CHAPTER 1

INTRODUCTION

Chitosan, a biocompatible and biodegradable polysaccharide, is a deacetylated product derived from chitin. The deacetylation process provides sufficient free amine groups on polymeric chain to render the polymer soluble in certain aqueous acid systems. Whereas chitin, due to its limited solubility in aqueous solutions, has limited utilization, chitosan is emerging to play an important role in wide scope of applications i.e. agriculture, bio-medicine, biotechnology and industry. Areas such as textile finishes, chelating agents, dietetics and photographic products, have attracted the bulk of the research thrust. A variety of pharmaceutical applications of chitosan have also been proposed. It can be applied into tablets, beads, membranes, microcapsules, gels and so on. Extensive investigation on chitosan as pharmaceutical excipients has been conducted (Upadrashta, Katikaneni and Nuessle, 1992; Thacharodi and Rao, 1993 a, b; Theodora, 1993; Skaugrud, 1989; Ritthidej et al. 1994).

Chitosan can readily dissolve in dilute non-corrosive aqueous acids which the mostly used as standard solvent is dilute acetic acid. On solubilization, the amine groups in chitosan molecules are quarternized with carboxylic acids. Various acids can be used to solubilize chitosan. These acids may have different effect on the pH, viscosity or the expansion of this polymeric chains in solution, and the physicochemical properties in solid state (Demarger-Andre and Domard, 1994).

Due to its cellulose-like chemical structure, chitosan exhibits good filmable property. Various pharmaceutical applications of chitosan film have been proposed (Nakatsuka and Andrady, 1992; Bonvin and Bertorello, 1993; Thacharodi and Rao, 1993 a; b; Remunan-Lopez and Bodmeier, 1997; Ikeda, Takayama and Nagai, 1997; Bolgiil et al., 1998). Salt formation or interaction between chitosan and carboxylic acid simultaneously occurs in cast film. Most chitosan salt forms are water soluble. The solubility is reported to be depended on the polymorph in the chitosan film. Crystals of anhydrous polymorph result in water insolubility.

Many researchers attempted to prepare chitosan in insoluble form by converting its functional groups (Hall and Yalpani, 1980; Koyama and Taniguchi, 1986; Holme and Hall, 1991) or crosslinking process (Mayer and Kaplan, 1991, Wei et al., 1992; Kim et al., 1992; Saha et al., 1998; Suto and Ui, 1996). The introduction of hydrophobic group on chitosan was complicated process and had to involve organic solvent in reaction. Whereas the crosslinking was more frequently utilized, however the residues of crosslinking compounds were not amenable to human use due to their toxicity.

Recently, Phaechamud, Koizumi and Ritthidej (1997 a, b) found poor solubility of film prepared with chitosan in dilute acetic acid when stored at room temperature for a long time or after exposure accelerated temperature and humidity. Whereas Ritthidej, Kusonwiriyawong and Phaechamud (1994) previously found the good stability of water soluble film obtained from chitosan in dilute citric acid. This evidence of difference in

solubility of chitosan films due to the type of acids employed and storage condition has not been profoundly characterized.

Tablet film coating is a process which involves the deposition of a thin plastic-like material consisting of polymer upon the tablet surface. The purpose of tablet film coating includes : masking undesirable taste, odor and color; imparting a more glossy and elegant appearance; protecting the active ingredients against environment (light, air and moisture) ; increasing mechanical stability and prevent dust formation during subsequent packing and shipment; separating incompatible active ingredients; and ensuring the controlled or modified release of drug (e.g. fast, enteric and sustained release). Nowadays, because of the expense of organic solvents used in the coating process and the problem of the release of these potentially explosive and toxic agents into atmosphere, or the high cost of solvent recovery system, the manufacturers are actually favoring the use of aqueous-base film coating (Porter, 1979; Stern,1983; Pondell, 1984; Porter and Saraceni, 1988; Ansel and Popovich, 1990; Edgren and Theeuwes,1990; Seitz, 1990; Phuapradit, 1995). The polymeric matters that are widely used in film coating are the cellulose derivatives. Chitosan has a close chemical relative of cellulose and also has the ability to dissolve in aqueous medium, thus this material should be capable to be used as film former with aqueous base system for tablet film coating approaching to both fast or extended controlled drug release depended on characteristics of selected films that are soluble or insoluble forms.

The physicochemical properties of polymeric film are a function of the composition in coating formulation. Apart from the polymer employed as film former, film coating formulations are normally composed of plasticizer to enhance film forming characteristics, opacifier to improve appearance and stability and colorant to provide a unique identity (Radebaugh, 1988). The effect of coating formulations on chitosan cast film and especially on film coated tablets has not been reported.

Propranolol hydrochloride, a beta blocker, is pharmaceutically used in the treatment of hypertension. It has a short plasma half life, about 2-6 hours. Consequently, it has to be frequently taken in order to maintain the plasma concentration in therapeutic range. The main purpose of extended release product is to reduce side effects and prolong drug intake interval and thus it is also convenient for drug administration. This drug is manufactured both in the rapid and extended release dosage forms in the dosage unit of 40 and 80 mg respectively. The drug is also very high water soluble which is suitable used as model drug for this study since the efficacy of chitosan film to control the release can be assessed.

Basically, the cumulative of drug release-time profiles contain elementary information exemplified the structure and mechanisms of a delivery system on a microscopic scale. Possibly, mutual interactions and other subtle relationships between encapsulated component and its carrier can be elucidated. However, more detailed information's on the microstructure and properties of the delivery system appear to be necessary. Ideally, the release profiles can be corrected to understand the microstructure of the carrier. Hence, the manufacturer can predict the release characteristic and thereafter can design the device with the more desired release pattern (Gopferich,1996; Phares, Cho and Swarbrick, 1996).

Suitable mathematical release model is practically useful to elucidate the drug transport through the film coat. Such release model for describing the drug transport should be developed and applied for the release from tablets coated with chitosan film. The reasonable assumption based on physical characteristic of controlled release device is necessary in model construction. The assessment of release data fitting to conventional models selected and created model will be useful to obtain the best release model suitable for the release behavior of drug from chitosan film coated tablet.

By comparison, the use of linear regression for fitting the release data to tested models may not be mathematically accurate due to data transformation, meanwhile the nonlinear fitting does not distort the original data and the standard deviations are usually taken into consideration (Lu, Abu-Izza and Mao,1996). For this study, drug release profiles were nonlinear fitted to equation derived from different models. Least squares fitting is performed using a modified Powell algorithm to find a local minimum.

This investigation was aimed to characterize the cause of change in solubility of chitosan film due to type of organic carboxylic acid used and condition of film treatment especially the influence of temperature and humidity. This study selected mono-, di- and tri-functional organic acids to investigate the effect of amount of carbonyl group on acid molecule on the properties of chitosan solution and film. Organic acids would serve as solvents as well as reactants. Additionally, this study was also emphasized on the feasibility to employ chitosan as film former approaching to fast and extended release coated tablets using aqueous based system and conventional pan coating technique. Propranolol hydrochloride was used as model drug in the dosage unit of 40 and 80 mg. for fast and extended release dosage forms respectively. The effect of type and amount of plasticizer and water soluble colorant on physicochemical properties of chitosan cast films and film coated tablets was examined. The effect of opacifiers such as titanium dioxide and talcum which have different particle shape on the physicochemical properties of chitosan cast films and film coated tablets were investigated. Some hydrophobic substances such as magnesium stearate and talcum, and hydrophilic substances such as urea and HPMC were added to modify the extended release dosage form. The heat treatment was applied to alter the release characteristics of chitosan film coated tablet. The physicochemical characteristics of chitosan cast films were assessed as the measurement of film swelling index, film dissolution, mechanical properties, UV and FT-IR absorption, powder X-ray diffraction, solid-state ^{13}C NMR spectra and thermal property. The evaluation of chitosan film coated tablets was undertaken as followed: surface topography, weight variation, hardness, disintegration, film thickness, adhesion between film and tablet surface, and drug release. The stability of prepared coated tablets was tested upon both long term storage at room temperature for one year and after exposure accelerated condition. This study also created suitable mathematical models including necessary parameters for describing the transport of drug through chitosan film coated tablet of fast as well as extended release characteristics. The composite of geometrical shape of delivery device, diffusion coefficient of drug in each part of device, surface area, film thickness and film dissolution rate are crucial consideration for model development. The nonlinear regression analysis was used to compare the degree of curve fitting between conventional models and developed models, and select the best fitted model for drug liberation from prepared film coated tablets both in the case of fast and extended release dosage forms.

