CHAPTER I

INTRODUCTION

Pellets dosage form is one of several methods for providing controlled release of drugs in the gastrointestinal tract. These because of they minimizes the risk of local irritation, and makes the formulation independent of the variable effects of gastric emptying with constant drug release. Controlled release pellets usually consist of a drug entrapped in a sustaining matrix or of a drug core encapsulated with a low permeability film (Harris and Ghebre-Sellassie,1989), followed by compression to tablets or filled within gelatin capsules.

For the encapsulating layer, various materials can be used and classified into water–soluble polymers such as hydroxypropyl methylcellulose and it derivatives, (Siepmann and Peppas,2001) and water-insoluble polymers such as ethylcellulose (EC), acrylate derivatives and waxes (Barthelemy et al., 1999 ; Faham et al.,2000). The use of wax seems to bring attention to many researchers, due to chemically inert with other excipients. The number of researchers have reported on the effect of wax coating generated by spray-congealing of drug/molten wax slurries (John and Becker,1968; Hamid and Becker, 1970), solvent evaporation (Shanawany,1993) or the spraying technique of hot molten wax (Achanta et al., 1997).

In this study we intended to develop controlled release DTZ HCl 90 mg/150 mg dose pellets, and coated with organic solvent-based solutions of waxes such as carnauba wax, glyceryl monostearate (GMS) and Compritol 888 ATO [®] . The suitable wax was selected, then combined with EC in proper ratios and coated by using fluidization

technique. Dissolution profiles of these formulas were conducted, and permeability coefficients were calculated. In addition, interaction of Compritol 888 ATO [®] (selected wax) and EC was also determined.

Objectives of this study

1. Prepare DTZ HCl sustained release pellets by extrusion and spheronization process.

2. Study the effect of types and amounts of wax and polymer on the release characteristic of drug from coated pellets.

3. Determine the suitable coating conditions of wax, ethylcellulose and mixture of them by fluidized bed technique.

4. Develop the 12 hours sustained release DTZ HCl capsule which meet the release requirements of USP 24 specification in term of the release behaviour including mechanism of release.

Literature Reviews

1.   Pelletization Technology (Ghebre-sellassie, 1989)

Pelletization is an agglomeration process that produces small, free flowing, spherical or semi-spherical units from fine powders or granules of bulk drug and excipients, referred to pellets. The classification of pelletization process is shown in Figure 1

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                              Pelletization
                                   |
      ┌──────────────┬─────────────┴──────────┬──────────────────┐
   agitation     compaction              layering           globulation
      |              |                       |                   |
   balling   ┌───────┴──────┐        ┌───────┴──────┐     ┌──────┴──────┐
          compression   extrusion/   powder      solution/  spray drying  spray
                        spheronization           suspension             congealing
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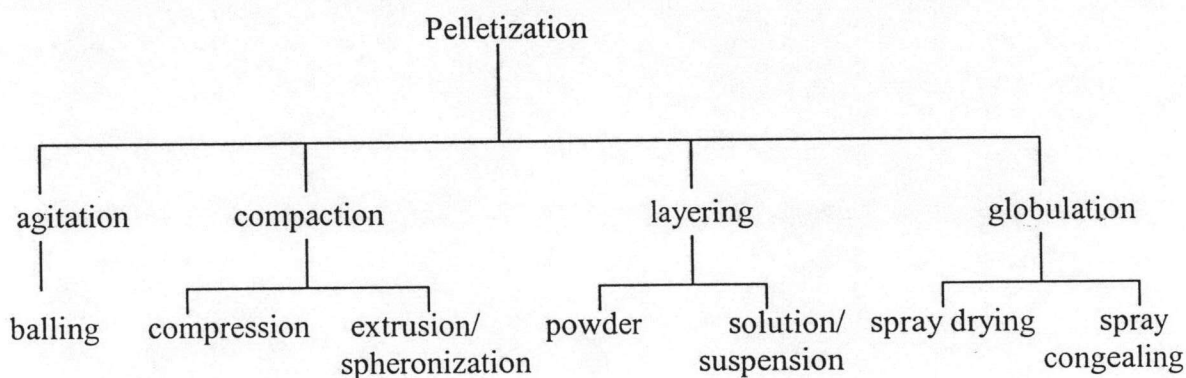
Figure 1   Classification of various pelletization processes

Extrusion and spheronization is currently one of the most techniques used to produce pharmaceutical pellets. With each production technique, pellets with specific characteristics are obtained. The preparation of spherical granules or pellets by extrusion and spheronization is now a more established technique because of its advantages over the other methods. For example, pellets forms by extrusion-spheronization show a narrow particle size distribution, low friability, uniformity of dosage unit, each of operation, suited for film coating and more sustained and better controlled drug- release profile when compared with other techniques.

The extrusion-spheronization process involves four steps:

- granulation- preparation of the wet mass

- extrusion- shaping the wet mass into cylinders extrudate

- spheronization- breaking up the extrudate and rounding off the particles into spheres

- drying- drying of the pellets

Granulation

Granulation is the first step consisting of the preparation of the wet mass by mixing of the powder blend and the granulation liquid. The most commonly used granulator is a planetary mixer although the use of high shear or sigma blade mixers has also been reported (Vervaet et al., 1995).

Extrusion

Extrusion is the second step of the process and consists of shaping the wet mass into long rods, which are more commonly termed 'extrudate'. The extrusion process, used in pharmaceutical industry, can be performed using four main classes of extruders: that is, screw, sieve and basket, roll and ram extruders. A screw extruder, as the name implies, utilizes a screw to develop the necessary pressure to force the material to flow through the uniform openings, producing uniform extrudates. In the sieve and basket extruders, the granulate is fed by screw or by gravity into the extrusion chamber, where rotating or oscillating device pushed the plastic mass through the screen. A sieve extruder, the screen positioned at the bottom of the extruder chamber, while in the case of basket type extruder the vertical walls of the extruder chamber make up the extrusion screen. The third class of

extruders are the roll extruders and these are also known as 'pellet mills'. Two types of roll extruders are available. One extruder is equipped with two contrarotating wheels, of which one or both are perforated, and the second type of roll extruder has a perforated cylinder that rotates around one or more rollers that discharge the materials to the outside of the cylinder. The final type of extruder is an experimental device called the ram extruder. The ram extruder is believed to be the oldest type of extruder and features a piston riding inside a cylinder or channel that is used to compress material and force it through an orifice on the forward stroke.

