CHAPTER I

INTRODUCTION

Literature Review

The bioavailabilites of many poorly water soluble drugs are limited by their dissolution rates (1). Since absorptions normally occur only after drugs are in solution, solid dosage forms administered orally must first dissolve in the gastrointestinal tract (2). If the absorption process of a drug is dissolution rate limited, an enhancement in the dissolution rate should facilitate its gastrointestinal absorption (3). Several methods can be used to improve the dissolution properties of poorly water soluble drugs (2, 4-5), these include particle size reduction, reduction in hydrophobicity such as coating and granulation with a hydrophilic material or surfactants, formation of polymorphs and salts, complexation, surface adsorption and solid dispersion.

Solid Dispersion

The concept of solid dispersion was first introduced by Sekiguchi and Obi (1,6) in 1961 as a novel method for reducing drug particle size. They showed that formation of a eutectic mixture of the poorly water soluble drug, sulphathiazole, and the physically inert, water soluble carrier, urea, produced an increased dissolution and

absorption of sulphathiazole. Subsequent publications have developed the research area of solid dispersion to envelop both fast release and sustained release products.

1. Terminology

A solid dispersion was defined by Chiou and Riegelman (6) as "a dispersion of one or more active ingredients in an inert carrier or matrix at a molecular level in a solid state prepared by the melting (fusion), solvent, or melting-solvent method". Complexes formed in situ by any of these processes which is not simple mechanical mixed may also be classed as solid dispersion (1, 6-7).

2. Methods of Preparation (1, 6-8)

Broadly speaking, there are two methods of preparing solid dispersion, namely by melting (fusion) and solvent method.

2.1 Melting (Fusion) Method. This method was first proposed by Sekiguchi and Obi (1, 6) and was subsequently modified by a lot of investigators (9-12).

Procedure

Melt the drug-carrier mixture, cool to form a homogeneous solidified dispersion, and deminute the resolidified product.

Advantages

-simplicity and economy.

-no use of toxic solvents.

-possible to obtain a supersaturation of a drug in the system by quenching the melt rapidly from high temperature.

Disadvantages

-immiscibility between drug and molten carrier may occur during fusion.

-only low melting point drugs or carriers can be used due to the problems of thermal degradation or sublimation of drugs or carriers.

-the solidified melts may be tacky or unhandable.

2.2 Solvent Method. This method was initally used by Tachibana and Nakamura (1).

Procedure

Dissolve drug and carrier in suitable organic solvent, evaporate the solvent (with or without aids of heat or vacuum), and pulverize the solid product (which may be called "coprecipitate" or "coevaporate" (1)).

Advantages

-thermal decomposition of drugs or carriers can be prevented.

-high melting point carriers can be used.

Disadvantages

-higher cost of preparation.

-difficulty in selection of a common volatile solvent since the chosen carriers are generally hydrophilic but the drugs are hydrophobic.

-difficulty in completely removing liquid solvent which may lead to toxicity problem.

-effect of solvent on chemical stability of drug.

-supersaturation of the solute in the solid system cannot be obtained except in a system showing highly viscous properties.

-large scale batches present many problems such as solvent recovery, drying of the sample, uniformity in rates of evaporation, solvent flammability and toxicity, and batch reproducibility (5).

Problems such as thermal instability and immiscibility of melting method have resulted in the development of the "melting-solvent" method. Small quantities of organic solvents were used to dissolve the drug, the solution was added to the molten carrier and the resultant solution was evaporated to dryness. This method has the advantages of both melting and solvent methods. However, it is only limited to drugs with a low therapeutic dose, e.g. below 50 mg. The feasibility of this method has been demonstrated for spironolactone and griseofulvin dispersions in polyethyleneglycol 6000 (1, 6).

3. Influence of Carriers on Drug Release (6, 8)

The selection of the carrier has an ultimate influence on the dissolution characteristic of the dispersed drug. A water-soluble carrier combined with a poorly water-soluble drug results in a fast release of the drug from the matrix and a poorly soluble or insoluble carriers combined with a good water-soluble drug leads to a retardation of drug release from the matrix.

If the water-soluble carrier was used, when the solid dispersion was exposed to water or gastrointestinal fluids, the soluble carrier would dissolve rapidly and the finely dispersed drug particles would then be released in very fine, almost in the micron or submicron range (11).