Objectives of the Study

1. To characterize the mechanism of chitosan film alteration to water insoluble form or unaltered water soluble characteristic under influence of type of organic carboxylic acids and condition of film treatment

2. To develop propranolol hydrochloride fast and extended release film coated tablets using chitosan as film former

3. To study the effect of chitosan film coating components on physicochemical properties of both chitosan cast films and coated films

4. To study the stability of the obtained chitosan film coated tablets

5. To create the mathematical model and equation describing the release behavior of fast and extended release chitosan film coated tablets

6. To elucidate the release mechanism of propranolol hydrochloride from tablet through chitosan films.

Literature Review

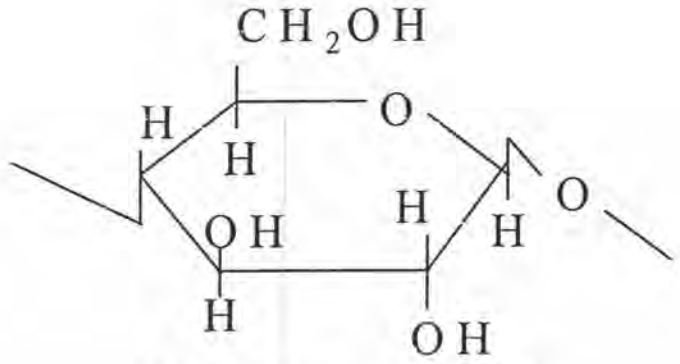
Chitosan

Chitosan is a linear bio-polysaccharide obtained by deacetylating chitin which is the major constituent of the exoskeleton of crustaceous animals. This polymeric matter was firstly reported by Rouget in 1859 (Muzzarelli, 1977) when he boiled chitin in a concentrated potassium hydroxide solution. Commercially, nowadays chitosan is prepared by purification and then N-deacetylation of chitin with an aqueous solution of sodium hydroxide.

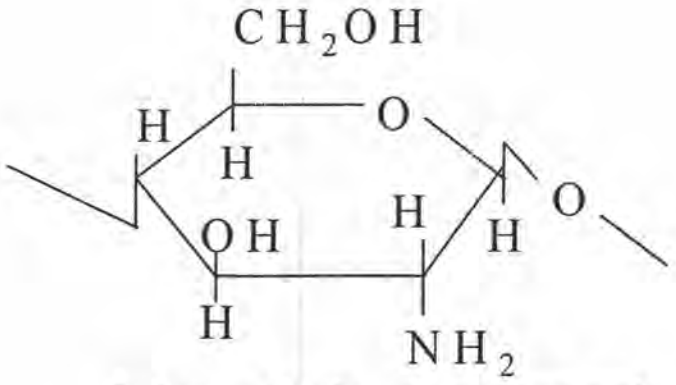
Main available sources for production of chitosan is the chitin derived from the shells of crab, shrimp and krill which are bio-waste from shellfish processing industry. The abundant source of chitosan makes it an excellent candidate polymer for various applications. In addition, chitosan has potentially manufactured by artificial culturing, thus it has the possibility further mass produced by biotechnological methods (Hall, 1996).

The main driving force in the advanced investigation and application of chitosan comes from the actuality that this biopolymer is not only naturally abundant, but it is also satisfactorily biocompatible, biodegradable and nontoxic. The metabolic degradation of exogenous or regenerated chitosan *in vivo* and biocompatibility of chitosan administered orally and intravenously in animal was presented by Hirano, et al. (1988) and Muzzarelli (1993). Gradual degradation of chitosan can occur *in vivo* by lysozymic hydrolysis (Sanford, 1989). The biodegradability of chitosan could be determined from the lowering of viscosity of chitosan solution in various buffers (Pantaleone, Yalpani and Scollar, 1991) or by checking the weight loss of chitosan (Struszczk, Wawro, Niekraszewicz, 1991) after immersion in incubating medium. As above mentioned the products made from chitosan are variously useful, and especially safety to human beings.

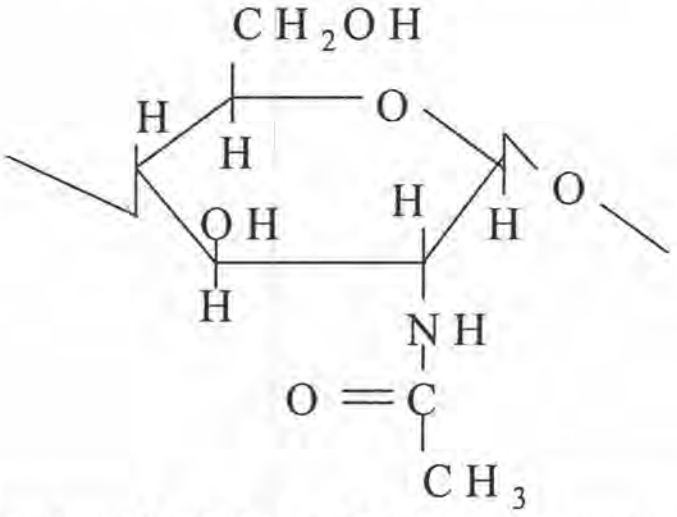
Cellulose chain mostly consists of β-(1-4)-D-glucopyranose units. Meanwhile, chitin has the same backbone but the 2-hydroxyl has been replaced by an acetamide group, resulting in mainly β-(1-4)-2-acetamido-2-deoxy-D-glucopyranose units. Chitosan is the N-deacetylated derivative of chitin. Commercially used chitosan is a unbranched binary heteropolysaccharide mostly consists of β-(1-4)-2-deoxy-D-glucopyranose units, but still remains acetamido structure units in polymeric chain. Structures of D-glucopyranose unit of cellulose, 2-acetamido-2-deoxy-D-glucopyranose unit of chitin and 2-amino-2-deoxy-D-glucosamine unit of chitosan are shown in Figure *1*. Main properties of chitosan such as source of the material, crystalline form, degree of N-deacetylation, molecular weight and solvents should be actually considered.



D-glucopyranose unit



2-deoxy-D-glucopyranose unit



2-Acetamido-2-deoxy-D-glucopyranose unit

Figure 1. Structures of D-glucopyranose unit of cellulose, 2-deoxy-D-glucopyranose unit of chitosan and 2-acetamido-2-deoxy-D-glucopyranose unit of chitin.

A flurry of applications and researches have been focused on chitosan since its structure is cellulose like, and the free amino groups on this polymeric chain contribute the reactive and polycationic nature. The potential application of chitosan as an excipient in oral formulation, as vehicle for parenteral drug delivery devices and the application of

this polymer to produce sustained-release system deliverable by other routes (nasal, ophthalmic, transdermal, and implantable devices) are reported (Felt, Buri and Gurny, 1998). Typically, chitosan degrades before melting due to the feature with extensive hydrogen like other polysaccharides. Therefore, the film fabrication cannot be made by molding with thermal processing. For industrial application it is necessary to dissolve chitosan in an appropriate solvent to spin fibers and films. Or the film was fabricated by casting the chitosan solution and then allowing to solidify by solvent evaporation. Owing to its peculiar glycosidic linkage on chitosan structure, its conformation is relatively rigid. As a consequence, it is easily filmable and the obtained transparent cast film or membrane shows the dominant characteristic to apply in many fields.

A plentiful research works on the investigation and application of chitosan film and membrane indicate the high potential use of this material in pharmaceuticals. These research works are mentioned as the following:

A. Utilization as Vehicles for Controlled Drug Delivery

Many investigators manifested the efficiency of crosslinked chitosan membrane for controlling the transport of diffusive molecules such as oxprenolol hydrochloride (Bolgiil et al., 1998); nifedipine (Thacharodi and Rao, 1993 a); propranolol hydrochloride (Thacharodi and Rao, 1993 b); sodium salicylate (Bonvin and Bertorello, 1993); indomethacin, lidocain and caffeine (Ikeda, Takayama and Nagai, 1997); chlorpheniramine maleate and guaifenasin (Remunan-Lopez and Bodmeier, 1997); vitamin B12 (Nakatsuka and Andrady, 1992); small organic compounds such as benzoic acid, benzenesulfonic acid ; nucleic acids such as uracil, cytosine, adenine and quanine; and amino acid such as L-phenylalamine (Uragami, 1994).

The transport behavior of some diffusive molecules through uncrosslinking chitosan membranes was also investigated by some investigators such as Sawayanagi, Nambu and Nagai (1982); Kanke et al. (1989); Qurashi, Blair and Allen (1992 a); Wanichpongpan (1997); Lim and Khor (1998). Angelova et al. (1995) loaded antimycotic drug (8-hydroxy-7-iodoquinoline-5-sulfonic acid) in chitosan membrane and tested the drug release and pharmacological efficiency. The determination of drug transport through the uncrosslinked membrane usually performed by using phosphate buffer or deionized water as extraction medium to avoid the swelling and dissolution of membrane.

