CHAPTER I

INTRODUCTION

The rate - determining step in the absorption process for drugs of poor solubility is generally their dissolution rate in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall (Gibaldi, 1971). When an insoluble drug is administered orally, the rate and/or the extent of biological availability can be controlled. If the bioavaibility of such a drug is enhanced, the dose required, and consequently the side effects may be reduced. Therefore, great efforts have been made to improve the dissolution rate of sparingly soluble drugs (Geneidi et al., 1980).

A large number of publications have reported on various techniques to enhance dissolution of poorly soluble drugs. These reviews examine many systems with particular reference to their methods of preparation. The poor dissolution characteristics of relatively insoluble drugs can be modified through use of soluble salts, polymorphism, hydrates and solvates, molecular complex, eutectic and solid dispersions, micronisation, microcrystallization as well as co-precipitation with inert carriers and adsorption onto inert compounds (Chiou and Riegelman, 1971).

Even though drug dissolution from solid dispersions depends on the technology employed to prepare the dispersion, the proportion and properties of the carrier used should be concerned. Over thirty different materials have been examined as potential carrier substance. They vary widely in chemical and physical properties. The selection of these carriers has an ultimate influence on the dissolution characteristics of the dispersed drug. The two most commonly used carriers are polyethylene glycols and polyvinylpyrrolidones (Craig, 1990; Corrigan et al., 1979).

Nowadays, there has been a great deal of effort to study the utilization of natural polymers. In this respect, chitin and its derivatives are the desirable choices of natural polysaccharides. Being as biodegradable and non-toxic polymers, they have plenty of potential applications. Moreover, the sources of raw materials are obtained from waste products which can reduce the environmental problems. Many reports on their application in the

pharmaceutical field were published. Sawayanagi et al. (1982,1983) reported that chitin and chitosan can improve dissolution properties of griseofulvin, phenytoin, and prednisolone by grinding in a ball-mill. In addition, Shiraichi et al. (1990) studied on enhancement of dissolution rate of several drugs by low molecular weight chitosan. Also studies on complexation between low molecular weight chitosan and indomethacin for enhancement of dissolution were investigated by Imai et al. (1991).

Hydrochlorothiazide, HCTZ, an important diuretic has a potential for poor gastro-intestinal absorption due to its limited aqueous solubility. Thus, it is not surprising that it has been identified in the U.S. Federal Register as a class of drugs with a potential for bioavialability/bioequivalence problems and for which dissolution standards should be developed (Augsburger et al., 1983).

In an earlier study, a number of in vitro studies on the influence of formulation factors on the dissolution properties of HCTZ were published (Alam & Parrott, 1981). These showed that coprecipitates and melt of HCTZ with polymers PVP or PEG significantly improved the dissolution rate (Kassem et al., 1982). Other methods have been reported by several dispersion techniques and by adsorption on various clays (Monkhouse and Lach, 1972; Ford, 1978).

Since the drug has relatively high melting point and heat fusion, and low intrinsic solubility, it may exist in amorphous form . Its behavior in the presence of different methods and/or carrier materials has previously been investigated (Millar and Corrigan, 1991).

Therefore, this study concentrated on the survey application of chitin, chitosan, and low molecular weight chitosan in dispersion systems of hydrochlorothiazide to enhance its dissolution by means of solid dispersion, solid surface dispersion, and kneading method. The carriers PVP and PEG were also used as comparative dispersed systems. Then the suitable dispersion mixtures were selected for directly compressed tablets and compared with commercial tablets.

The objectives of the present study are:

1. to prepare dispersion mixtures of HCTZ with different carriers of chitin (CT), chitosan (CS,CSU), low molecular weight chitosan (LMCS), PVP K30, and PEG 4000 via various dispersion techniques such as physical method (PM), kneading method (KM), solvent methods (SM,SMD), and ball milling method (BM).

2. to compare the results of the dissolution enhancement obtained from various dispersion systems.

3. to investigate the influence of types and fraction of carriers on drug dissolution.

4. to compare the effect of different sources of chitosan on dissolution enhancement .

5. to prepare HCTZ tablets from selected dispersion mixtures and evaluate the prepared tablets by comparison with commercial products.

6. to elucidate mechanisms of increasing dissolution of HCTZ from the prepared dispersion mixtures.

LITERATURE REVIEW

Solid dosage forms are usually designed for oral ingestion and this mode of administration can often result in inefficient and erratic drug therapy (Mayersohn, 1979). Since absorption normally occurs only after the drug is in solution, solid dosage forms must first dissolve in the gastrointestinal tract. After ingestion of a tablet or capsule dissolution occurs from three structures, i.e. intact dosage form, disintegrated granules, and fine particles. Dissolution occurs fastest from the fine particles, followed by granules and tablets or a capsule slug. Since dissolution is the primary step which affects drug absorption, the prime objective of formulation is to ensure that the formulation ingredients or processing do not inhibit the intrinsic dissolution rate of the drug. In some cases a product may be formulated with the objective of enhancing dissolution. This may apply particularly to insoluble and hydrophobic drugs.