A carrier chosen for dispersions designed to increase the dissolution rates of drugs should meet the following criteria (1)

-freely water soluble with intrinsic rapid dissolution properties.

-non-toxic.

-for fusion processes, it should be chemically, physically and thermally stable with a low melting point. The carrier and drug should be miscible in the liquid state.

-for solvent processes, it should be soluble in a variety of organic solvents.

-preferably increase the aqueous solubility of the drug.

-chemically compatible with the drug and in the solid state it should not form strongly-bonded complexes with a strong association constant which may reduce dissolution rates.

-pharmacologically inert.

The interesting carriers which were broadly used are polymers, especially polyethyleneglycols (PEGs) and polyvinylpyrrolidone (PVP), sugars (dextrose, glucose, sucrose, lactose, galactose, fructose, maltose, mannitol, sorbitol, zylitol), urea, surface-active agents (poloxamers and myrjs), citric acid and succinic acid, bile acids, sterols and related compounds, globular compounds (pentaerythritol and pentaerythritol tetraacetate), urethan, fatty materials, cyclodextrins, etc. Combination of carriers have also been examined including citric acid-succinic acid, sugar mixtures, sugar-PEG, and sterols-surfactants (1).

Carriers used in this investigation are briefly reviewed in Appendix A.

4. Physicochemical Structures of Solid Dispersions (1, 5-8)

The physicochemical structures of these dispersions play an important role in controlling their drug release. Six representative structures have been outlined (6, 10) as representative of interactions between carrier and drug:

1) Simple eutectic mixtures.

2) Solid solutions.

3) Glass solutions and glass suspensions.

4) Amorphous precipitations in a crystalline carrier.

5) Compounds or complex formations.

6) Combination.

Regarding the physical nature of a solid dispersion system, many methods can be used to evaluate the dispersion in the powder and in the final dosage form. These methods include thermal analysis, X-ray diffraction, electron microscopy, spectroscopy, thermodynamic methods and dissolution-rate determination. Results from these methods, due to their different sensitivities, may often be conflicting and care is required for their accurate interpretation.

5. Mechanisms of Increased Dissolution Rates (1, 6, 8)

The increased dissolution rates from solid dispersion were attributed to

1. The reduction of particle size of the drug within the dispersion.

The increase of specific area due to this particle size reduction generally increases rates of dissolution.

2. The amorphous form precipitate of the drug in the crystalline carrier.

Since the amorphous form is the highest energy

form of a pure drug, it produces faster dissolution and absorption rates than the crystalline form. However the presence of metastable, crystalline form which has a higher solubility can also increase dissolution rate.

3. The absence of aggregation and agglomeration between hydrophobic drug particles.

4. Many carriers increase the aqueous solubility of drugs and may have led to microenvironmental solubilization of drug in the static fluid layer surrounding the dissolving dispersion.

5. Increased wettability and dispersibility of a drug.

6. Formation of soluble compound or complex between drug and carrier.

A solid dispersion does not always fall neatly into any of the fast-release machanisms mentioned above. The observed increase in dissolution and absorption rates may be the contribution of different machanisms.

6. Advantages and Disadvantages of Solid Dispersion

Advantages

Many of advantages claimed derive from their rapid dissolution rates which produce increases in vivo rates and extent of absorption of many drugs (10-22). Therefore, the dosage of solid dispersed drugs could be decreased (1, 15). The increased dissolution and associated rapid absorption may reduce proportion of drug metabolized presystemically

(23). Moreover, it is possible that the solid dispersion technique can be used to obtain a homogeneous distribution of a small amount of drugs at solid state, to stabilized unstable drugs (1, 6), to dispense liquid or gaseous compounds (24), to formulate a fast-release priming dose in a sustained-release dosage form, and to formulate sustained-release or prolonged-release regimens of soluble drugs by using poorly soluble or insoluble carriers (6, 25-26).

Disadvantages

Despite the advantages of increasing dissolution and absorption rate of numerous drugs, solid dispersion resulted in decreasing rate of dissolution of many drugs (23, 27-28). Formulation problems, e.g. tackyness and unhandable characteristic of some dispersions made it difficult for pulverization (17), wet granulation techniques are unacceptable for tableting the solid dispersion, and the solid dispersion may exacerbate interactions between drugs or carriers with tablet excipients (29-30). Stability of the dispersion is also an important problem.