Above investigations revealed that the permeability of chitosan membrane was ostensibly affected by different parameters, including the acid or base nature of the diffusive molecule (Sawayanagi, Nambu and Nagai, 1982), degree of crosslinking (Thacharodi and Rao, 1993 a; b), pH of extraction medium (Uragami, 1994), molecular size of diffusive molecule (Sawayanagi, Nambu and Nagai, 1982) and membrane thickness (Nakatsuka and Andrady, 1992).

B. The Other Application of Chitosan Film or Membrane

Among many coating materials, chitosan has been also listed as one of coating materials used in column film coating (Hall and Wallace, 1988). Recently, the technique of coating core medicament with chitosan film and subsequently over-coated with selected enteric-soluble polymer was also reported. Chitosan capsules coated with enteric film former were manufactured in order to deliver insulin to colonic absorption site of rat (Tozaki, 1996, 1997). This investigation demonstrated that chitosan capsule might be useful carriers for colon-specific delivery. This technique for producing oral capsule releasing drug in lower digestive tract was also listed on the patent of Yamada (1992 a, b). Another report employed this technique was from Jujio and Yoshiro (1992) who coated core solid medicament with chitosan and then top-coated with a specific enteric-soluble polymer such as hydroxypropyl methyl cellulose acetate succinate and hydroxypropyl methyl cellulose hexahydrophthalate.

Core tablets containing triamcinolone and other diluents were firstly coated with chitosan acetate film composed of the lubricants, magnesium stearate and talcum, and thereafter top-coated with enteric-soluble polymer. The rate of drug liberation could be manipulated by suitably adjusting the mixture ratio between chitosan and selected lubricant. The prolongation of drug release was achieved to about 4 hours in basic extraction medium (Yamada b, 1992). The study of Chen and Tsaih (1997) demonstrated that the preparation procedures (orifice method and complex coacervation method) and the characteristic of chitosan (molecular weight and chain flexibility) affected the mechanical and permeability properties of the prepared chitosan capsule.

Partially deacetylated chitin and chitin derivatives (carboxymethylchitin and dihydroxy propylchitin) were employed to coat onto oxytetracycline HCl core tablet by dipping method. The sustainable drug liberation from coated tablet into phosphate buffer was obtained (Sashiwa et al., 1994). The time when drug level in canine blood reached maximum after *in vivo* subcutaneous implantation of this dosage form was remarkable shifted to longer times (Morimoto et al., 1995). N-phthaloylated chitosan was prepared by Duc, Chau, Ha and Hung (1997) and used as enteric film former for tablets. This was insoluble in water, 0.1 N HCl , but readily disintegrated in phosphate buffer solution pH 6.8.

Chitosan acetate film was claimed to be a potential candidate material for electrooptic application due to its good thermal stability which was higher than 200°C and morphological observations disclosed that prepared film possessed a dense and homogenous amorphous structure (Jiang, 1996).

Method to Prepare Chitosan in Insoluble Form

Recently, many investigators attempted to prepare chitosan that became insoluble by crosslinking chitosan chain with crosslinking agent or converting its functional group with chemical reaction.

A. Chemical Crosslinking

The chemical crosslinking is the most recurrently method to prepare insoluble chitosan. The crosslinking agents used for this purpose are glutaraldehyde (Kim et al., 1992; Thacharodi and Rao, 1993 a,b; Jameela and Jayakrishnan, 1995; Berthold and Kreuter, 1996; Suto and Ui, 1996; Saha et al., 1998), glyoxal (Suto and Ui, 1996), tripolyphosphate (Mayer and Kaplan, 1991; Kawashima, et al., 1985; Puttipipatkhachorn and Anantakul, 1996; Remunan-Lopez and Bodmeier, 1997; Bolgiil et al., 1998) and epichlorohydrin (Wei et al., 1992).

This chemical crosslinking notably enhances the flexibility, reduces the swelling index and also affects the permeability of membrane. An enhancement of degree of crosslinking will usually reduce the membrane permeability. The residual of crosslinking agents is not amenable to human use due to its toxicity. Glutaraldehyde crosslinked chitosan microspheres were cytotoxic at all concentrations used toward B16 F10 cell (Carreno-Gomez and Duncan, 1997).

B. Modifying Chitosan Functional Group

The addition of hydrophobic functional groups on chitosan structure by chemical reaction is useful such as to enhance the metal chelating ability (Hall and Yalpani, 1980; Koyama and Taniguchi, 1986; Holme and Hall, 1991). A wide range of chitosan derivatives have been synthesized of which the mixed derivatives gave the most promising results. These chemical modifications of chitosan by introduction of suitable groups are rather complicated fabrication and had to utilize organic solvent involved in the reaction. The chemical reaction frequently used to synthesize insoluble chitosan is acetylation in suitable organic solvent using acid anhydride as main reactant (Kanbara and Iljima, 1988; Zhang, Kohr and Hirano, 1993; Luyen and Rossbach, 1995; Xu et al., 1996).

Mechanical Properties of Chitosan Film

Due to glycosidic linkage and long polymeric chain like cellulose, chitosan exhibits the property as a filmable material. Neutralized chitosan acetate membrane showed higher values of stress, strain and modulus than cellulose acetate membrane (How, Wanichpongpan and Chandrkrachang, 1997). The thermoelastic and equilibrium stress-strain properties of chitosan film slightly crosslinked with glutaraldehyde had a higher stress than expected and this result was attributed to an energetic component of the tensile force caused by hydrogen bonding interactions and/or to strain-induced crystallization (Andrady and Xu, 1997). As mentioned by many researchers, mechanical properties of chitosan film were notably affected by some factors as followed.

A. Effect of Electric Charge

Electric charge generated and utilized during casting of chitosan acetate film caused a parallel orientation of chitosan molecules due to its cationic nature of polymeric chain. In addition, this cast film showed the break point after yielding by stretching. This behavior was reported close to the inter-macromolecular sliding during elongation (Ikeda et al., 1995). Additionally, the estrangement of the diffracting planes in powder X-ray diffractogram confirmed that the orientation of chitosan film was changed by an electric charge (Ikeda et al., 1996).

B. Effect of Irradiation

An attempt to sterilize the products produced from chitosan was recently described. The gamma irradiation was arised as one of such methods. Gamma irradiation reduced the mechanical strength of the neutralized chitosan film as a result of polymeric chain scission, whereas the films after exposure to moist heat at temperature 121°C under the pressure of 15 lb/in^2 (as using in autoclaving process) retained their original tensile strength to a greater extent, though the film elongation rates were considerably lowered (Rao, 1995). However, Lim and Koo (1998) suggested that gamma irradiation might be an attractive sterilization method since the biocompatibility of neutralized chitosan acetate film was not affected by this irradiation dose of 25 kGy. While Lim, Khor and Koo (1998) reported that gamma irradiation in air enhanced both the Young's modulus and the tensile strength of film but not significantly altered the percent strain at break point or the energy to break point, and this irradiation in anoxia did not exhibit significant changes in mechanical properties.

C. Effect of Temperature and Moisture

Lim and Khor (1998) demonstrated that the extent of changes in mechanical strength and permeability of neutralized chitosan acetate films was influenced by temperature and moisture content of the heat applied. Dry heat treatment at 120°C lowered the strain at break point, but the Young's modulus remained relatively unchanged. The autoclaved film showed the weakest mechanical properties, but showed the lowest permeability to indomethacin compared to film heated in air or in anoxia. The investigators claimed that the autoclaving process might induce rearrangement of molecular chain which did not allow for chain slippage during stretching, but was structured enough to reduce the permeability of drug through the film. Maillard-type reaction was also mentioned that it was the cause of discoloration of chitosan film during heat treatment.

D. Effect of Incorporated Substance

Some substances was incorporated into chitosan film to modify its mechanical properties. These substances were such as potassium hydrogen phthalate and monosodium glutamate which provided the higher tensile strength of prepared film than

that of the plain chitosan film (Chandrkrachang and Wanichpongpan, 1997). Sucrose and sorbitol added to the blended chitosan/poly(vinyl alcohol) film could lower the melting point and percentage crystallinity. The tensile strength of film decreased proportionally to the plasticizer content whereas the percentage elongation increased considerably, particularly in the case of sorbitol (Arvanitoyannis et al., 1997). The tensile strength and percent elongation at break decreased as the amount of PVP (Qurashi, Blair and Allen, 1992 b) or PVA (Blair et al., 1987) in the blends was increased.

