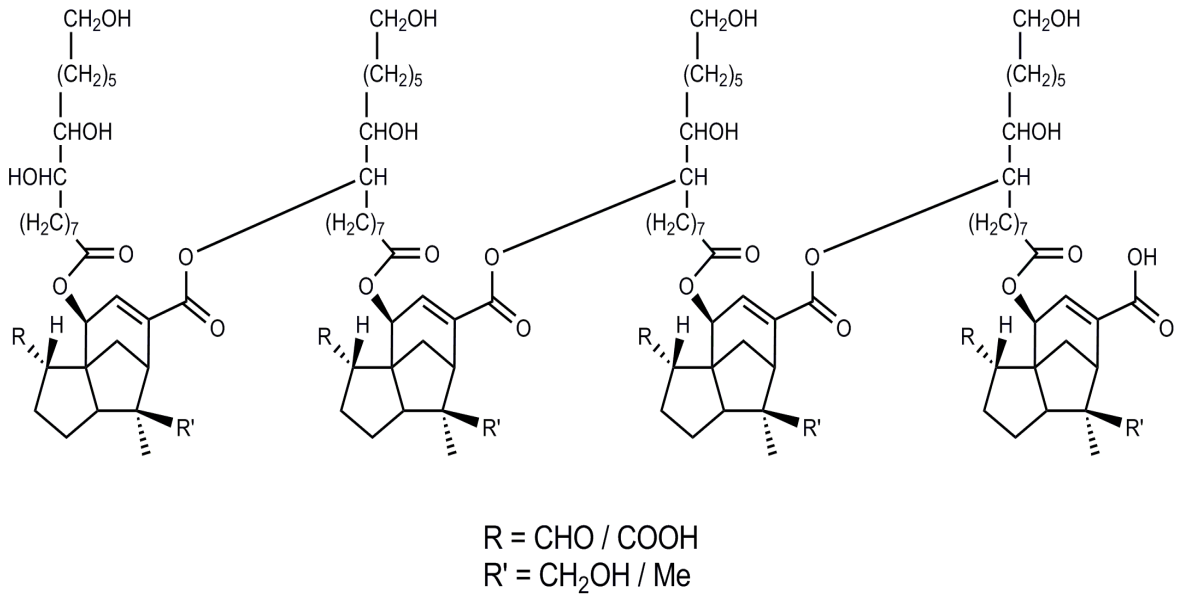
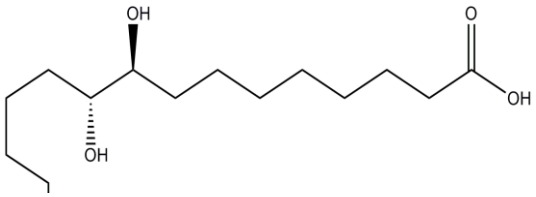
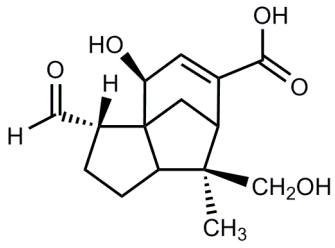


Figure 7: Chemical structure of shellac according to A. N. SINGH .

Aleuritic acid



Jalaric acid



Shellolic acid

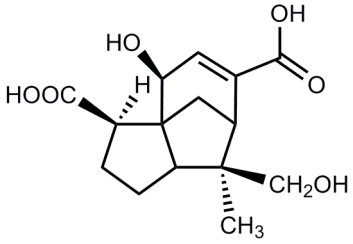


Figure 8: Chemical structure of the main shellac components

1.8. Applications of shellac

Lac is a multipurpose resin that has been applied for many different applications. In order to expand its application fields, various formulations were developed, some additives were employed in the modification of lac properties and many lac products with special functions were produced [99].

1.8.1. Application in wood coatings

Shellac dissolved in alcohol (varnish) can be easily obtained and is convenient to use [99]. The varnish film has good gloss property with good adhesive strength and good elasticity [99]. It has been used for a long time, since it was widely applied in wood varnishes. A great number of recipes and preparation procedures are documented in literature [110, 122-127].

Resins mixed with a drying oil were the earliest type of varnish blend, whereas spirit varnishes were introduced only in the sixteenth century [110].

1.8.2. Applications in food industries

Shellac has a long history of use in food and it is listed as food additive by the FDA (Food and Drug Administration) [128] and it has been approved as a food additive in the European Union (E904) [129], this regulatory status allows its use as additive in food products which is the most common application of shellac [7]. In food application it is mainly applied to confections, fruit coatings, nutritional supplements, nutraceuticals and used for microencapsulation [130-134]. It's used as an edible coating started about the beginning of the last century [135-136]. Further applications of shellac are coating for nutraceuticals supplements (tablets and capsules) enteric or retard coatings, for example vitamins and it can be used as sub-coat or gloss coat [137-138].

The main uses of shellac in the confectionery industry are for the coating of chocolate goods, such as extruded chocolates, chocolate covered nuts and similar products [139-140]. Shellac adds beneficial properties to confections, including high gloss, hard surface for protection and increased stability [141]. Shellac glaze has been used for

many years as a protective and decorative coating for various types of confections [76, 142-144]. For nutritional supplements shellac from aqueous solutions has a market of growing interest for the coating of tablets, capsules, pellets and for microencapsulation [138, 145].

Because of its unique ability to provide a high gloss in relatively thin coatings with moisture protection, shellac is widely used in coating for citrus and other fruits [130, 146]. These coatings were designed primarily due to low water vapor permeability of shellac films from aqueous solutions, so it reduces the loss of water and volatile flavoring substances from citrus fruits, also to impart high-gloss [56, 130, 147-152].

Shellac- and wood resin-based coatings also tend to increase prevalence of post harvest pitting of white grapefruit, as pitting increased with decreasing internal O_2 level and decreased with increasing CO_2 level [153-155]. Gan Jin et al, used shellac for film-coating preservation of apples and their results indicated that bleached shellac revealed obvious effects on reduction of respiration intensity, inhibition of water loss and slow decay of the fruits [156]. It has been used to prevent postharvest decay by supporting populations of bacterial and yeast antagonists [132, 149, 157].

Chauhan et al., applied surface coatings made up of shellac and aloe gel, singly as well as in combination, on apple slices and the coatings were found to minimize the firmness and the activity of the oxidizing enzymes polyphenol oxidase (PPO) and peroxidase (POD), thus maintaining the quality of apple slices during storage [158].

Shellac used as encapsulating agents for high potency sweeteners in chewing gum composition, provides an impermeable, hydrophobic coating which is not soluble in the chewing gum base [159]. Encapsulation and targeted delivery of Nattokinase (NKCP) in shellac beads prepared by cross-linking aqueous shellac solution with calcium ions was reported by Law and Zhang [160]. More recently, a systematic study of the mechanical properties of thin-walled liquid-filled pectinate capsules and the influence of the addition of shellac to the polymer solution was made and showed that, precipitation of shellac under acidic conditions has increased the flexibility and softness

of the capsules against deformations [144]. Xue and Zhang [161-162] prepared and characterized calcium–shellac microspheres loaded with carbamide peroxide (CP) as a tooth whitening agent [162]. Stummer *et al.* they have improved the enteric coating properties of shellac by coating probiotic bacteria with formulation of shellac and various plasticizers such as Glycerol and polyvinylpyrrolidine for protection of the individual microorganisms against acidic pH of stimulated intestinal fluid [163-164].

Shwan and co-workers, prepared composite microcapsules of shellac and yeast cells, they demonstrated the versatility of shellac as a microencapsulating material for protection of cells under acidic environments and reported that the composite shellac–cell microcapsules could be used in formulations for protection and delivery of probiotics [163].

Due to the fact that synthetic excipients are limited in the preparation of nutritional supplements, an increasing trend for using excipients from natural sources exists. In this regards shellac as a natural polymer and for the development of enteric coating formulations containing shellac were of interest [165].

1.8.3. Pharmaceutical applications of Shellac

The first application of shellac for enteric coatings was done by Milton S. Wruble in 1930 [37], who stated that the ammoniacal solutions of shellac prove to be far more effective as enteric coatings than alcoholic solutions [37]. Due to the lack of suitable equipment for aqueous coatings at that early time, shellac was applied from ethanolic solutions for coatings of tablets [7]. These organic solutions used for coatings, require special care (e.g. equipments, coating parameters). The hazard of explosion of organic solvents and chemical problems like the esterification and the polymerization of the dry shellac film (hardening), after storage, has lead to the development of aqueous shellac solutions [59].

However, these changes finally affect the release properties from the shellac coated dosage forms but not to the desired needs in pharmaceutical technology, hence its use in pharmaceutical applications declined [7, 59]. In 1992, the work on shellac from aqueous

solutions begins and first paper on shellac from aqueous solution was published by Manfred Penning in 1996 [59].

Shellac contains carboxyl groups. It is not soluble in water, but it can dissolve at higher pH, so it is possible to prepare aqueous shellac solutions of alkali salts. This has been done by using volatile alkali like ammonia or ammonium bicarbonate. In it shellac is dissolved directly in the ammoniacal solution and the excess ammonia evaporates as CO_2 and NH_3 [59]. This attempt solved the main problems of using organic solvents and shellac in acid form [59, 76, 166].

Aqueous shellac solutions have several advantages when compared to organic solvents, they are not sticky, stable with low viscosity and can be easily diluted with demineralised water to the desired concentration [59]. The application of aqueous shellac solutions does not avoid the problems with organic solvent systems, but also improve the performance of the polymer film by stable dissolution characteristics after extended storage time and result in improved mechanical properties compared to films from ethanolic shellac solutions [59]. By applying shellac from aqueous solutions, shellac has regained importance in pharmaceutical application [133].

Several other methods were suggested to overcome the problems of organic solvents. One approach was to use it as pseudolatex dispersions and colloidal dispersions [145], but it still contains organic solvent.

Another approach is to apply shellac as micronized powder with high amounts of plasticizer [7], which is then used for powder polymer coating [143, 167] or powder layering technique [168], but it is not applicable.

Shellac is mostly used for enteric coating [166, 168-170]. Due to its pKa values of 5.6–6.6 it is assumed to remain undissolved in the stomach [57]; it requires high pH for dissolution, usually pH 7.2 [171] or even more.

Because of it is high dissolution pH and low solubility in the intestinal fluid, shellac is not suitable for conventional enteric coating [170-176]. It needs to be modified to

enhance its dissolution at lower pH. It has been modified by partial hydrolysis by alkali treatment [166] and its solubility was found to be improved, but polymerization still occurred [166, 172, 177]. Esterification with succinic acid also enhances shellac solubility at pH of the small intestine and also improves film flexibility [177].

Additional materials to improve its intestinal solubility have also been applied. These materials act as pore formers or swelling agents [175, 178]. Addition of sodium alginate, Hydroxypropyl methylcellulose and Polyvinylpyrrolidine result in increased solubility of shellac films in simulated intestinal fluid [164]. Organic acids have also been used [176].

For sustained release applications, shellac is combined with polyamidoamine (PAA). The combination has shown good sustained release behavior [179]. Shellac used in multiple types of floating dosage systems composed of effervescent layers, it used as swellable coated membrane between the layers [180-181]. Also shellac is used as a matrix former for sustained release tablets and pellet formulations [133, 182-183].

Due to its high dissolution pH, shellac coating is suitable for colon targeting [61, 184-185]. It is used for topical treatment of colonic diseases. Shellac-coated pectin microspheres have been investigated as carriers for colon-targeted delivery of Tramadol TMD [186].

However shellac coat remains intact during the passage through the gastrointestinal tract (GIT) from the mouth until it reaches the colon, where the pH is more than 7 [187]. Moreover, the potential of shellac and shellac combined with HPMC coated anthocyanin amidated pectin beads as dietary colon targeting systems was demonstrated [188]. Combination of shellac/ Inulin coating, was successfully developed to obtain colonic release of Ibuprofen [189].

Shellac is used for microencapsulation of vitamin B 12 [190]. It is also used for microencapsulation of sulphadiazine and it is found to be able to produce microcapsules with varying core to coat ratio, which is required for controlling the release rate by shell thickness [191]. In microencapsulation it produces free flowing microcapsules, which

are then blended with other excipients and compressed into tablets [192], it increases the stability of the drug [192] and to mask the taste of bitter drugs [193-194].

Shellac was often used as a water insoluble polymer for microencapsulation, either to modify the release or to mask unpleasant taste. For this purpose, it is used as natural material or modified, also in combination with other materials [105, 161-162, 191, 194-205].

2. Aims of the thesis

Although considerable research has been performed in the area of shellac coatings, several important questions remain unanswered. One of these is the question related to differences that may occur between shellac grades which are all prepared by the solvent extraction process and designed for pharmaceutical application. No previous investigation has addressed the physicochemical characterization and dissolution properties of these shellac samples from different origins and ages.

Furthermore, I aim at comparing commercially available aqueous shellac solutions (SSB AQUAGOLD, based on shellac SSB 57 Dewaxed Orange shellac, Bysakhi-Ber type and refined in a solvent extraction process) prepared with different bases (ammonia solution versus ammonium bicarbonate) as well as studying the influence of shellac age on the quality of the shellac-coated metoprolol tartrate pellets which themselves have been stored for various times.

Additionally, in this thesis, the enteric properties of shellac films from aqueous shellac solutions should be compared following addition of different aqueous polymeric solutions of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxy methylcellulose (CMC), gum arabic and polysaccharide (Pullulan®). These water soluble polymers which will act as pore formers to enhance drug release from pellets coated with the combination of shellac and these polymers. The influence of these polymers on the gloss of the shellac films, mechanical properties of the films and the drug release from metoprolol tartrate pellets coated with these polymeric solutions were studied.

Finally, the potential of ethanol to alter the rate of drug release from shellac coated dosage forms should be studied in order to estimate the risk associated with the concurrent intake of shellac coated dosage forms and alcohol containing beverages.

3. Materials and Methods

3.1 Materials

Metoprolol tartrate pellets containing 80% metoprolol tartrate, with particle size 500 µ< X >1000 µm were kindly donated by ACINO PHARMA AG, Liesberg Switzerland.

Samples of different shellac types with different manufacturing dates and origins were investigated (Table 1)

Table 1: Shellac types investigated and their vendors

Shellac grade	Origin	Manufacturing date	Vendor
Shellac SSB 55	Kushmi	June. 2008	Stroever GmbH & Co. KG, Bremen, Germany
Shellac SSB 55	Kushmi	Nov. 2009	Stroever GmbH & Co. KG, Bremen, Germany
Shellac SSB 55	Kushmi	May. 2010	Stroever GmbH & Co. KG, Bremen, Germany
Shellac SSB 55	Kushmi	Nov. 2010	Stroever GmbH & Co. KG, Bremen, Germany
Shellac SSB 57	Bysakhi-Ber	Sep. 2009	Stroever GmbH & Co. KG, Bremen, Germany
Shellac SSB 57	Bysakhi-Ber	Feb. 2010	Stroever GmbH & Co. KG, Bremen, Germany
Shellac SSB 57	Bysakhi-Ber	May. 2011	Stroever GmbH & Co. KG, Bremen, Germany
Shellac AT 10-1010.	Kushmi	Unknown	Hindustan Shellac Pvt. Ltd., Howrah, India
Shellac AT 10-1210.	Kushmi	Unknown	Hindustan Shellac Pvt. Ltd., Howrah, India
Shellac Gifu PN20-F	Thai	Jan. 2010	Gifu Shellac co. Ltd, Japan
Shellac Gifu PN20-F	Thai	Jan. 2012	Gifu Shellac co. Ltd, Japan

Aqueous ready for use shellac solutions

1- SSB AQUAGOLD (25% w/w) based on SSB 57, a dewaxed and decolorized shellac were donated by HARKE Pharma GmbH Food Tec Division (Germany) and produced by Stroever GmbH & Co. KG, Bremen (Germany).

The following samples of ready for use aqueous shellac solutions and their manufacturing dates were investigated:

(1) September 2009; (2) August 2010; (3) October 2010; 4) May 2009;

(5) July 2011 and (6) September 2011.

2- AQUALACCA 25 (25% w/w) were based on a Bysakhi type dewaxed orange shellac and were donated by Chemacon GmbH, Bühl, Germany.

Water soluble polymers

The following water soluble polymers were used in combination with aqueous shellac to improve the shellac film properties.

Hydroxypropyl methylcellulose (HPMC), Pharmacoat 606, ShinEtsu, Tokyo, Japan, was donated by HARKE Pharma GmbH Food Tec Division (Germany).

Hydroxypropyl cellulose (HPC, Klucel® EF Pharma), was obtained from Aqualon, a Division of Hercules incorporated Hopewell, VA (USA), it was kindly donated by Hercules BV Samples Store, noordweg 9, zwijndrecht 3336 (Netherlands)

Gum arabic, instant gum (AA &BA), was donated from CNI Colloides Naturels international (France).

Carboxymethyl cellulose sodium CMC (Walocel® 30 & 100) was donated from Biogrund GmbH, Hünstetten, Germany.

Polysaccharide (Pullulan®), was produced by Hayashibara Co., LTD. Okayama, Japan and kindly donated by George GmbH Königstein, Germany.

Table 2: Water soluble polymers, their manufacturers and suppliers.

Material	Manufacturer	Supplier
HPMC (Pharmacoat 606)	Shin-Etsu Chemical Co., Ltd. Japan	HARKE Pharma GmbH Food Tec Division (Germany)
HPC (Klucel® EF Pharma)	Aqualon, a Division of Hercules incorporated Hopewell, VA (USA)	Hercules BV Samples Store, noordweg 9, zwijndrecht 3336 (Netherlands)
Gum arabic	CNI Colloides Naturels international (France)	CNI Colloides Naturels international (France)
CMC (Walocel® 30 & 100)	Dow Wolff Cellulosics GmbH, Bomlitz (Germany).	Biogrund GmbH, Hünstetten, Muster, Germany
Polysaccharide (Pullulan®)	Hayashibara Co., LTD. Okayama,Japan	George GmbH Königstein, Germany

All other reagents used were of analytical grade and used as received

3.2 Methods

3.2.1. Preparation of different shellac grades

All shellac flakes were ground and prepared by milling and passed through a 500 mesh sieve. The ground shellac was then used for determination of the acid values, glass transition temperatures, as well as for the preparation of shellac solutions which were then used for color testing and for coatings.

3.2.2. Physicochemical properties of different shellac grades

3.2.2.1. Gardner color / Iodine color

3.2.2.1.1. Alcoholic solutions

Samples from shellac grades were dissolved in ethanol 96% to produce a concentration of 20% (w/w). Thereafter they were subjected to color testing, using a photometric method. All measurements were done using the color tester Lico 50 (Dr. Lange GmbH, Düsseldorf, Germany) in 11 mm cylindrical glass cuvettes.

3.2.2.1.2. Aqueous solutions

Shellac is not soluble in water; however, as it is containing carboxyl groups it is possible to prepare aqueous shellac solutions using alkali salts. A volatile alkali is preferable, therefore, ammonium hydrogen carbonate was chosen as the base. The selection of the base used and the method for dissolving will influence the properties of the film [76].

Ground shellac was dissolved in 2.5% (w/w) ammonium bicarbonate solution at 40°C under continuous mechanical stirring to produce a final concentration of 20% (w/w). The solution was heated up to 70°C for 30 minutes under continuous stirring, to evaporate excessive ammonium in order to reach the optimum pH 7.3. Then water was added to achieve the concentration of 20% (w/w).

3.2.2.2. Surfaces of coated pellets

The shellac coated pellets were coated with a thin layer of Pd with a SC7620 sputtering machine (Quorum Technologies, East Sussex, UK). Electron images were taken with a Phenom SEM (FEI, Eindhoven, Netherlands) at 3kV accelerating voltage.

3.2.2.3. Glass transition temperatures

Each sample (9–10 mg) was accurately weighed into an aluminium pan. The caps were perforated once and then samples were heated at 10°C/min from −30°C up to 200°C with 80 mL/min of nitrogen purge. Glass transition temperatures of all samples were analyzed using a Mettler Toledo DSC 30. The data were analyzed using Mettler Graphware software. (*T*g) was reported as the turning point of the curve progression.

3.2.2.4. Acid Values

The acid value was determined by an acid-base titration method adapted from the *European Pharmacopoeia* 6.2. One gram of ground shellac was dissolved in a mixture of diethyl ether and ethanol (1:1) and titrated with 0.1 M potassium hydroxide (KOH) solution. Instead of using a color indicator, the endpoint was determined potentiometrically [3] due to the dark color of the shellac solutions. The AV is expressed as (mg/g) of KOH/shellac. The data reported represents the average of five measurements.

3.2.2.5. DLS for size measurement

Dynamic Light Scattering DLS (also known as PCS - Photon Correlation Spectroscopy) measures Brownian motion and relates this to the size of the particles.

The particle size distribution of the shellac solutions (1.0 g/l alcoholic shellac solution) were analyzed by DLS Malvern® Zetasizer Nano (Malvern Instruments, Malvern, England), at room temperature. A backscattering arrangement was used, the scattering angle being 173°. Laser light (lambda = 632.8 nm) was used as the incident beam and the scattered light was detected by a single photon detection unit. Measurements for 5 min duration of the autocorrelation function were performed.

Calculation of intensity fluctuation of scattered photons and particle size distribution was done via an autocorrelation method using Malvern® Zetasizer Software.

3.2.3. Preparation of polymeric solutions

3.2.3.1. Preparation of HPMC solution:

The HPMC solutions were prepared by adding HPMC to demineralized water under mechanical stirring. HPMC was slowly added to prevent foam formation. The solution was heated at 50 °C under stirring for 2 hours in order to mix properly, and then the solution was allowed to cool and to de-foam for several hours before use. 10% w/w solutions were prepared.

3.2.3.2. HPC solution:

The HPC solutions were prepared by adding HPC slowly to demineralized water under mechanical stirring at room temperature. Thereafter, the solution remained under continuous stirring for 2 hours in order to mix properly followed by cooling and defoaming for several hours before use. 10% w/w solutions were prepared.

3.2.3.3. Polysaccharide (Pullulan®) solution

Pullulan® solution was prepared by dissolving the Pullulan® in demineralized water. The material was added gradually to the demineralized water under stirring at 50 °C for 2 hours. Then the solution was allowed to cool at room temperature. 5% w/w solutions were prepared.