Spheronization (Merumerization is trademark of the Fuji Denki Kogzo Co., in Osaka)

The third step of the extrusion and spheronization process involves the dumping of the cylinders onto the spinning plate of the spheronizer, called the friction plate, where the extrudate is broken up into smaller cylinders with a length equal to their diameters.

The pellet-forming mechanism may be divided into two types. The different stages can be distinguished depending on the shape of the particles. The first mechanism, according to Rowe (1985) starts from a cylinder over a cylinder with roughed edges, dumbbells and elliptical particles to eventually perfect spheres (Figure 2a). Baert and Remon (1993) suggested that another mechanism might exist. In this mechanism a twisting of the cylinder occurs after the forming of cylinders with round edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have around and flat side. Due to the rotational and the frictional forces involved in the spheronization process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets (Figure 2b). The overall process usually takes less than 15 minutes.

Drying

The fourth and final step of the process is the drying of the pellets. The pellets can be dried at ambient temperature or at elevated temperature in a fluidized bed, a hot air oven or a microwave oven.

2. Air suspension coating (Jones, 1988)

In pharmaceutical solid dosage form development, many products require coating to provide release characteristics. Recent advance in film coating equipment have made it possible to coat particles ranging from crystals to tablets reproducibly. Films may be applied to provide sustained or controlled release, taste making, enteric release, improved stability, or aesthetics.

The fluidized bed is well known for its drying efficiency, as it has been used for drying and granulating for many years. It has recently been given increased interest owing to its ability to apply virtually any type of coating system (solution, suspension, emulsion, latex and hotmelt) to a wide range of particle size. Coatings can be applied to fluidized particles by a variety of techniques, including spraying from the top, from the bottom, or tangentially.

The fundamental of film coating and general process are common to the three types of fluidized bed processing. During the application of a film to the substrate; granules, pellets, or tablets, a layer of coating does not occur during a single pass through the coating zone, but droplet formation, contact, spreading, coalescence, and evaporation are occurring almost simultaneously as illustrated in Figure 3. Liquid is supplied at a low pressure and is
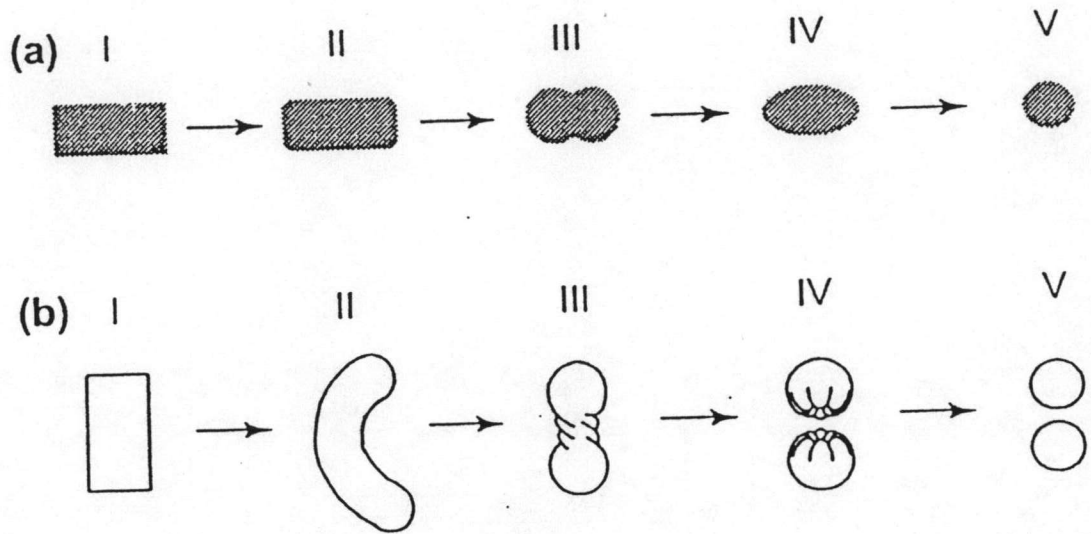
Figure 2   Pellet-forming mechanism according to: (a) Rowe; I cylinder, II cylinder with round edges, III dumb-bell, IV ellipse, V sphere (b) Baert; I cylinder, II rope, III dumb-bell, IV sphere with cavity outside, V sphere.

sheared into droplets by air. Droplet size and distribution are controllable with nozzle. However the air used for atomization also contributes to evaporation of the coating solvent. The evaporation results in increasing the droplet's viscosity, thus inhibiting spreading and coalescence upon contact with the core material. Another factor affecting droplet viscosity is the distance that the droplet travel through the primary evaporation media (the fluidization air) before impinging on the core. In all three processes techniques, the nozzle is positioned to minimize droplet travel distance.

2.1 Top spray coating

A top spray coater was developed from conventional fluidize bed dryer for coating pharmaceutical dosage forms. The spray nozzle equipped in the fluidized powder bed is shown in Figure 4. The coating suspension was sprayed downward onto the substrate as it was randomly fluidized by air from air distribution plate below the coating chamber. The films from top spray process gains smoothness and continuity of coating surface over pellets coated in a conventional or perforated pan due to its greater drying efficiency of the fluidized bed technique.