Glycerin, propylene glycol, polyethylene glycol and triethyl citrate were also assessed as plasticizer for chitosan film (Remunan-Lopec and Bodmeier, 1996). The plasticizing efficiency of these plasticizers depended on the compatibility between them and chitosan film. It was also found that the diffusion of chlorpheniramine maleate through crosslinked chitosan glutamate film increased with increasing concentration of glycerin (Remunan-Lopec and Bodmeier,1997).

Polymorphism and Crystallinity of Chitosan Film

Recent investigations revealed that the function of chitosan depended on its crystallographic characteristics (Koyama and Taniguchi, 1986; Qurashi, Blair and Allen, 1992 a; Ritthidej et al., 1994; Ikeda, et al., 1996; Ikeda, Takayama and Nagai, 1997). Powder X-ray diffraction was the useful method to characterize the crystallographic characteristics of this polymer. Reflection peaks at around 10°(2θ) and 15°(2θ) were attributed to the presence of hydrated and anhydrous crystals of chitosan respectively (Ogawa, 1991). The characteristics of unit cell such as dimension, composition, density and chain conformation and arrangement in crystal structure of anhydrous form of chitosan were profoundly elucidated by Yui(1994). The chitosan in a salt form was reported that it was essentially in amorphous phase compared to that of neutral form (Ratto, Chen and Blumstein, 1996; Samules, 1981).

The crystallographic characteristic of chitosan differed essentially in the lateral packing of the chains, corresponded either to chitosan alone or to chitosan in interaction with various molecules such as water, inorganic acids, organic acids, or salts. A flurry of in-depth researches on crystalline polymorphs of chitosan have been undertaken (Ogawa, 1984; Ogawa, 1991; Ogawa, Yui and Miya, 1992; Mazeau, Winter and Chanzy, 1994; Yui, 1994; Yamamoto et al., 1997; Kawada, 1998).

Crystallinity of chitosan film was affected from the method of preparation and heat treatment. Chitosan acetate film prepared on cast plate loaded with an electric charge had a higher crystallinity than normal cast film since the former promoted the greater degree of macromolecular orientation and crystallized formation (Ikeda et al., 1996). The proportion of hydrated and anhydrous crystal occurred in chitosan film was also affected from the neutralization technique (Ogawa, Yui and Miya, 1992). The loss of chain alignment of film after exposure to a negative pressure in anoxia detected in diffractogram was useful to explain the lowering tensile strength of treated film (Lim and Khor, 1998).

An enhancement of heating temperature of an aqueous suspension of chitosan increased an anhydrous crystal of chitosan. The occurrence of this crystal started to appear at 100°C and chitosan with a low molecular weight or low degree of N-acetylation had a greater tendency to crystallize in anhydrous form than that of high molecular weight and high degree of N-acetylation (Ogawa, 1991). The higher temperature of dry heat utilized to treat the chitosan acetate film induced a more peak intensity and the peak around 20° 2θ was more shifted nearly to anhydrous peak (Lim and Wan, 1995). The alteration in powder X-ray diffractogram especially whether the presence of anhydrous form will be useful to explain the change physicochemical properties of chitosan.

Film Coating

The oral route has been claimed to be the most popular route of drug administration regardless of the essence of the dosage form or drug delivery systems. The major considerations in the development of oral controlled release drug product include: the system or device for drug delivery; transit time in gastrointestinal tract and hepatic first pass elimination or presystemic elimination.

An application of a polymeric film coat is one of common practices in the preparation of dosage forms. In relatively simple terms, film coatings is the application and deposition of a thin layer of polymeric material on the core material. Film coating for tablet came into use in the 1950s as an alternative to traditional sugar coating procedures. Sugar-coating had much more effect, especially, on dissolution rate of fast release product than film coat (Pariyawatee, 1998). Many polymeric films, both natural, semisynthetic and synthetic, are virtually scrutinized and improved the range of utilization in pharmaceutical research. The purpose of coating includes : masking undesirable taste, odor and color; imparting a more glossy and elegant appearance; protecting the active ingredients against environment (light, air and moisture); increasing mechanical stability and prevent dust formation during subsequent packing and chipping; separating incompatible active ingredients; and ensuring the controlled or modified release of drug (e.g. fast, enteric and sustained release). Since diffusion of medicament through a membrane is a simple approach to obtain a predictable release rate, membrane-controlled systems are extensively interesting. The transport of medicament through permeable coating membranes is controlled by the permeation of water into the device and diffusion of medicament through the membrane into the extraction medium.

Because of both the expense of non-aqueous solvents used in the coating process and the problem of the liberation of these potentially explosive and harmful agents into atmosphere especially the high toxic or even cancerogenic chlorinated hydrocarbons, or the high cost of solvent recovery system, the manufacturers are actually favoring to use of aqueous-base film coating (Porter, 1979; Stern, 1983; Pondell, 1984; Phuapradit, 1995; Porter and Saraceni, 1988; Ansel and Popovich, 1990; Edgren and Theeuwes,1990; Seitz, 1990).

Although nowadays the use of aqueous colloidal dispersion coating formula is more interesting , these coating systems having some disadvantages that should be essentially considered and noted. Aqueous colloidal dispersions are generally expensive

and are prepared with rather complicated technique. The residual emulsifiers and remained monomers may produce detrimental effects to the properties of prepared film and may be harmful to human beings. Additionally, the stability is limited under certain conditions. The alteration of temperature, pH, ionic strength, and the high mechanical or shear during mixing can potentially alter the stability of the dispersion such as flocculation and coagulation (Bodmeier and Chen, 1991; Tamai, Oyanagi and Suzawa, 1991; Coffin and McGinity, 1992).

The film forming substances are usually the cellulosic derivatives, such as HPMC, HPC or EC, or acrylate polymers. Actually, the film cast from these materials is rather hard and brittle, therefore it is necessary to add a plasticizer which lowers glass transition temperature of the polymer. Coloring agent or pigment may also be incorporated (Lund, 1994). In order to enhance and complete the coalescence, the curing of film coated tablets is usually recommended after coating, especially in case of using aqueous colloidal dispersion as film former (Bodmeier and Paeratakul, 1994; Singh and Khan, 1997). Various coating variables, equipment type, film coating defect and solutions which should be considered in coating technology are described in many reports (Porter, 1979; Seitz, Mehta and Yeager, 1986; Seitz, 1990; Rowe, 1992).

Film Formation

In general, the spraying technique is employed to layer the coating solution on tablet surface. The process of film formation from aqueous film coating solution is relatively simple process. The conversion of a viscous into a visco-elastic film involves three main steps. Firstly, the solvent rapidly evaporates from the surface of sprayed droplets causing an increase in film former concentration in the solution and contraction in volume of the coating liquid. Secondly, the further loss of solvent by diffusing to the surface of coating make the coating increased and then the concentration is more increased to the point when the polymer molecules notably become immobilized (solidification point). Finally, there is additional loss of solvent resulting from the slow diffusion of residual solvent (time-dependent) through the coat (Porter, 1989).

As the droplets of polymeric solution are sprayed onto the surface of core tablet, they have to spread and set the force occurring between the film former molecule (cohesion), and between film and surface of tablet (adhesion). Great cohesive force will obtain if there is sufficient cohesive strength of film former, molecule to molecule, and the coalescence process is enough. The process of film formation is fulfilled when the individual droplets coalesce, thereafter providing the macromolecules opportunity to penetrate each other during solvent evaporation. The inherent film properties depend on the mesh size of the network and the strength of the bonds, especially in the area of entanglement (Banker, 1990)

Apart from the coalescence property, the coated film has to exhibit a tendency to proper adhere to the surface of core tablet. The degree of adhesion bases on the chemical and physical interaction between polymer, solvent, plasticizer and surface of tablet, as well as on diffusion behavior (Bauer, et al. 1998). The smaller the contact angle, the better the droplet will spread on the surface and the distribution of the coating around the

core. The latter case relates to the promotion of adhesive property of film coating (Bauer et al., 1998; Banker, 1990). The surface free energy determined from contact angle data is greatly influenced by the degree of interaction between the forces in the solid surface and in the adhering liquid. Hence, this value can be utilized to indicate the operative cohesional forces in the tablet surfaces that are effectively interacting with the liquid and can be exploited to predict the adhesion of film coating to tablets surface (Harder, Zuck and Wood, 1971; Janule, 1995).

General Composition of Coating Formulation Including:

A. Film Former

The film former may be categorized into three types including: (1) the natural compounds such as polysaccharides like starch, dextrin, malodextrin, gelatin, pectin, alginate and carrageenan; (2) the semisynthetic compounds such as methyl-, ethyl-, hydroxypropyl-, hydroxypropylmethyl cellulose and several esters, especially cellulose acetate phthalate; and (3) the synthetic compounds such as polyacrylates, -methacrylates, -aminoalkyl methacrylates and- methacrylesters.