3.2.3.4. Gum arabic solution

Solution of gum arabic was prepared by adding the spray-dried powder to 1% (w/w) ammonium bicarbonate solution in demineralised water at 50°C and stirring mechanically until the gum was dissolved completely. The ammonium bicarbonate was added to increase the pH of the gum solution to above 7, which is required to make a clear solution when mixed with the shellac solution. 10% w/w solutions were prepared.

3.2.3.5. Carboxymethy lcellulose solution

CMC was carefully added to demineralised water in portions under stirring at room temperature, the solution was mixed for 3 hours until complete solubilization of the CMC and formation of a clear solution. 5% w/w solutions were prepared.

3.2.3.6. Shellac-polymers solutions

The required amount of plasticizer (Glycerol)**,** which has good plasticization property with shellac [164] was added to the shellac solution. Then the polymeric solution (HPMC, HPC, CMC, Gum arabic or Pullulan®) was mixed with the shellac/plasticizer solution under stirring for one hour and water was then added to achieve the desired concentration that was used for coating. The solution was then stirred for an extra additional 30 min to ensure good mixing.

3.2.4. Free shellac films

10 ml of each formulation was poured into circular polyacetal (POM) molds of 10 cm diameter. Thereafter, the solvent of the formulations was evaporated, by drying the films for 5 hours at 65°C in a laboratory oven. Using a scalpel the films were removed from the molds and cut into strips of width 1 cm. By storing the cutted shellac stripes in a desiccator above a saturated potassium acetate solution, films were conditioned at room temperature and 22% relative humidity for at least 2 days. Subsequently the thicknesses of the films were determined using the thickness measuring gauge 412 B-F (Sony Precisions Technology, Stuttgart, Germany). For this, each film was measured 5 times and the mean was calculated. The measurement points were equally distributed over the area used for the tensile tests (1 cm x 1 cm).

3.2.4.1. Tensile tests

The tensile tests were performed using the Universal Testing machine LRX (Ametek Precision Instruments Europe GmbH, Meerbusch, Germany) equipped with a LRX load cell of 100 N upper range value. As clamp distance 1 cm was chosen, consequently the film area between the clamps was 1 cm x 1 cm. To avoid damages at fixing the films between the clamps, the contact areas of the films were strengthened by means of an

adhesive tape. The stress-strain profiles of the films were recorded at traverse speed of 10 mm/min. The elongation at break and the elastic modulus of the films were calculated using the following formulas [178, 206]:

$$\text{Elongation at break } [\%/\text{mm}^2] = \frac{\text{Increase in length [mm]} \times 100}{\text{Original length [mm]} \times \text{Cross-sectional area [mm}^2\text{]}}$$

$$\text{Elastic modulus [MPa]} = \frac{\text{Force at corresponding strain [N]}}{\text{Corresponding strain} \times \text{Cross-sectional area [mm}^2\text{]}}$$

Elastic modulus is defined as the ratio of the stress to the strain applied on a material. The practical unit mainly used is megapascals (MPa or N/mm²) . It predicts how much a material sample extends under tension or shortens under compression. Elastic modulus can vary due to differences in sample composition and test method. An elastic material requires a smaller force to flow.

Elongation at break is a good relative indicator of ductility. High levels of elongation indicate good energy-absorbing capabilities. This means that the higher the elongation at break of a material, the greater the force it can withstand and the more ductile it is.

3.2.4.2. Gloss measurements

Shellac and shellac-polymer films were prepared using the casting/solvent evaporation technique. The solution was poured onto plastic foils (19 * 12 cm), using a stainless steel spiral film applicator (ERICHSEN-Germany). Two thicknesses films (100 and 200 µm) were made and the casted films allowed to evaporate at room temperature for 2–3 days. Then the films were kept dried at room temperature until the measurement of the gloss. The gloss was measured using a PICOGLOSS 560 MC (ERICHSEN-Germany) in different areas on the films surfaces and the mean ± S D were calculated.

3.2.5. Coating of Metoprolol tartrate pellets with different shellac grades

3.2.5.1. Preparation of coating solution

After the preparation of aqueous shellac solutions and shellac-polymers solutions, the shellac coating solutions were diluted with demineralised water to 10% (w/w) solid content before coating.

3.2.5.2. Coating of metoprolol tartrate pellets with aqueous shellac solutions

Different coating levels were applied to the pellets, using a Ventilus 1 air suspension coating machine (Innojet, Steinen, FRG) by applying an inlet temperature of 50°C, air pressure of 1.2 - 1.5 bar, pump rate of 0.85g/min and inlet air rate of 50 m^3/ h.

For one randomly selected batch, the coating process was repeated three times on different days and the coated pellets were compared to ensure the reproducibility of the coating process.

3.2.5.3. Coating of metoprolol tartrate pellets with aqueous shellac-polymer solutions

Different coating levels were applied to the pellets, using a Ventilus 1 air suspension coating machine (Innojet, Steinen, FRG) by applying an inlet temperature of 50°C. Air pressure, pump rate and inlet air rate were adjusted depending on the polymer used.

3.2.6. Characterization of ready for use shellac coating solution

The pH of the aqueous shellac solution was checked using a pH meter. Then the 25% w/w solution was diluted with demineralised water to a 10% w/w solution, the final concentration used for coating.

3.2.7. Dissolution tests

Dissolution tests were performed according to the United States Pharmacopoea (USP) paddle method, with approximately 60 mg pellets in 900 ml dissolution medium. Gastric resistance was tested in simulated gastric fluid at pH 1.2 using the paddle apparatus (PharmaTest Type PTW III) at 50 rpm and 37 ± 0.5°C for 2 hours. Drug

release from the coated pellets in enteric medium was measured in phosphate buffers at pH 6.8, 7.2 and 7.4 for six hours. The samples were withdrawn directly from the dissolution vessels and analyzed spectrophotometrically at λ_{max} 222 nm.

For colon targeting formulas, the dissolution was conducted in 0.1 N HCl for the initial two hours, followed by dissolution at a pH of 6.5 for five hours, then for three hours at pH 7.2.

For evaluation of alcohol consumption on drug release from shellac hated pellets, the dissolution was carried in 900 ml 0.1 N HCl media containing ethanol (v/v) at 0%, 5%, 10%, 15%, 20% and 30%, with sampling every 15 minutes until 2 hours.

For each batch six samples were tested, for two batches, an additional confirmatory test was performed on three subsequent days with n = 6 on each day to ensure reproducibility of the dissolution results.

4. RESULTS

4.1. Physicochemical properties of different shellac grades

4.1.1. Gardner color / Iodine color

All shellac grades showed Gardner color and Iodine numbers within the accepted range (≤ 100 units for Iodine color number and ≤ 12 for Gardner color). The three batches of SSB 55 showed almost the same color number for ethanolic solutions and with slight differences for the aqueous solutions. Results for color number are shown in Table 3. For all the tested brands, aqueous solutions were darker than ethanolic solutions.

4.1.2. Glass transition (Tg)

The Tg of all shellac types ranged from 38 to 46, the three SSB 55 brands showed lowest Tg with very little effect for the age. Similarly, the two SSB 57 brands almost had the same Tg (Table 3).

4.1.3. Acid values (AV)

The acid value (AV) for all tested brands ranged from 71.5 to 74.6, with no significant differences (P value = 0.112). Results for AV are shown in Table 3.

Table 3: Color numbers (ethanolic and aqueous solutions), glass transition and acid value for different shellac grades.

Shellac grade	Ethanolic solution 20% w/w		Aqueous solution 20% w/w		Tg [°C]	Acid Value	
	Gardner	Iodine	Gardner	Iodine		Tested	In Certificate Of Analysis
Gifu PN20-F	11.2	83.2	11.9	95.7	44	72.8±0.4	71.9
SSB55(June 2008)	6.2	9.3	7.4	15.2	38	71.0±0.5	71
SSB55(Nov. 2009)	6.2	9.3	7.6	15.7	38	73.5±0.0	74
SSB55(May 2010)	6.3	9.9	6.9	12.6	40.9	73.5±0.3	73
SSB57(Feb. 2009)	9.7	47.8	11.3	55.9	43	74.6±0.3	73
SSB57(Sep. 2010)	8.7	31.1	9.9	52.8	43.3	73.5±0.6	73
AT. 10-1010.	5.4	6.4	6.8	12.1	46	73.5±0.3	x

x not available.

Color number measured as gardner and iodine number for 20% w/w concentrations, Tg: Glass transition and S D: Standard deviation.

For AV the reported results represent the average of five measurements, while for Tg and color number the results are constant with no variations.

4.2. Coating of metoprolol tartrate pellets

All different shellac grades produced similar coated metoprolol tartrate pellets. All grades resulted in pellets with smooth surfaces without cracks (Figure 9).

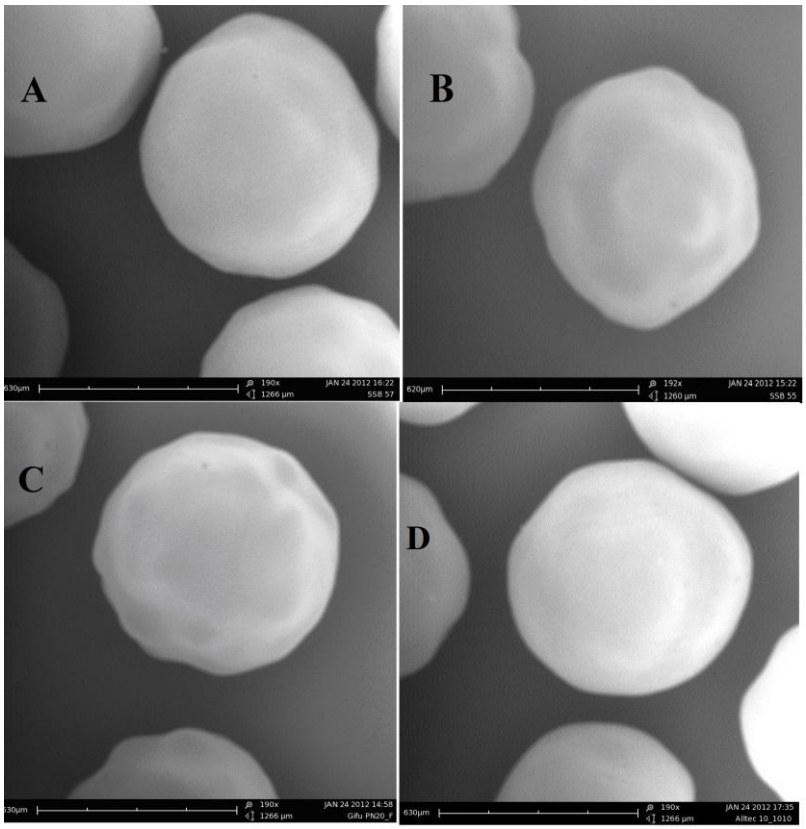


Figure 9: Scanning electron microscope (SEM) pictures of metoprolol tartrate pellets coated with different shellac types (20% w/w); SSB 55 (A), SSB 55 (B), Gifu PN-20 (C) and AT 10-1010 (D).

4.3. DLS for size measurement

The particle size diameters for the tested shellac grades are shown in Figure 10. Gifu PN20-F showed the largest particle diameter (318.60 nm), whilst AT 10-1010 and SSB 55 had average sizes of 6.02 and 7.36 nm, respectively and SSB 57 showed an average size of 13.60 nm which was larger than SSB 55 and AT 10-1010.

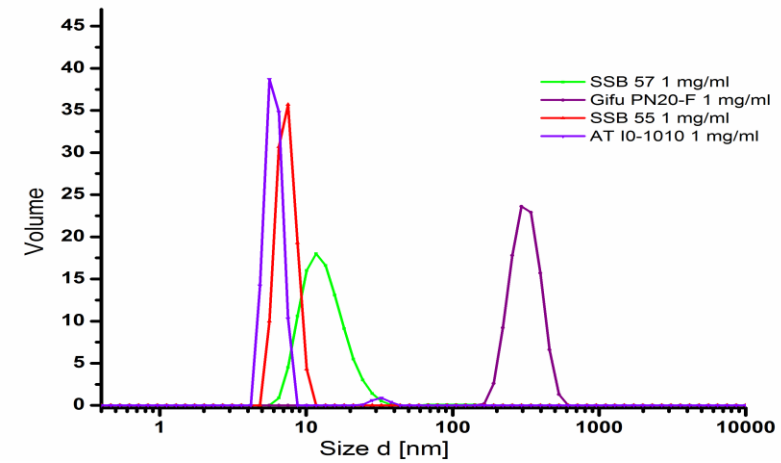


Figure 10: Molecular size of the different shellac grades used. The analysis was done in alcoholic solutions of 1 mg/ml. The diameters of the particles are presented in nanometers (nm).

4.4. Release of metoprolol from pellets coated with different shellac grades

At pH 1.2, the release of the active ingredient from the coated pellets was less than 2%, after five hours from the two coating levels, 20% and 25% (Figure 11).

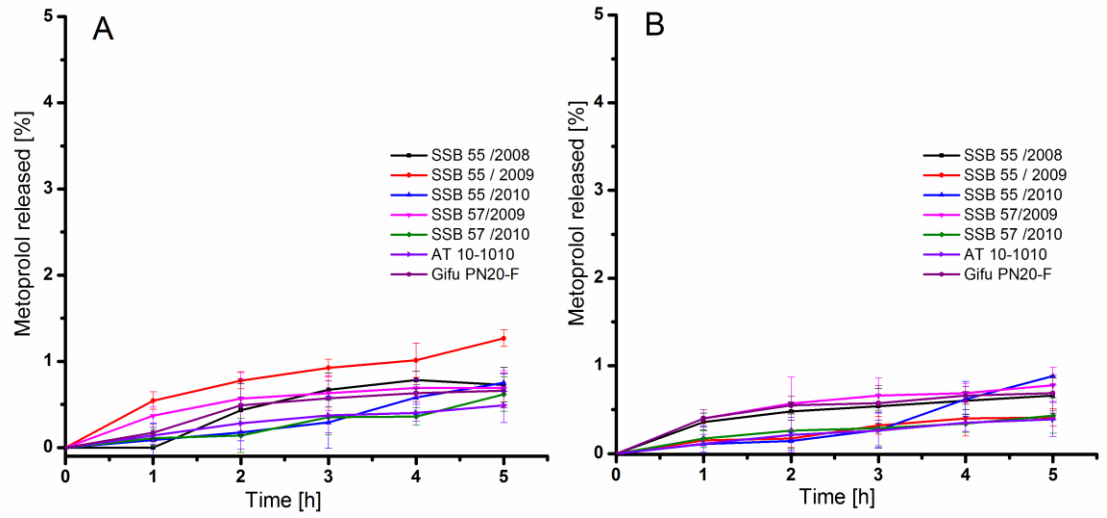


Figure 11: Metoprolol released from pellets coated with different shellac grades at pH 1.2, at coating level 20% w/w (A) and 25% w/w (B). Values presented are means of six observations. Vertical bars donate standard deviation.

At pH 6.8, the % released from the coated pellets was ≤ 30% within the first hour and ≤ 60% after six hours. The amount released was reasonably increased with the pH of the dissolution medium as shown in Figure 12.

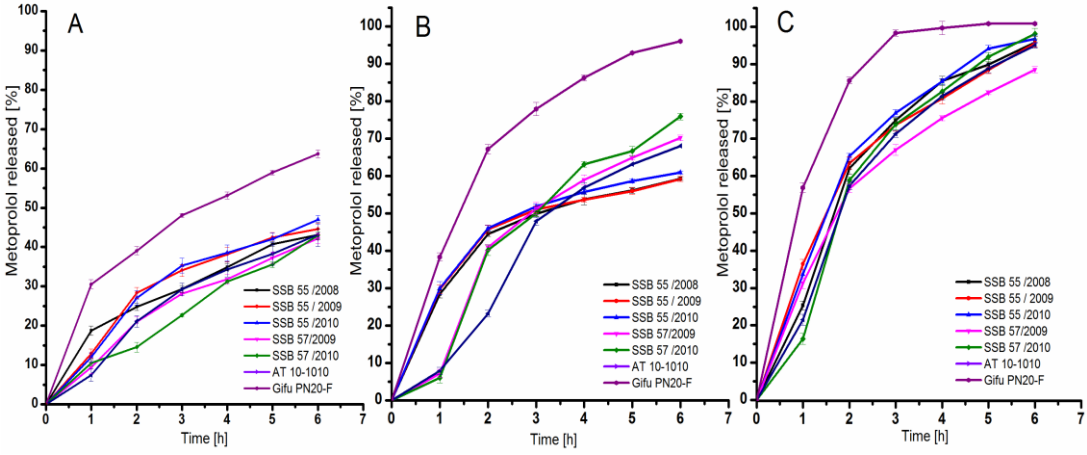


Figure 12: Metoprolol released from pellets coated with different shellac grades at a coating level of 20% w/w at different pH values. (A) pH 6.8, (B) pH 7.2 and (C) pH 7.4. Values represent means of six observations; vertical bars donate standard deviations.

The effect of coating level and dissolution medium pH on the release of metoprolol is shown in Figure 13. Gifu PN20-F shows the highest release among the tested shellac brands. Differences in release between brands are inversely proportional with the pH. A 5% higher coating level resulted in a slight increase in dissolution times. This is also demonstrated by the mean dissolution times (Table 4)

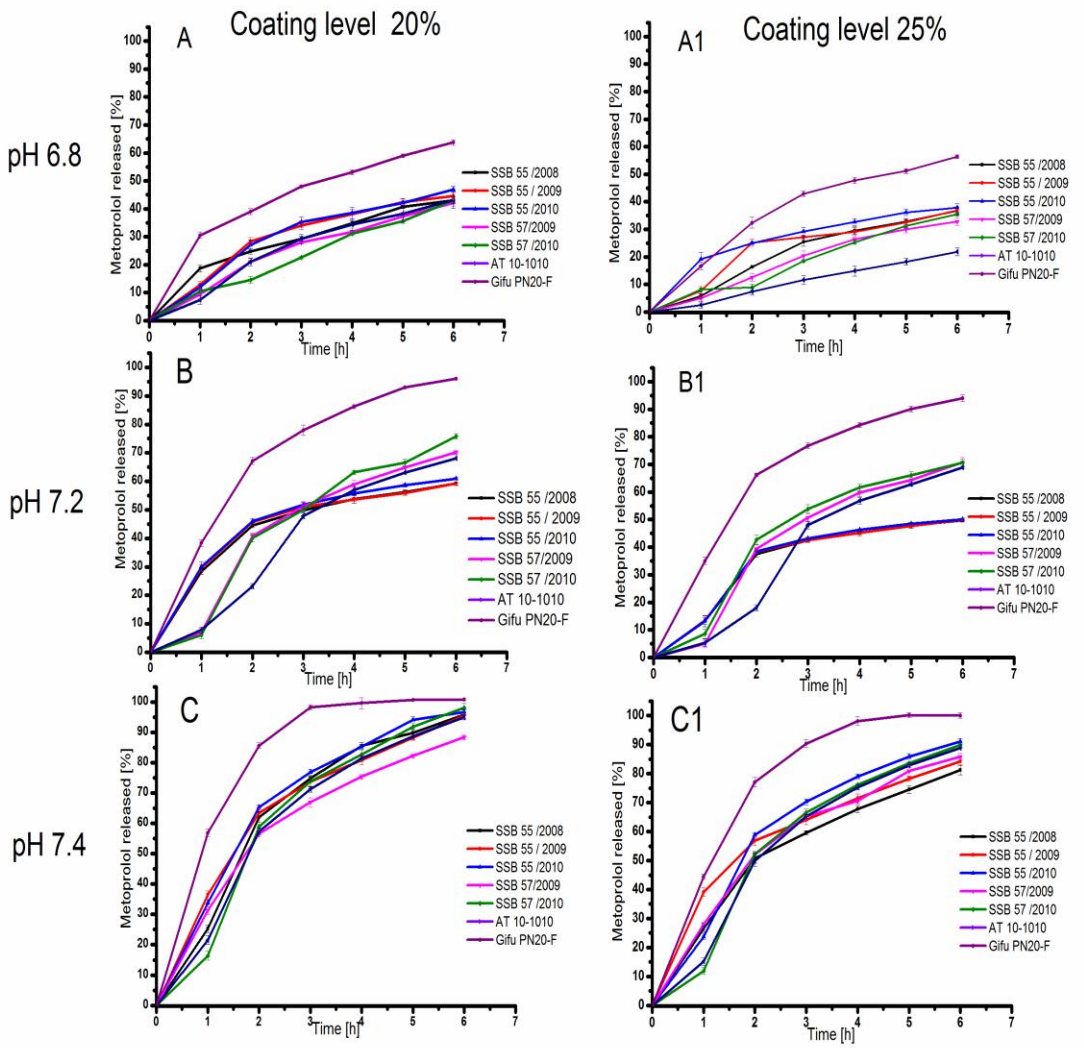


Figure 13: Metoprolol released from pellets coated with different shellac grades. Two coating levels were used at different pH values. (A & A1) 20% and 25% w/w coating levels at pH 6.8, (B & B1) 20% and 25% w/w coating levels at pH 7.2 and (C & C1) 20% and 25% w/w coating levels at pH 7.4. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

The variability of dissolution for batches (from freshly prepared shellac solutions) produced on different days was small (f_2>50), f_2 is equal to 79.15, 96.13 and 77.71. The release profiles are shown in Figure 14 A, which demonstrates that the pellets exhibited uniform coating layers indicating a robust and reproducible process. Likewise, the reproducibility of the dissolution method was good with high reproducibility of the results between different days; f_2 is equal to 84.93, 94.25 and 85.25 (Figure 14 B).