1. Method to Enhance Drug Dissolution

Some of the favourable methods which can be used to enhance dissolution are (Khan, 1981):

1.1 Physicochemical modification (e.g. prodrug approach, polymorph, complexation, particle size reduction).

1.2 Solid dispersion (e.g. coprecipitated of drug using inert water - soluble carriers).

1.3 Solid surface dispersion (e.g. mechanical deposition, solvent deposition).

1.4 Hydrophobic reduction (e.g. coating and granulation with hydrophilic materials or surfactants).

1.1 Physicochemical modification.

The alteration in physical properties and/or modification of the chemistry of active drug substances can in certain instances lead to easier pharmaceutical processing and is one of the most widely used approach to improving dissolution rate and bioavailability. If it is known that dissolution is the rate limiting step in absorption, then the rate of availability will increase as dissolution rate increases. Since the salt form of a drug is more soluble in an aqueous medium than its unionized form, the bioavialability can be improved by making readily soluble salts. Miyazaki and co-workers(1981) improved the apparent solubility and dissolution rate of berberine by forming with sulfate salt. In practice, however, the selection of a desirable salt form depends upon various factors e.g. drug stability, its toxicology, ease of processing, cost, and of course, the actual extent and significance of improvement in bioavailability.

Polymorphism is known to affect the solubility of drugs, thus the use of polymorphic properties of poorly soluble drugs to enhance the dissolution rate may be useful . Mullins and Macek (1960) worked on two polymorphic forms of novobiocin, one of which crystalline and the other amorphous. They found that the crystalline novobiocin acid was poorly absorbed and did not provide adequate therapeutic blood levels following oral administration, but the amorphous novobiocin acid was readily absorbed and therapeutically active. This was due to difference in solubility of different polymorphs. The application of polymorphic properties of poorly soluble drugs may be used in a pharmaceutical formulation, i.e. selecting a polymorph having the desired rate of dissolution . However, in practice, it is often difficult to produce a desirable polymorphic form which is both thermodynamically and pharmaceutically stable.

The formation of molecular complexes can increase the apparent solubility of many drugs, thus increase the dissolution rate of the drugs from the solid dosage forms. Many studies have been made on the formation of molecular complexes. Imai et al.(1991) reported that the dissolution of indomethacin was markedly increased from kneaded mixture with low molecular weight chitosan. They suggested that the acetyl group and amino group of chitosan played an important role in complexation. In 1992, Tasic and co-workers complexed paracetamol with β-cyclodextrin to improve the solubility and dissolution rate of the drug. Moreover, it is known that inclusion complexes with cyclodextrin often result in improved stability of the guest molecules (Nakai, 1986). However, the formation of molecular complexes may also decrease the apparent solubility of many drugs. Bettis et al.(1973) found that complexes of theophylline and barbiturate resulted in a significant decrease in dissolution rate of theophylline .

Reduction of particle size to expose larger surface area to the dissolution medium is perhaps the most obvious choice for improving dissolution. The literature contains several examples where bioavialability was increased following particle size reduction. Ridolfo et al. (1979) had shown that the bioavailabllity of benaxoprofen, an antiinflammatory agent, was increased by reducing particle size. Although particle size seems to be the most easily controllable factor, in practice, reduction of the particle size is often associated with the following problems:

a. increased particle - particle interaction resulting in a reduction in the effective surface area.
b. dustiness and difficulties of handling fine particles, poor flow properties.
c. for tablets, compaction problems and changes in particle size after tabletting, effect on disintegration.
d. increased rate of degradation of relatively unstable drugs.

Particle size reduction is usually achieved by conventional trituration and grinding, ball milling, fluid energy micronisation, controlled precipitation by change of solvents or temperature, application of ultrasonic waves, and spray drying, etc. Although the reduction of particle size can be easily and directly accomplished by the first four methods, the resultant fine particles may not produce the expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger Van der Waals' attraction between nonpolar molecules. This was demonstrated

by Lin et al.(1968) who showed that the in vitro dissolution rates of micronized griseofulvin and glutethimide were slower than those of their coarser particles.

Another inherent disadvantage associated with micronization of hydrophobic drugs is their poor wettability. The wetting of powders is the first step for them to dissolve and sometimes disperse in fluids. This problem may be overcome by the addition of a wetting or surface active agent for reducing the hydrophobicity of poorly soluble drug (Reddy et al.,1976). Furthermore, drugs with plastic properties are difficult to subdivide by method of trituration, ball mill, and fluid energy. They have more tendency to stick together. If the material compacts by plastic deformation, a reduction in the surface area may occur. The effect of particle size reduction during processing should be examined as early as possible.

1.2 Solid dispersion

A solid dispersion was defined as dispersion of one or more ingredients in an inert carrier or matrix in the solid state prepared by melting (fusion), solvent, or melting - solvent method (Chiou and Riegelman, 1971).