However, the top spray coating always have imperfections of films in a finished product. Although the spray nozzle immersed in the fluidized pellets, the fluidized pattern was still disorganized. As a result, droplets travel random distances before impinging on the substrate. Coating solution was sprayed downward against the heated air stream, counter-current style, which generated viscosity changed as the solids content of the droplet increases with high evaporation rate of solvent used and spray dried occurs. Since a top
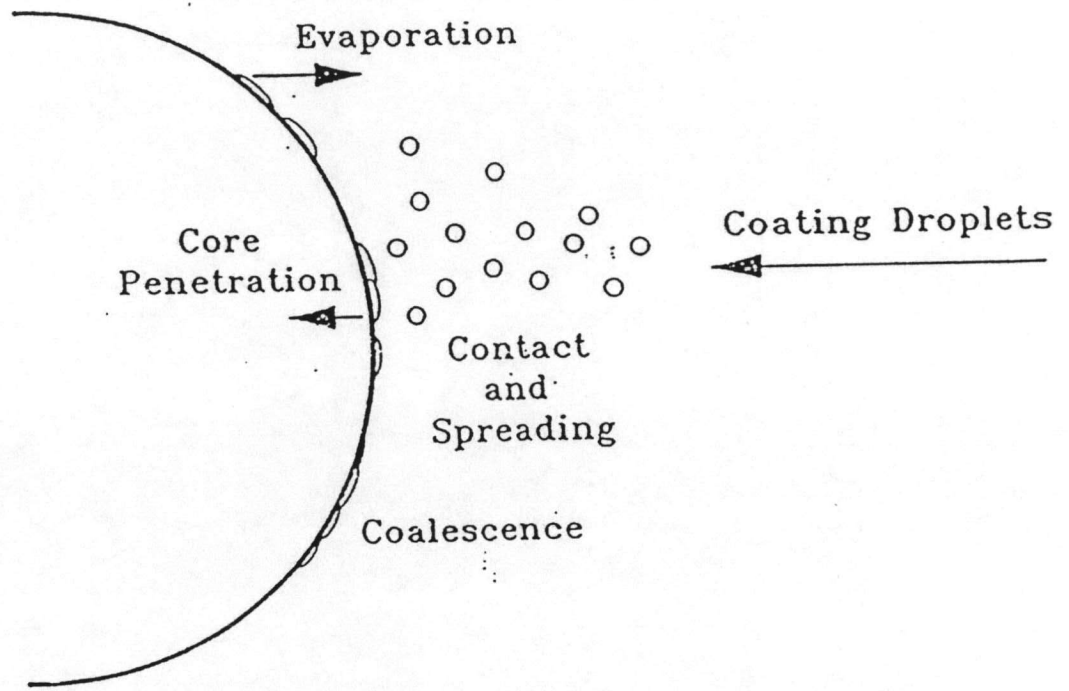
Figure 3   Dynamics of film coating on surface of solid

spray film always involves imperfections, this method is nowadays primary used for barrier (protective) coating, but less for controlled release films.

2.2   Bottom spray coating

Another type of fluidized-bed coating process was introduced by Wurster. The spray nozzles was equipped at the bottom of coating chamber as in Figure 5. This system is currently widely used for film coating of particles, pellets and tablets.

The coating chamber is an unbuffled cylinder that contains another cylinder, half its diameter, known as a partition. At the base of the coating chambers a fine screen and an air distribution (orifice) plate. In the center of the plate, a nozzle is positioned to spray upwardly. The holes in the plate in the area beneath the partition are larger in diameter than those outsides. Air passes through this of the plate at a high volume and velocity, pneumatically transporting particles vertically the partition and spray zone. The sprayed particles exit the partition and begin to decelerate in the expansion chamber. When the air velocity is such that the particles can no longer be entrained, they drop into the area between the partition and the wall of the coating chamber known as the down bed. The horizontal transportation of particles toward the spray zone, which completes the cycle, is accomplished by the proper selection of the distance between the base of the partition and the air distribution plate (known as partition height). Particles are recycled through the spray zone in a mater of seconds as in a conventional top spray technique. But, in contrast, the fluidization pattern is much more controlled in a Wurster system.
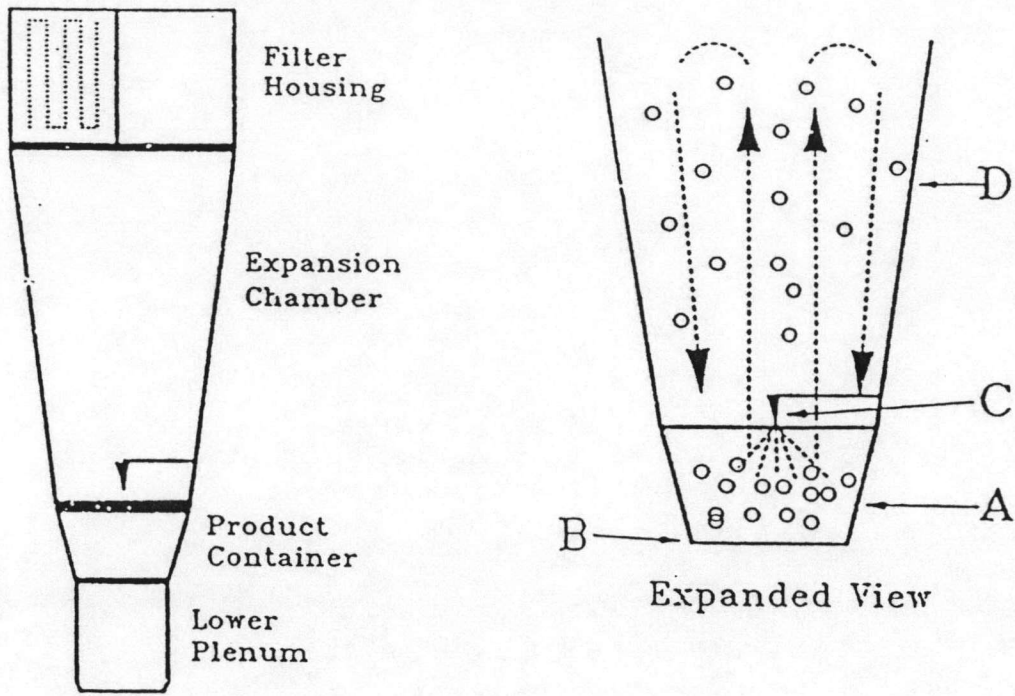
Figure 4   Top spray coater: (A) product container; (B) air distribution plate; (C) spray nozzle; (D) expansion chamber.
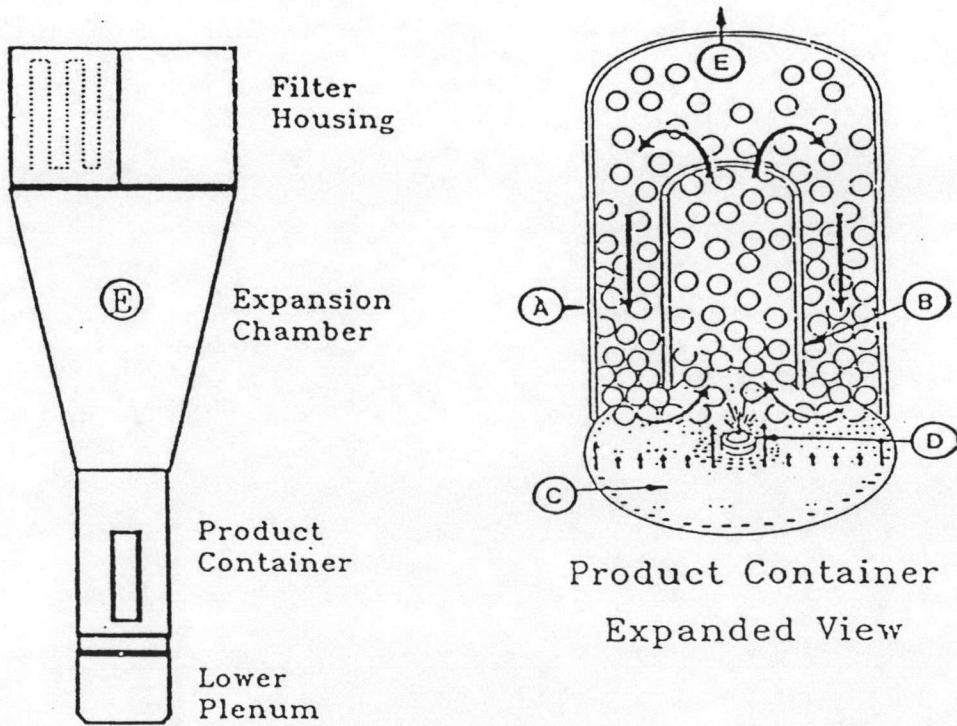