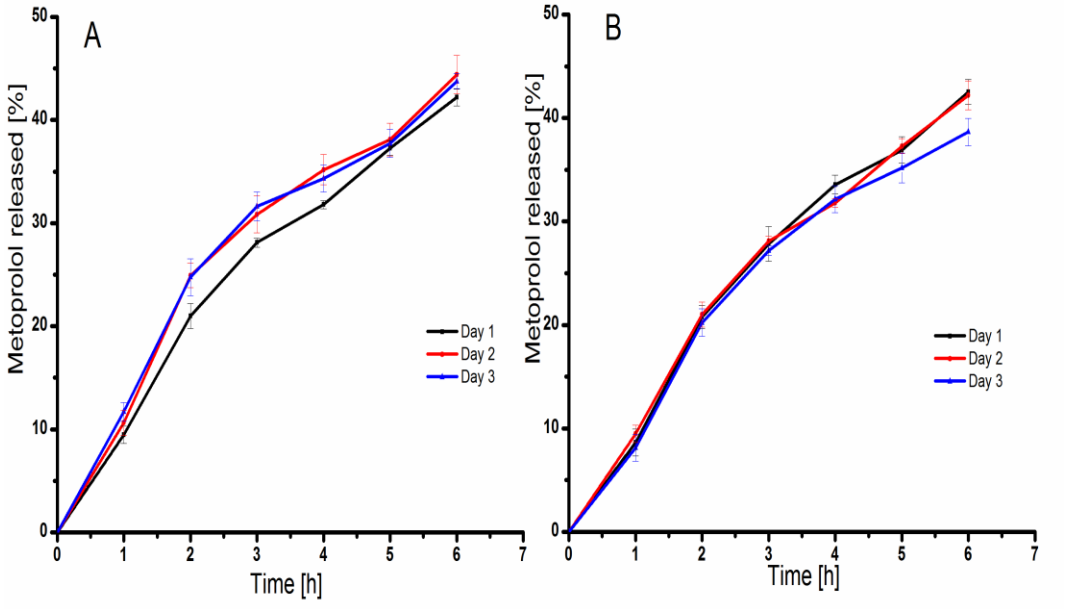


Figure 14: Metoprolol released at pH 6.8 from pellets coated with SSB 57 (20% w/w). The coating process was repeated on three different days (A). Metoprolol released at pH 6.8, from the same batch of pellets coated with SSB 57 (20% w/w) on three subsequent days (B).

The confirmatory dissolution tests for the batches (from ready for use aqueous shellac solutions) prepared on different days revealed that the coated pellets exhibited uniform coating layers (Figure 15 A) with a uniform dissolution behaviour on different days (Figure 15 B).

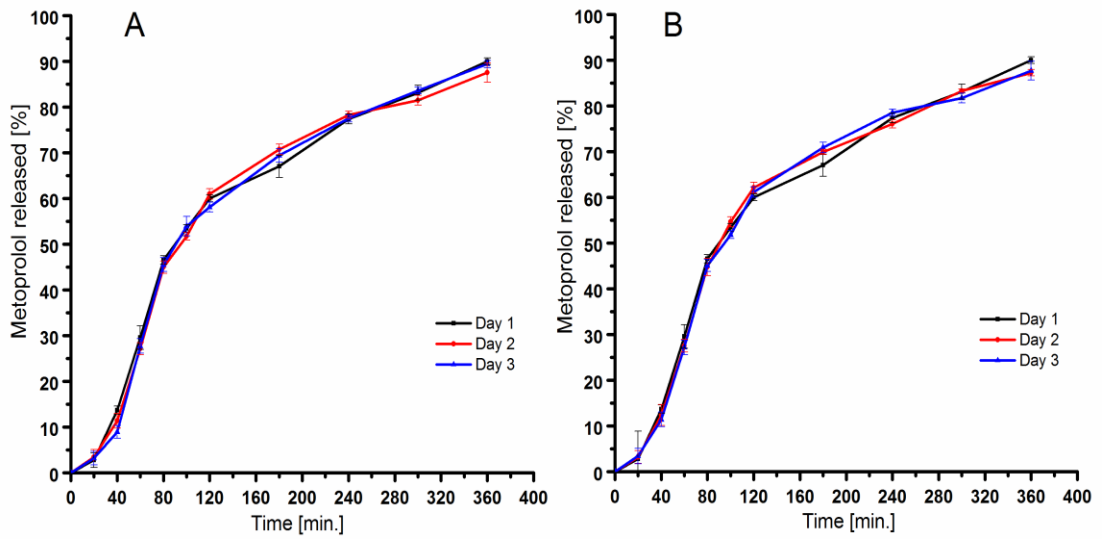


Figure 15: Metoprolol released from pellets coated with shellac solution (20% w/w) at pH 7.4. The coating process was repeated on three different days (A). Metoprolol released from pellets coated with shellac solution from the same batch (20% w/w) on three subsequent days for dissolution testing at pH 7.4 (B).

Table 4: Mean dissolution times of metoprolol for the shellac coated pellets for the two coating levels 20% and 25% w/w at pH 6.8, 7.2 and 7.4.

Shellac brand	MDT at pH 6.8		MDT at pH 7.2		MDT at pH 7.4	
	20% w/w	25% w/w	20% w/w	25% w/w	20% w/w	25% w/w
Gifu PN20-F	1.90 ± 0.05	2.11 ± 0 02	1.71 ± 0 02	1.76 ± 0 01	1.13 ± 0 01	1.43 ± 0 02
SSB 55 (Jun 08)	2.06 ± 0 01	2.51 ± 0.03	1.94 ± 0.05	2.69 ± 0.03	1.62 ± 0 02	2.05 ± 0 01
SSB 55 (Nov 09)	2.01 ± 0 02	2.20 ± 0 01	1.87 ±0.03	1.84 ± 0 04	1.51 ± 0 02	1.66 ± 0 01
SSB 55 (Mai 10)	2.20 ± 0 01	2.30 ± 0.05	1.82 ± 0 01	1.98 ± 0.03	1.54 ± 0.03	1.63 ± 0 02
SSB 57 (Feb 09)	2.47 ± 0 02	2.63 ± 0 01	2.32 ± 0.03	2.50 ± 0.04	1.97 ± 0 01	2.03 ± 0.05
SSB 57 (Sep 10)	2.84 ± 0.03	2.90 ± 0 02	2.20 ± 0.05	2.61 ± 0.03	2.16 ± 0.04	2.23 ± 0 01
AT 10-1010	3.08 ± 0.03	3.34 ± 0 04	3.02 ± 0 02	3.24 ± 0.06	3.37 ± 0.03	3.40 ± 0 04

Shellac AT 10-1010 showed the highest MDT among the tested brands for the two coating levels, whilst Gifu PN20-F has the shortest MDT. As expected the 20% w/w coatings, showed slightly shorter MDT than pellets coated with 25% w/w. The MDT is inversely proportional to the molecular size as shown in Figure 16 below.

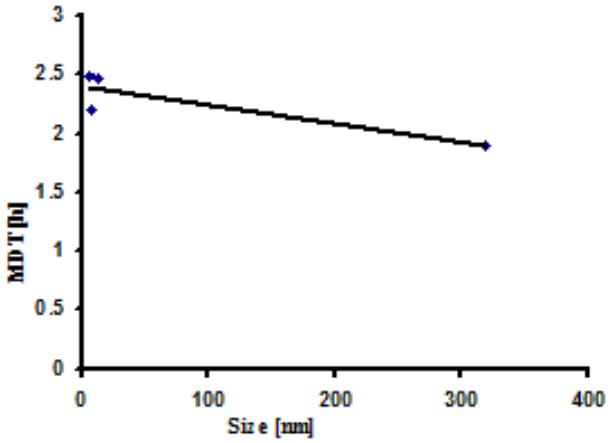


Figure 16: Mean dissolution times MDT of metoprolol pellets coated with different shellac grades, for the coating level 25% w/w at pH 6.8. The X axis represents the molecular size in nm for the shellac grades.

4.5. Effect of storage time on ready for use aqueous shellac solutions (SSB AQUAGOLD)

4.5.1. pH measurements

pH measurements indicate that older batches have a lower pH than the new ones. This may be due to the fact that there is some evaporation of CO_2 and NH_3 from the ammonia used in preparation of these solutions from the bottles, which then leads to the decrease in the pH of the shellac solution with time.

The pH values of all tested solutions were less than 7.3, with the lowest value for the oldest sample (September. 2009). The shelf life given by the manufacture is 12 months and the specification for the pH in the certificate of analysis is 7.5 ± 0.2.

The pH values for the ready for use aqueous shellac solutions (SSB AQUAGOLD) are reported in Table 5

Table 5: The pH of the tested SSB AQUAGOLD solutions at the time of use.

Shellac solution samples	pH	Testing date
(1) September. 2009	7.00	November. 2010
(2) August 2010	7.2	November 2010
(3) October 2010	7.2	November 2010
(4) May 2010	7.2	December 2011
(5) July 2011	7.25	December 2011
(6) September 2011	7.28	January 2012

4.5.2. Dissolution results for metoprolol tartrate pellets coated with different batches of different ages of ready for use shellac solutions (SSB AQUAGOLD)

Dissolution results of the coated pellets showed enteric resistance according to USP/Ph. Eur. For all tested shellac solutions ≤ 2% was released from coatings of 20% w/w after six hours dissolution at pH 1.2. Thus complete enteric resistance was achieved (Figure 17).

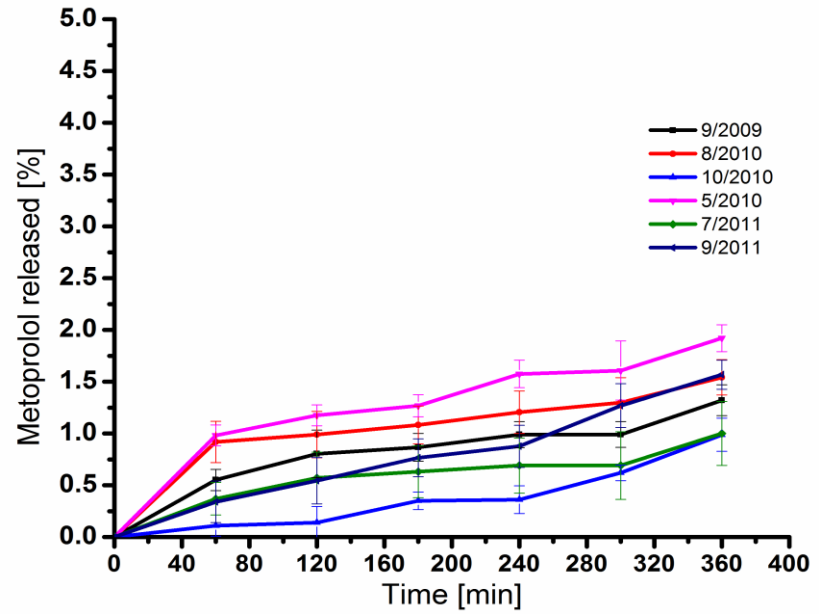


Figure 17: Metoprolol released from pellets coated with different aged shellac solutions (SSB AQUAGOLD) at pH 1.2 using 20% w/w coating level. Values presented are means of six observations. Vertical bars donate standard deviation.

The dissolution results of the coated pellets at higher pH values 6.8, 7.2 and 7.4 are shown in Figure 18. Each data point represents a mean of six measurements. Uncoated pellets completely dissolve after 5 minutes at all tested pH conditions. The out of date solution (Sep. 2009) shows release profile different from the other solutions at pH 6.8.

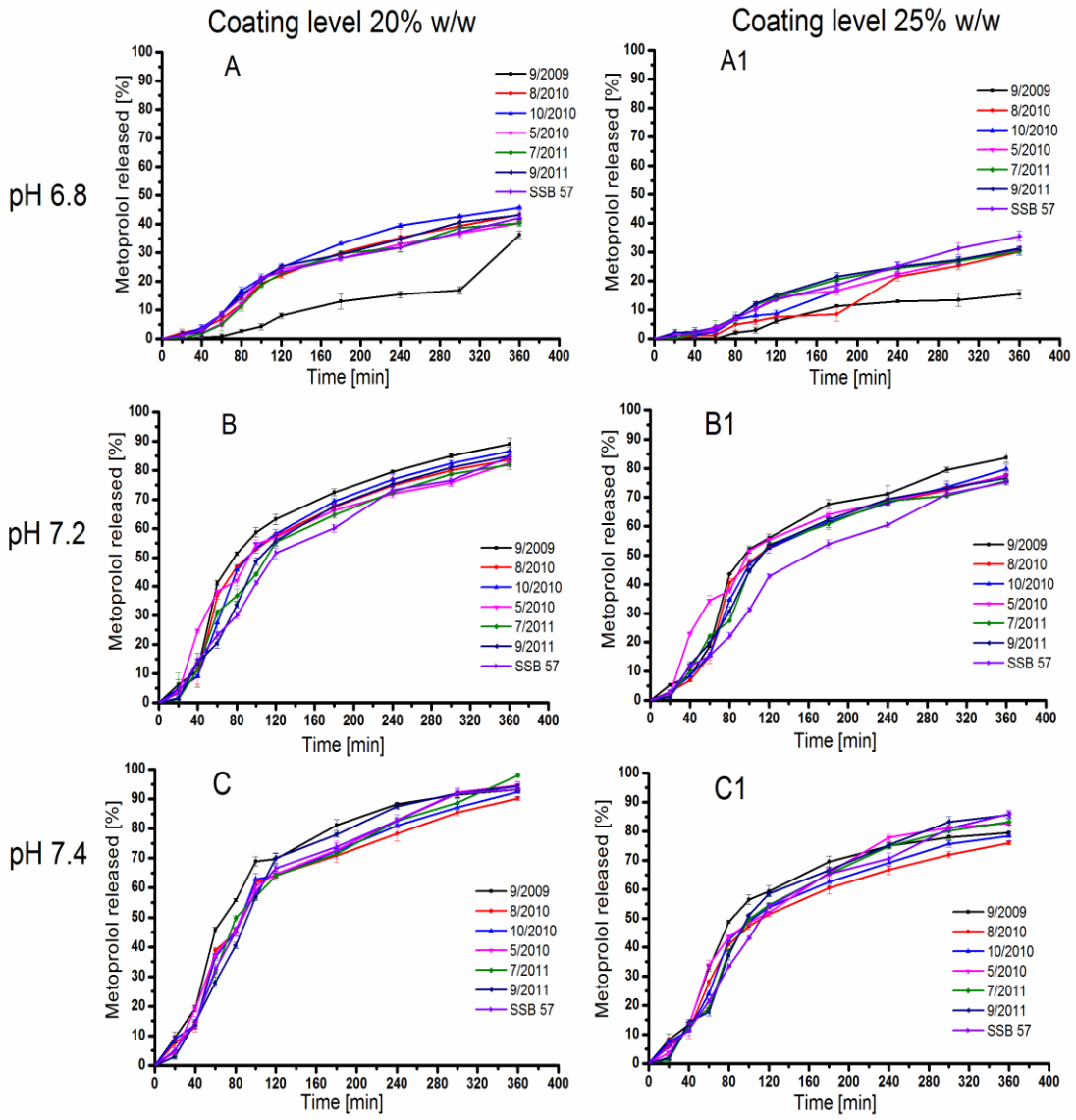


Figure 18: Metoprolol released from pellets coated with differently aged shellac solutions (SSB AQUAGOLD) at different pH, (A, A1), (B, B1) & (C,C1) at pH 6.8, 7.2 & 7.4 respectively, using coating levels of 20% w/w (A, B &C) and coating levels 25% w/w (A1, B1 & C1). Each data point represents a mean of six measurements, while vertical bars indicate standard deviation (S D).

4.5.3. Effect of the pH of shellac solution on its release characteristics

When the pH of the old solution (September 2009) was adjusted to 7.3 by addition of ammonia solution with the aid of heating, the turbidity of the solution disappeared. The dissolution profile of pellets coated with the new solution at pH 6.8 showed no significant difference from the reference SSB 57. (f_2 is equal to 83.3, while it is 44.4 before adjusting the pH). The old shellac solution (September 2009), showed higher and faster release after five hours dissolution and this because of the softening and swelling of the shellac film after long dissolution time, followed by drug diffusion through the coating layer. The dissolution profiles are shown in Figure 19.

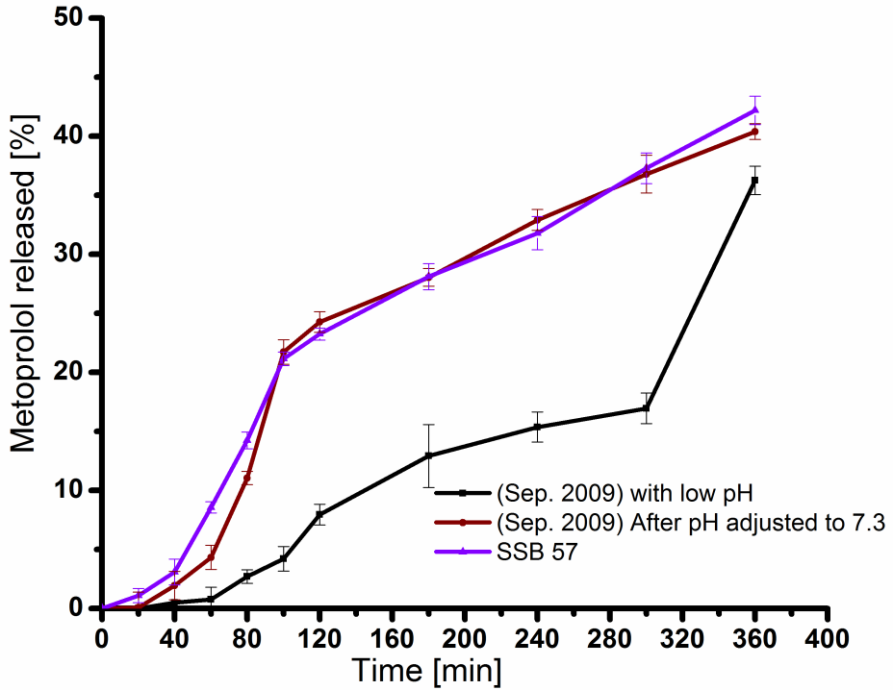


Figure 19: Dissolution profiles of metoprolol released (at pH 6.8) from pellets coated with the old aqueous shellac solution with low pH, with the same solution after adjusting the pH to 7.3 and from pellets coated with the reference SSB 57. Each data point represents a mean of six measurements, while vertical bars indicate standard deviation (S D).

The dissolution test is the most obvious way to evaluate coated pellets physically [175, 207]. It is used for the comparison of dissolution profiles [208-209]. Several methods for the comparison of dissolution profiles were proposed in the literature [210-214]. f_2 is extensively used as the United States Food and Drug Administration (US FDA) endorses it [208]. An f_2 parameter is commonly used to establish similarity of two dissolution profiles [215], the two profiles are considered identical when f_2=100. An average difference of 10% at all measured time points results in a f_2 value of 50; value between 50-100 indicate similarity between two dissolution profiles.

With exception of the low pH out of shelf life shellac solution, there are no significant differences between the dissolution profiles of the tested ready for use shellac solutions at the three pH values and for the two coating levels as the f_2 values are higher than 50, except for one sample (May. 2010) 25% w/w at pH 7.2, where f_2 is equal 45.6. This solution showed fast release in the first hour, compared to SSB 57; this is the reason why the f_2 is < 50.

Table 6: Similarity factors f_2 of metoprolol dissolution from metoprolol tartrate pellets coated with shellac coating solutions compared to the reference SSB 57, for two coating levels (20% & 25%) w/w at pH 6.8, 7.2 & 7.4.

Shellac sample	f_2 at pH 6.8		f_2 at pH 7.2		f_2 at pH 7.4	
	20% w/w	25% w/w	20% w/w	25% w/w	20% w/w	25% w/w
(1) Sep. 2009 (without adjusting the pH)	44.4	49.0	45.4	45.2	56.6	54.2
(2) Aug. 2010	84.1	64.7	53.2	51.6	70.2	61.2
(3) Oct. 2010	70.9	75.3	54.9	54.5	75.7	65.8
(4) Mai. 2010	86.7	79.3	53.3	45.6	79.2	60.8
(5) July. 2011	82.7	79.7	68.1	57.2	76.7	72.1
(6) Sep.-2011	85.2	81.0	68.0	56.4	73.9	69.3

From the results of the mean dissolution time (MDT) for the tested brands, the old shellac solution with low pH showed the highest MDT for both coating levels at pH 6.8 and the lowest MDT at pH 7.4 among the tested solutions.

Table 7: Mean dissolution times of metoprolol from metoprolol tartrate pellets coated with shellac coating solutions for two coating levels (20% & 25%) w/w at pH 6.8, 7.2 & 7.4.

Shellac sample	MDT at pH 6.8 [h]		MDT at pH 7.2 [h]		MDT at pH 7.4 [h]	
	20% w/w	25% w/w	20% w/w	25% w/w	20% w/w	25% w/w
(1) Sep. 2009 (without adjusting the pH)	4.0 ± 0 01	3.4 ± 0.04	1.7 ± 0.01	1.9 ± 0.02	1.5 ± 0.02	1.5 ± 0.03
(2) Aug. 2010	2.4 ± 0 01	2.7 ± 0.03	1.8 ± 0.01	2.0 ± 0.01	1.8 ± 0.04	1.8 ± 0.03
(3) Oct. 2010	2.2 ± 0.02	2.9 ± 0.05	1.9 ± 0.04	2.1± 0.03	1.8 ± 0.02	1.8 ± 0.01
(4) Mai. 2010	2.3 ± 0.0	2.8 ± 0.02	1.8 ± 0.04	1.7 ± 0.06	1.8 ± 0.04	1.8 ± 0.02
(5) July. 2011	2.2 ± 0.16	2.5 ± 0.07	1.9 ± 0.05	1.9 ± 0.08	2.1± 0.06	1.9 ± 0.04
(6) Sep.-2011	2.3 ± 0.03	2.5 ± 0.07	2.0 ± 0.04	1.9 ± 0.05	1.8 ± 0.03	1.9 ± 0.02

4.6. Comparison between different ready for use aqueous shellac solutions from different manufacturers

For comparison between different ready for use aqueous shellac solutions, two (4 months old) aqueous ready for use shellac solutions based on Bysakhi-Ber shellac type, AQUALACCA 25 and SSB AQUAGOLD were used. The two solutions were used for coating metoprolol tartrate pellets and then dissolution tests were carried out at different pH values.

Dissolution results of the coated pellets showed enteric resistance according to USP/Ph. Eur. For all tested shellac solutions ≤ 2% was released from coatings of 20% w/w after two hours dissolution at pH 1.2. Thus complete enteric resistance was achieved (Figure 20).