Practically, film formers are most widely divided according to their solubility properties as water soluble, water insoluble and enteric film former. The commonly used polymers for rapidly disintegrating film coating are water soluble film formers such as cellulose ethers like hydroxypropyl methyl cellulose, methylcellulose, hydroxypropyl cellulose, hydroxy ethylcellulose, sodium carboxy methylcellulose; the other synthetic polymer such as polyvinylpyrrolidone and vinyl pyrrolidone/ vinyl acetate copolymers; and water soluble salts form of acrylate polymer. Film coatings for sustained release usually employ the water insoluble polymer such as ethyl cellulose and polymethacrylates as release rate controlled membrane. Enteric polymers are hydroxypropyl methyl cellulose phthalate, methacrylic acid-methacrylic acid ester copolymers, cellulose acetate trimellitate, cellulose acetate phthalate, carboxymethyl ethylcellulose and hydroxy propyl methyl cellulose acetate succinate, polyvinyl acetate phthalate. This latter group of polymers is soluble in basic environment such as in small intestine, thus it can be used as protective barrier for drug that sensitive to acidic environment in stomach.

Some investigators evaluated some materials such as maltodextrin (Porter and Woznicki, 1989), cereal solid hydrolysate (Small and Jeffries, 1973), substance isolated from the root of *Salacia macrospera* (Venkateswarlu et al., 1993) and zein (Beck, Tomka and Waysek, 1996) as pharmaceutical film former. The first two materials were utilized as water soluble film former and the last two materials were applied as water insoluble film.

B. The Plasticizer

The mechanical properties of polymeric film can be modified by an incorporation of internal or external plasticizing techniques. Internal plasticizing pertains to the chemical modification of basic polymer such as an alteration degree or type of substitution and chain length of polymer. Meanwhile, external plasticization is achieved by the incorporation of a plasticizer to the pre-formed polymers. Practically, the manufacturer utilizes external plasticizers as additives in coating formula. The substances are usually high boiling point liquids or low molecular weight solids and polymeric substances which should homogeneously disperse in the film formers. The plasticizer alters the polymer-polymer interactions resulting in decreasing molecular rigidity. Plasticizer can alter the flexibility, tensile strength or adhesive properties of the plasticized film. Usually, these substances can minimize the brittleness, increase film flexibility and facilitate film distribution on tablet surface.

Since plasticizer molecule is rather small, it can penetrate and distribute between polymeric chain, thereby reducing the physical or chemical interaction on among the polymeric chain in the film coat. The flexibility of polymeric film is enhanced because plasticizer molecules push polymeric chain segments further apart or alter the average chain conformation through molecular effects. The plasticizer can enhance the segmental mobility of polymer. This effect promotes the lowering of the glass transition temperature (Tg) of polymer, and that the film can become plastic like behavior in the temperature range for processing (Seitz, Mehta and Yeager, 1986; Bauer et al., 1998). Lim and Wan (1994) mentioned that the plasticizer not only reduced the degree of crystallinity in the films, but also lowered the crystalline melting temperature probably by introducing defects into the crystal lattice.

The definition and more explanation about glass transition temperature are mentioned in many reports (Okhamafe and York, 1987; Radebaugh, 1988; Misev, n.d.). Thermal analysis is the effective method to determine and study about the effect of additives on the Tg of the film coat. The thermal analysis embraces a group of various methods to determine a physical property e.g. enthalpy, mass, volume or birefringence as a function of temperature. Gedde (1990) briefly presented the differential scanning colorimetry (DSC), differential thermal analysis (DTA), thermalgravimetry (TGA), thermal mechanical analysis (TMA) and thermal optical analysis (TOA) as analysis methods and also mentioned in more detail their useful application on investigation in polymer. DTA and DSC provide discrepancies with Tg values, due partly to the poor resolution of these techniques which record Tg as slight changes in the baseline. Basically, the Tg determinations are sensitive to the molecular structure, the presence or degree of crystallinity, heating rate, residual solvent, diluent and molecular weight variation. Differential mechanical thermal analysis (DMTA) is generally recognized as being more sensitive to molecular motion, hence, this technique is quite useful for determining subtle transitions in polymer (Rials and Glasser, 1988). Johnson, Hathaway, Leung and Franz (1991) demonstrated that the DMTA results further confirmed TMA results by showing that for the same percentage of plasticizer, PEG 400 reduced the softening temperature of HPMC film to a greater extent than did triacetin. Torsional braid analysis (TBA), a dynamic method, can produce data of high precision and resolution and can provide higher values than static methods such as DSC and DTA (Sakellariov, Rowe

and White, 1985; Radebaugh, 1988; Ford and Peter, 1989). The plasticizing efficiency of PEG 6000 on HPMC/PVA blends has been scrutinized by TBA. PEG 6000 exhibited a poor plasticizing effect on the two pure homopolymers, and had no effect on the behavior of either HPMC-rich or PVA-rich phases of the blends (Sakellarion, Hassan and Rowe, 1994).

Attempt to explain the mechanism of plasticization is described in main three theories called the lubricity theory, gel theory and free volume theory. The detail about concept in each theory is proposed and explained by Doolittle (1954) and Seara and Darby (1982). Sasty et al. (1988) found that there was an increase in free volume fraction from 5.000 to 6.082 as the diacetin concentration increased from 90 to 170 % in film prepared from cellulose acetate pseudolatex. This free volume was estimated by positron annihilation spectroscopy.

Antiplasticizing effect is often found when the low level of plasticizer is added in polymeric films. This phenomenon arises from an interaction between polymer and the plasticizer molecules and minimizes the molecule mobility of the polymer and also plasticizer (Guo, 1993; Wang et al., 1997). More investigations found that at temperature raised above Tg, the films would contain sufficient energy to disappear the antiplasticizing effect. The additional proposed mechanism of antiplasticization was perhaps a combination of several factors. These included the interaction between the molecules of polymer and of the plasticizer with hydrogen bonding, Van der Waal's force or steric hindrance. Hence, there is the reduction of free volume of the polymer and a physical stiffening resulting from the presence of rigid antiplasticizer molecules adjacent to the polar groups of the polymer (Guo, 1994 a, b; Wang et al.,1997).

The direct relationship between plasticizer content and rate of solvent evaporation was reported by Gutierrez-Rocca and McGinity (1993). Due to the strong molecular interaction forces between the polymer and the plasticizer than between the polymer and the solvent, high level plasticizer incorporated on acrylic aqueous dispersion or solvent was found to augment the evaporation of the solvent.

The choice of plasticizer selected to modify mechanical properties of polymer film depends upon the ability of plasticizer to solvate the polymer and to alter the polymer-polymer interactions, and at proper proportion to the polymer, it should impart flexibility by lower glass transition temperature and molecular rigidity. The type and concentration of plasticizer used should be seriously considered to achieve the desired film properties.

C. The Colorant

The colorant can provide a distinctive color and can give a unique identity for products. The choice of this substance approved for application in pharmaceutical, food and cosmetic is severely restricted. The most colorants are provided by certified Food, Drug, and Cosmetic (FD&C) or Drug and Cosmetic (D&C) dyes (Goldemberg, 1983; Seitz, 1990). The various shade of color can be obtained by combination of primary colors according to the trichromatic theory of color vision.

The amount of soluble dyes added in coating solution is normally lower than pigments. The dye molecules potentially migrate to the surface of film coating during solvent evaporation resulting in the mottled and marbled appearance and causing it to rub off (Bauer, 1998). The retardation of disintegration time and drug liberation from tablets (coated with HPMC, HPC and sodium ethylcellulose sulfate) due to an incorporation of water soluble dyes such as FD&C Red No.3, No.4, No17, et al. in the film was detected (Prillig, 1969), however the cause of this occurrence was not in-depth investigated.

D. The Pigment

Pigment is a solid dyestuff or inorganic color which unfolds its color and hinding power when homogeneously mixed and finely dispersed. It is often incorporated in coating formulation to increase solid-loading, to accelerate correspondingly the build-up of the film coat structure, and to reduce coating time. Occasionally pigment is added to minimize tackiness or stickiness. Particle size, source and type of pigments are the main factors affected the covering power and tinctorial strength.

