CHAPTER I

INTRODUCTION

RATIONALE

There is such a wide variance in the nature of the active raw materials used in pharmaceutical manufacturing. One of the most important decisions to be made in active raw material control is the degree of purity that will be maintained for each material. There are variations in the degree of purity between samples of the same active raw material purchased from different commercial sources. The selection then must be one which results in the highest purity practical for each active raw material, consistent with safety and efficacy of the final oral dosage form. Its specifications normally consist of a description, solubility, identification, melting range, loss on drying ...etc. However, it should be indicated that these compendial tests are intended as the minimum required from the legal point of view.

Many of those active raw materials are available from more than one source. Although active raw materials from alternate sources may have similar chemical composition, there is no guarantee that they will exhibit similar physical behavior when used in solid dosage form formulation. For certain tablet or capsule products, it may be necessary to

obtain an active ingredient with special specifications far tighter than those of the comparable compendial standard. Even when highly purified and well characterized raw materials are involved, specifications should include additional critical features such as particle size, crystal shape ,bulk and tap density and some other physical peculiarities.

Characteristics such as drug morphology, particle size, and other physical and chemical characteristics are important in assessing drug availability and reproducibility of subsequent manufacturing process (Kumkumian, C. 1980).

This present study intend to evaluate some physical properties and the dissolution characteristics of some active raw materials from various sources in the market.

LITERATURE REVIEW

THEORETICAL CONCEPTS FOR THE RELEASE OF A DRUG FROM DOSAGE FORMS

In determining the dissolution rate of drugs from solid dosage forms under standardized conditions, one has to consider several physicochemical process in addition to those previously discussed under dissolution of pure chemical substances. Wagner proposed the scheme in Figure 1 for the processes involved in the dissolution of solid dosage forms.

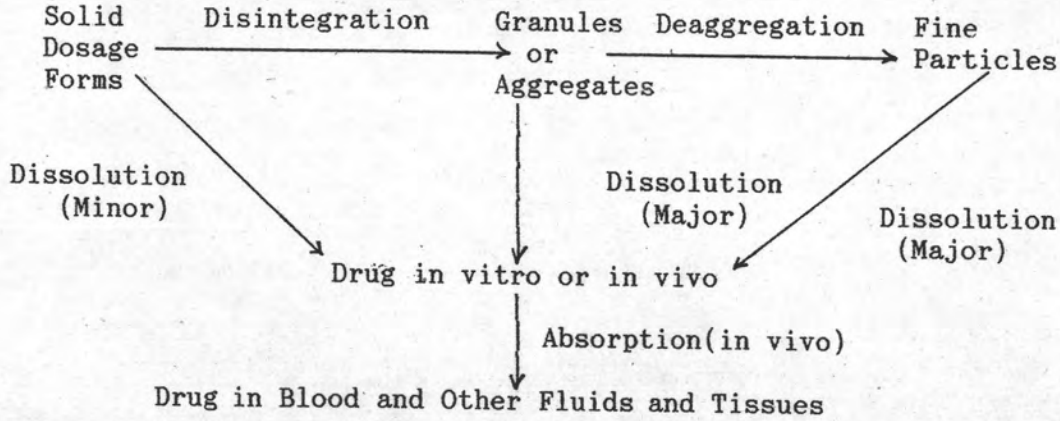

Figure 1 Wagner's schematic diagram illustrating the processes involved in the dissolution of solid dosage forms.

FACTORS AFFECT DRUG RELEASING FROM THE DOSAGE FORM

PROPERTIES OF THE DRUG

Physical characteristics of the drug which can have an effect on the rate of disintegration, deaggregation, and dissolution of the drug. As such, these can affect the rate of absorption and resultant blood levels of the drug. These physical characteristics of the drug consist of the following:

The polymorphic crystal form

The microscopic examination gives a gross indication of particle size and characteristic crystal properties. The photomicrographs are useful in determining the consistency of particle size and crystal habit from batch to batch, especially during the early periods of chemical synthesis of the drug. If any synthesis step is changed, they may also effect on crystal habit. Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystalline species. As a result, polymorphs may differ substantially with respect to certain physicochemical properties: for example, crystal shape, density, melting point, hardness, solubility, dissolution rate, as well as bulk behavior characteristics such as flow properties and compaction behavior (Peter York, 1983).

Several interesting studies have examined the processing characteristics of different polymorphs. Two

polymorphic forms of tolbutamide, which did not reveal significant in vivo differences, have been reported to possess different powder flow and compression characteristics(Simmons et al., 1972; Sekiguchi et al., 1973). Working with different crystal forms of phenylbutazone, Tuladhar et al.(1981) reported differences in dissolution characteristics for the polymorphs following compaction with excipients. However, the application of polymorphism properties of poorly water-soluble drugs can be used to choose for a pharmaceutical formulation, that polymorph having the rate of dissolution desired. On the other hand, a small difference was seen with mefenamic acid , polymorphism did not appear to affect the absorbability of the drug (Aguiar et al. 1969).