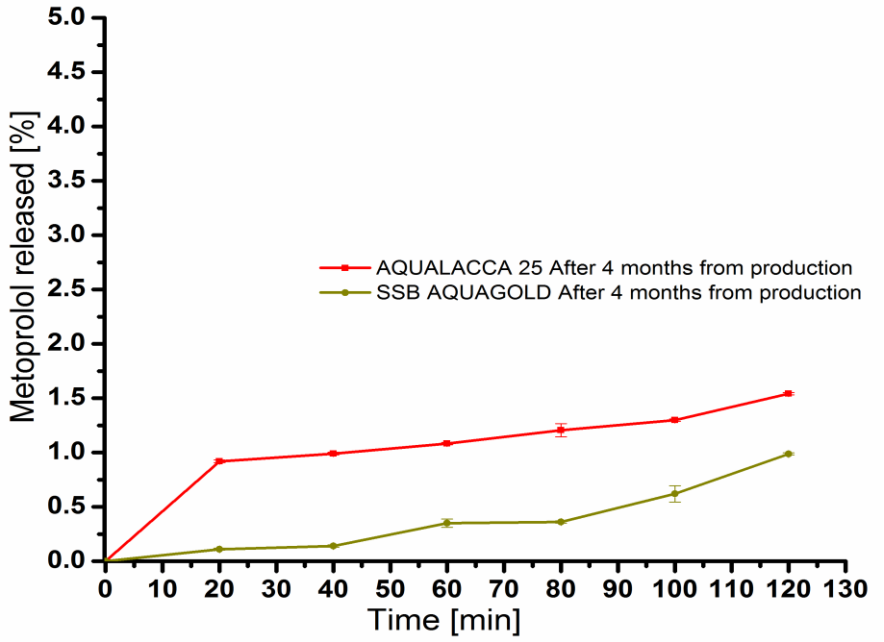


Figure 20: Metoprolol released from pellets coated with two different ready for use shellac solutions (AQUALACCA 25, SSB AQUAGOLD and SSB 57) at pH 1.2, using coating level 20% w/w. Values presented are means of six observations. Vertical bars donate standard deviations.

The dissolution results showed no significant changes, between the two shellac solutions AQUALACCA 25 and SSB AQUAGOLD (Table 8). Release profiles at pH 6.8 and 7.4 are shown in Figure 21. As expected drug released increased with pH.

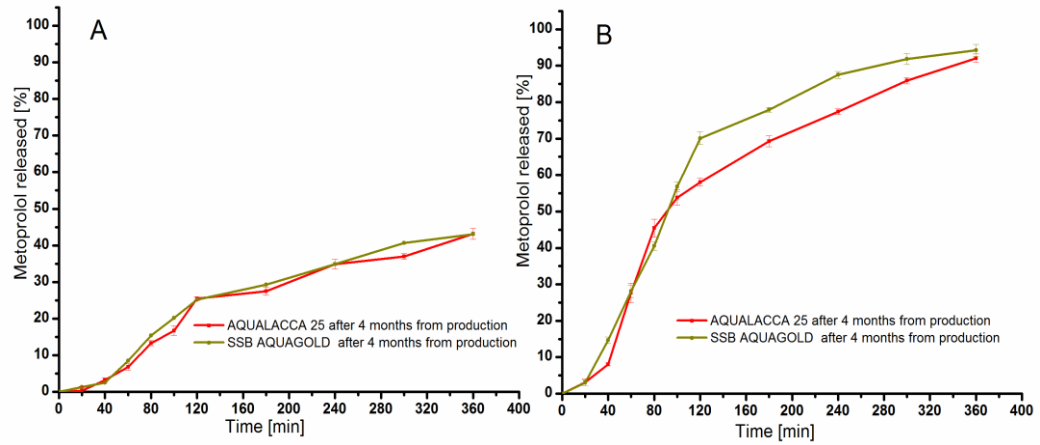


Figure 21: Metoprolol released from pellets coated with 20% w/w of two different ready for use shellac solutions (AQUALACCA 25 and SSB AQUAGOLD). (A) At pH 6.8, (B) at pH 7.4. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

Table 8: Similarity factors f_2 and mean dissolution times of metoprolol from metoprolol tartrate pellets coated with two different ready for use shellac solutions (AQUALACCA 25 and SSB AQUAGOLD), for the coating level 20% w/w at pH 6.8 and 7.4.

Shellac solution	**AQUALACCA 25**		**SSB AQUAGOLD**	
Dissolution pH	**6.8**	**7.4**	**6.8**	**7.4**
f_2	86.1	88.37	86.1	88.37
MDT [h]	2.50 ± 0.01	2.05± 0.01	2.37 ± 0.03	1.85 ± 0.03

4.7. Influence of incorporation of water soluble polymers on shellac films properties

4.7.1. Mechanical properties

The incorporation of HPMC, CMC and HPC into the shellac films resulted in an increase in the percent of elongation at break and a decrease in the elastic modulus. For the enteric coating formula (Pencoat 912.1) based on shellac: soluble polymer: Glycerol (62.5: 25:12.5), the HPC showed the best results. It increased the elongation at break percentage to about 20% and decreased the elastic modulus to < 50, whilst the other two soluble polymers HPMC and CMC showed an increase in the elongation at break percentage < 2% and decreased the elastic modulus to > 75 MPa for HPMC and > 100 MPa for CMC (Table 9).

Table 9: Elongation at break and elastic modulus of the measured free shellac films

Type of film	Number of samples measured	Standard deviation of thickness of the individual films [%] *	Thickness range of samples [µm]	Elongation at break [%/mm²] ± S D.	Elastic modulus [MPa] ± S D.
AQUAGOLD 62.5% + HPMC 25% + Glycerol 12.5%	17	1.40 – 7.03	106-130	0.86 ± 0.20	87.25 ± 13.07
AT 10-1010 62.5%+ HPMC 25% + Glycerol 12.5%	22	0.55 – 9.78	54 - 151	1.20 ± 0.62	78.55 ± 11.22
SSB 55 62.5% + HPMC 25% + Glycerol 12.5%	16	0.61 – 4.63	100 - 147	0.96 ± 0.40	78.45 ± 5.69
SSB 57 62.5% +HPC 25% + Glycerol 12.5%	21	0.78 – 3.47	93 - 138	14.89 ± 4.23	46.23 ± 3.13
AT 10-1010 62.5% + HPC 25% + Glycerol 12.5%	21	0.88 – 8.18	83 - 154	22.09 ± 7.88	24.11 ± 4.23
SSB 55 62.5% + HPC 25% + Glycerol 12.5%	20	0.82 – 4.63	92 - 155	20.86 ± 6.84	36.80 ± 3.31
SSB 55 62.5% + CMC 25% + Glycerol 12.5%	24	0.82 – 14.02	71 - 139	1.97 ± 0.65	116.05 ± 16.58
SSB 57 62.5% + CMC 25% + Glycerol 12.5%	20	0.97 – 5.40	72 - 144	1.42 ± 0.18	108.93 ± 12.89
AT 10-1010 62.5% + CMC 25% + Glycerol 12.5%	18	1.96 – 5.51	96 - 150	1.75 ± 0.33	104.83 ± 8.75
SSB 55 75% +HPC 17.5% + Glycerol 7.5%	16	0.50 – 3.23	80 - 121	1.75 ± 4.87	103.24 ± 6.34
SSB 57 75%+ HPC 17.5% + Glycerol 7.5%	17	1.40 – 6.10	58 - 140	1.77 ± 1.01	102.25 ± 18.54
AT 10-1010 A 75% + HPC 17.5% + Glycerol 7.5%	17	0.98 – 5.99	43 - 101	2.41 ± 1.67	108.05 ± 22.74
AT 10-1010 75%+ HPC 12.5% + Glycerol 12.5%	18	0.62 – 4.83	89 - 149	12.82 ± 5.58	34.67 ± 4.39
SSB 57 75% + HPMC 17.5% + Glycerol 7.5% (A)	9	1.51 – 5.72	53 - 125	0.61 ± 0.34	113.23 ± 21.41

A = The dried films were extremely brittle, hence the most material was destroyed at removing the films from the forms and at cutting the films into stripes
* The standard deviation range of measurements on different sites on each film.

4.7.2. Gloss

Gloss is an important quality factor of many food products such as apples, citrus fruits, vegetables and confectionery products which are coated with shellac and waxes to provide a high gloss [216-218]. Shellac from alcoholic solutions has been used for glazing in the pharmaceutical industry [171], films from aqueous shellac solution produced gloss in the same range that showed from films from alcoholic solution or even higher (Table 10).

Table 10 shows the results of gloss measurements of shellac and shellac with water soluble polymer films. Two film thicknesses were used (100 and 200 µm) and the results showed no large differences between the two used film thicknesses. The incorporation of CMC to shellac showed a drastic drop in the gloss of shellac films. Gum arabic also decreases the gloss of the shellac film and there is a direct proportion between the concentration of the gum and the drop in the gloss**.** The incorporation of 50% gum in the shellac decreased the gloss by 50%. HPMC, HPC and Pullulan® left the gloss rather unaffected.

Table 10: Measured gloss of films from aqueous shellac solutions (SSB 57) in gloss unit GU at 60°. The data represent mean of five ± standard deviations. 100 µm and 200 µm refer to the thickness of the film respectively.

Polymer	Shellac: polymer (62.5:37.5)		Shellac: polymer (50:50)	
	100 µm	**200 µm**	**100 µm**	**200 µm**
HPMC	184.0 ± 1.4	183.8 ± 12.7	203.0 ± 0.8	183.3 ± 2.5
HPC	182.3 ± 1.5	188.0 ± 1.8	197.3 ± 3.3	180.3 ± 2.2
Pullulan®	185.3 ± 1.7	185.5 ± 0.6	192 ± 2.8	187.3 ± 3.1
Gum arabic	148.5 ± 4.2	128.4 ± 0.8	103.4 ± 2.6	88.7 ± 14.7
CMC	73.3 ± 6.7	36.9 ± 10.6	12.2 ± 1.1	8.3 ± 0.6

HPMC	**Shellac: HPMC (25:75) 200** µm	**Shellac: HPMC (75:25) 200** µm
	187 ± 8.8	186 ± 2.9
Pullulan®	**Shellac: Pullulan® (25:75)100** µm	**Shellac: Pullulan® (75:25) 100** µm
	199.8 ±3.5	189.3 ±4.6

Shellac SSB 57	**100 µm**	**200 µm**
Aqueous solution	200.5 ± 2.6	186.5 ± 3.3
Alcoholic solution	189 ± 1.8	187.0 ± 1.8

4.7.3. Optimizing the coating composition for enteric coated release

Coating of a solid dosage form is often designed to perform desired functions like taste masking, moisture protection and controlled released films. The controlled releases are either pH or time controlled. Water soluble polymers were added to shellac/plasticizer, to promote the dissolution of shellac at higher pH values, while retaining good resistance in simulated gastric fluid The addition of these water soluble polymers resulted in an enhancement of the permeability of shellac films (pore formers). The dissolution of such polymers in the aqueous media and leaching out leads to creating a micro porous membrane that enhances the release through the film coat.

To achieve the desired formula for shellac enteric coating, different concentrations from shellac, plasticizer and HPMC were used. The desired formula needed consist of a higher concentration of HPMC with low coating level and the amount of drug released from these coatings after two hours dissolution at pH 1.2 should be less than 10%.

The results of the dissolution of coated metoprolol tartrate pellets coated with shellac, plasticizer and HPMC with different ratios of the components and different coating levels are shown in Table 11.

Table 11: Metoprolol released after two hours dissolution at pH 1.2 for shellac, shellac/plasticizer and shellac/plasticizer and HPC coatings using different coating levels.

Coating formula (% Solid content)		Coating level%(w/w)	% Released after two hours Dissolution at pH 1.2
SSB 57	100%	25% w/w	≤ 1
HPMC	0%	30% w/w	≤ 1
Glycerol	0%	35% w/w	≤ 1
		40% w/w	≤ 1
SSB 57	95%	25% w/w	≤ 1
HPMC	0%	30% w/w	≤ 1
Glycerol	5%	35% w/w	≤ 1
		40% w/w	≤ 1
SSB 57	90%	25% w/w	≤ 1
HPMC	5%	30% w/w	≤ 1
Glycerol	5%	35% w/w	≤ 1
		40% w/w	≤ 1
SSB 57	85%	25% w/w	≤ 1
HPMC	10%	30% w/w	≤ 1
Glycerol	5%	35% w/w	≤ 1
		40% w/w	≤ 1
SSB 57	80%	25% w/w	1.5
HPMC	15%	30% w/w	1
Glycerol	5%	35% w/w	≤ 1
		40% w/w	0≤ 1
SSB 57	75%	25% w/w	12
HPMC	20%	30% w/w	10
Glycerol	5%	35% w/w	4.5
		40% w/w	1
SSB 57	65%	25% w/w	4.5
HPMC	20%	30% w/w	2
Glycerol	15%	35% w/w	2
		40% w/w	1
SSB 57	80%	25% w/w	2
HPMC	0%	30% w/w	1
Glycerol	20%	35% w/w	1
		40% w/w	≤ 1

Glycerol has a good plasticization effect on shellac films [164] and from the results in Table 11, the incorporation of 20% from the total solid content, achieved excellent gastric resistance, while the incorporation of HPMC increased the percentage of metoprolol released. The addition of 20% HPMC with 5% plasticizer increased the release to more than 10% for 25% w/w coating level. The increased concentration of plasticizer from 5% to 15% in the formula then decreased the percent released from 12 to 4.5%.

This formula was then selected and the ratios of its component were slightly changed and then further tested for dissolution at pH 6.8. A formula containing Shellac: HPMC: Glycerol, in ratios of 62.5:22.5:15, respectively, was found to be the best for enteric coating using shellac and HPMC. The results for the different shellac types are shown in Figure 22.

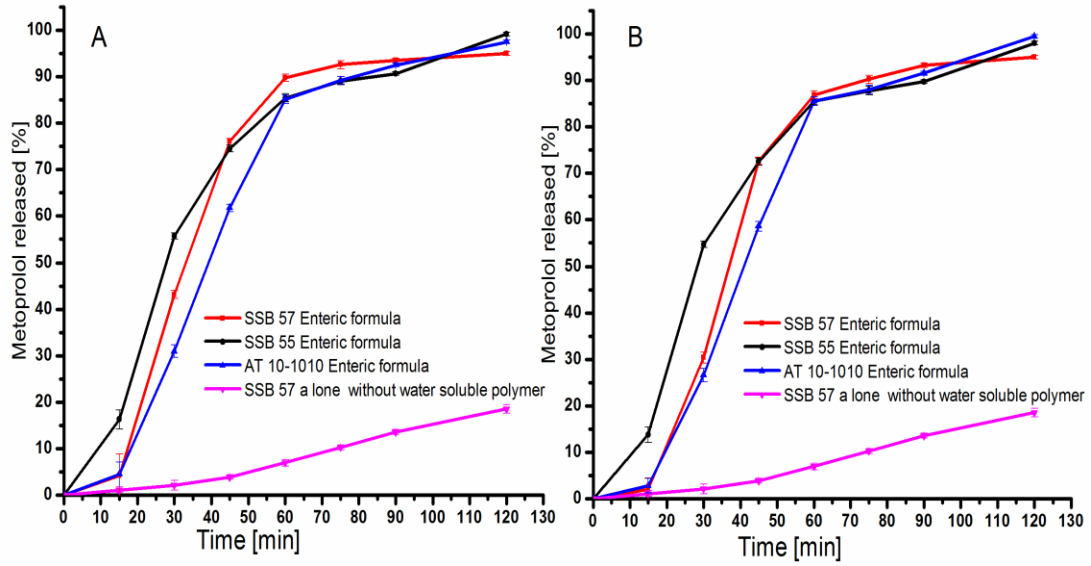


Figure 22: Dissolution profiles of metoprolol from metoprolol tartrate pellets coated with enteric coating formula containing (Shellac: HPMC: Glycerol) in ratios of 62.5:22.5:15 at pH 6.8. Three types of shellac were used and two coating levels were applied. (A) 25% w/w coating level, (B) 27.5% w/w coating level. Pellets coated with 25% w/w SSB 57 without added water soluble polymer were included as reference. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

The incorporation of HPC instead of HPMC in the above tested formula which was slightly modified to shellac: HPC: Glycerol, in the ratios of 62.5:25:12.5, respectively, was found to be the best for enteric coating using shellac and HPC. Results with different shellac types are shown in Figure 23.

The USP requirements for enteric-coated formulation are less than 10% dissolved in 2 hours in simulated gastric medium and not less than 80% dissolved after one hour in simulated intestinal medium. The two formulas for shellac/plasticizer and the water soluble polymer HPMC and HPC complied with these regulations as shown in Figures 22&23. Not more than 7% was released from the thin coating level 25% w/w after two hours at pH 1.2 and ≥ 80% from the thicker coat 27.5 % w/w after one hour at pH 6.8.

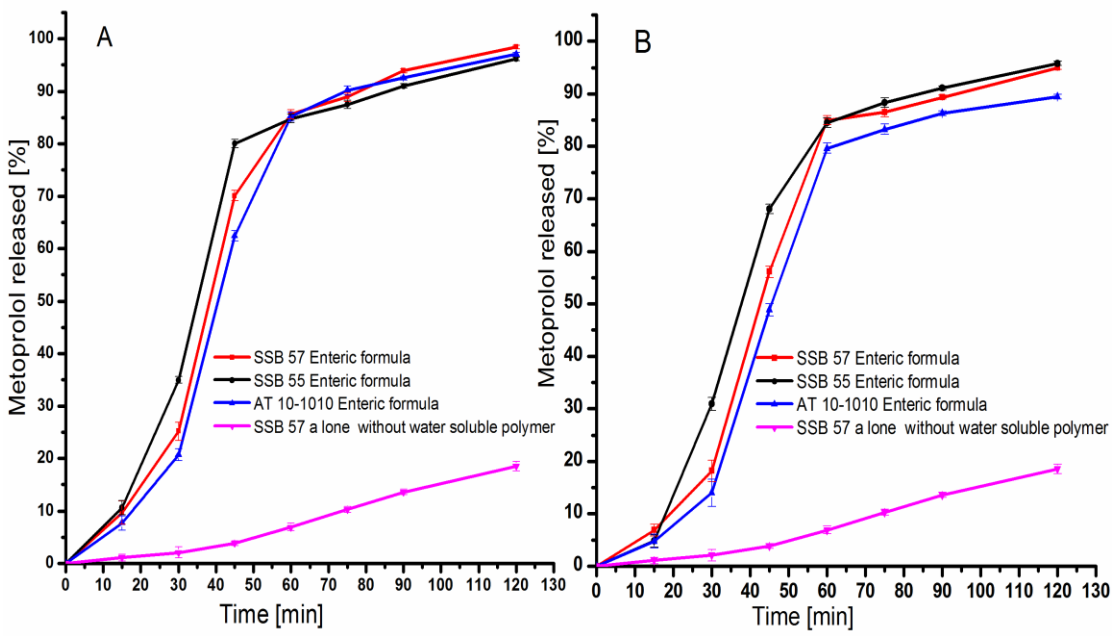


Figure 23: Dissolution profiles of metoprolol from metoprolol tartrate pellets coated with enteric coating formula containing (Shellac: HPC: Glycerol) in ratios of (62.5:22.5:15), at pH 6.8. Three types of shellac were used (A) **25% w/w coating level,** (B) **27.5% w/w coating level. Pellets coated with 25% w/w SSB 57 without added water soluble polymer were included as reference. Values presented are means of six observations, while vertical bars donate standard deviation (S D).**

Three different shellac types were used in the current investigation. For HPMC formula SSB 55 showed faster release in the first 30 minutes, which is significantly different from the other two types SSB 57 and AT 10-1010. f_2 are equal to 42.5 and 38.4 respectively. Whilst SSB 57 and AT 10-1010 are not significantly different (f_2 = 66.5). For the HPC, SSB 55 also showed faster release in the first 30 minutes, whilst AT 10-1010 showed the slowest release; the two release profiles are significantly different (f_2 = 40.9). SSB 57 showed release profile not significantly different either from SSB 55 (f_2 = 52.2) or from AT 10-1010 (f_2 = 50.6)

For CMC and Pullulan® which both have high water solubility the coated pellets showed dissolution at pH 1.2 ≥ 20% dissolved in 2 hours at pH 1.2. Even thicker coating levels (30% w/w and more) failed to prevent the higher release at pH 1.2.

Gum arabic, is slightly different from these polymers in that the pH of its solution is low (4 - 5 for 20% w/w solution). This low pH makes it immiscible with shellac. Thus its solution was prepared using 1% (w/w) ammonium bicarbonate in demineralised water instead of demineralised water. This method increased its pH to ≥ 7.3 which then made it miscible with shellac solution and formed a clear solution. Gum arabic showed high solubility at pH 1.2. Using different ratios of shellac/gum arabic and thicker coating levels (30% w/w), the drug released after two hours at pH 1.2 was decreased to less than 10%. However, the % released after one hour at pH 6.8 was found to be less than 80%.

4.7.4. Optimizing coating composition for targeting of release to the distal small intestine and large intestine

Water-soluble polymers may be added to shellac to aid in controlling its release characteristics and to provide channels or pores in the film. HPMC & HPC were used for this application. The release patterns can be modified by addition of different amounts either of the soluble polymer or of the shellac/plasticizer ratio. Figure 24 shows the effect of incorporation of a constant amount of HPMC and different ratios of shellac/plasticizer. Different release rates were obtained with the same coating level

(25% w/w) with lower release rates from shellac coat when a higher percentage of shellac in the spraying solution was used.

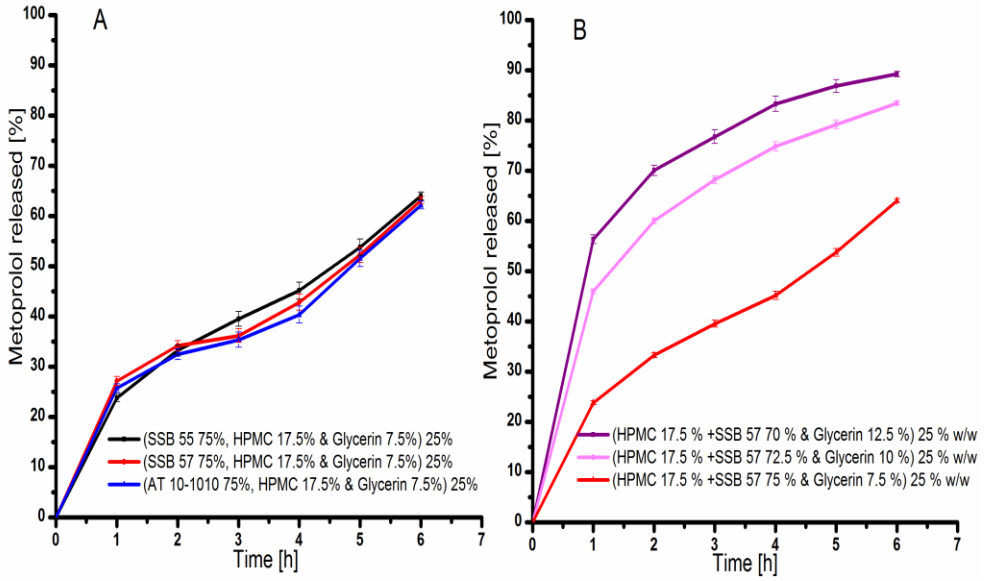


Figure 24: Metoprolol released from 25% w/w coated metoprolol tartrate pellets at pH 6.8 for 6 hours. (A) Coating formula Shellac: HPMC: Glycerol (75%:17.5%:7.5%). Three different shellac types were used. (B) Coating formula containing HPMC 17.% and SSB 57/Glycerol in ratios of 70%/12.5%, 72.5%/10% and 75%/7.5%. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

Materials which have been found suitable for an appropriate polymer coat for colon specific drug delivery include incorporation of 80% shellac, 10% water soluble polymer and 10% Glycerol in one system coating formula and the application of two coating levels (27.5 & 30% w/w). This formula was found to prevent the dissolution of drug in simulated gastric juice pH 1.2 for two hours and for five hours at pH 6.5. As shown in Figure 25, by increasing the concentration of shellac in the coating film, the release at pH typically found in the small intestinal region decreased. Films containing higher concentrations of shellac (more than 75% w/w from the total solid contents), can delay or withstand release at pH less than 7. As shown Figure 25, the selected formula for colon targeting prevents the release at both pH 1.2 & 6.5 for 2 & 5 hours respectively, with ≥ 90% rapid drug release at pH 7.2.