7. Aging of Solid Dispersion

Since many dispersions contain amorphous or molecularly dispersed drugs, they are often susceptible to changes during storage (1). Hardening on storage of the melts of griseofulvin with either PEG 6000 or citric acid (11), brittleness of hydroflumethiazide-PEG system (1), crystallization in indomethacin-PEG 6000 solid dispersions

(1) which led to reduction of dissolution rates are examples of aging effect.

Solid dispersions are temperature-sensitive (22, 31) and are very moisture sensitive too. This is because the chosen carriers are usually water soluble and hygroscopic. Consequently high humidities have induced changes resulting in dissolution decreases from many dispersions (22, 32).

However, age-induced changes may be system specific. Despite crystallization, unchanged dissolution rates were obtained from many dispersions (1, 33). Similarly the bioavailability of a nabilone-PVP dispersion was unchanged after two year storage (34). Certain systems, e.g. chlorpropamide-urea , may display an increased in dissolution rates following storage (19).

In conclusion, although there are many stability and technology problems, the advantages provide scope for the continued interest in the solid dispersion. The pharmaceutical scientist's challenge is to prepare, formulate, and stabilize these high energy forms of poorly water soluble drugs and to use this new approach in providing a sustained or controlled release of drugs (1, 5).

Rationale

Ibuprofen (35-38) (see also Appendix A) is a phenylpropionic acid derivative which has analgesic, anti-inflammatory, and antipyretic actions. It is extensively

used in the treatment of rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders. In Great Britain, there was a reclassification of ibuprofen from prescription-only medicine (POM) to pharmacy-only (P) medicine, available as over-the-counter (OTC) drug in 1983 (39). The Food and Drug Administration (FDA) also approved the OTC marketing of ibuprofen (40). In Thailand, ibuprofen has been widely used and the cost of treatment is not expensive. It is one of the drugs in the National List of Essential Drugs of Thailand.

Gillespie and co-workers (41) conducted relative bioavailability of commercially available ibuprofen oral dosage forms in Canada. They found that though all of the commercially available products studied were equivalent with respect to the amount of drug absorbed from the dosage forms, they differed markedly in terms of absorption rate. So, ibuprofen may be formulation dependent. Moreover, although ibuprofen is well tolerated than other nonsteroidal anti-inflammatory drugs, e.g. aspirin, indomethacin or phenylbutazone, gastrointestinal disturbances such as nausea, heartburn, and epigastric pain are still the most frequent adverse effects. Some patients may experience more severe gastrointestinal reactions, such as ulceration and bleeding (38). If the dissolution rate of the water insoluble ibuprofen can be improved, the absorption rate (i.e. bioavailability) may be increased and its dosage may be decreased. Thus, the possibility of local gastrointestinal irrition may also be reduced because of the shorter resident

time of the drug in the gut (42).

In this study, the dissolution rate of ibuprofen was expected to be increased through the preparation of solid dispersion in popular carriers, i.e. polyethyleneglycols (PEG 4000, PEG 6000 and PEG 20000), polyvinylpyrrolidone (PVP K-30 and PVP K-90), urea and mannitol. Cross-linked insoluble polyvinylpyrrolidone (PVPP), an excellent tablet disintegrant, which has been used as an effective carrier of some solid dispersion systems (13, 43) was also used in this work. Both fusion and solvent methods were utilized. The expected product is the solid dispersion which composes of the appropriate type and ratio of carrier and ibuprofen, easy to prepare, stable and can markedly improve the dissolution rate of the drug.

The purposes of the present investigation were to :

1. obtain solid dispersion of ibuprofen in various carriers using both fusion and solvent methods.

2. select the carrier of choice and its appropriate amount to increase dissolution rate of ibuprofen from solid dispersions.

3. investigate the influence of types of carriers on the dissolution of ibuprofen from solid dispersions compared to ibuprofen alone.

4. compare the effect of preparation method of solid dispersion on dissolution rate of ibuprofen.

5. study the effects of other factors such as particle size and storage of solid dispersion on dissolution rate of ibuprofen.

6. demonstrate an approach of dissolution rate enhancement of poorly water-soluble drugs.