Figure 5   Wurster bottom spray coater: (A) product container; (B) partition; (C) air distribution plate; (D) spray nozzle; (E) expansion chamber.

2.3 Tangential spray or rotary fluidized bed

For tangential spray or rotary fluidized bed coating, three forces are combined to provide a pattern best described as a helix. Centrifugal force generates by the rotating disc causes the product to move toward the wall of the chamber (Figure 6), air velocity through the gap provides acceleration upward, and gravity cascades the products inward and toward the disc once again. The coating suspension is sprayed tangentially in the same direction, concurrently, as the movement of the pellets in chamber, similar to those of the coating applied using the Wurster bottom spray method. Film applied using the rotor tangential spray system are high in quality, similar to those found using the Wurster process. However, the process is more susceptible to adhesion of particles to upper wall of the product container owing to static electricity; hence, coating of smaller and lighter particles is difficult, especially with organic solvents.

Additionally, the higher kinetically energy produced by the centrifugal forces of the fast rotating disc makes the rotor more suitable for the film coating of powders and tablets. The process also has more mechanical stress than other methods thus it is discouraged for use with friable substrates.
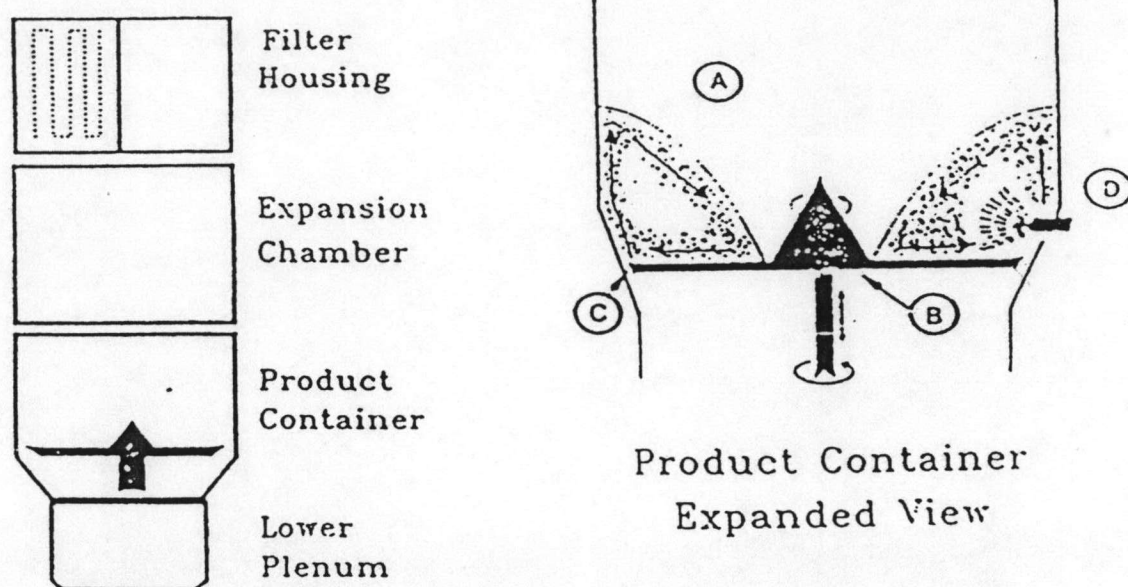
Filter
Housing

Expansion
Chamber

Product
Container

Lower
Plenum

Product Container
Expanded View

Figure 6   Rotor tangential spray coater: (A) product chamber; (B) variable speed
disc; (C) gap or slit; (D) spray nozzle.

3.   **Lipid in Pharmaceuticals** (Banakar and Speake, 1990)

Fats and Waxes have been important adjuvants in the preparation of various types of pharmaceutical product for many years. Initially, they were simply used to enhance and improve the properties of dosage forns.By yhe late 1960s people realized the therapeutic value as nutritional supplements and started using them intravenously administered fat emulsions. Around the same time it was found that waxes were good matrix-forming agents that could be used in prolonged release formulations.