1.2.1 Melting method (Fusion method)

This method is prepared by heating the physical mixture of drug and water-soluble carrier to a temperature at which melting occurs and a solution forms. The melted mixture is then usually cooled rapidly to entrap the drug particles in the matrix in as fine a state as possible. The cooling rate of a eutectic mixture can influence the physical state of the solid obtained and the particle size of the crystals formed.

The main advantage of this method is its simplicity and economy. In addition, supersaturation of a drug solute in a system can often be obtained by quenching the melt rapidly from a high temperature and a much finer dispersion of crystallites is obtained for systems of simple eutectic mixtures if such quenching techniques are used. The disadvantage of this procedure is the possibility of decomposition and/or evaporation of a component at the elevated temperatures required. This method was first proposed by Sikiguchi and Obi and was subsequently employed with some modifications by many investigators such as the process involving spray - congealing from a modified spray - drier onto cold metal surfaces. The melting method also has been used for dispersions containing mannitol (Kanig,1964). The feasibility of melting has been demonstrated for many dispersions. For

example, glibenclamide was dispersed in different polyol systems such as mannitol, sorbitol, PEG6000 (Geneidi, Adel, and Shehata, 1980), griseofulvin in different PEG systems (Chiou and Regelman, 1969).

1.2.2 Solvent method (Coprecipitation method)

This method is prepared by dissolving the drug and a water soluble carrier in a common solvent. The solvent is then taken off by evaporation with or without the aid of a vacuum pump. Sometimes heat is used to assist in the evaporation of the solvent.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effects of the supposedly negligible amount of the solvent on chemical stability of the drug, the selection of a common volatile solvent and the difficulty of reproducing crystal forms. This method was used to prepare several solid dispersion systems. For example, Resetarits et al.(1979) increased dissolution of 17 β - estradiol (E_2) by coprecipitating with povidone. Geneidi et al.(1980) also enhanced dissolution of glibenclamide by coprecipitating with PVP of different molecular weights.

1.2.3 Melting - solvent method

The melting - solvent method is prepared by first dissolving a drug in a suitable solvent and then incorporating the solution directly into the melt of water-soluble carrier. The solvent is then taken off by evaporation with or without the aid of heat. This method possesses the advantages of both the melting and solvents methods. However, it is possible that the selected solvent or dissolved drug may not be miscible with the melt of water-soluble carrier, and the polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used. The feasibility of the melting - solvent method was demonstrated on spironolactone - PEG 6000 and griseofulvin-PEG 6000 systems (Chiou and Riegelman, 1971).

The various possible mechanisms of increasing dissolution rate from solid dispersion are (Ford, 1986)

1. reduction of particle size
2. deaggregation or deagglomeration of particles
3. soluble complex formation
4. changing crystallinity of active ingredients.
5. changing the microenviroment of powder in solid dispersion.
6. increasing wettability of powder.
7. combination of the aforementioned mechanisms.

It is believed that the solid dispersion can play an important role in increasing dissolution, absorption and therapeutic efficacy of poorly water-soluble drugs in future dosage forms. However, the solid dispersion systems often have some limitations upon application to manufacturing process. For example, the potential processing problems were formation of sticky masses such as those of chlorpropamide and urea systems (Wells, Rubinstein and Walters, 1975). Other problems include the physicochemical stability which is generally poor or compaction process which often destroys the enhancement of dissolution by solid dispersion. Chiou and Riegelman found that melts of griseofulvin with either PEG 6000 or citric acid hardened on storage.

1.3 Solid surface dispersion systems.

The dissolution characteristics of a drug can be altered by dispersing it on the surface of an inert carrier. The solid surface dispersion system is defined as the system in which the drug is distributed on the surface of an inert carrier to increase dissolution rate of the drug. The new approach of solid surface dispersion to increase the dissolution rate of poorly soluble drugs is based on the concept of increasing the surface area of the drugs available for contact with the dissolution medium.

The solid surface dispersion systems are achieved by two methods, frictional deposition (or mechanical deposition) and solvent deposition (coevaporation). Frictional deposition method is accomplished by grinding the drugs with inert carrier. Solvent deposition is prepared by dissolving the drugs in a suitable organic solvent and then the solution of drug is dispersed on the surface area of an inert carrier with extensive surface area. The solvent is taken off by evaporation with or without the aid of heat.