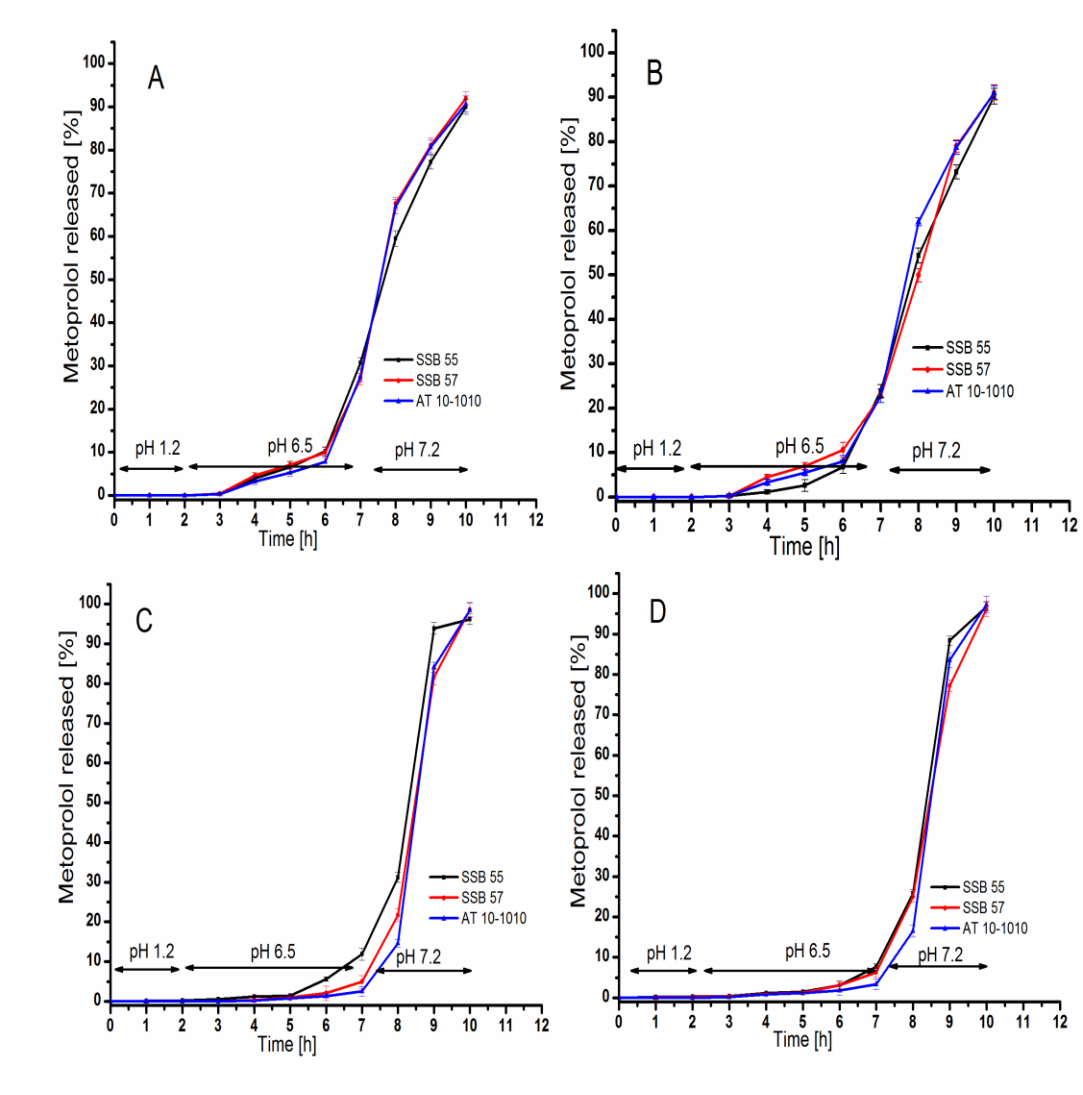


Figure 25: Dissolution profile of metoprolol tartrate pellets coated with formula containing Shellac: Water soluble polymers: Glycerol (80:10.5:10) at pH 1.2 for two hours and at pH 6.5 for 5 hours and at pH 7.2 for 3 hours. Three types of shellac were used. (A) &(B) 27.5% w/w and 30% w/w coating level using HPMC as the water soluble polymer; (C) &(D) 27.5% w/w and 30% w/w coating level using HPC as the water soluble polymer. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

Three different shellac types were used in the current investigation. f_2 similarity factor was chosen as statistical parameter for comparison between the shellac types. The results showed no significant differences between the three shellac types, as all the values are > 50. The results are shown in Table 12.

Table 12: Similarity factor f f_2 for the three shellac types (SSB 55, SSB 57 and AT 10-1010), that were used in the coating formulas for targeting release to the distal small intestine and large intestine.

Formula **Shellac type**	**Shellac: HPMC: Glycerol (62.5%: 22.5%: 15%)**		**Shellac: HPC: Glycerol (62.5%: 25%: 12.5%)**	
	(27.5% w/w)	**(30% w/w)**	**(27.5% w/w)**	**(30% w/w)**
SSB 55 – SSB 57	58.58	74.55	71.99	71.73
SSB 55 – AT 10-1010	56.97	65.86	73.55	71.32
SSB 57 – AT 10-1010	69.56	76.36	89.71	67.25

Formula **Shellac type**	**Shellac: HPMC: Glycerol (75%: 17.5%: 7.5%) 25% w/w**
SSB 55 – SSB 57	80.12
SSB 55 – AT 10-1010	87.42
SSB 57 – AT 10-1010	75.14

4.8. Effect of alcohol on drug release from shellac coated pellets

For evaluation of alcohol consumption on drug release from shellac coated pellets, three shellac types were used (SSB 55, SSB 57 and Gifu PN20-F) for coatings of metoprolol tartrate pellets. The three shellac types failed to withstand dissolution in alcohol concentrations > 10% v/v and more than 10% from the drug were released after 2 hours.

The metoprolol released from shellac coated metoprolol tartrate pellets, after dissolution at 0.1 N HCl containing different concentrations of alcohol was increased as the concentration of alcohol in the dissolution media increased. The cumulative metoprolol released after two hours dissolution at pH 1.2 are shown in Figure 26.

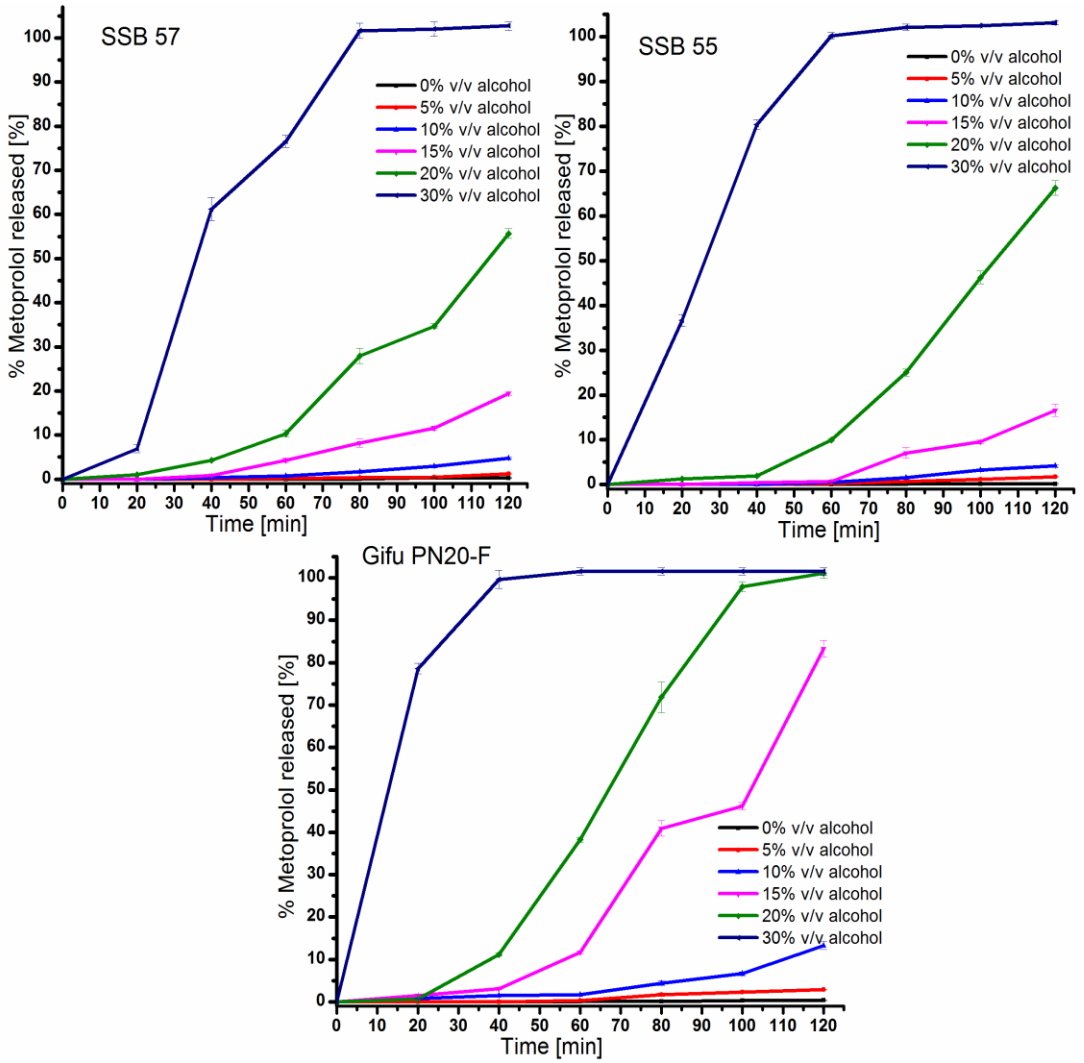


Figure 26: Dissolution profiles of metoprolol from metoprolol tartrate pellets coated with different shellac types in 0.1 N HCl containing 0%, 5%, 10%, 15%, 20 & 30% v/v alcohol respectively, for two hours. Three types of shellac were used. Bysakhi-Ber SSB 57, Kushmi SSB 55 and Thai type Gifu PN20-F. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

4.9. Effect of shellac salt type on drug release

Two shellac salts were used for coating metoprolol tartrate pellets. Ammonium salt for which ammonium bicarbonate was used as base and sodium salt where sodium bicarbonate was used. Three different shellac types SSB 57, AT 10-1210 and Gifu PN20-F were used. Dissolution profiles of metoprolol tartrate pellets coated with 20% w/w coating level at pH 6.8 and 7.2 are shown in Figures 28 and 29 respectively. The metoprolol released from the sodium salt coatings were significantly higher than that released from the ammonium salts at pH 6.8 (Table 13), whilst at pH 7.2 the difference in the release depends on the shellac type used. Shellac Gifu PN20-F showed release profile higher and faster than the other two types for the two salts types and at the two tested pH values.

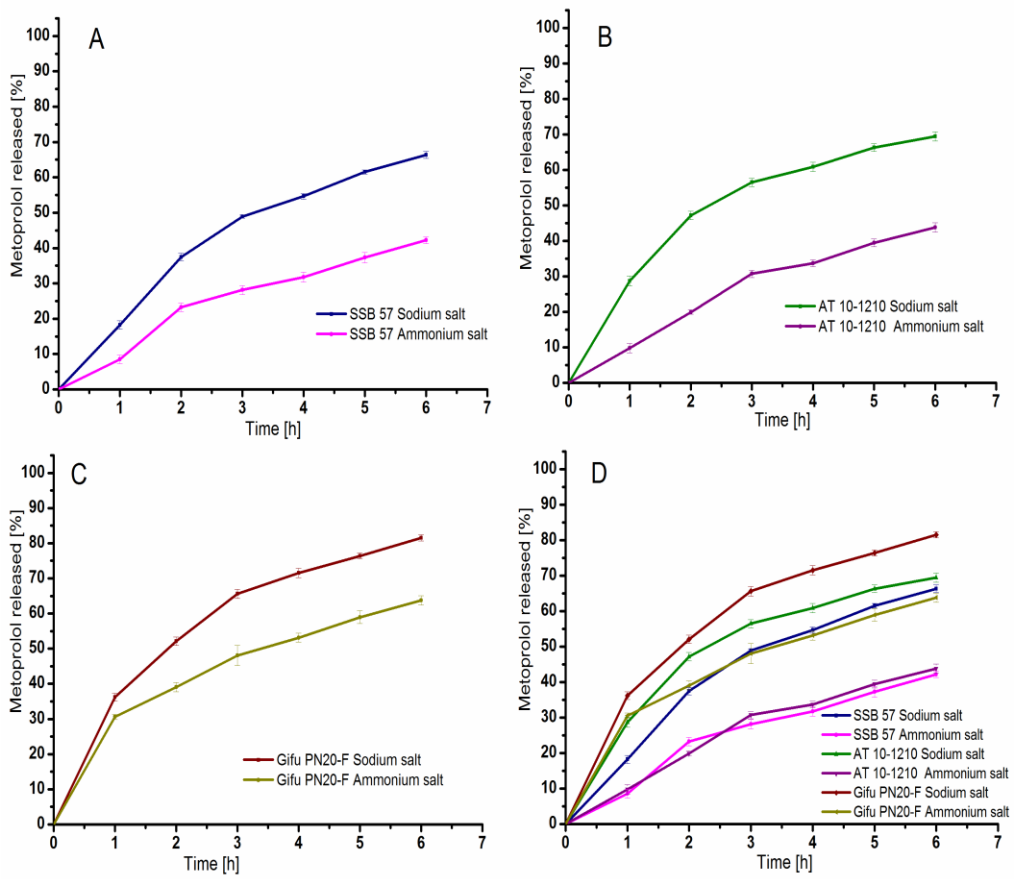


Figure 27: Dissolution profiles of metoprolol from metoprolol tartrate pellets coated with 20% w/w of two different shellac salts, ammonium salt and sodium salt at pH 6.8. (A) SSB 57, (B) AT 10-1210, (C) Gifu PN20-F and (D) the three shellac types together. Values presented are means of six observations, while vertical bars donate standard deviations (S D).

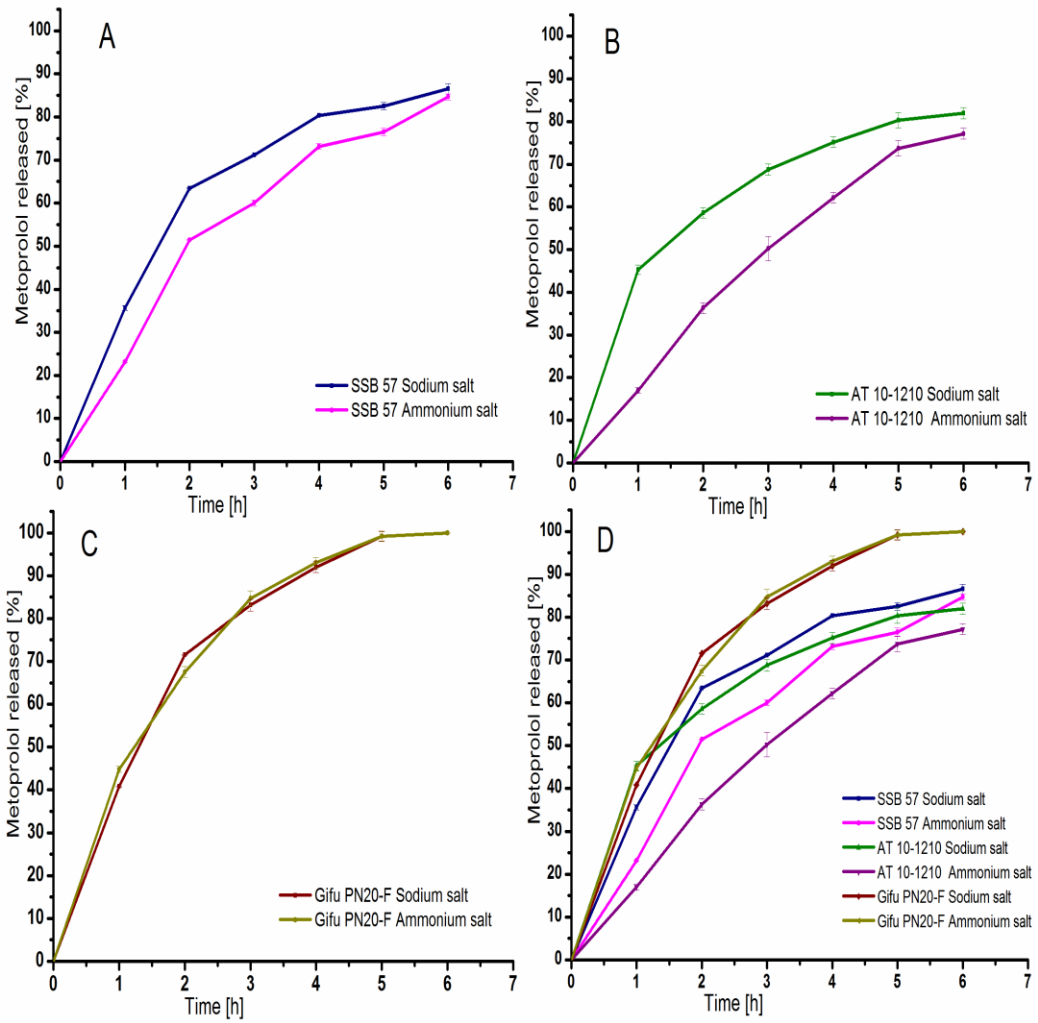


Figure 28: Dissolution profiles of metoprolol from metoprolol tartrate pellets coated with 20% w/w of two different shellac salts, ammonium salt and sodium salt at pH 7.2. (A) SSB 57, (B) AT 10-1210, (C) Gifu PN20-F and (D) the three shellac types together. Values presented are means of six observations, while vertical bars donate standard deviations (S D).

Table 13: Similarity factors f_2 of metoprolol dissolution from metoprolol tartrate pellets coated with two different shellac coating solutions (ammonium salt and sodium salt) of three different shellac types, for the coating level 20% w/w at pH 6.8 and 7.2.

Shellac type	SSB 57	AT 10-1210	Gifu PN20-F
At pH 6.8	34.82	29.72	40.24
At pH 7.2	51.59	37.39	78.97

Table 14: Mean dissolution times of metoprolol dissolution from pellets coated with two different shellac coating solutions of three different shellac types. The coating level is 20% w/w at pH 6.8 and 7.2.

Shellac type	SSB 57		AT 10-1210		Gifu PN20-F	
	Ammonium salt	Sodium salt	Ammonium salt	Sodium salt	Ammonium salt	Sodium salt
At pH 6.8	2.44 ± 0.01	2.14 ± 0.02	2.45 ± 0.02	1.76 ± 0.01	1.90 ± 0.02	1.80 ± 0.02
At pH 7.2	2.17 ± 0.02	1.65 ± 0.01	2.40 ± 0.01	1.50 ± 0.02	1.63 ± 0.01	1.61 ± 0.00

4.10. Stability

Stability tests were conducted for different shellac coated metoprolol tartrate pellets, by storing the coated metoprolol tartrate pellets at room temperature (22–25°C), for one year followed by testing metoprolol dissolution.

4.10.1. Stability for different shellac grades

4.10.1.1. Coating stability

Three shellac types (SSB 55, SSB 57 and Gifu PN20-F) were used in this investigation. The metoprolol released from the coated metoprolol tartrate pellets was measured one day after coating and after storage duration of one year. The results are shown in Figure 29; the drug released from the coated pellets after storage for one year did not change. Gifu PN20-F showed higher and faster release than the two SSB types.

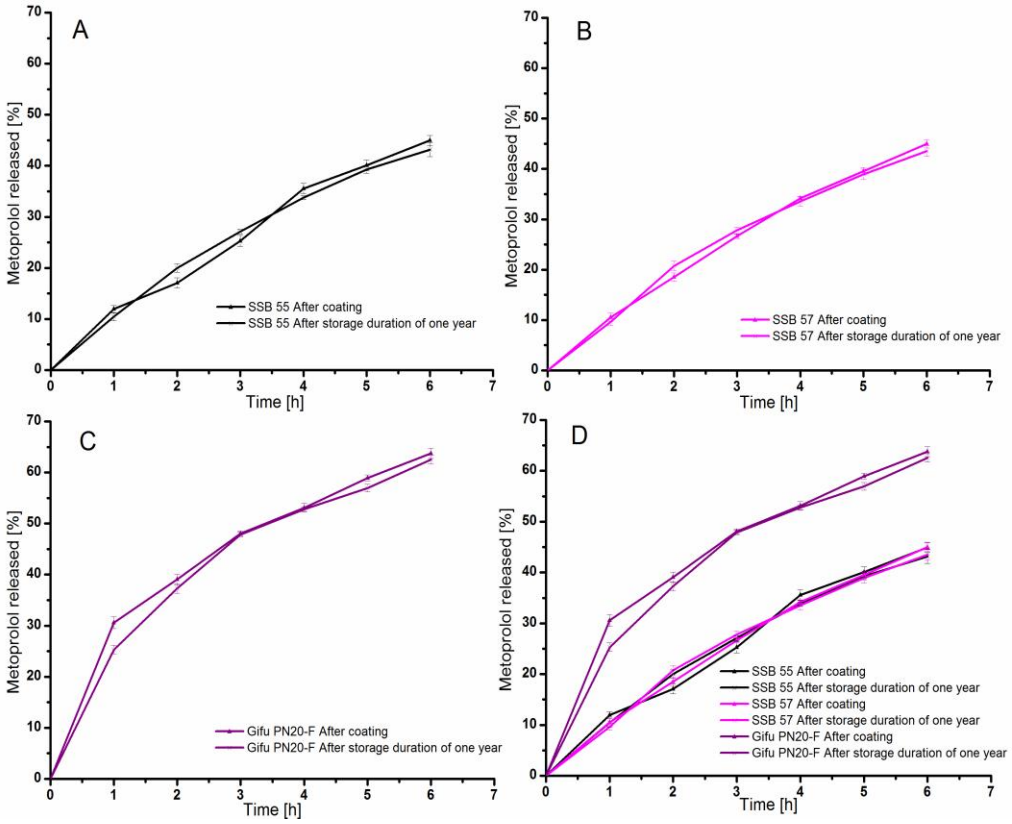


Figure 29: Dissolution profiles of metoprolol tartrate pellets coated with three different shellac types (A) SSB 55, (B) SSB 57, (C) Gifu PN20-F and (D) the three types in one plot. The dissolution was carried out at pH 6.8 for six hours, one day after coating and after storage duration of one year.Values presented are means of six observations, while vertical bars donate standard deviation (S D).