Fats and waxes are importance in the preparation of pharmaceutical products, both as excipients and as therapeutic agents. Althrough they are already widely used, new applications are still being found and existed uses improved upon. Classified as lipids, they encompass a wide spectrum of organic compounds that vary considerably in their chemical and physical properties.

Fats are greasy to the touch, lighter than water and insoluble in water. However, they are soluble in ether, chloroform and some other water immiscible solvents. As they contain carotene, fats often have a yellowish colour.

Waxes, like fats, are esters of high-molecular weight, monohydric alcohols and high molecular weight fatty acids. The alcohols found in waxes are one of the higher even number monohydric alcohols fromC_{16} to C_{36} such as cetyl alcohol($C_{16}H_{33}OH$), ceryl alcohol ($C_{26}H_{53}OH$) and myricyl alcohol ($C_{30}H_{61}OH$). While waxes often contain these alcohols and fatty acids C_{24} to C_{36} in the free state as the major components, some waxes obtained from plants contain paraffin hydrocarbons.

3.1   Characterization

Characteristics of fats that are important in their identification are the iodine value, the acid value, and the saponification value. The iodine value is the number of grams of iodine that will react with 100 g of fat. The acid value is the number of milligrams of potassium hydroxide required to neutralize the free acids in 1 g of sample, while the saponification value is the number of milligrams of potassium hydroxide required to neutralize the free acids and to saponify the esters in 1 g of sample. Specific gravity, color, odor and congealing point are also worth considering.

The major component of fat is the triglyceride. The triglyceride typically represents over 95% of the weight of most food fats. The other minor components are mono- and diglycerides, free fatty acids, phosphatides, sterols, cerebrosides, fat soluble vitamins, and other substances. The triglyceride is composed of glycerol and three fatty acids.Both the physical and chemical characteristics of fat are greatly influenced by the kinds and proportions of the component fatty acids and the way in which these are positioned on the glyceryl radical.

3.2   Lipid uses in pharmaceutical dosage forms

Overall prospective the uses of lipids in pharmaceutical dosage forms can be grouped in to four categories:

1.   An improvement in the processing or stability of the formulation in the preferred physical state.

2.   Enhancement or reduction in cellular or systemic absorption of the drug from the formulation.

3.   More effective drug targeting to efficacy sites and away from toxicity sites.

4.   Slower or more controlled delivery of drug from the formulation.

3.2.1 Conventional dosage forms

When used in emulsion, suspension and ointments, fats and waxes can give the product a dry formulation and suitable consistency or form.

Fats and waxes are also widely used as emulsifiers in the preparation of emulsions. Whether a substance is a good emulsifier depends on the value of its hydrophile-lipophile balance(HLB). This HLB value, which was developed by Griffin, gives a means of selecting the appropriate emulsifying agent. Compounds with HLB values of between 4 and 6 are shown to yield water-in-oil (W/O) emulsions while those with HLB values between 8 to 18 generally suitable for preparation of oil-in-water (O/W) emulsion.

3.2.2 Modified release

There are many situations that require an alternative to the conventional rapid release formulations. Possibilities include sustained-, prolonged-, and controlled-release systems, which are generally obtained either by modifying the chemical structure of the active ingredient to alter its physicochemical properties or by careful selection of excipients.

In some formulations fats and waxes are used to interfere with the release of the medicament, causing it to deviate from the conventional rapid release characteristic to modified release behavior. This interference might involve producing a hydrophobic environment for drug release, coating drug particles to give an additional barrier to dissolution or providing a matrix-type structural environment that entraps the drug. Coating and preparation of wax-matrix systems are both widely used.

3.3   Production of sustained release products using fats and waxes

Fusion and congealation (Dakkuri et al., 1978; Kumar et al., 1975; Dave et al., 1974) The lipid substance, singly or mixture, is melted at the temperature close to the melting point which is then filled into capsule while hot. For incorporating an active ingredient, its size should be reduced to fine. Adjuvant is incorporated to the melt little by little under agitation. The agitation is maintained until the total mixture is congealed and they are granulated by sieving with suitable equipment.

In a novel way, Bodmeir et al. (1990) studied the sustained release wax matrices by filled the drug-wax powder blends in hard gelatin capsule. The waxes will melted within the capsules in a heated fluidized bed and formed solid drug-wax matrices upon cooling.

Evaporation (Dakkuri A. et al., 1978) This method involves dispersing the under agitation, and the mass remaining is further treated according to the procedure of fusion and congealation method.

Spray congealing (John and Becker, 1968; Hamid and Becker, 1970) In this process, the drug is allowed to melt, disperse, or dissolve in hot melt of lipid substance. The mixture is then sprayed into an air chamber where the temperature is below the melting point of the formulation components. Depending on the physicochemical properties of the ingredients and the formulation, various pellets with immediate or controlled release behavior can be produced by this process. Products from this process come in the form of powder or pellets.

Spray drying (Asker and Becker, 1966) The process is different from spray congealing in that the drug is dispersed in a solution of lipid dissolved in organic solvent. The resulting suspension is sprayed in an atmosphere of warm air, and the product is formed on evaporation of the solvent.

Aqueous dispersion (Draper and Becker, 1966; Emori et al., 1984) The procedure of this method involves adding an active ingredient under agitation control into a molten lipid excipient. The mixture is then dispersed in the water, often containing dispersant, at the same temperature. After cooling this system to an optimum temperature, the drug lipid particles are flitered, washed and dried.

Wet granulation (Capan, 1989; Parab et al., 1987) In wet granulation, drug mixture of the lipid excipient and active ingredient is damped by water or organic solvent. The damped mass is then granulared in conventional manner, dried and sieved.

Direct compression (Capan, 1989; Parab et al., 1987) The active ingredient is mixed with the pulverized lipid excipient and other adjuvant. The resulting mixture is then compressed a^t high pressure.

Melt pelletization (Thomsen et al., 1993) A melt pelletization process proceeds by agitation of a mixture of particulate solid and a meltable binder in amixer, preferably a powerful high shear mixer. As the binder is liquified by the heat developed by the agitation or by a heating jacket, it causes agglomeration similar to an aqueous binder solution.