In manufacturing powdered preparation, grinding is generally used for reducing the particle size of a solid, since the dissolution rate of poorly soluble drug is strongly affected by particle size. It had been reported that a

strong grinding force may give crystalline solid an increase in the activation energy on the surface and in the distortion of crystal lattice together with reducing the size. This had been reported by many researchers. Nakai et al.(1977) studied that upon grinding of benzoic acid with microcrystalline cellulose, the drug became amorphous and its dissolution rate was markedly improved. Yamamoto et al.(1978) also reported that a mixture of griseofulvin and microcrystalline cellulose prepared by grinding in a vibration ball mill was shown to dissolve and absorb significantly faster than those from micronized griseofulvin powder. They proposed that the possible transformations taking place during the vibration ball mill process were initial size reduction of drug crystalline powder and its interaction with cellulose which had also become amorphous during the milling process, or by production of lattice defects due to shear stress and impact stress. Moreover, Sawayanagi et al.(1983) reported that amorphous state of some crystalline drugs such as prednisolone, griseofulvin, and phenytoin, was obtained by grinding with chitin or chitosan.

Law and Chiang (1990) reported that the dissolution of griseofulvin was markedly enhanced by the solvent deposition method on the three types of disintegrants of primogel (modified starch), mobile starch (unmodified wheat starch), and nymcel (modified cellulose). The solution of the drug in suitable organic solvent was dispersed on the surface of the support material and the solvent was taken off by evaporation. The resulting material contained the drug in a molecularly micronized state on the surface of the carrier. It was suggested that the dissolution rate of the drug can be improved by combination of the disintegration and the solvent deposition effects. Another publications such as solvent deposited systems of piroxicam using five excipients of lactose, soluble starch, microcrystalline cellulose, silicagel and kaolin also showed markedly increase in the dissolution rate (Chowdary and Madhusudhan, 1990).

In conclusion the solid surface dispersion systems can be regarded as drug in a microparticulate form molecularly dispersed on the surface of an inert carrier. The resulting decrease in particle size and the concomitant increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the dissolution rates. The solid surface dispersion system is a potential pharmaceutical technique which can play an important role in increasing dissolution rate of poorly soluble drugs.

1.4 Hydrophobicity reduction

A major problem of traditional particle size reduction of the poorly water soluble drugs is that it results in a very cohesive powder. The high surface energy may lead to the formation of aggregates and agglomerates. The drug particle aggregates tend to be hydrophobic and thus, are difficult to wet. This problem is overcome by reduction in hydrophobicity of the drugs. The approach "reduction in hydrophobicity" of the poorly soluble drugs to enhance the dissolution rate based on the concepts of reducing theirs particle size may give greater problems with wetting and liquid penetration in solid dosage form. Since liquid penetration is the first step in the disintegration and dissolution of the solid dosage forms, the overall process may be penetration limited, thus reduction in hydrophobicity of the drugs may be an effective method. In an ideal situation, the drug would be continuously released from the solid dosage forms as well-wetted particles, so that the maximum surface area afforded by the powder would be exposed to the dissolution medium. For hydrophobic drugs, such a situation may be difficult, but it may be possible to achieve if the surface properties of the drugs are changed from hydrophobic to hydrophilic ones. The changes of hydrophobicity of the drugs may be accomplished by several methods, such as by coating with a hydrophilic material, using a surface active agent, and mixing with a hydrophilic material.

Lerk et al. (1978) successfully used a technique for reducing the hydrophobicity of drugs with a hydrophilic polymer (hydroxyethyl cellulose)to enhance dissolution rate of poorly water - soluble drugs. They also found that the dissolution rate was dependent on the amounts of hydrophilic polymers used and there is the optimum percentage of the hydrophilic polymers used to increase the dissolution rate of the drugs. The method appeared similar to a conventional granulation technique and simply relied on improving the wettability and solubilization of a hydrophobic drug partially coated with hydrophilic polymer.

Many investigators had reported that the surface active agents could also enhance the dissolution rate of many poorly soluble drugs by reducing hydrophobicity of the drugs. Khalafullah et al. (1975) used dioctyl sodium sulfosuccinate to reduce the hydrophobicity of phenol sulfonphthalein. The addition of surface active agents could lowered the surface tension and decreased the contact angle. Reddy et al.(1976) also used dioctyl sodium sulfosuccinate and poloxamer 188 for enhancing the dissolution of sulfadiazine and sulfisoxazole. Therefore the dissolution rate of poorly soluble drug may be enhanced by administering with a surface active agent.

Another method to reduced the hydrophobicity of the drugs is mixing with a hydrophilic filler, such as starch, microcrystalline cellulose, polyvinylpyrrolidone, etc. Starch, has been shown to enhance the dissolution of poorly water-soluble drugs, particularly when it was granulated with the drug. Marlowe and Shangraw (1967) prepared sodium salicylate tablets by wet granulation techniques using either lactose or a mixture of lactose and corn starch as filler. They found that the presence of starch dramatically increased the dissolution rate of the poorly soluble drug.

2. Determination of Mechanisms of Increasing Dissolution

Many methods can give information as to the mechanism of increasing dissolution with respect to the physical nature of a dispersion system. In most cases, combinations of several methods are required. The commonly used methods are the following (Bloch and Speiser, 1987):

2.1 Thermal analysis

This is the most common approach used to study the physico-chemical interactions of two or more component systems. Several modified techniques utilizing the principle of change in thermal energy as a function of temperature are cooling-curve method, thaw-melt method, thermomicroscopic method, differential thermal analysis (DTA), differential scanning calorimetry (DSC).