4.10.1.2. Coating reproducibility

For three shellac types (SSB 55, SSB 57 and Gifu PN20-F) the coating process was repeated using the same shellac types after one year from the first coating. The dissolution results for the two coatings are shown in Figure 30.

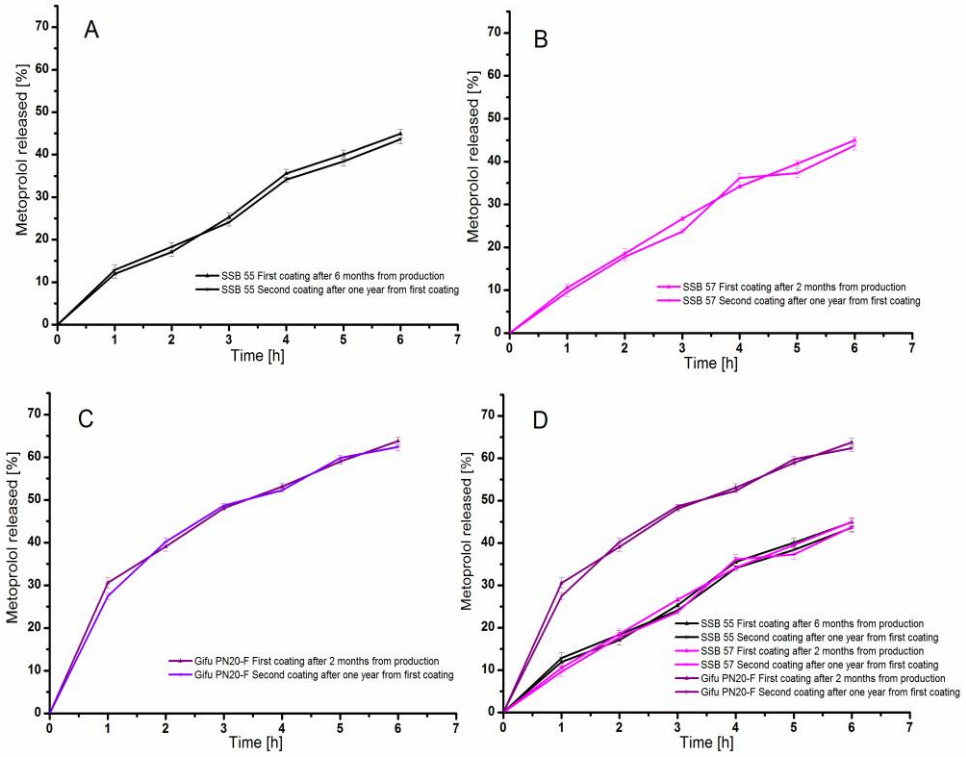


Figure 30: Dissolution profiles of metoprolol tartrate pellets coated with three different shellac types. The coating processes were repeated after one year from the first coating and the dissolution carried out at pH 6.8 for six hours. (A) SSB 55, (B) SSB 57, (C) Gifu PN20-F and (D) the three types in one plot. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

4.10.2. Stability for ready for use shellac solutions

Two aqueous ready for use shellac solutions based on Bysakhi-Ber shellac type, AQUALACCA 25 and SSB AQUAGOLD were used. AQUALACCA 25 with labeled shelf-life for 6 months after date of production and SSB AQUAGOLD with labeled shelf-life for one year. The coating processes for metoprolol tartrate pellets were done using AQUALACCA 25 solution 5 days old (0 time), 4 months old and after 8 months old, while for the SSB AQUAGOLD it was done by using 4 months old solution, 8 months and 12 months old solution.

The dissolution results showed no significant changes between identical but different aged solutions and between the two shellac solutions AQUALACCA 25 and SSB AQUAGOLD (Table 15). Release profiles of the different ages AQUALACCA 25 and SSB AQUAGOLD solutions at pH 6.8, 7.2 and 7.4 are shown in Figures 31 and 32 respectively.

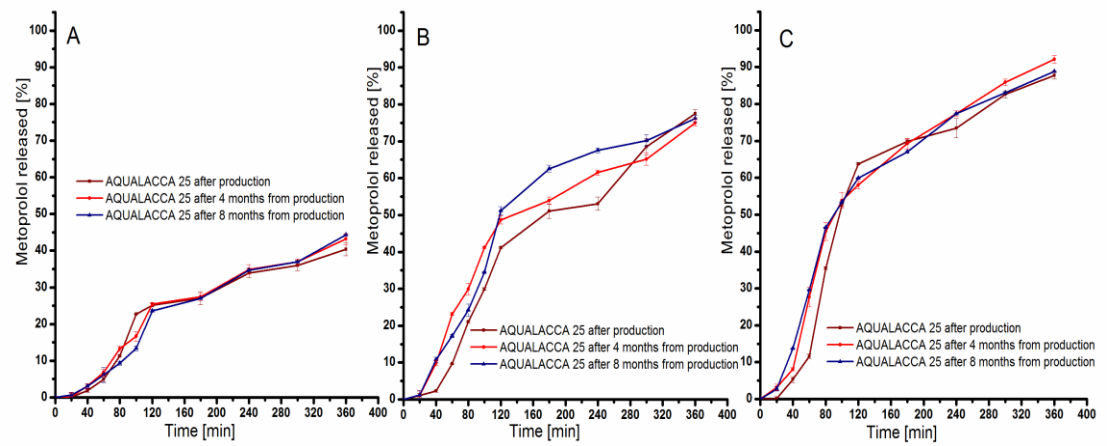


Figure 31: Metoprolol released from pellets coated with 20% w/w ready for use shellac solution AQUALACCA 25 (0, 4 and 8 months old) at different pH values. (A) at pH 6.8, (B) at pH 7.2 and (C) at pH 7.4. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

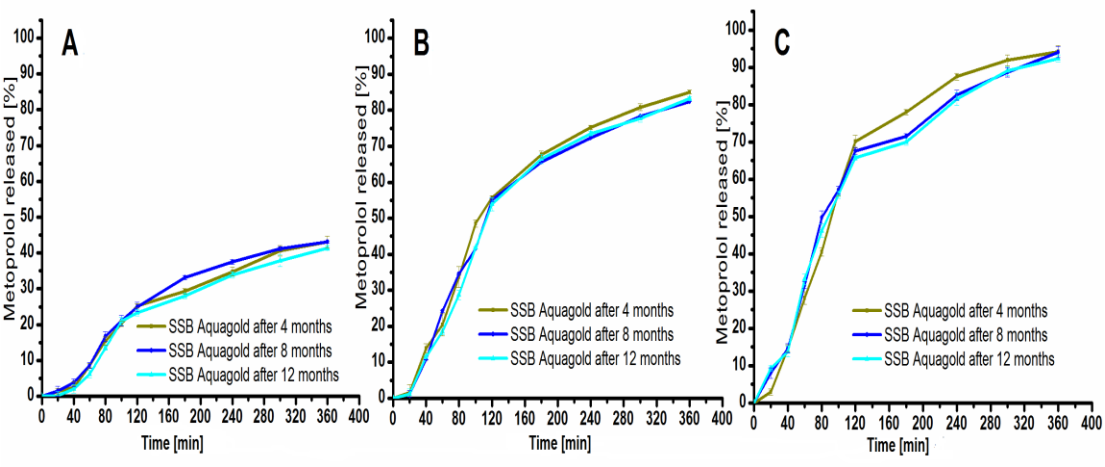


Figure 32: Metoprolol released from pellets coated with 20% w/w ready for use shellac solution SSB AQUAGOLD (4, 8 and 12 months old) at different pH values. (A) at pH 6.8, (B) at pH 7.2 and (C) at pH 7.4. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

Table 15: Similarity factors f_2 of metoprolol dissolution from pellets coated with two ready for use shellac solutions. AQUALACCA 25 (0, 4 and 8 months old) and SSB AQUAGOLD (4, 8 and 12 months old), for the coating level 20% w/w at pH values 6.8, 7.2 and 7.4.

Shellac solution	AQUALACCA 25		SSB AQUAGOLD	
Dissolution pH	After 4 months	After 8 month	After 8 month	After 12 months
6.8	79.43	72.58	86.10	86.10
7.2	55.39	55.26	73.88	73.84
7.4	58.34	56.07	66.73	65.47

Table 16: Mean dissolution times of metoprolol dissolution from pellets coated with two ready for use shellac solutions, AQUALACCA 25 (0, 4 and 8 months old) and SSB AQUAGOLD (4, 8 and 12 months old), for the coating level 20% w/w at pH values 6.8, 7.2 and 7.4.

Shellac solution	AQUALACCA 25			SSB AQUAGOLD		
Dissolution pH	0 month	4 months	8 month	4 months	8 month	12 months
6.8	2.35 ± 0.03	2.50 ± 0.01	2.57 ± 0.02	2.37 ± 0.03	2.31 ± 0.02	2.13 ± 0.01
7.2	2.64 ± 0.02	2.19 ± 0.02	2.04± 0.01	1.97 ± 0.01	2.08 ± 0.02	2.05 ± 0.02
7.4	2.04 ± 0.01	2.0 5± 0.01	1.94 ± 0.01	1.85 ± 0.03	1.77 ± 0.02	1.87 ± 0.01

4.10.3. Stability for enteric release formulas

A stability test was conducted by storing the enteric coated metoprolol tartrate pellets with the two enteric coating formulas (Shellac: HPMC: Glycerol, in ratios of 62.5:22.5:15 and shellac: HPC: Glycerol, in the ratios of 62.5:22.5:15) at room temperature (22–25°C), for one year followed by testing metoprolol dissolution.

The dissolution results showed that less than 5% was released after two hours at pH 1.2 for 25% w/w coatings and more than 80% was released after one hour at pH 6.8, which complies with the USP requirements for enteric-coated formulations (less than 10% dissolved in 2 h in simulated gastric medium and not less than 80% dissolved after one hour in simulated intestinal medium). The results are shown in Figure 33.

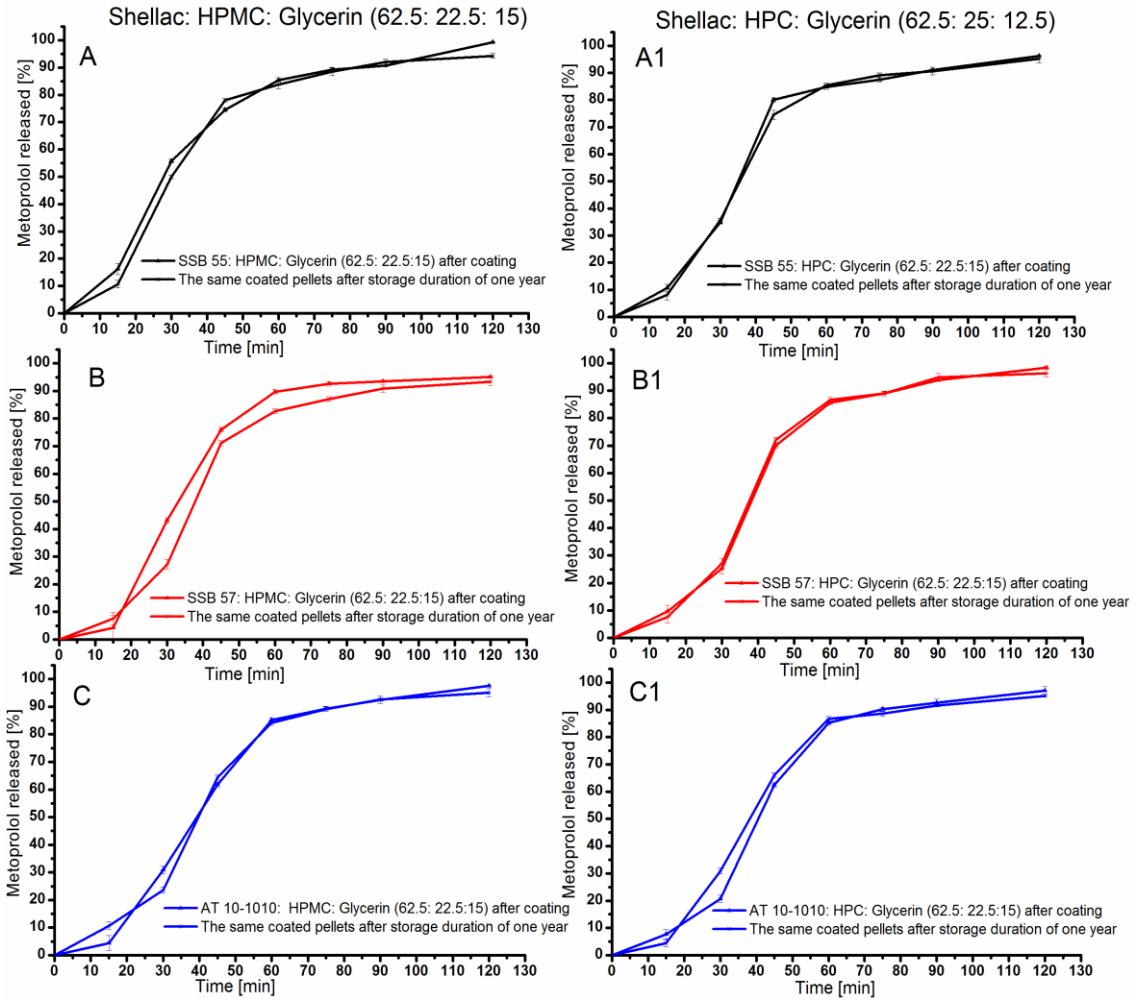


Figure 33: Dissolution profiles of metoprolol tartrate pellets coated with 20% w/w enteric formula (A, B and C) containing Shellac: HPMC: Glycerol (62.5:22.5:15) after coating and after storage duration of one year. (A1, B1 and C1) containing Shellac: HPC: Glycerol in ratios of 62.5:25.5:12.5 after coating and after storage duration of one year. Three types of shellac were used. The dissolution was carried out at pH 6.8. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

4.10.4. Stability for colon targeting formula

The stability tests for colon targeting formulas were performed just like for enteric release formulas. The coated pellets were kept at room temperature (22–25°C), for one year followed by testing metoprolol dissolution. The formulas containing HPMC showed slightly lower release at pH 7.2, whilst that containing HPC showed no considerable change in the release after one year as shown in Figure 34.

Although shellac coatings have been used as enteric coatings against gastric acidic media and provide sustained release products, there has been concern that film hardening could occur as a function of time and lead to a reduction in drug release rate. Reproducible release rates were obtained when shellac coated pellets were stored at room temperature. Stability data on metoprolol tartrate pellets stored at room temperature over a period of 12 months indicated that shellac/Glycerol coatings containing different amounts of HPMC or HPC are stable during storage at room temperature (22–25°C) and did not show large deviations in dissolution profiles.

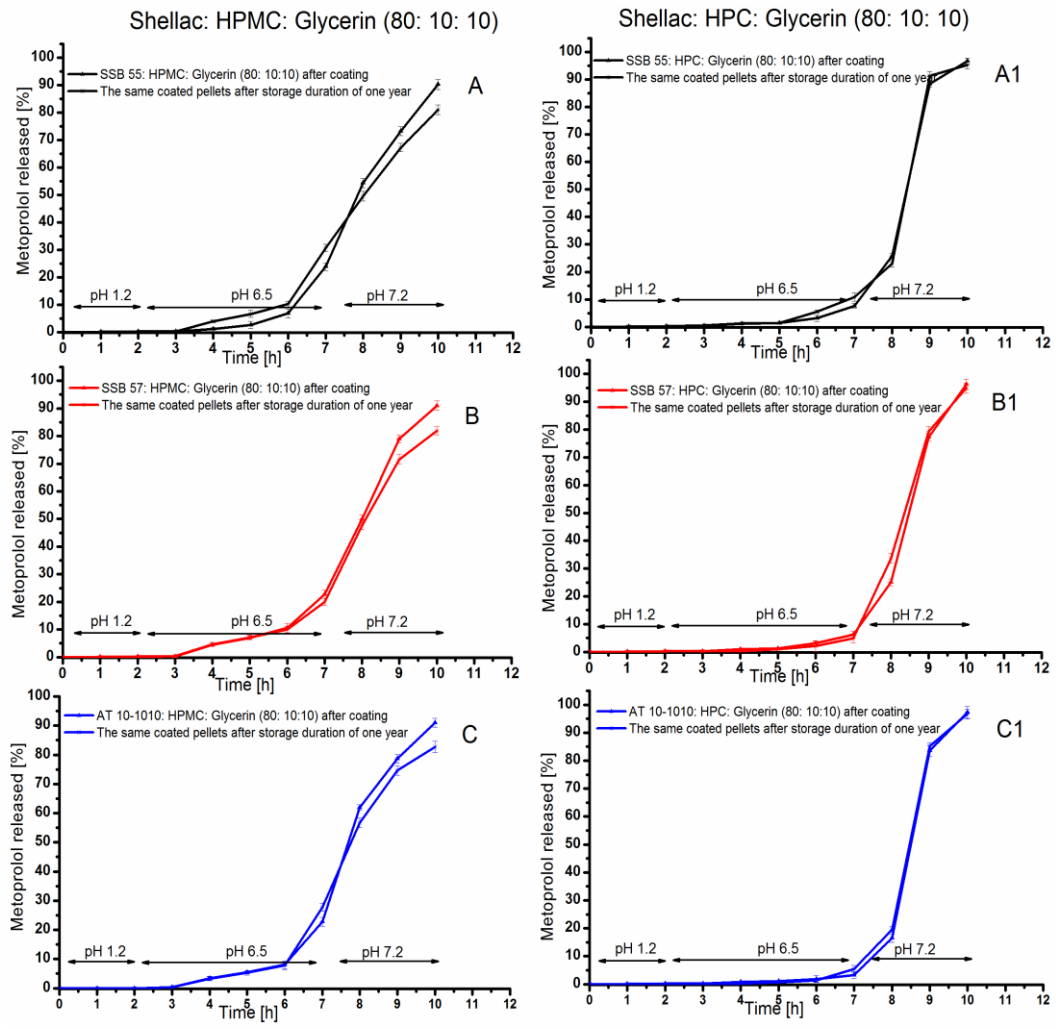


Figure 34: Dissolution profiles of metoprolol tartrate pellets coated with 30% w/w colon targeting formulas containing Shellac: Water soluble polymers: Glycerol (80:10.5:10) directly after coating and after storage duration of one year. The dissolution was carried out at pH 1.2 for two hours, at pH 6.5 for 5 hours and at pH 7.2 for 3 hours. Three types of shellac were used. (A, B &C) 30% w/w coating level using HPMC as the water soluble polymer, while (A1, B1 &C1) are 30% w/w coating level using HPC as the water soluble polymer. Values presented are means of six observations, while vertical bars donate standard deviation (S D).

5. Discussion

An acceptable color is an important parameter in pharmaceutical shellac coatings as it improves the appearance and facilitates product identification [219-221]. The color results are inline with *Buch et al.*, who reported that the color number can be used to differentiate between the different types of shellac. Colorants are mainly used to impart a distinctive appearance to pharmaceutical dosage forms [222]. In shellac coatings there is no need for the addition of coloring agents, since the shellac imparts color. Shellac is natural material and is accepted as food grade, thus making it safe, also saves the cost of adding a colorant.

Shellac thermal behavior (Tg) can serve as indicator for the level of degradation since outdated shellac shows an increase in the glass transition temperature [72]. The grades investigated here were not negatively affected by age (SSB 55), whilst small differences were observed between the different brands. This is attributed to the different sources of the tested grades. The method of purification affects substantially the thermal behavior of shellac. This was shown when two grades from the same source were purified by different processes. SSB 55 and AT 10-1010 are from the same host tree but they differ in Tg by more than 6 °C, most probably due to the method of purification.

The acid value (AV) is found to be a good indicator for the quality of the shellac raw material. During storage a slow polymerization takes place, resulting in a decrease in the AV. Therefore, the quality of the product can be estimated by comparison with the manufacturers certificate of analysis [72]. No significant differences in AV were seen between the tested brands, either from the same source or from different sources. This may be attributed to the fact that, all these brands were prepared by the solvent extraction method. These findings are agree with Buch et al [57] who reported no differences in AV between different shellac grades. They do not agree with data reported by Farag and Leopold[72], where the AV decreased during storage. The difference may be due to the storage conditions, where the tested brands in this study

were kept in a cool place and also the difference in the age of the shellac which was less than two years in this study.

Dissolution behavior of the coated pellets showed enteric resistance according to USP/Ph. Eur. for all shellac type coating. Shellac coatings of 20% w/w and higher, resulted in complete enteric resistance.

Drug release from shellac coated pellets, was not a result of shellac dissolution and subsequent liberation of the drug but rather of swelling of the shellac film coat followed by metoprolol diffusion across the coating layer as reported by Farag and Leopold [197]. Since film integrity was proven in the dissolution studies at pH 1.2, the drug flux through the coating film layer may be described by Fick's first law of diffusion [72, 171, 197, 223].