Extrusion (Ghali et al., 1989; Miyagawa et al., 1996) With this method, the medicament and molten material are intimately mixed and placed in the extruder. The mass is extruded by means of a piston through small holes and processed to pellets in the spheronozer. The kneading during the process can heat the molten material and disperse it through the mass. The controlled release matrix will occur when the mass is cooled.

Coating procedure (Porter and Ghebre-sellassie, 1994) Waxes have also been used as coatings for granules and pellets. Solid dosage forms are often to sustain drug release, improve the stability, or mask the taste of poorly tasting drugs. Wax coatings have various advantages over coating with polymer solutions or dispersions. The waxes can be applied without organic solvents, and, in the case of hot melts, at a high application rate and therefore shorter processing time.Waxes can be applied onto solid dosage forms in the forms of hot melts, hot emulsions, aqueous suspensions (colloidal wax particles), or organic solutions. Coating processes include dip coating, pan coating, and fluidized-bed coating. Table 1 lists probable release mechanisms of the core substance and properties of these coating materials. The coating materials are selected for their ability to protect a

Table 1   Properties of some of the most common coating materials

Type of coating	Examples of coating type	Most Suitable dosage forms	Probable drug release mechanism
Barrier coating	Beeswax Glyceryl monostearate Acetylated monoglycerides	Film coated products (tablets, pellets) Compressed tablets containing mixtures of barrier coated particles	Diffusion and dialysis, pH dependent dissolution and possible enzymatic breakdown
Embedding in a fatty coating	Glyceryl palmito stearate Beeswax Glycowax Castor wax Carnuba wax Glyceryl monostearate Stearyl alcohol	Compressed granules (tablets) Compressed granules placed in capsules Multilayered tablets Compression coated tablets	Gradual erosion of coat Coating may contain portion of dose for quick release upon hydrolysis with subsequent slow release from erosion of the core

given substrate from a specific type of environment and to release that substrate, either gradually or instantly, in reaction to specific stimuli or via a deliberately altered environment. Substrate release may be accomplished as a function of heat, moisture, shear, pH, or enzymes. It has been reported that the release of substrates, barrier coated with beeswax, glyceryl monostearate, and acetylated monoglycerides, is probably due to diffusion and dialysis, pH dependent dissolution, and possible enzymatic breakdown (Provost et al., 1989).

The wax can be dissoved in an organic solvent and sprayed onto the solid dosage form. The wax film around the solid substrate forms upon solvent removal. In most studies, waxes such as beeswax, hydrogenated castor oil, microcrystalline wax, or glyceryl mono- or distearate were dissolved in chlorinated organic solvents such as chloroform, carbon tetrachloride, or trichlorethane and applied in coating pans at elevated temperatures. Mixtures of ethylcellulose with different waxes such as castor, carnauba, or paraffin wax in chloroform were evaluated as sustained-release coatings.

Sugao et al. (1998) studied the preparation of wax-coated microparticles containing hydrogenated oil and surfactants in a fluidized bed using the side spray method. The result showed that the dissolution rate of coated particles was significantly delayed. Heat treatment of coated particles comprising hydrogenated oil and PPG at a temperature above the melting point point of PPG was applied. It was found that dissolution rate was enhanced. The mechanism of this effect of heat treatment is throught to involve rediffusion of PPG in the coating layer due to the melting of PPG.

Prinderre et al. (1997) studied the effect of protective agents using fluidized bed technique on stability and controll-release of jasomycin and paracetamol. The protective

agent composed of Eudragit L30D, Eudragit RS30D, Sepifilm LPO10 and Compritol 888 ATO ® were coated in fluidized bed. The Sepifilm LPO10 were prepared by disperse in water before coating, Eudragit L30D and Eudragit RS30D, ready for use, supplied as latex formulations and Compritol 888 ATO ® atomized powder usable after dissolving in an organic solvent before coating. It was found that, Compritol 888 ATO ® applied with an organic phase presented a better efficacy against humidity than the polymers applied with aqueous solvents. The dissolution profiles of coated granules from Eudragit L30D, Eudragit RS30D and Compritol 888 ATO ® showed that the release of the drugs was sustained and the dissolution curves were best fitted by the HIGUCHI model.

4. Mechanism of Release from Coated Pellets (Ozturk et al.,1990).

There are some possible mechanisms by which release from capsule-type controlled release dosage forms coated with water insoluble polymers may occur.

A. Solution/Diffusion through the continous plasticized polymer phase

In the case of A), the disolution rate of a drug from coated pellets in the steady state can be described by:

$$J = \frac{P_m}{h} \times (C_s - C_b) \qquad (1)$$

where J is the flux (release rate per unit surface area of coating), C_s and C_b are the concentrations of drug at the drug-coating interface and bulk, respectively, and h is the coating thickness. The permeability coefficient (P_m) can be written as

$$P_m{}' \quad = \quad \frac{D \times V \times k}{\tau \times \beta} \qquad (2)$$

Where D is the molecular diffusivity of the drug, k the distribution coefficient of the drug between the polymer membrane and fluid in the core (imbibed water), V the volume fraction of the chain opening, β a chain immobilization factor, and τ the tortuosity factor.

B. Solution/diffusion through plasticizer channels.

The release rate for this model can be described by equation 1, but with the permeability coefficient, P_p represented as,

$$P_p \quad = \quad \frac{D_p \times V_p \times k_p}{\tau_p} \qquad (3)$$

In this case, k_p is the distribution coefficient of the drug between plasticizer ant the core fluid (imbibed water), τ_p the tortuosity of the plasticizer channels and V_p the volume fraction of plasticizer channels.

C. Diffusion through aqueous pores.

The transport mechanism in these pores can range from pure molecular diffusion to convection, depending on the pore size. For diffusion through aqueous pores, the permeability coefficient, P_a , is given by:

$$P_a \quad = \quad \frac{D_a \times V_p}{\tau_a} \qquad (4)$$

Where D_a is the aqueous diffusivity of the drug, V_p the volume fraction of the aqueous channels. And τ_a the toutuosity of the aqueous channels. The partition coefficient, K, will unity, as there is no partition between the channels and the aqueous environment in the bulk.