An incorporation of pigment mostly affected the mechanical properties of film. Because of the adsorption of polymer on pigment surface, the polymer chain will tend to restrict the motion or even totally immobilize some of polymer chain. This evidence promotes the localized stress and also possibly to induce the localized thermal stress due to the difference between the thermal expansion of the pigment and film coating (Parker, Peck and Banker, 1974; Rowe, 1982; Okhamafe and York, 1985 a)

Hydrodynamic and reinforcing effect are the two main types which are noted as the factors of localized stress. This first effect comes from the physical nature of pigment such as size, shape, volume, concentration and orientation and the latter effect appears from stress physical and sometimes, chemical bonding between surface of pigment and polymer chain (Parker, Peck and Banker, 1974; Rowe, 1982; Okhamafe and York, 1985 a). The developed model to evaluate and simulate the crack propagation for tablet film coating containing pigment was useful. From this model it was found that crack velocity was highest at small particle size (Rowe and Roberts, 1992; Rowe, Rowe and Robert, 1994)

Generally, pigment incorporation reduces both an extensibility as well as a tensile strength at break. An addition of suitable plasticizer or utilization of the high molecular weight polymer as film former effectively minimize the localized cracking (Funke, Zorll and Murthy, 1969; Okhamafe and York, 1984 a)

Mechanical Properties

Coated polymeric film around the core tablet practically supplies a physical protection to the tablet and have to, therefore, remain intact and have suitable mechanical properties. The coating must be durable and resistant to chipping and cracking during

handling or transport. Basically, mechanical properties are associated with the response that results after applying the force or load to test specimen. Mechanical properties include compressive strength, tensile strength, shear strength, fatigue and flexing, hardness, indentation, and friction. These mechanical properties of polymeric matter are depended on its nature and composition. In linear polymers, generally the chains tend to pack closely, enhancing density with an increased percentage of crystallinity. Meanwhile bulky side groups in branched polymers keep the polymer chains farther apart, thus decreasing the tendency to crystallize. Amorphous regions of polymer have a long-range disorder of liquids and isotropic in nature. An enhancement of molecular mass and crystallinity generally increases in softening temperature, strength, stiffness, hardness, creep resistance, and impermeability to gas and liquid and vice vesa.

There are three direct kinds of stress commonly applied to test specimens ; compression, tension and shear. Force applied should be utilized as suitable rate. Due to viscoelastic properties, therefore, when polymeric material subjected to load for a period of time it tends to deform (strain). The degree of deformation depends on the load duration. Tension is the most commonly used to test the film coating specimen, and tensile strength, modulus of elasticity, area under the stress-strain curve are the useful indicative parameters. Practically, the film coat should be hard and tough without being brittle. These mechanical properties are reflected in a high value of tensile strength, a high modulus of elasticity and substantial elongation and resulted in high area under the stress-strain curve (Nagarsenker and Hegde, 1999).

A. Tensile Strength and Elongation

When the stress is applied to a material by pulling until broken, tensile strength can be calculated by dividing the maximum load (force) by the original cross-section area. Pulling stress usually causes material to deform by thinning and stretching in length. The alteration of length, is called strain which is usually measured in percent of elongation. Elongation is defined as a measure of the capacity of the specimen to deform prior to failure. Stress-strain profile is typical means of expression and plotting the strength of test specimen. The classification of the great various stress-strain behaviors of materials is described by Aulton (1982).

B. Modulus of Elasticity

The modulus of elasticity, also called Young's modulus, is the ratio between the stress applied and the strain, within the elastic range. This value can be calculated by dividing the stress (load) in pascals by the strain in millimetre. This ratio is useful in specifying how far a stiffness and rigidity under a given load. A great modulus indicates that the specimen is rigid which will be resistant to stretch and elongation (Nash and Sturgess, 1977).

C. Area Under the Curve

This is a function of the work done (force X displacement) in the breaking the film and is representative of the film toughness. Toughness is much more a function of stress, elasticity and internal damping. The work done is the energy to break point and the toughness is calculated by dividing the energy to break point by specimen volume.

The Adhesion Between Film Coat and Tablet Surface

Adhesive force is the force required to pull a film coating from the tablet surface. Adhesiveness may be defined as the force required to remove the film coating from a unit area of the tablet surface using specially designed tensile tester (Fung and Parrott, 1980).

Good adhesion of coating substance onto tablet surface is desirable for a pharmaceutical product. Loss of adhesion may reduce the mechanical protection of film-coat and may enhance an accumulation of moisture at the film-tablet interface, probably affecting the stability of active ingredient susceptible to degradation by hydrolytic mechanism (Felton and McGinity, 1997).

Typically adhesion theories are based on the effects of adsorption and wetting, on diffusion, on electrostatic interaction, and mechanical blocking of surfaces to the substrate by adhesive force. Numerous investigations have established that adhesion occurs through different sophisticated style. The processes of mechanical entanglement, physical adhesion, formation of a chemical bond, shrinkage, forces, metallurgical interaction or diffusion have been formed at the contact boundary. Several types of adhesive bonds are classified and described by Sperling, 1992. The first stage of adhesion is migration of polymer toward the surface of the tablet and the second stage is adsorption of polymer as a result of which the distance between its functional groups and the surface of tablet is comparable with the radius of action of molecular force (Koryagain, 1997). Many investigations about adhesion between film coating and tablet surface have been reported (Fisher and Rowe, 1976; Rowe, 1978,1980; Okhamafe and York, 1985 b; Felton and McGinity, 1996,1997). The nature of tablet surface such as hydrophobicity, roughness and the composition of coating formulation, and also the test method affect the adhesion property.

Propranolol Hydrochloride

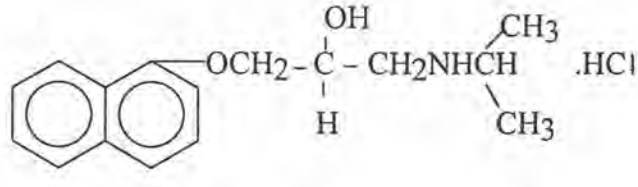


Figure 2. Structure formula of propranolol hydrochloride.

Chemical name of propranolol hydrochloride is (±) 1-isopropylamino-3-(1-naphthyloxy)-propane-2-ol hydrochloride. The empirical structure is $C_{16}H_{21}NO_2$, HCl with molecular weight of 295.8. Propranolol HCl is white or almost white crystalline powder, odorless, nonhygroscopic and bitter taste. It has melting point at 163-166°C and pKa of 5.0-6.0. It is classified as water soluble drug. It is soluble in 20 parts of water and slightly soluble in chloroform, and practically insoluble in ether (Reynold, 1994).

This model drug is a beta blocker clinically used in the treatment of hypertension and to improve the tolerance to exercise in patients with angina pectoris. It has been given for the prevention of re-infarction. It is also used in the treatment of cardiac arrhythmias and it is often effective in supraventricular tachyarrhythmias (John,1990; Lund, 1994).

In aqueous solution, the oxidation of the isopropylamine side chain, accompanied with the reduction in the pH of the solution decomposed the compound. This drug is most stable at pH 3 and decomposes rapidly under alkaline condition. Propranolol HCl is sensitive to light, but stable to heat. It should be preserved in well-closed containers. The USP requires the preparations to be protected from light (The United States Pharmacopeial Convention, 1990).

Release Mechanism

The liberation of medicament from prepared dosage form is mostly detected from the dissolution test. The release behavior can be observed from the amount of drug released and time profile. In general, the obtained release profiles contain elementary information exemplified the structure and mechanisms of a delivery device on a microscopic scale. Possibly, interactions and other subtle relationships between encapsulated component and its carrier can be obviously known. More detailed information on the microstructure and properties of the selected device appears to be necessary to understand the release mechanisms. Ideally, the release profiles can be corrected to understand the microstructure of the carrier, hence, the manufacturer can predict the release characteristic and can design the device with the more desired release pattern.

Additionally, practical methods such as optimization techniques combined with above data will be useful in designing or construct the desired drug delivery system (Gopferich,1996; Phares, Cho and Swarbrick, 1996). The mathematical model is developed to describe the drug release behavior and is also useful for aiding the understanding of delivery system. The development is based on a composite of geometrical shape to predict drug release

The Release Model

For this study, the selected conventional mathematical models for comparison with new adapted derived models were cube root, first order, Higuchi, power law expression, zero order models. Each mathematical model consists of independent and dependent variables, constants and parameters that have to be related or estimated.

A. Cube Root Model (Wagner and Permarowski, 1971; Abdou, 1989).

Hixson and Crowell carried out research to investigate the subject of agitation and establishing a basis which might serve for a quantitative comparison of different agitations (Wagner and Permarowski, 1971). They derived the well-known cube root law by modifying equation of Noyes and Whitney :

$$dc/dt = K_1S(Cs-Ct) \quad \text{.....(Eq. 1)}$$

where dc/dt=dissolution rate of the drug, K is the dissolution constant, Cs is the equilibrium concentration of the drug and Ct is the concentration at time t and S is the surface area.