DTA and DSC are effective thermal methods to study the phase equilibria of either a pure compound or mixture. Differential effects, associated with physical or chemical changes are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate. In addition to thawing and melting, polymorphic transitions, evaporation, sublimation, desolvation and other types of decomposition can be quantitatively detected. These techniques are especially valuable in detecting the presence of a small amount of eutectic in the mixture, because its melting at the eutectic temperature can be sensitively detected, the observation of such small fractions of melting at eutectic temperature can often be missed when employing thaw - melt or thermomicroscopic methods (Chiou and Riegelman, 1971). Ford(1987) used DTA for studying the properties of several drugs such as chloramphenicol, glutethimide, griseofulvin, indomethacin or paracetamol with PEG6000 from solid dispersions. Another solid dispersions or mixtures studied by DTA or DSC have been reported by many researchers (Guillaume, 1992 ; Millar and Corrigan, 1991 ; Geneidi, Adel, and Shehata, 1980).

2.2 X-ray diffraction

In this method, the intensity of the X-ray diffraction (or reflection) from a sample is measured as a function of diffraction angles. The diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. It detects in a simple way crystalline and amorphous components. For example, the utilization of X-ray diffraction could indicate the amorphous character of oxidipine in coprecipitate with PVP, the X-ray diffraction pattern of coprecipitate was flat which was different from pure oxidipine or its physical mixture (Guillaume et al., 1992). This technique is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly different from those of pure components. It has been used to study quantitatively the concentration of a crystalline component in the mixture. The height of diffraction peaks may be attenuated by a reduction of crystallite size. In addition, this method has been used to study the stability of dispersions. The amorphous form is transformed into a crystalline form after annealing at high temperatures, as shown by the appearance of its sharp diffraction peaks (Chiou and Riegelman, 1971). This study was used to study various dispersion systems (Shiraishi, Imai, Iwaoka and Otagiri, 1991 ; Nakai, 1986 ; Corrigan , Timoney and Whelam, 1976).

2.3 Dissolution rate determination.

Allen and Kwan (1969) proposed the dissolution rate method to study the degree of crystallinity in solid-solid equilibria, especially in temperature regions below solid-liquid equilibria. The method involves comparing the in-vitro dissolution rates of the solute component from a constant-surface tablet made from molecular dispersion with a physical mixture of the same chemical composition.

The application of this method also requires:(a) the observed dissolution rate to be proportional to the surface area, (b) a reasonably large difference between the dissolution rate of the physical mixture and the corresponding solid solution, and (c) the use of the same polymorphic form of a drug in the tablet of the physical mixture as that precipitated out from the solid dispersions. Furthermore, one must assume in this dissolution method that the distribution of particle size (may be as small as on the subcolloidal

range) precipitated from the solid solution or glass solution dose not affect the dissolution rate. Such assumption needs to be proved experimentally. In most cases dispersions cause an acceleration of dissolution in gastric fluids. (Mishra, Varma and Jain, 1983 ; Deshpande and Agrawal, 1982; Sawayanagi, Nambu and Nagai, 1982).

2.4 Electron Microscopy

This method often used to get a primary information of the systems, for example the morphology, polymorphism, particle size, shape, surface appearance, agglomeration or deaggregation, and to detect amorphous and crystalline structures.

Scanning electron microscope (SEM) was used to study many of the dispersion system characteristics such as the surface of compacts before and after dissolution testing of frusemide/PVP solid dispersions (Doherty and York, 1987). Kaneniwa and Watari (1977) used SEM to observe the particle surface and to determine the amount of sulfonamide dissolved.

3. The Drug

Hydrochlorothiazide (HCTZ)

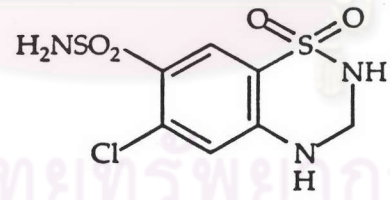

Figure 1 The structure of HCTZ

The molecular structure of HCTZ is shown above. The empirical formula is $C_7H_8C1N_3O_4S_2$ with a molecular weight of 297.73. The chemical name is 6-chloro-3, 4-dihydro-7-sulfamoyl-2H-1, 2, 4-benzothiadiazine 1, 1-dioxide.

HCTZ is a diuretic drug of the benzothiadiazine group. HCTZ occurs as a white or practically white, practically odorless, crystalline, powder and has a slightly bitter taste. The drug is slightly soluble in water and insoluble in ether. Its solubility in some commonly used organic solvents are: acetone (13.7 g/100 ml.), acetonitrile (2 g/100 ml), ethyl acetate (0.59 g/100 ml), acetic acid(0.15 g/100 ml),chloroform(0.1 g/100 ml). It is soluble in aqueous solution of inorganic bases like sodium hydroxide or ammonium hydroxide. HCTZ has two pka of 7.9 and 9.2. Its melting points vary within the temperature range from 263 to 275°C (Deppeler, 1981)

Storing of HCTZ at room temperature for five year shows no degradation and heat affects it very slowly, e.g. treatment for 2 hours at 230°C gives a yellowish discoloration but no significant change of the physical properties.