This mechanism is often accompanied by other mechanisms. The most usual combination is diffusion through the continuous polymer phase in parallel with diffusion through aqueous channels. Assuming that two mechanisms operate independently, the resultant permeability is given by equation 5

$$P_t \quad = \quad P_m + P_a = \quad \frac{D \times V \times k}{\tau \times \beta} + \frac{D_a \times V_p}{\tau_a} \tag{5}$$

Where P_m and P_a are the permeability in the polymer and the aqueous phase, respectively.

D. Osmotically driven release

When pellets come into contact with an aqueous environment, water is imbibed through the coating, creating a solution in the core. The excipients and/or drug dissolve in the imbibed water, generating the interior osmotic pressure. The osmotic pressure difference between the core and the external medium then provides the driving force for efflux through pores in the coating. The release for this process can be described by equation 6.

$$J = \frac{L_P}{h} \times (\sigma \times \Delta \pi - \Delta P) \times (C_i - C_m) \qquad (6)$$

Where L_P is the filtration coefficient, σ the reflection coefficient of the coating, $\Delta \pi$ the osmotic pressure difference across the coating, ΔP the hydrostatic pressure difference and C_i and C_m are the interior and media drug concentrations, respectively.

Materials Information

1. Model Drug

1.1 Diltiazem Hydrochloride (DTZ HCl) is a calcium ion influx inhibitor (slow calcium channel blocker).

1.1.1 Physico-Chemical Properties (David et al., 1994)

Chemical name : (2S-cis)-3-(acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothia-zepin-4(5H)-onemonohydrochloride.

Empirical name : $C_{22}H_{26}N_2O_4S \cdot HCl$

Molecular weight : 450.98 g/mole

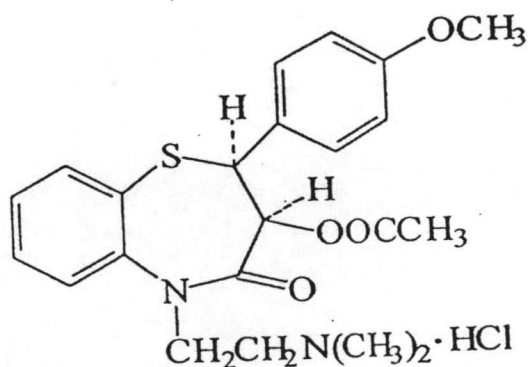**Structural formula** : is shown in Figure 7

Figure 7   Chemical structure of diltiazem hydrochloride

Description : DTZ HCl is a white to off-white crystalline powder. It is odorless and has a bitter taste

Solubility : The solubility of DTZ HCl in a varity of solvents is presented in Table 2

Table 2   Solubility of DTZ HCl in various solvent systems at 25 °C

Solvent	Solubility
Chloroform	Freely soluble
Formic acid	Freely soluble
Methanol	Freely soluble
Water	Freely soluble
Dehydrated alcohol	Sparingly soluble
Benzene	Practically insoluble
Ether	Insoluble

1.1.2   Pharmacology (Micaela et al., 1990)

DTZ HCl is a calcium antagonist effective in treatment of stable, variant and unstable angina pectoris and mild to moderate systemic hypertension, with a generally favourable adverse effect profile. It is also effective in terminating supraventricular tachycardia and in controlling the ventricular response to atrial fibrillation/flutter.

1.1.3   Pharmacokinetic

Approximately 90% of an orally administered dose of DTZ HCl is absorbed. After administration of single oral doses , including a sustained release tablet, the mean absolute bioavailability is about 30 to 40% and is dose related. The area under the plasma concentration-time curve (AUC) increases after multiple dosing , indicating that first-pass metabolism decrease with multiple dosing.

DTZ HCl undergoes substantial first pass metabolism to form several metabolites. The most important of these are N-monodemethyldiltiazem, with an estimated 20% of the potency of diltiazem and deacetyl diltiazem, which is about half as potent as the parent drug. Steady state diltiazem concentrations in plasma are achieved within 3 to 5 days. The pharmacokinetics of DTZ HCl are unaffected by renal disease.

Table 3   Pharmacokinetics of DTZ HCl

	Diltiazem
Absorption (%)	>90
Bioavailability (%)	~40
Onset of action : oral (min)	<30
Peak effect	3-5 hrs.
Protein binding (%)	90
Plasma half life	5 hrs.
Metabolism	60% of first dose ; 10% steady state
Excretion	
- Renal (%)	30
- Fecal (%)	70

1.1.4 Dosage and preparation

Oral dosages employed in the treatment of systemic hypertension and angina pectoris. In systemic hypertension, oral dosages between 90 to 180 mg/day are employed in Japan and Southeast Asia.

Treatment of stable or variant angina pectoris should be initiated at 120 mg/day divide with stepwise titration up to a maximum of 360 mg/day. The dosage in angina pectoris in Southeast Asia a dosage of 90 mg/day is normally employed.

DTZ HCl (Cardizem ®, Dilacor ®) is available as tablets, sustained release capsules, and injectable forms. Therapy is individualized and generally begins with 30 mg four times a day up to a maximum of 360 mg daily. Intravenous therapy usually begins with a dose of 0.2 mg/kg over 2min, followed by an additional dose of 0.3 mg/kg. Infusions are usually given in dose of 10 mg/hr and can be maintained for up to 24 hrs.

2.   Materials Used in Coating Formulations

In this investigation, the coated systems consist of carnauba wax, glyceryl monostearate, Compritol 888 ATO®and ethylcellulose as coating materials. In this action, the organic solvent systems are employed by using chloroform to prepare coating solutions. Triethyl citrate (TEC) was selected to be the plasticizer of ethyl cellulose of the coating materials.

Brief descriptions of the materials used in the experiment are delineated in the following sections.

2.1 Carnauba wax

Physico-Chemical Properties

Chemical name   :   Carnauba wax

Empirical formula : Carnauba wax consists primarily of a complex mixture of esters of acids and hydroxyacids. Also present are acids , oxypolyhydric alcohols , hydrocarbons , resinous matter and water.