Drug released from coatings of 20% w/w was slightly higher than that from 25% w/w coatings, as it is inversely proportional to the thickness of the coating layer. Differences in drug released at the same coating levels from the pellet were mainly due to differences in the permeability coefficient of the coating layers and thus to the differences in the shellac types.

The mean dissolution time (MDT); is a parameter used for comparing the formulations. It is calculated from the amount of drug released at various times to the total cumulative drug released [224]. Shellac AT 10-1010 which showed the highest MDT among the tested brands, has the slowest release rate over all the shellac tested brands, whilst Gifu PN20-F has the fastest release rate. The difference may be explained based on physicochemical principles. Many basic functions of particles depend on their size and smaller particles adhere to each other more easily. On the other hand, the film formed from larger particles, may consist of larger voids between the particles which enhances swelling and drug diffusivity. This may be the reason that why Gifu PN-20 showed a faster release compared to the other shellac types.

In addition to the known physicochemical characteristics of shellac, its acid value, glass transition temperature and color number which are the main characteristics for

differentiation of shellac today, the molecular size of the shellac has also an important influence on the functional properties of shellac films. Shellac from Thai origin (Gifu PN20-F) showed a larger molecular size, while shellac from Kushmi origin (SSB 55 and AT 10-1010) showed smaller molecular size and shellac from Bysakhi-Ber (SSB 57), showed molecular size larger than that of Kushmi origins (SSB 55 and AT 10-1010) and smaller than that from Thai origin (Gifu PN20-F).

Besides the various seedlac types, the influence of different activated carbons and processing parameters during solvent extraction of the shellac may be important, so that grades from the same origin (seedlac type), may show different release properties.

In addition, the age of shellac may have an effect on its release properties. It has been reported that drug released from new shellac grade is faster and more complete than from old shellac grades of the same type [72]. This is not obvious from the present study and may be due to the fact that the shellac samples in the present study were not remarkably different in their age.

Aqueous shellac solutions are prepared by dissolving shellac in demineralised water with ammonium carbonate or ammonium bicarbonate added under stirring and heating. At higher temperatures (40 - 50 ºC) the formation of CO_2 and NH_4 occurs since both compounds are volatile and excessive base, which is not used for the ammonium salt formation of shellac, evaporates from the solution. The pH of the clear shellac solution is preferable in the range of 7.3 - 7.5 to avoid hydrolysis of the OH group of shellac at higher pH values [59].

For ready for use aqueous shellac solutions, pH measurements indicate that older batches have a lower pH than the new ones. This may be due to the fact that there is some evaporation of CO_2 and NH_3 from the ammonia used in preparation of these solutions from the bottles, which then leads to the decrease in the pH of the shellac solution with time. The shelf life given by the manufacturer is 12 months and the specification for the pH in the certificate of analysis is 7.3 ± 0.2. The effect of the pH becomes apparent when the dissolution is carried out low pH 6.8 (pH is lower than the

pH of the shellac solution). In that case the release from the pellets coated with the old shellac solution was significantly lower than that obtained when using shellac solution in accordance with the specifications

From the results of the mean dissolution time (MDT) for the tested ready for use aqueous shellac solutions (SSB AQUAGOLD), the old solution with low pH showed the highest MDT for both coating levels at pH 6.8 and the lowest MDT at pH 7.4 among the tested solutions. The MDT for the 25% w/w coatings are higher than those obtained by 20% w/w coatings in most of the cases. This is due to the thickness of the coat since thicker coats need more time to dissolve [72, 132, 225]. At pH 7.4, the MDT for the two coating levels are almost the same. Here the effect of solubility of the coating film is higher than that of the thickness of the film. As the shellac begins to dissolve at pH $\geq$ 7.2 pores may be formed in the coating film. In this case the release of drug through the film does not depend on the thickness of the coating film. Furthermore, the thickness of the coating film is decreased and the dissolution of the coated pellets is increased.

The incorporation of HPMC, CMC and HPC into the shellac films resulted in an increase in the percent of elongation at break and a decrease in the elastic modulus. The addition of the plasticizer (Glycerol) resulted in a decrease in the elastic modulus of shellac films, whereas the elongation at break was increased. This because obvious when comparing the ratio between HPC (the best mechanical properties water soluble polymer used) and Glycerol, in the shellac films that contains 75% w/w shellac. When the concentration of Glycerol is increased to about 12.5% w/w and that of HPC is decreased, the elongation at break increases with a decrease in the elastic modulus. Thus the use of Glycerol (plasticizer) offer better mechanical properties than increasing the concentration of the water soluble polymer.

The incorporation of CMC to shellac showed a drastic drop in the gloss of shellac films and the incorporation of 50% CMC to shellac dropped the gloss from more than 185 GU to less than 15 GU. Gum arabic also decreases the gloss of the shellac film and there is a direct proportion between the concentration of the gum and the drop in the

gloss. The incorporation of 50% gum in the shellac decreased the gloss by 50%. HPMC, HPC and Pullulan® left the gloss rather unaffected.

Water-soluble polymers may be added to shellac to aid in controlling its release characteristics and to provide channels or pores in the film. HPMC & HPC were used for this application. The release patterns can be modified by addition of different amounts either of the soluble polymer or of the shellac/plasticizer ratio. Figure 24 shows the effect of incorporation of a constant amount of HPMC and different ratios of shellac/plasticizer. Different release rates were obtained with the same coating level (25% w/w) with lower release rates from shellac coat when a higher percentage of shellac in the spraying solution was used.

A quantitative model describing the mechanism and kinetics of drug release from enteric-coated tablets was developed by Ozturk et al., who stated that the dissolution rate for drug release from enteric coating is dependent on several parameters, from which the polymer pK_a and ionization are most important. Polymers used for enteric coatings are weak acids containing carboxyl groups in a substantial proportion of their monomeric units [27].

Shellac is often used as an enteric coating polymer, as it possesses carboxylic acid groups that are un-ionized in the relatively low pH of the stomach (normally about 1.5 to 4.5), but ionize and thus repel one another as the pH rises when the coating system enters the small intestine, thus causing coating disruption and release of the drug across the diffusion layer [27, 226]. The release velocity can be decreased during dissolution, by increasing the concentration of shellac in the coat. In this case a zero-order release profile may be obtained as seen in Figure 24.

Application of a thicker coat causes a delay in drug release in the small intestine and slows down drug release, which is both pH and time controlled. This time-controlled drug release may be retarded by additional 3–4 hours. This insures drug delivery to be colon specific. For the preparation of such tailor- made formulations, the selection of a polymer with a suitable coating level is crucial [26, 227]. Shellac is pH sensitive in that

it dissolves at pH higher than 7.2 and variations in its coating thickness can facilitate drug delivery to the terminal ileum, proximal or distal colon [228-229].

Pronounced differences were observed in the drug release from the pellets coated with different coating levels at pH 6.5. By increasing the shellac concentration in the coat, drug release was decreased. At pH 7.2 a rapid drug release was observed, which became more than 90% after 3 hours. The typical drug release of shellac can be explained by the fact that at a lower shellac concentration in the coat and after introduction into a medium of pH 6.5, there is a slow solubilization of shellac whereby channels are formed within the film through which the drug diffuses [26]. However, when the coat mass was increased, due to the slow solubilization of this polymer, formation of channels through thicker coat took more time, which in this case was 4–5 hours. The ability of shellac to resist drug release for 4–5 hours, followed by a rather rapid drug release, can be exploited for delivery of various drug molecules to the large intestine [26].

Although shellac coatings have been used as enteric coatings against gastric acidic media and provide sustained release products, there has been concern that film hardening could occur as a function of time and lead to a reduction in drug release rate. Reproducible release rates were obtained when shellac coated pellets were stored at room temperature. Stability data on metoprolol tartrate pellets stored at room temperature over a period of 12 months indicated that shellac/Glycerol coatings containing different amounts of HPMC or HPC are stable during storage at room temperature (22–25°C) and did not show significant differences in dissolution profiles ($f_2 > 50$).

From the results obtained for evaluation of alcohol consumption on drug release from shellac coated pellets, the three shellac type coatings failed to withstand dissolution in alcohol concentrations and more than 10% was released after 2 hours. Thus care must be taken when shellac coated dosage form intended for enteric or MR formulations are co-administered with alcoholic beverages contains more than 10% v/v alcohol. This may cause destruction of the drug by gastric enzymes or by the acidity of the gastric

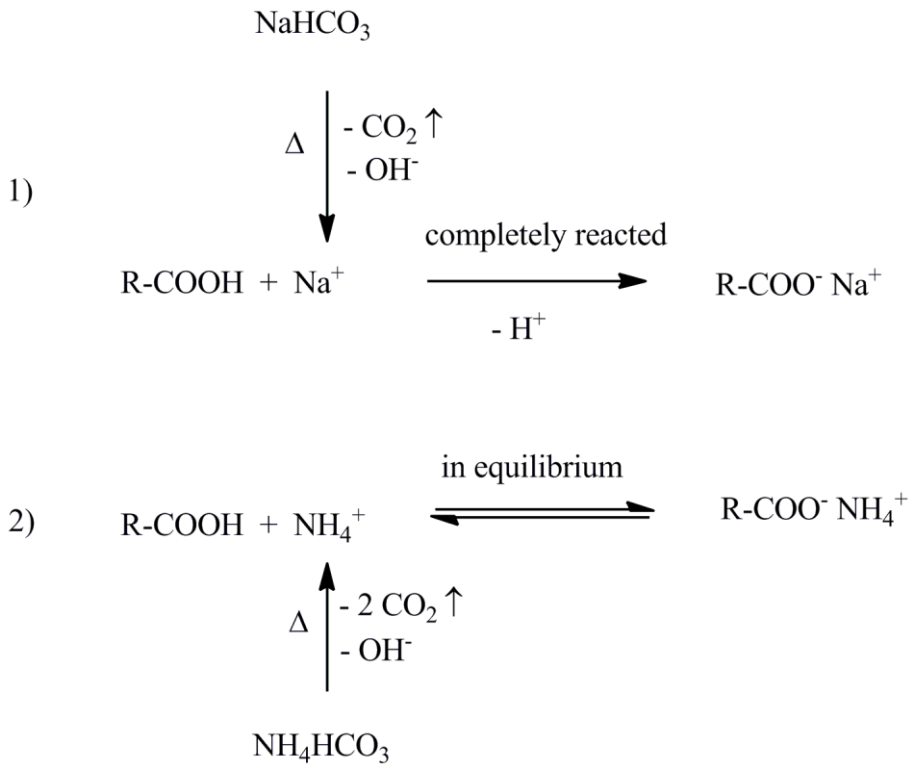
fluids for gastric sensitive drugs, nausea and vomiting when the drug irritates the gastric mucosa, thus impaired the delivery of the drug to its local site of action in the intestine and alter the delayed release property when the coat is applied for delayed release action. At lower alcohol concentrations of 5% v/v alcohol, the % released after 2 hours from the three shellac type coatings was found to be less than 3%. Thus shellac coated dosage forms can be co-administered with alcohol beverages containing ≤ 5% with no effect of alcohol on the shellac coat.

For 10% v/v alcohol concentration, the % released after 2 hours from the pellets coated with shellac types Bysakhi-Ber (SSB 57) and (Kushmi SSB 55) was less than 5%, which is acceptable according to the USP requirements for enteric-coated formulation. However, pellets coated with shellac based on Thai type (Gifu PN20-F) released more than 10% and may fail to pass the USP requirements for enteric-coated formulations when co-administered with alcoholic beverages containing more than 10% v/v alcohol. Here the shellac type used for coating affects the drug released and different shellac types differ in their solubility in alcohol. Hence selection of the shellac type is also important.

The study data indicates that this modified in vitro DDA assay, is adequate to assess the potential of ethanol to alter the rate of drug release from shellac coated dosage forms. In this case the nature of shellac (solubility in alcohol) suggests the potential rather than the rules used by the OGD for MR drug products.

Stability results in this study, are in agreement with Penning's findings who stated that the drug release of the pellets coated with the aqueous shellac solution did not change and storage for one year had no influence on drug release [59]. Also the results are complying with Qussi and Suess findings, who indicated that shellac/plasticizer coatings containing different amounts of PVA or HPMC are stable during storage at room temperature (22–25°C) and did not show large deviations in dissolution profiles [175].

For the two shellac salts, sodium bicarbonate reacts with the carboxylic groups of shellac and forms the sodium salt of shellac by an ionic bond, leading to complete formation of sodium salt, while for NH_4HCO_3 the reaction with the carboxylic groups of shellac leads to partial and not complete formation of the ammonium salt of shellac and some of the shellac remains in the acid form as the dissociation needs an equilibrium and more time than when sodium is used instead. The formations of the two salts are shown in the equations below:



The sodium salt of shellac is more basic than the ammonium salt of shellac and also more water soluble. These may be that why pellets coated with shellac solution prepared by sodium bicarbonate, showed faster release than the pellets coated with shellac solutions prepared using ammonium bicarbonate.

For shellac sodium salts, even it showed higher release than ammonium salt, these results needs to be clarify by an extra stability tests. Ammonium salts are volatile while

sodium is not volatile and by the time the effect of time on its release properties still unknown.

Pellets coated with shellac based on Thai type (Gifu PN20-F), which showed a larger molecular size than the other shellac types (SSB 55 and AT 10-1010) from Kushmi origin and SSB 57 from Bysakhi-Ber, showed a higher and faster release either using ammonium salts or sodium salts of shellac. The molecular size of shellac has a pronounced effect in that shellac types with larger molecular size show a higher and faster release. This may be the fact that at pH 7.2 which is near the dissolution pH of shellac, there is no significant difference between the two salt forms of shellac Gifu PN20-F (f_2 = 78.97)

6. Summary

Different shellac types (Bysakhi-Ber, Kushmi & Thai), all refined by the solvent extraction process, with different manufacturing dates and source of raw materials were compared in this study. The physicochemical properties of these investigated shellac types such as the Tg and color number vary to a certain extent. These differences may be partially due to the different sources of the shellac like insect species and host tree and processing parameters during solvent extraction of the shellac. The use of activated carbon resulted in production of a light-colored and lower Tg grade shellac. Pellets coated with these different types differ significantly in their drug release profiles.

Beside these differences in physicochemical properties, shellac types also differ in their molecular size, which may have the most pronounced effect on drug release from coated metoprolol tartrate pellets in that higher molecular size grades showed the fastest release of metoprolol, whilst the smaller molecular size grades showed slower release profiles. A molecular size determination should thus serve as important shellac quality attribute, a finding which has not been highlighted in the past.

Aqueous ready for use shellac solutions based on the same shellac type SSB 57 have been used. A decrease in the pH due to storage time was noticed after longer storage times, this decrease in the pH is due to evaporation of the volatile alkali from the shellac solution. If the pH is decreased, it can be overcome by addition of ammoniacal solution to adjust it to the specified range (7.3±0.2). Dissolution profiles for metoprolol tartrate pellets coated with these shellac aqueous solutions showed no significant differences in the drug released from these coated pellets at different dissolution pH values.

The incorporation of water soluble polymers (HPC and HPMC) to aqueous shellac solution was found to improve the mechanical properties and release characteristics of the films. By incorporation and modulating the amount of these water soluble polymers and the aqueous shellac, film coatings with different release properties were obtained.

Different coating formulas containing different concentrations of shellac, Glycerol and polymers were used. Formulas containing low shellac concentration and high concentrations of soluble polymers were found suitable for enteric coatings, while high concentrations of shellac and low concentrations of soluble polymers were found to be suitable for colon targeting. After one year storage at room temperature (22–25°C), dissolution results showed that drug released from the coated pellets was not changed.

The study data indicate that the modified in vitro dose dumping in alcohol (DDA) assay, can adequately assess the potential of ethanol to alter the rate of drug release from shellac coated dosage forms. In this case the nature of shellac (solubility in alcohol) suggests the potential rather than the rules used by the OGD for MR drug products. Shellac coated dosage forms can be co-administered with alcohol beverages containing ≤ 5% with no effect of alcohol on the shellac coat.

Stability data on shellac coated metoprolol tartrate pellets stored at room temperature over a period of 12 months indicated that shellac coatings containing are stable during storage at room temperature (22–25°C) and did not show significant differences in dissolution profiles (f_2 >50).

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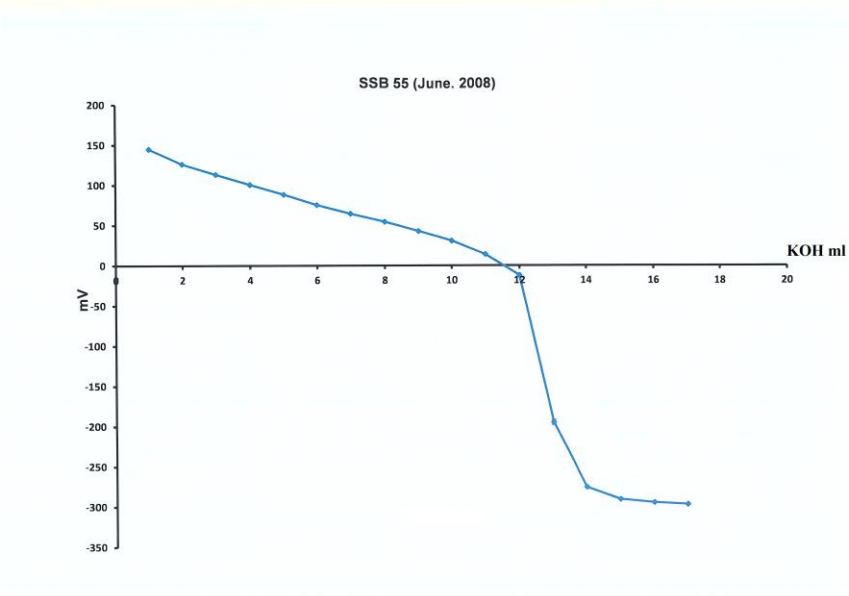
Acid Values titration curves; mill volts (mV) vs. Potassium hydroxide (KOH) in ml.

SSB 55 (June.2008)



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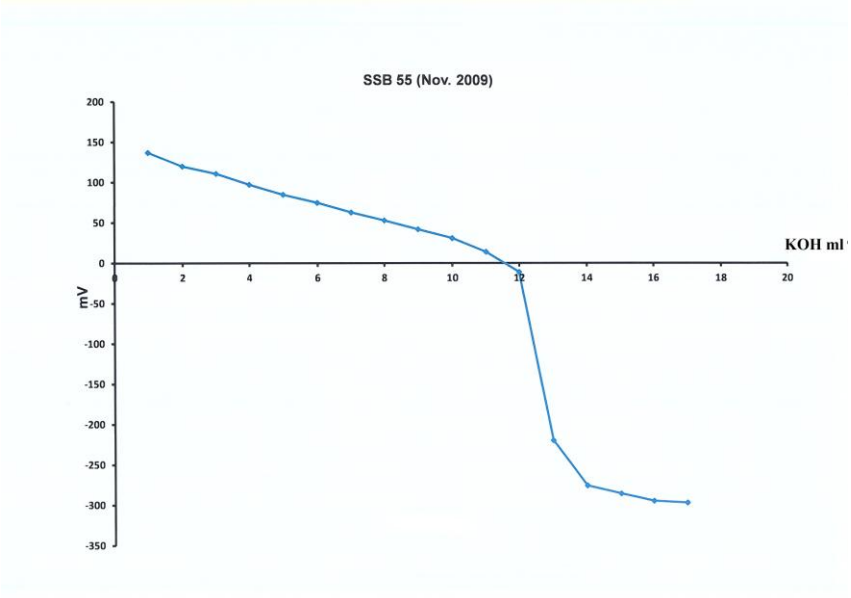

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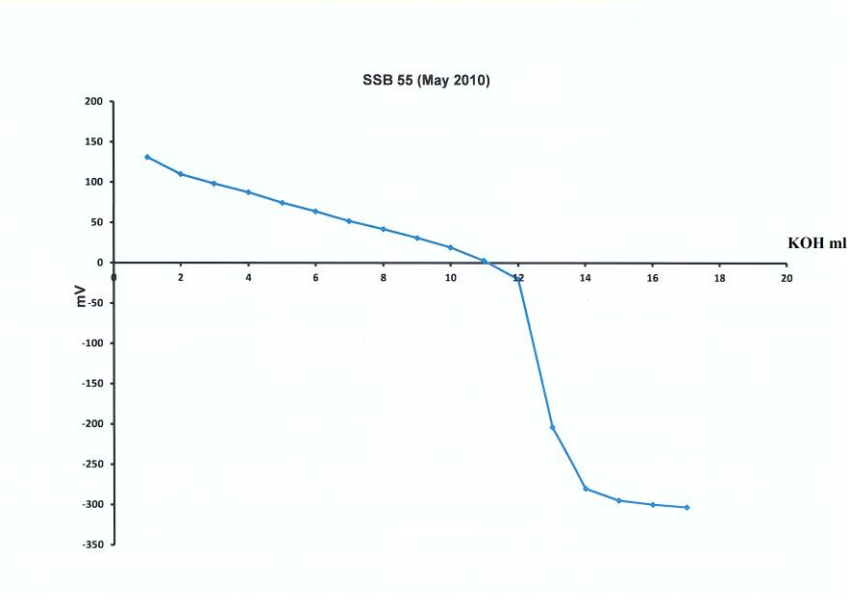

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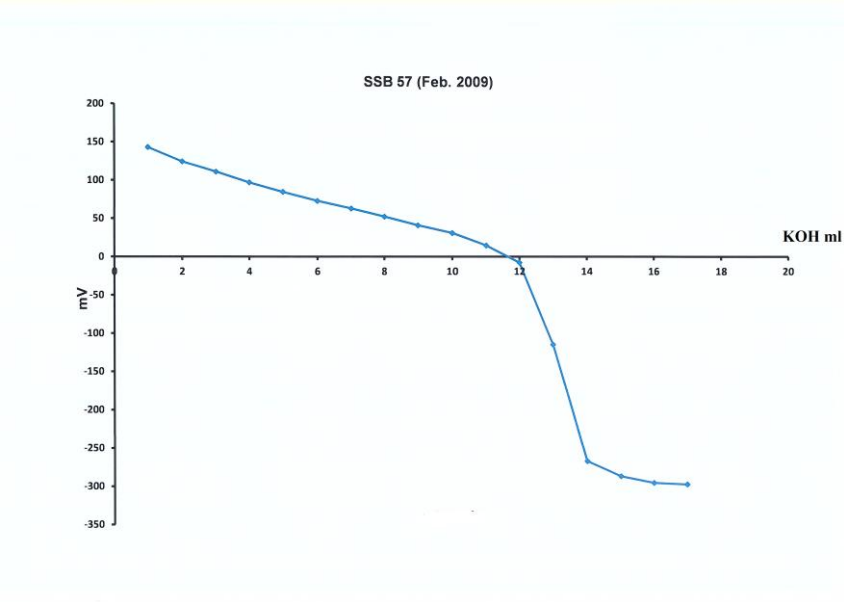