Shangraw et al. (1980) demonstrated that chemically equivalent materials from alternate source exhibited different behavior. In addition, differences in the morphology of chemically similar materials were revealed by the use of scanning electron microscopy (Shangraw et al. 1981a,b). For the manufacturer confronted with several sources for various active raw materials, it was thought that a comparative evaluation of tableting or capsuling characteristics as well as of the physical properties that could influence the behavior of the materials would be helpful.

The choice of the salt form

Salt-forming agents often are chosen empirically by the pharmaceutical chemist primarily on the basis of the cost of raw materials, ease of recrystallization and percentage yield. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound in dosage forms. Furthermore, even when many salts of the basic compound have been prepared, there are no effective screening techniques which make the selection process of the salt an easier task for the pharmacist. The fundamental consideration which may have some influence on salt selection are physical and chemical stability, hygroscopicity, flowability and solubility.

The particle size

The rate of dissolution of small particles is usually faster than that of larger ones because rate of dissolution is dependent on the specific surface area in contact with the liquid medium. This is usually described by the modified Noyes-Whitney equation for dissolution rate dA/dt.

$$\frac{dA}{dt} = KS(C_s - C)$$

Where A is the amount of drug in solution, K is the intrinsic dissolution rate constant, S is the surface area, C_s is the concentration of a saturated solution of the drug, and C is the drug concentration at time t.

Dittert et al. 1968, reported data for an experimental drug, 4-acetamidophenyl 2,2,2-trichloroethyl carbonate, which demonstrated that the dissolution rate and in turn bioavailability were affected by particle size.

Shah et al. (1983) showed that chemically equivalent compressible acetaminophen from alternate suppliers were found to be very different in sieve size distribution and compressibility profile.

The use of the hydrated or anhydrous form

The state of hydration have been also shown to have significant influence on the dissolution rate. The different state of hydration may also show some differences in physical properties of the powder. Bolhuis G. K. 1988, showed that different types of hydrous and anhydrous lactose powder were different in particle size and shape therefore influenced the flow properties of the powder.

Wettability and solubility of the drug

Wetting is an important factor in the dissolution process but the extent of that role has not been clearly defined(Florence and Attwood, 1981). Some drugs particle

aggregate tend to be hydrophobic and are difficult to wet. Reducing the particle size of hydrophobic drug may give greater problems with wetting and liquid penetration in solid dosage form and 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 released from the solid dosage form as discrete, well-wetted particle, 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 into a hydrophilic drugs. The changes of hydrophobicity of the drugs may be accomplished by several methods, such as by coating the hydrophobic drugs with a hydrophilic material, using surface active agent, and mixing with a hydrophilic material (Lerk et al., 1978).

The aqueous solubility of the drug is the major factor which determines its dissolution rate because the rate-controlling step in absorption process is the rate for the drug to transferred from solid state into the solution. The rate of dissolution of general substances is proportion to its solubility (Hamlin et al., 1965). Therefore when the drug substance has a low aqueous solubility the rate of dissolution will be low and the absorption is also. Newton, J.M. and

Razzo, F.N. 1977, also studied the dissolution properties of many drugs and many additive that prepared in hard gelatin capsule dosage form and found that rate of dissolution is proportion to the log of drug solubility. Their experiments can serve as a guideline for the pharmaceutical scientist especially when slightly water soluble drugs are concerned.

PROPERTIES OF THE DOSAGE FORM

Additives, other than the active ingredient. For a capsule dosage form, a sufficient volume of inert diluents such as lactose, mannitol or calcium carbonate, may be mixed before filling into capsules. Granular powders do not pack readily in capsules and crystalline materials, especially those which consist of a mass of filamentlike crystals are not easily fitted into capsules unless powdered. Since the flow of material is of great importance in the rapid and accurate filling of the capsule bodies, lubricants such as the stearates are also frequently used. However, it is now realized that the additives present in the capsule formulation, like the compressed tablet, can influence the release of the drug substance from the capsule.

Marlowe and Shangrew, 1967., demonstrated the hydrophilic excipient, such as starch, enhanced the dissolution rate of the dosage form.

Newton, J.M. and Razzo, F.N. 1974, also demonstrated the influence of additives on the in vitro release of drugs from

hard gelatin capsules that the higher level of diluent will usually increase drug release but not by a constant ratio between drugs. A reversal of an effect was shown by the addition of magnesium stearate, which in some instance increase rather than decrease drug release (its more usual effect).

Timmins et al.(1986) indicated that batch-to-batch variation in an active raw material, trimethoprim was evaluated following a production process change by the raw material supplier. Physicochemical and physicomechanical tests were applied and indicated that polymorphism or solvate formation was not occurring but changes in crystal properties in terms of size and degree of aggregation were involved. Other more subtle differences in crystal properties were also possible. The deleterious effect of the raw material process change on production of the dosage form was noted and a method of overcoming the problem identified. The necessity for comprehensive preformulation studies including physicomechanical screening is underlined. Such studies are also necessary if changes in raw material production methods occur to avoid process problems related to the marked batch-to-batch variation that can occur in these instances. A process validation of raw materials may be introduced during the early development of a formulation to avoid processing or quality problems.