Structural formula : -

Description : Carnauba wax occurs as a light brown to pale yellow colored powder , flakes , or irregular lumps of a hard , brittle wax. It possesses a characteristic bland odor and practically no taste. It is free from rancidity. Commercially , various types and grades are available.

Solubility : Soluble in warm chloroform and warm toluene , slightly soluble in boiling ethanol (95%) , practically insoluble in water.

Stability : Carnauba wax is stable and should be store in a well-closed container , in a cool , dry , place.

2.2 Glyceryl monostearate (GMS)

Physico-Chemical Properties

Chemical name : Octadecanoic acid, monoester with 1,2,3-propane-triol

Empirical formula : $C_{21}H_{42}O_4$

Structural formula

$$CH_2\text{-}OOCC_{17}H_{35}$$
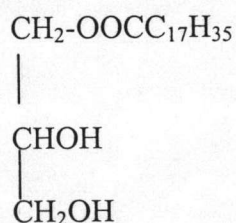$$|$$
$$CHOH$$
$$|$$
$$CH_2OH$$

Figure 8   Chemical structure of glyceryl monostearate

Description : The USPNF XVII describes glyceryl monostearate as consisting of not less than 90% of monoglycerides, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$)and glyceryl monopalmitate ($C_{19}H_{38}O_4$). It should be noted that glyceryl monostearate from European sources usually refers to glyceryl monostearate 40-50. Glyceryl monostearate is a white to cream-colored, wax-like solid in the form of beads, flakes or powder. It is waxy to the touch and has a slight fatty odor and taste.

Solubility : Soluble in hot ethanol (95%) , ether , chloroform , hot acetone , mineral oil and fixed oils. Practically insoluble in water , but readily dispersible in hot water with the aid of an anionic or cationic agent.

Stability : Glyceryl monostearate increases in acid value upon aging , if stored atwarm temperatures , due to the saponification of the ester with trace amounts of water. Effective antioxidants that may be added are butylated hydroxytoluene and propyl gallate. Glyceryl monostearate should be stored in a light-resistant , tightly sealed container at a cool temperature.

2.3 Glyceryl behenate (Compritol 888 ATO [®])

Physico-Chemical Properties

Empirical formula : $C_{69}H_{134}O_6$

Structural formula :

$$
\begin{array}{c}
\overset{\displaystyle O}{\overset{\displaystyle \|}{}} \\
H_3C(CH_2)_{20}COCH_2 \\
|\\
H_3C(CH_2)_{20}COCH_2CHOC(CH_2)_{20}CH_3 \\
\underset{\displaystyle O}{\|} \qquad \underset{\displaystyle O}{\|}
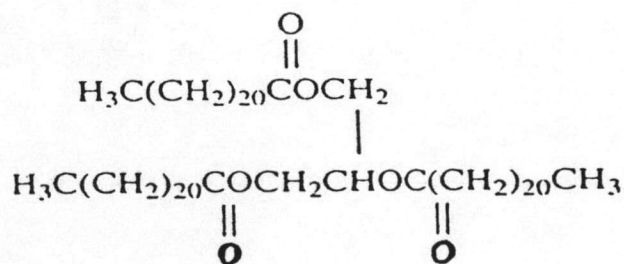\end{array}
$$

Figure 9 Chemical structure of glyceryl behenate

Chemical description : Compritol 888 ATO® is synthesized by esterification of glycerol by behenic acid (C22 fatty acid). The raw materials used are of strictly vegetable origin and the reaction process involves no catalyst. The product is then atomized by spray-cooling. Compritol 888 ATO® is composed of mono, di and triglycerides of behenic acid, the diester fraction being predominant.

Appearance : fine white powder with a faint odor.

Solubility : It can be soluble in chloroform, methylene chloride when heated and insoluble in ethanol, n-hexane, water and mineral oils.

Stability : -

2.4 Ethylcellulose

Physico Chemical Properties

Chemical name : Cellulose ethyl ether

Empirical formula : Ethylcellulose is an ethyl ether of cellulose, a long chain polymer consisting of anhydroglucose unit joined together by acetyl linkages. Each anhydroglucose unit has three replacable hydroxyl groups which are substituted to the extent of 2.25-2.60 ethoxyl groups per unit, equivalent to an ethoxyl content of 44-51%
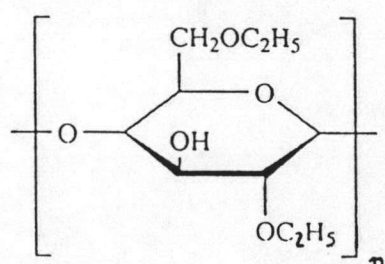
Structural formula

Figure 10   Chemical structure of ethylcellulose

Description : Ethylcellulose is a tasteless , free flowing , white to light tan colored powder.

Solubility : Practically insoluble in glycerine, propylene glycol and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform , methyl acetate , tetrahydrofuran, and in mixture of aromatic hydrocarbons with ethanol (95%) . Ethlycellulose that contains not less than 46.5% of ethoxyl group is freely soluble in chloroform, ethanol (95%) ethyl acetate , methanol and toluene.

Stability : Ethylcellulose is a stable , slightly hygroscopic material . It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions , although it is more sensitive to acidic materials than cellulose esters.

2.5 Triethyl citrate (TEC)

Physico-Chemical Properties

Chemical name : 2-Hydroxy-1,2,3-propane tricarboxylic acid, triethy ester

Empirical formula : $C_{12}H_{20}O_7$

Structural formula

$$
\begin{array}{c}
CH_2COOC_2H_5 \\
| \\
HO-\overset{}{C}-COOC_2H_5 \\
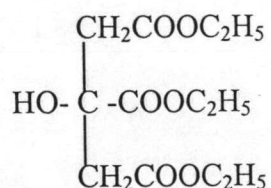| \\
CH_2COOC_2H_5
\end{array}
$$

Figure 11   Chemical structure of triethyl citrate

Description : Triethyl citrate occurs as a bitter tasting, odorless, practically colorless, oily liquid.

Solubility : Soluble 1 in 125 of peanut oil, 1 in 15 of water . Miscible with ethanol (95%) and ether.

Stability : Triethyl citrate are stable if stored in a well-closed container in a

cool, dry, place.