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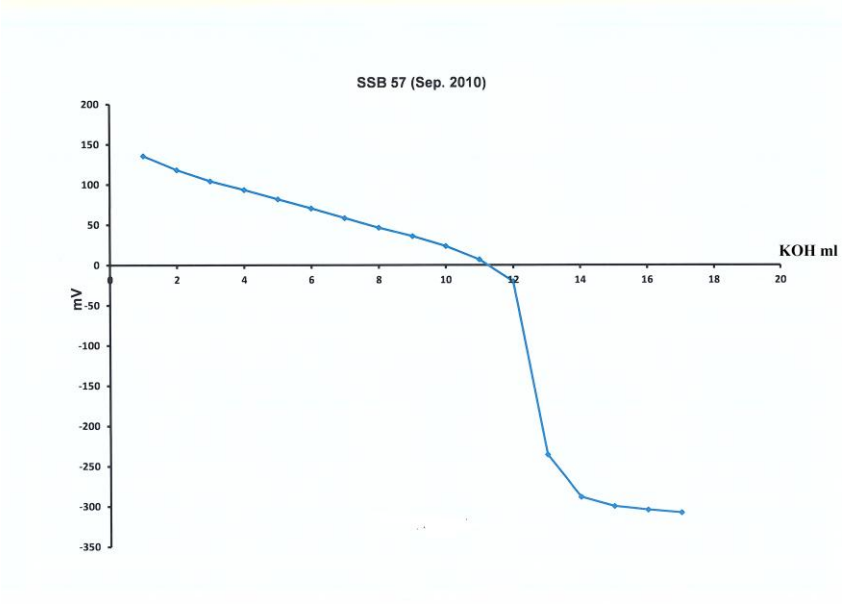
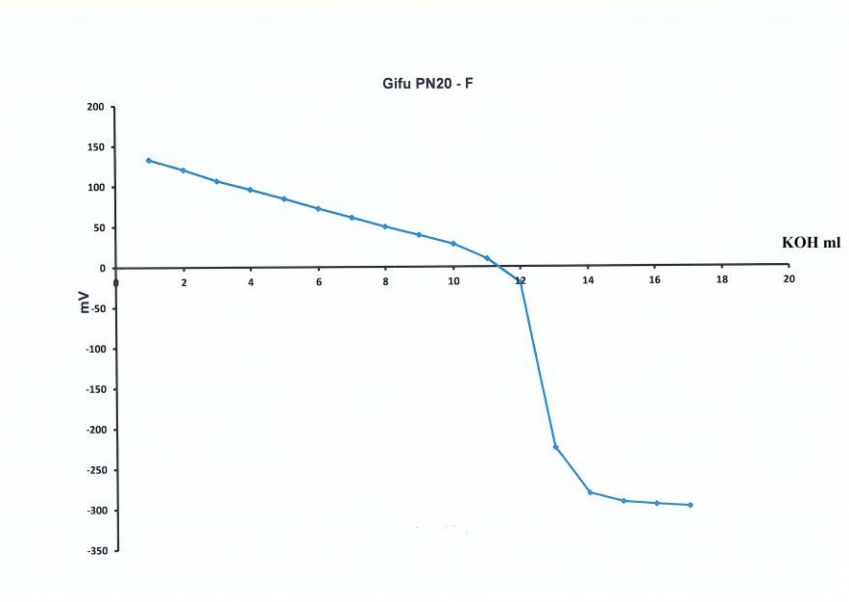
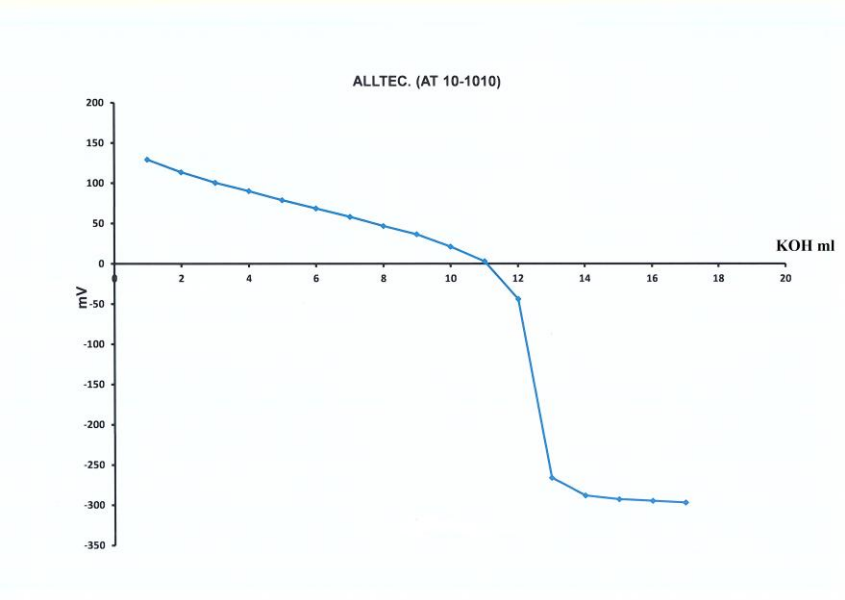


Gifu PV20-F (2010)

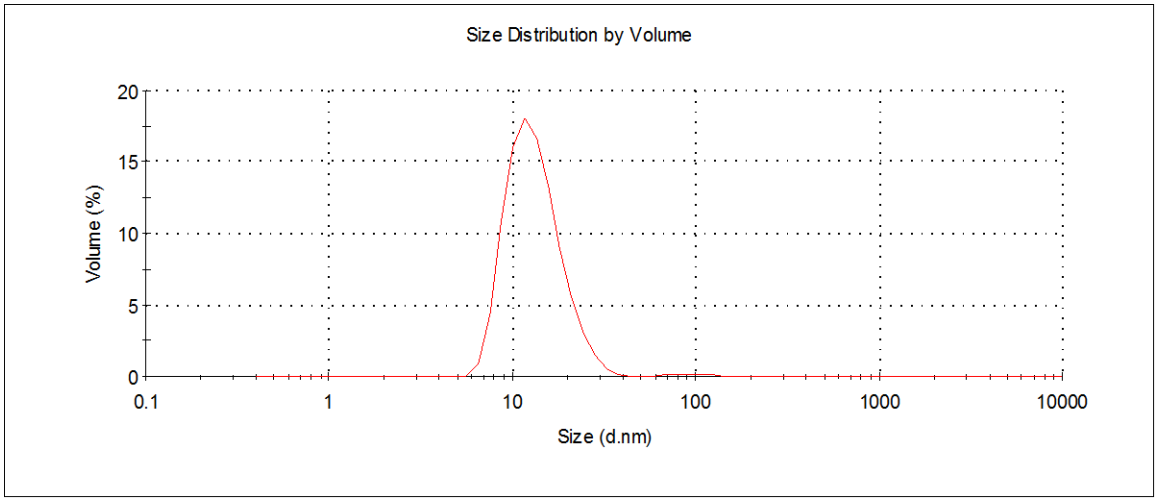


ALLTEC (AT 10-1010)



DLS Curves:

SSB 57



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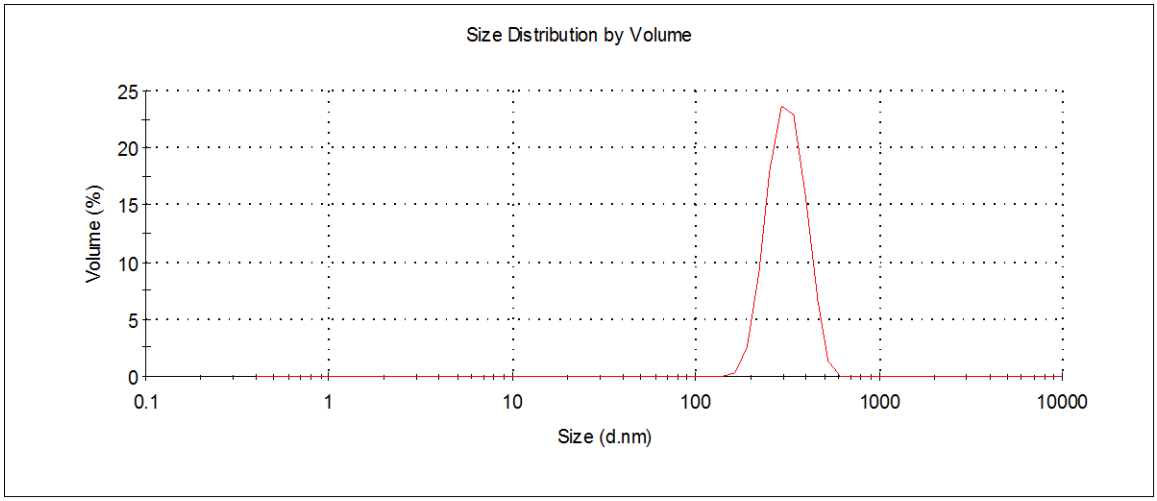

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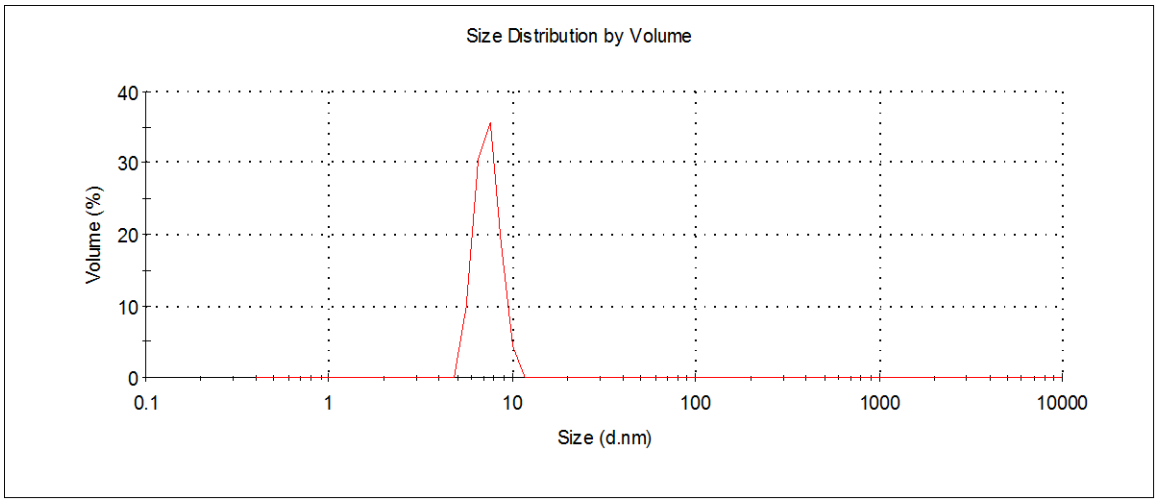

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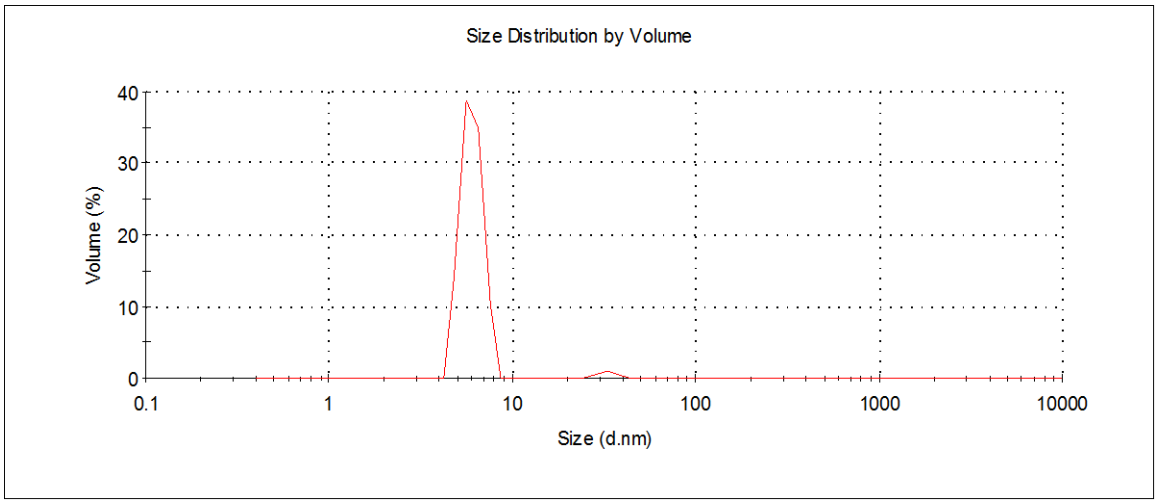

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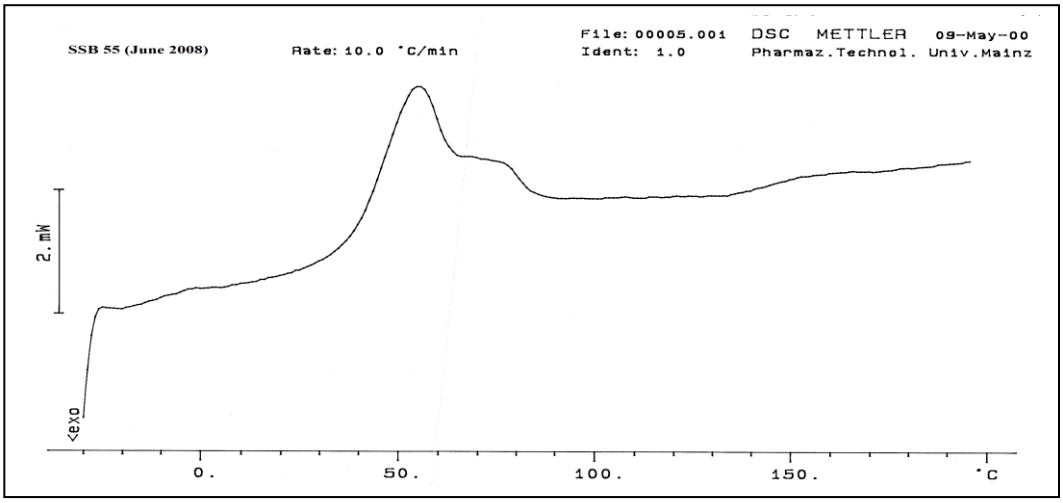

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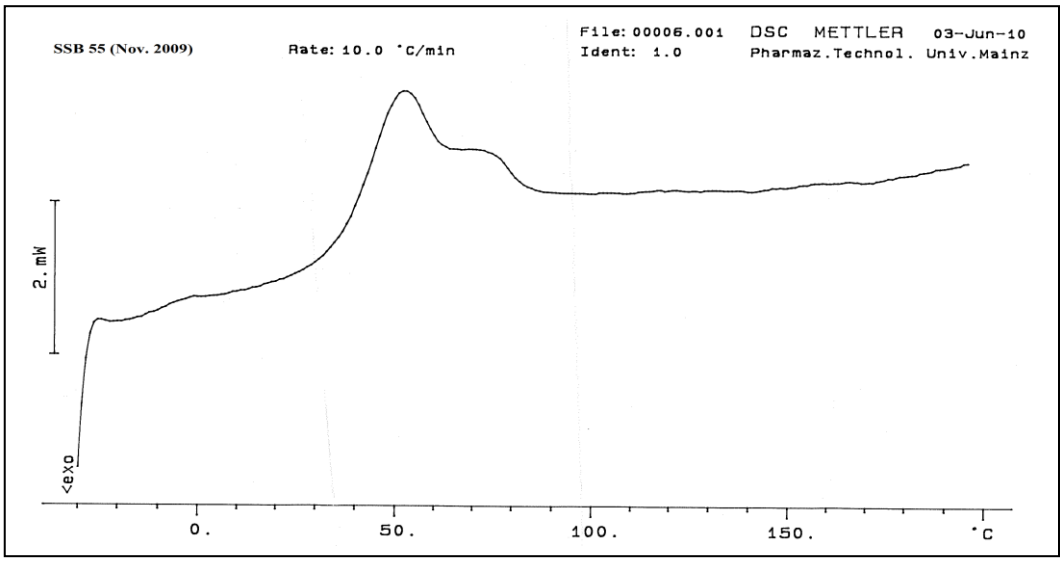

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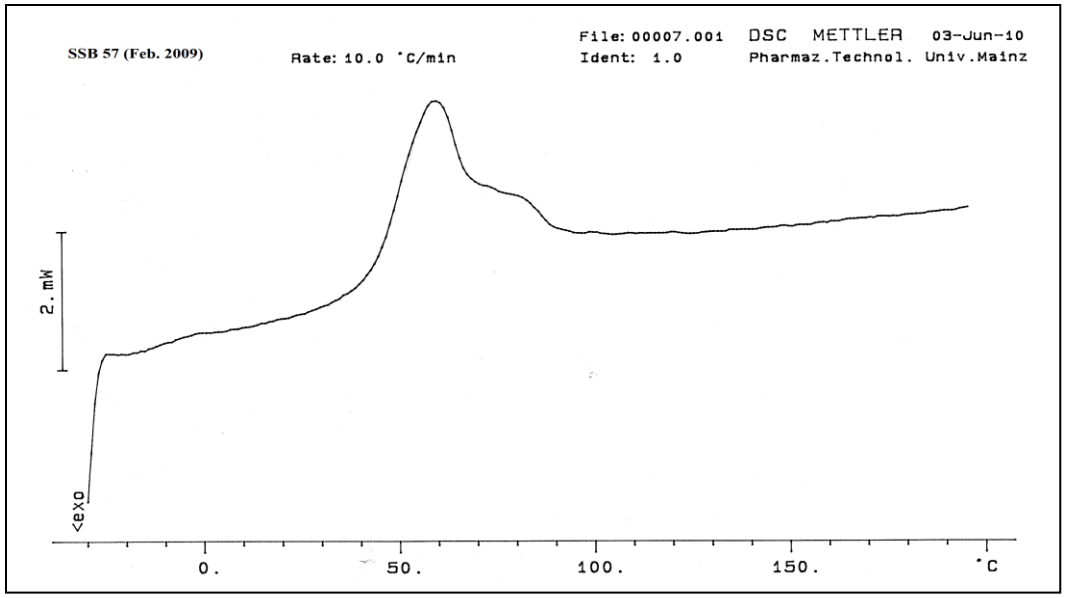

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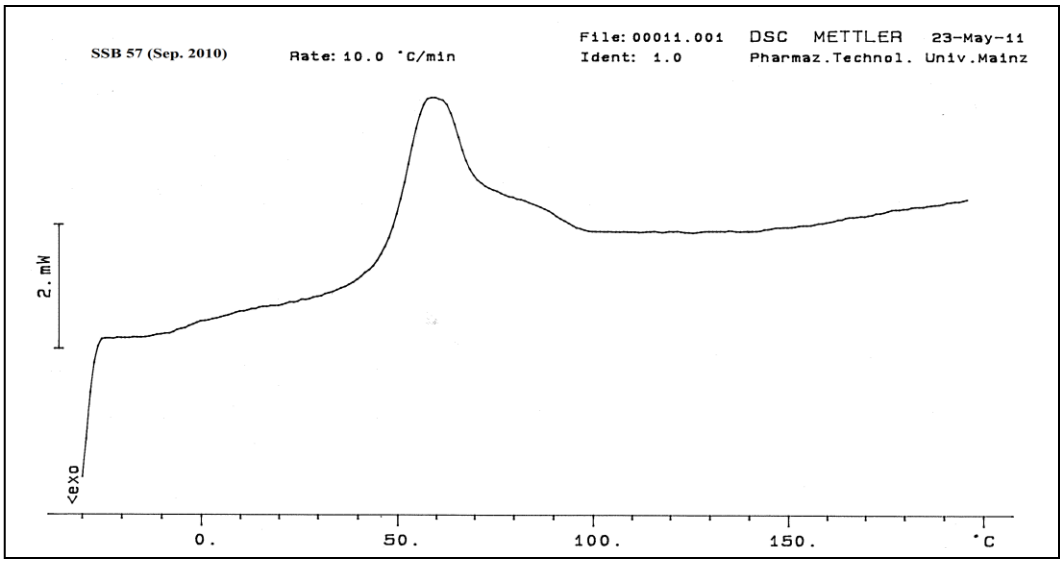

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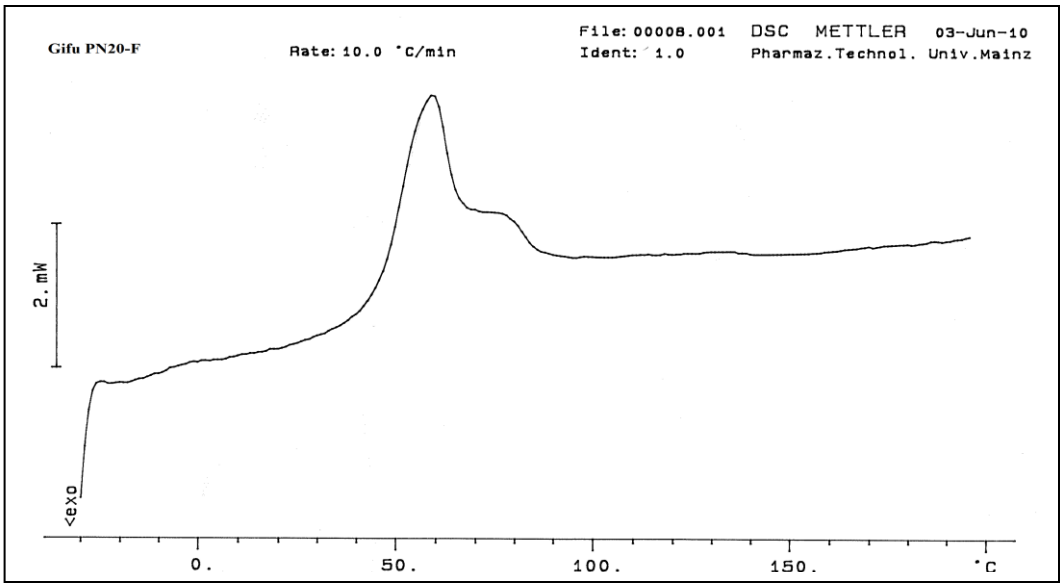

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