HTCZ is a thiazide diuretic used for the treatment of edema associated with congestive heart failure, renal and hepatic disorders. It is also used in the treatment of hypertension either alone or as an adjunct to other hypertensive agents. Its mechanism of action is to increase the renal excretion of sodium and chloride and an accompanying volume of water (Mudge, 1980). The drug is absorbed from the GI tract. The peak plasma concentration reached within 1.5-5 hours and the area under the concentration curves was linearly correlated with the dose. Absorption of an oral drug dose was in the range of 60-80%. More than 95% of the absorbed HCTZ is excreted unchanged in the urine. It's half-lives is 5.6-14.8 hours. Excretion of the drug is essentially complete within 24 hours (Marvola, 1979).

HCTZ is administered orally. The most common dosage schedule among hypertensive patients is one tablet (50 mg) per day. Dosage can vary from 25 to 200 mg as a single dose or 2 divided dose. For management of edema, the dosage is 25-200 mg daily in 1-3 divided doses. Pediatric dosage may range from 37.5-100 mg for children 2-12 years and 12.5-37.5 mg for children up to 2 years of age. Dosage forms were tablets of 25, 50 and 100 mg. Preparations of hydrochlorothiazide in Thailand were 50 mg tablet. (Gwendolene, 1990).

4. Carriers

4.1 Chitin

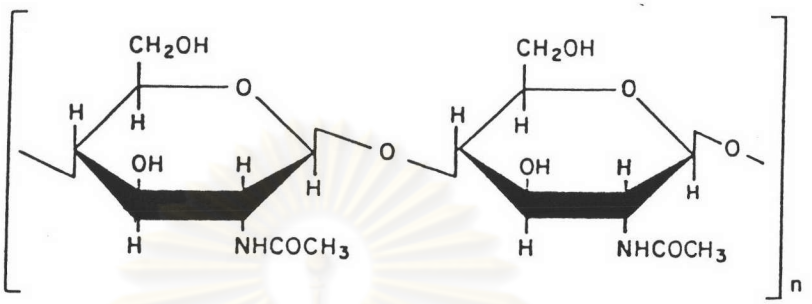

Figure 2 N-acetyl-D-glucosamine repeating unit.

Chitin is the most plentiful natural polymer next to cellulose and it is widely distributed throughout nature. Chitin occurs as a major cuticular or skeletal component in all arthropods, in some other invertebrate, and in some fungi.

It's structure is a crystalline polysaccharide. Like cellulose, chitin is a β(1-4) - linked glucan, but is composed of 2-acetamide-2-deoxy-D-glucose (N-acetylglucosamine), as shown above. Three crystalline forms of chitin are α, β and γ chitin. α-Chitin is the tightly compacted, most crystalline polymorphic form where the chains are arranged in an anti- parallel ; β- Chitin is the form where the chains are parallel ; and γ-Chitin in the form where two chains are "up" to every one "down". The three forms of chitin have been found in different parts of the same organism. In plants it serves as an alternative to cellulose ; in animals as an alternative to collagen. The γ - chitin is usually found, frequently sclerotized and encrusted with mineral deposites ; β and γ - Chitins seem to be associated with collagen type proteins providing toughness, flexibility and mobility, and may have physiological functions other than that of support, such as control of electrolytes and transport of a polyanionic nature.

The solubility study of chitin showed that it can be dissolved in the concentrated mineral acids, anhydrous formic acid but insoluble in water, diluted acids, diluted and concentrated alkalis, and many commercial solvents. Chitin is hygroscopic but thermally stable up to about 260°C (Muzzarelli, 1977).

Chitin is primarily obtained from invertebrates and fungi. The most easily exploited sources are the protective shells of crustaceans such as crabs and shrimps. Thus, the natural sources of chitin would be the waste products of other industrial processes. Since waste disposal is becoming an immediate problem, chitin appears to be a very desirable source of new material. In addition, it possesses favorable characteristics such as biodegradable, biocompatible, biopolymer (aminopolysaccharides), almost nontoxic, changeable in the molecular conformation, and have amino and hydroxyl groups which are chemically modifiable. These properties consequently make it a very attractive biomaterial. Some applications of chitin in the pharmaceutical field are as follows :

a) used as a disintegrant in directly compressed tablets and wet granulation tablet containing about 2-20 % (w/w) of chitin (Bruscato and Danti, 1978)

b) used as a directly compressible diluent with friction-lowering properties for chewable, sublingual, or oral mucosal tablets prepared by direct compression (Sawayanagi et al., 1982).

c) used as a dissolution enhancer of poorly soluble drugs such as prednisolone, griseofulvin, phenytoin from ground mixtures by lowering the degree of crystallinity of such drugs (Sawayanagi, et al. 1983).

d) used in controlled release preparations

Miyazaki and co-worker (1981) prepared dried gel of chitin containing indomethacin or papaverine hydrochloride for sustained release preparation.