This allows for the change in the surface area that usually presents during dissolution and to represent the rate of appearance of the drug in the medium by multiplying each side by volume (V) and letting $K_2=K_1V$

$$dW/dt = K_2S(Cs-Ct) \quad \text{.....(Eq. 2)}$$

$$VdW/dt = -K_2S(Ws-Wo+W) \quad \text{.....(Eq. 3)}$$

where W is the weight of the remained solid drug at time t, Ws is the weight of solid needed to saturate the volume of a medium at a given temperature and Wo is the initial weight of the particle.

Fick's first law is added into the above equation and allowing the surface to alter with time and assumed $S = KW^{(2/3)}$. From the sphere assumption, the radius ; $r = (3 W/4\pi\rho)^{(1/3)}$ and surface area; $S = 4\pi r^2$. Therefore K is a constant involved the shape and density of the substrate. Then by integrating under the condition that W is equal to Wo at time zero, results

$$Wo^{(1/3)}-W^{(1/3)} = (4\pi\rho\eta/3)^{(1/3)} * DCs\ t/h\rho \quad \text{.....(Eq. 4)}$$

where Wo is the initial weight, W is the weight at time t, ρ is the substrate density, η is the viscosity, D is the diffusivity, Cs is the solubility and h is the diffusion layer thickness. Thus, incorporating all constants into the constant K.

$$Wo^{(1/3)} - W^{(1/3)} = Kt \quad \text{.....(Eq. 5)}$$

B. First Order

The first order model selected for the case of the release rate is proportional to the mass of drug contained within the device. The release rate could be expressed as

$$dW/dt = k (W_0-W) \quad \text{.....(Eq. 6)}$$

where W_0 is the mass of drug in the device, W is the drug remaining in device and k is the rate constant. On rearrangement, this model can be expressed as:

$$W = W_0e^{-kt} \quad \text{.....(Eq. 7)}$$

In case of coated dosage form, typically, constant drug release can be achieved up to about 70-80% of drug release after which the release rate will decline. Presumably, the gradually declined rate of a constant-thermodynamic activity reservoir system in late stage of drug release is due to the decreased drug concentration inside the device below the saturation level resulting in a loss of thermodynamic activity and release rate. This release behavior can be described as first order characteristic (Chien, 1983; Husson, 1991; Rekhi, Porter, and Jambhekar, 1995).

C. Higuchi's Model

Higuchi (1963) introduced a mathematical model for the drug released from an inert matrix by plotting the percentage of drug liberated as a function of the square root of time:

$$F = K(t)^{(1/2)} \quad \text{.....(Eq. 8)}$$

where F is the fraction of drug released, t is the time and K is the release constant defined as

$$K= [((D\varepsilon)/\tau)(2A-\varepsilon Cs)Cs] \quad \text{.....(Eq. 9)}$$

where D is diffusion coefficient, ε and τ are the porosity and tortuosity factor of matrix respectively, A is the amount of drug in the matrix (weight/volume) and Cs is the solubility of drug.

The level of film coating sometimes related to the change in release mechanism. The drug release from incompletely coated bead at low levels of Aquacoat could be described with the square root of time model, while that from high level of coating appeared to be best described by zero order (Zhang, Schwartz and Schnaare,1991). Samani et al. (1999) also applied this model as one of release models to study the release kinetic of atenolol from film-coated tablets.

D. Power Law Expression

The kinetics of drug liberation can be analyzed by the following commonly used exponential equation:

$$F = K(t)^n \quad \text{.....(Eq. 10)}$$

while F is the fraction of drug released up to time t, K denotes as a constant incorporating the structure and geometric characteristics of the release device and n is the release component indicative of the mechanism of release (Ritger and Peppas, 1987 a; b). Mathai and Thomas (1996) investigated the transport behavior of aromatic hydrocarbons in crosslinked nitrile rubber membrane and applied the power law expression to analyze the transport mechanism. Chen and Hao (1998) applied this equation to analyze the release mechanism of verapamil released from insoluble gelatin capsule. A zero-order drug release profile could be achieved by simple inserting the mixture of verapamil and starch into this capsules.

The relationship between the diffusional exponent n and the corresponding release mechanism is dependent upon the geometry employed as presented in Table *1*.

Table 1 Diffusional exponent and mechanism of drug from various non-swellable and swellable controlled release systems.

Diffusional Exponent (n)			Drug Release Mechanism
Thin film	**Cylindrical Sample**	**Spherical Sample**	
0.5[a]	**0.45[a]**	**0.43[a]**	**Fickian Diffusion**
0.5<n<1.0[a]	**0.45<n<1.00 [b]** **0.45<n<0.89 [c]**	**0.43<n<1.00 [b]** **0.43<n<0.85 [c]**	**Anomalous (non-Fickian Transport)**
1.00[a]	**1.00 [b]** **0.89 [c]**	**1.00 [b]** **0.85 [c]**	**Case-II Transport**

* a: in case of both non-swellable and swellable controlled release system; b: in case of non-swellable controlled release system; c: in case of swellable controlled release system.

E. Zero Order

An ideal controlled release system is one which can manipulate the medicament released at constant rate until the system is exhausted. The drug transport through the membrane by simple diffusion should provide the constant release rate. Mathematically, the release rate from this device is expressed as

$$dW_t/dt = k \quad \text{.....(Eq. 11)}$$

where k is a constant; W_t is the mass of drug released and t is the time.

This release pattern is called zero-order release model. If the drug diffusion is the major release mechanism, the release rate should be directly proportional to the drug solubility.

F. Osmotically Driven Release

Basically, osmotic pumping mechanism should be included and considered when analyzing release behaviors of membrane coated products. When the polymeric film is porous or semipermeable, there is a tendency of release being driven by an osmotic driving force (Lindstedt, Sjoberg and Hjartstam, 1991; Herbig et al., 1995). After immersion the device in an extraction medium, aqueous is imbibed through the coat, creating a solution in the core and then generating the interior osmotic pressure. Because of the occurrence of osmotic difference, it then provides the driving force for efflux through pores in the film. The release rate for this process can be described by

$$J=K\sigma\Delta\pi(C_i-C_m) \qquad \text{.....(Eq.12)}$$

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

Even the case of very low osmotic permeability, as for pure ethyl cellulose film, it may be sufficient to induce osmotic pumping. When the membrane coat is more permeable to the drug, drug diffusion and osmotic pumping may both contributed to drug release (Theeuwes, 1987; Ragnarsson et al., 1992). The drug delivery rate combined between diffusion and osmotic pumping during steady-state zero order release rate of drug can be expressed as:

$$dm/dt = \frac{A.S.Lp\sigma.\Delta\pi}{h} + \frac{A.P.S}{h} \qquad \text{.....(Eq. 13)}$$

where A is the device surface area, h is the coating thickness, S is the drug solubility, $Lp\sigma$ is the fluid permeability of the coat, P is the permeability coefficient of the drug through the coat.

The first term represents the osmotic pumping component and the second term is the contribution from simple diffusion (Appel, Gaylen and Zentner, 1991). Typically, as long as a reservoir of undissolved drug is in the core surrounded by a saturated drug solution and enveloped by an intact membrane the constant drug release can be achieved up to about 70-80% of drug release, and this release pattern is frequently called "zero order release behavior", after which the release rate declined. Presumably, the gradually declined rate of a constant-thermodynamic activity reservoir system in late stage of drug release is due to the decreased drug concentration inside the device below the saturation level resulting in a loss of thermodynamic activity and release rate (Chien, 1983; Husson, 1991; Rekhi, Porter, and Jambhekar, 1995). In particular, osmotic release can be

observed even from the system coated with high porosity film, however, as porosity is greater, the osmotic effect on release kinetics decreases (Lindstedt, Sjoberg and Hjartstam, 1991)

Aqueous pores can be promoted by adding water soluble substances in the coating formulation. These substances are hydrophilic, water soluble substances such as methyl- and hydroxypropyl cellulose, polyethylene glycol, polyvinylpyrrolidone or water soluble solids. Urea is often chosen as a pore-forming agent because of its small, readily water soluble and also uncharged molecule. The pores can enhance the permeability of water insoluble film coating (Appel and Zentner, 1991).

Alteration the osmotic pressure in the dissolution medium is a convenient way to check the osmotically driven mechanism. However, it is important to consider the theoretical limitation about the suitability of osmotic pressure adjusting agent (Lindstedt, Ragnarsson and Hjartstam, 1989). Typically, the experiment should also determine that the drug solubility is not affected by the presence of high concentration of the osmogent in extraction medium. For instance, sodium chloride or potassium chloride are less preferable, since both osmotic pressure and ionic strength effects can contribute to change in the release behavior. These inorganic salts may also affect the film permeability through ion-exchanging. Therefore Narisawa (1997) utilized glucose as osmotic pressure adjusting agent to minimize the influence of drug solubility or drug permeability through Eudragit RS-based coating.