Validation may be defined as the means by which sound

support for the efficacy of a process is gathered. Processes are validated by challenge, that is, by manufacturing batches at the upper and the lower limit of an acceptable range of variation for each parameter.

There are three important reasons for validating a process and for establishing the acceptable range of variation for each raw material (Berry, I. R. 1981).

1. Manufacturers are required by law to conform with Good Manufacturing Practice (GMP) regulations.

2. Good business dictates that a manufacturer avoid the possibility of rejected or recalled batches.

3. Validation helps ensure product uniformity, reproducibility, and quality.

When establishing validation and control procedures, it must be considered that errors can occur at any point in the operation, from the receipt of components to the release of the final product.

Variations in raw materials constitute one of the major sources of such errors. Variations in materials may occur among different suppliers of the same product, depending upon the method of transportation chosen, the exposure of materials to undesirable conditions (such as heat, cold, humidity, or light), the reliability of supplier, and the individual supplier's conformance to regulatory requirements in terms of facilities, personnel, and operating procedures and controls.

Differences among batches of raw material from the same

supplier must also be taken into account. The manufacturer should check the supplier's assay process as a part of its own validation process. The manufacturer should also monitor the physical specifications of incoming materials, observing such properties as particle size, shape, and crystalline structure for applicability to the manufacturer's specific needs. Variations within a single batch of a raw material must also be considered. Different containers of one batch or even one container within a batch occasionally vary because of improper storage or incorrect expiration dating.

It would be financially prohibitive to examine every combination of the aforementioned variables, so only the most critical combinations or those most likely to cause problems will be considered. Since those parameters for a given raw material that are validated for one pharmaceutical product may not be important for another, each case must be studied separately, and in each case, the manufacturer's judgement must be carefully exercised.

The validation of a process is important today both from a regulatory and from a good-business standpoint. A manufacturer's most difficult determination in process validation is the proper method. In accordance with GMP regulations, a manufacturer must generate and follow written guidelines that may involve the following steps (Rudolph, J.S. 1984).

1. The first step, each raw material should be validated

by performing checks on several batches, preferably three, from the primary suppliers as well as the alternate supplier. The batches chosen should be selected to represent the range of acceptable specifications, both high and low.

2. Depending on the susceptibility of the raw material to aging,either physical, chemical or microbiological stability should be assessed. This is especially true for liquid or semisolid ingredients where interaction with the container or permeability of the container to air and moisture could have a detrimental effect on the raw material.

3. Once the samples of raw materials have been selected as having fallen into an established, acceptable range of specifications and stability, it should be used to manufacture a batch of final dosage form. It may be appropriate to manufacture several lots of final product with raw material at the low and high end of the specification limit. Such testing would be especially useful when it is known that the product may be sensitive to small changes in the characteristics of the excipients or active ingredient.

4. The final step of raw material validation should involve an on-site inspection of the supplier to review the vendor's manufacturing operations and control procedures. The reliability of each vendor and how well each conforms to regulatory requirements must be determined. It is also important that every vendor understands the necessity of informing the manufacturer of any changes in the vendor's

established procedures for manufacture, control, or distribution, since these changes may necessitate revalidation.

Hard gelatin capsule dosage form is frequently used to administer new drug substances for evaluation in initial clinical trials because of the absence of numerous additives and manufacturing processing. There are some other investigation concerned with hard gelatin capsule dosage form showed that solubility of active raw materials (Newton et al., 1977), the particle size of active raw materials (Georgarakis et al., 1988), the content of active raw materials and diluent (Newton et al.,1980) and the moisture content of the powder (York, 1980) are all effect on drug release from hard gelatin capsules and no report has been found on the use of comparing the same active raw materials from different sources.

The active raw materials used in this study can be classified into three types:

1. Water soluble drug: use Tetracycline Hydrochloride as the model drug.

2. Slightly water soluble drug: use Cimetidine as the model drug.

3. Water insoluble drug : use Mefenamic Acid as the model drug.

Tetracycline Hydrochloride, Cimetidine and Mefenamic Acid were chosen to be the model drugs, are due to the wide-spread used as antibiotics, peptic ulcer drug and analgesic drug, respectively.

PURPOSES OF THE STUDY

On the basis of the rationale mentioned previously, the objectives of this research are to:

1. Study some physical properties of water-soluble, slightly soluble and insoluble active raw materials from various sources.

2. Study some physical properties and dissolution rate of hard gelatin capsules prepared by using active raw materials from various sources.

3. Comparative study the effect of variation of active raw materials on physical properties of existing capsule formulations.