Nishioka and co-workers (1990) found that the incorporation of chitin in the carrier matrix of cisplatin chitosan microspheres produced a more pronounced increase in drug content which led to inhibition of the initial burst effect and retardation of the rate of drug released.

e) used as emulsion stabilizers in water emulsions

Magdassi and Neiroukh (1990) found that stable emulsions were obtained in the presence of 2.5% (w/w) chitin or 0.5% (w/w) chitin plus 0.005% (w/w) tween 80.

Moreover, chitin and its derivatives have found potential applications in several fields such as medical uses, personal care used, agricultural uses, biotechnology uses, food uses, clarification and waste management, etc (Lower, 1984 ; Sandford, 1989).

4.2 Chitosan

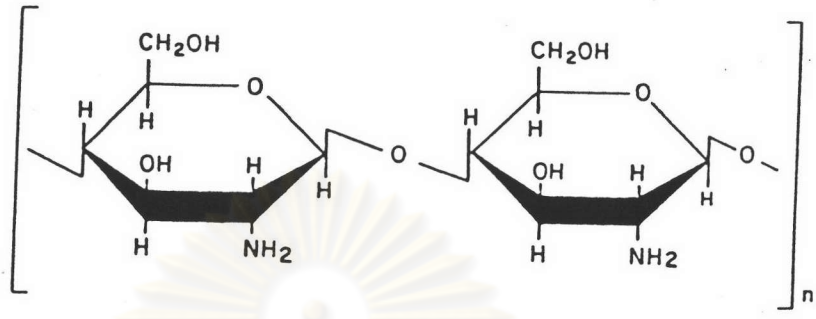

Figure 3 D-glucosamine repeating unit.

Chitosan, the deacetylated product of alkali treatment of chitin, is the name used for low acetyl forms of chitin and is composed primarily of glucosamine, 2- amino- 2- deoxy-D-glucose, the structure was shown above. It can be distinguished from chitin because of its solubility and higher percentage of nitrogen 7% or more in product. It is insoluble in water, organic solvents, alkali, mineral acids (except under certain conditions) and is soluble in diluted acetic acid, citric acid ; at acidic pH's the free amino groups ($-NH_2$) become protonated to form cationic amine groups ($-\overset{+}{N}H_3$) (Muzzarelli, 1977).

Like chitin, chitosan is a white, nontoxic, odorless, and biodegradable substance. The type of chitosan used commercially is determined by its physical form (flake, powder, solution), its purity (ultra pure, standard, industrial) and its molecular form (high to low viscosity, percent deacetylation > 75%; free amine or acid salt) and ultimately the cost. The molecular weight of chitosan depends on the processing conditions, and many grades within the range of 10,000 - 1,000,000 Dalton are available.

Chitosan has several properties relating to commercial uses and variety of applications. It has favorable characteristics like chitin and can be used in a variety of forms such as powder, solution, gel, film, fiber, bead, membrane which leads to a more attractive biomaterial than chitin. Some applications of chitosan in the pharmaceutical field are as follows :

a) used as excipient in tablet preparations : like chitin, chitosan has been used as a disintegrant in directly compressed tablets (Bruscato and Danti, 1978) ; as a directly compressible diluent (Sawayanagi et al.,1982) ; and as a dissolution enhancer of poorly soluble drugs (Sawayanagi et al., 1982, 1983).

b) used in controlled released preparations

Dried gels of chitosan containing indomethacin or papaverine hydrochloride were studied. Sustained release of the drug from the dried gels was obtained with a constant rate (Miyazaki et al., 1981).

Direct compression matrix of propranolol hydrochloride (water soluble drug) tablets were prepared by using chitosan as a vehicle and zero-order controlled release of the drug was obtained (Sawayanagi et al., 1982). In addition Nigalaye et al.(1990) found that the use of chitosan at a concentration of 50% of tablet weight produced a non-erosion type matrix system but when used chitosan at low concentration(10%) the sustained release properties were not observed.

Chitosan microspheres of cisplatin were studied, the results showed that the rate of cisplatin release decreased with increasing concentration of chitosan in the microspheres (Nishioka et al., 1990).