Theoretically, the reservoir type delivery system should be capable to release the encapsulated agent at a constant rate, but in practice the deviations from zero order kinetic can occur from several factors. Two such factors are boundary layer effect and the burst effect.

- Boundary layer effect arises when the rate of extraction of the active agent from the membrane is slow thus the concentration of the active agent in membrane surface gradually increases with time. Then the concentration gradient decreases and consequently the flux also decreases.

- Burst effect occurs in case of the membrane saturated with the active agent from core component during storage. As this device exposed to dissolution medium, the active agent will readily liberated from the membrane. The magnitude of this effect can be predicted from the diffusion coefficient of the active agent in the membrane, the membrane thickness, and the time interval of storage (Heller, 1987).

Classically, the osmotic pressure is given in atmospheres, however, in clinically practice, it is expressed in terms of osmols. When a solution containing one mole of a nonionizable substance in one kg of water (one molal solution) it is referred to as one osmolal solution. Basically osmolality measures total amount of particles dissolved in a kilogram of water, that is, the osmoles per kilogram of water, and depends on the electrolytic nature of the substance. Therefore m in Morse equation could be replaced by osmolality measured from osmometer.

G. Weibull equation

Weibull equation was originally designed to apply for a large variety of distribution such as yield strength of fibres and steels, size of beans and insects. This expression consists of a set of parameters related to scale, location, and shape (Langenbucher, 1972). The weibull equation has been applied successfully to various common type of dissolution curves and useful involving the quantitative interpretation of dissolution data. When applied to release data, the Weibull equation expresses the fraction of cumulative drug release, F, at time t, by

$$F = 1-e^{((-(t/Td)^B))} \quad \text{.....(Eq. 14)}$$

where $Td = A^B$, A is the scale parameter, B is the shape parameter and Td denotes the time interval when 63.2% of drug has been dissolved. The shape parameter, B, characterizes the curve as exponential when B=1 and sigmoidal curve when B>1. Racz, Dredan, Antal and Gondar (1997) mentioned about shape parameter as $B \simeq 1$ refers to first-order dissolution kinetics, and B>1 indicates the parallel moving courses in adding to diffusion (disintegration, erosion). Td reflects the degree of retardation of drug liberation, the greater the Td value the slower the liberation, however, there is no information signified the retardation mechanism (Jorgensen and Jacobsen, 1992; Mauger, Chiko and Howard, 1986). Christensen, Hansen and Bechgaard (1980) claimed that the flexibility of distribution in Weibull equation was obvious, and it had therefore also been applied a large variety of distribution such as yield strength of fibres and steels, size of beans and insects, and it was not designed to described drug release, and there are no obvious physical reasons for using particular distribution.

Mathematical Modeling for Drug Release Data

The advantage and reasons for construction the suitable and successful mathematical modeling for drug liberation data is to allow the exploration of mechanisms, simplify the recorded experiment results by the condensation of the data collected, and allow the useful prediction. The fitting of *in vitro* dissolution data to mathematical expression has performed and presented in many report (Christensen, Hansen and Bechgaard, 1982; Leary and Ross, 1983; Hariharan et al., 1994; Abu-khalaf and Soliman, 1996; Zimm, Schwartz and O'Connor, 1996; Narasimhan and Langer, 1997). Dissolution properties can be treated and analyzed by statistical and mathematical methods (Jorgensen and Christensen, 1996). Mathematical modeling of diffusion processes may serve two purposes: (1) the determination of release rate and the prediction of diffusion behavior (2) the elucidation of the physics of a particular drug transport phenomenon (Narasimhan and Langer, 1997). The understanding of the of drug liberation behavior may provide a useful means for designing the composition of constructed device with predetermined release profiles (Racz, Zelko and Bihari, 1996). Additionally the obtained release data may be summarized by means of the few main parameters in the suitable model.

The values of the numerically determined parameter that provided suitable prediction potential should be included in model. The proposed model should be simply to apply, as the necessary parameters such as rate constant could easily be determined (Leary and Ross, 1983). Generally the created model consists of the dependent variables measured during the experiments (y), independent variables (x), parameters (p) and constants (c). Therefore a general form of mathematical expression is $y = f(x, p, c)$. In order to define a model which will represent a better fit, the modified equation with mathematical adaptation had to be employed. Usually, the mathematical model construction for coated dosage form should compose of the following parameters: diffusion coefficient of diffusant in solution and membrane, partition coefficient, membrane thickness and a composite of geometrical shape consideration (Tahara, Yamamoto and Nishihata, 1996).

Fitting the Model Expression to Experimental Data

Fitting the obtained mathematical expression of developed model to the experimental drug release data is a next crucial procedure. The objective of this procedure is to minimize the overall difference between the experimental data and the calculated points by adjusting the values of the included parameters (Swarbrick and Boylan, 1988). Linear or nonlinear regression techniques is always chosen to fit the model to experimental data. The commentary on using these two techniques for data fitting is mentioned as below.

The drawbacks of data transformation using linear regression is that the fitting may not be mathematically accurate for the original data as noted by Lu, Abu-Izza and Mao (1996). When manipulating the model to obtain a straight line, the original experimental data have to be transformed with taking the logarithm or the reciprocal of the data point. The logarithm or semi-logarithm transforms will provide the visual distortion and the last few data point at the lowest concentration may dominate. This will distort the data and the error or variance of the data. Additionally, it can occur a source of error when generally applied linear fitting program fit the data to a straight line with an intercept that is different from the origin, however depends on the selected model applied for the data. The standard deviations of the data are usually not taken into consideration when linear fitting is done. For instance, linear transformation of Weibull equation markedly distorts the original scale of the observations particularly the deviations occurring in the lower and upper part are extremely over-concentrated, when compared with those in the middle of the curve (Langenbucher, 1972).

Nonlinear Model Fitting

In the case of mathematical expressions that are not naturally straight line, such as derivative type, nonlinear regression analysis is often the best approach. Since with this analysis technique the observed data and the corresponding dependent variable can be analysed without transformation, the data and error or variance are not distorted. Nonlinear regression analyses inclusively involve relatively complex calculations and

thus are well suited for computer assistance. Nevertheless, the computer must have a well-developed sequence of steps of algorithm to follow. The computer program, based on nonlinear least square analysis, determines the best model by minimization on a weighted sum-of-squares of experimental data with respect to the tested model (Rubinstein, Gonen and Friedman,1986; Weiner and Yuh, 1994). The objective of the nonlinear regression analysis is to reach the global minimum. Many basic algorithms, each with a number of refinements, are gainful in the search for a global minimum. Some of these fundamental methods are such as the grid search, steepest descent, Gauss-Newton, Marquardt, and the simplex methods (Swarbrick and Boylan, 1988).

The nonlinear fitting of actual drug dissolution profiles to equation derived from different model is conducted using a software package of nonlinear regression analysis program. This study applied the computer program named "Scientist®" for data fitting and determination of estimate parameters. While the selected mathematically models were cube root, first order, Higuchi, power law expression, zero order and newly derived mathematically models. Each mathematical model consists of independent and dependent variables, constants and parameters that have to be regarded. Even though there is derivative type equation, Scientist® which carries out numerical integration can provide the degree of fitting estimated on the basis of sum of squared difference between observed and calculated values. Thus, it can compare degree of fitting between derivative type equation and integrated type equation. The Scientist® program uses minimization of sum of square value as the criterion of best fit. The objective is to reduce the overall difference between the observed data and the calculated points by adjusting the values of the parameters. The estimated initial parameters have to first employed to generate estimates which result in relatively small sum of square. The initial estimated parameters are then refined via an iteration process to achieve a minimum sum of square.

Least squares fitting in Scientist® is performed using a modified Powell algorithm to find a local minimum, possibly the global minimum, of the sum of squared derivatives between observed data and model calculations. The Powell's method is the prototype of direction-set methods in multidimensional minimization. The detail of Powell's method and modified Powell's methods are described by Dixon (1973) and Press et al. (n.d). It is generally obvious from watching the performance of this algorithm whether convergence has been achieved. Failure is usually found in case that a convergence of the initial parameter estimates is so far removed from the solution and thereafter Scientist® cannot determine which direction to search. The usual behavior is that the algorithm takes anywhere from a few to several dozen iterations in converging to the solution. Sequently, this program graphically generates the presentation of the model fitting. Visual examination of the fraction released-time curve in the input data can help one to determine whether to reject the fitting results.

Several statistics parameters that may be used as indicators of goodness of fit are also reported by Scientist®. Coefficient of determination is selected for this purpose. The results of the analysis typically include "fitted" estimates of the parameters of the model, a graphical representation of the observed data and model predictions versus time (data/prediction-time plot), and statistics information.