Spherical pellets of poorly soluble drugs (micronized griseofulvin, ibuprofen, indomethacin, sulfadiazine, or tolbutamide) were prepared by using polyelectrolyte complex formation properties of chitosan. The drugs were dispersed in solution of chitosan and dropping these solution to the solution of counterion tripolyphosphate or calcium chloride, then the droplets of gelled spheres were obtained (Bodmeier and Paeratakul, 1989). This technique could probably be employed to prepare spherical agglomerates of the drugs for improving flow properties of drug crystals with fast disintegration time in 0.1 N HCL, and can be further developed to prepare a sustained release dosage form by coating the beads with organic polymers.

c) used in buoyant preparations

Chitosan also has a potential in the design of dosage forms that prolong the residence time in the stomach. It has gel-forming properties in the low pH range, that may prevent or weaken drug irritation to the stomach. Karlsen and collaborators (1991) were able to produce chitosan - drug containing granules with internal cavities, which will float in the gasrtric fluids and gradually swell in pH 1 to 8 . When this formulation was tried with prednisolone as a model drug, a sustained release effect was readily obtained.

d) used in film preparations

Miyazaki et al (1990), using diazepam as a model drug, produced a film composed of a 1:0.5 drug - chitosan mixture which might be an effective dosage form that is equivalent to the commercial tablet dosage forms.

e) used as bioadhesive polymer

Chitosan has been useful as a bioadhesive material. Takayama et al(1990) investigated bioadhesive properties of chitosan and sodium hyaluronate, the results suggested that the tablets containing both polymers have strong adhesive forces and the release rate of brilliant blue (as a model of water soluble drug) from chitosan - sodium hyaluronate tablets was greatly affected by the change of the polymer mixing ratio.

4.3 Low molecular weight chitosan (LMCS)

Low molecular weight chitosan is a hydrolysis product of chitosan. Its structure composed of glucosamine units, and showed shorter chains than those of chitosan. Due to the hydrolysis process, the molecular weight was reduced. In previous reports, its molecular weight ranged from 3,800-25,000 dalton (Imai et al., 1991). Also in this study, as kindly supplied by the same company (Kurita Water Industries Ltd.), the molecular weight of the tested material was about 1,000 dalton.

Low molecular weight chitosan has some physicochemical properties different from those of the original polymers such as the solubility. It is soluble in water, acid solution, and alkaline solution.

Due to its water-solubility, it has potential uses in pharmaceutical field to improve the biopharmaceutical and dissolution properties of many poorly - water soluble drugs. The improvement of dissolution from kneaded mixtures of LMCS and drugs such as phenytoin, diazepam, betamethasone, digoxin, and prednisolone has been studied by Shiraishi et al. (1990). Furthermore, Imai et al. (1991) also reported the interaction of indomethacin with LMCSs which improved some pharmaceutical properties such as dissolution rate and absorption behavior.

4.4 Polyvinylpyrrolidone K30 (PVP K30)

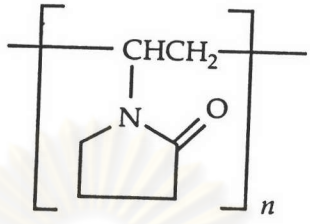

Figure 4 The molecular structure of PVP.

The molecular structure of PVP is shown above and its molecular weight is about 40,000. PVP K30 is a white to creamy white, odorless or almost odorless, hygroscopic powder. Its melting range is over 275 °C with decomposition. PVP K30 can be readily soluble in water up to 60% and freely soluble in many organic solvents, including monohydric (ethanol, methanol) and polyhydric alcohol, acids, esters, ketones, methylene chloride, chloroform. In addition, it is absolutely insoluble in ether, hydrocarbon, carbon tetrachloride, ethylacetate and mineral oil.

PVP K30 can be used as dispersing agent, suspending agent or viscosity builder, tablet binder, coating agent. Moreover, it can be utilized in preparing solid dispersions as a carrier such as oxodipine (Guillaume, 1992), frusemide (Doherty and York, 1987), hydrochlorothiazide (Kassem et al., 1982), reserpine(Stupak and Bates, 1972).

4.5 Polyethylene Glycol 4000 (PEG 4000)

$$HO\,CH_2\,(CH_2\,OCH_2)_{69\text{-}84}\,CH_2OH$$

Figure 5 The molecular structure of PEG

The polyethylene glycol 4000 is a water soluble synthetic polymers, the repeating unit being oxyethylcne(-OCH_2 CH_2-)with either end of the chain comprising an hydroxyl group. Its molecular weight is 3000-4000. PEG is an almost tasteless, creamy white, hard, wax-like solid or flakes or white free - flowing powder with a faint characteristic odour. Its melting range is 50 °C - 58 °C. It is soluble with 1:3 water, 1:2 alcohol, and chloroform and practically insoluble in ether.

Polyethylene glycol is used as stabilizers of emulsion, water miscible bases for ointments or bases for suppositories. Moreover, the aqueous solubility or dissolution characteristics of poorly soluble compounds can be enhanced by making solid dispersion such as diazepam (Anastasidou, Henry, Legendse, Soulean and Duchene, 1983), hydrochlorothiazide (Kassem et al., 1982), hydroflumethiazide (Corrigan et al., 1979), griseofulvin (Chiou and Riegelman, 1969).