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APPLICATION OF TECHNIQUES FOR IMPROVING EFFICACY OF SOLID DOSAGE FORMS

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ABSTRACT

The practical application of some standard and novel techniques used and intended to improve the clinical efficacy of solid dosage forms is discussed. It is suggested that many problems have yet to be overcome before novel drug delivery systems become practical realities. It is proposed that further research on novel dosage forms should be directed towards improving their stability, process reliability, ease of process control and manufacture at large scale.

NOTE

This paper is based on a presentation given to the Association Lilloise des pharmaciens Industriels on 26th April 1980 at University of Lille, France.

Recently, there has been considerable interest in new drug delivery systems and the maximising of clinical response by site targetting therapy(1). We have also seen significant progress in the fields of dosage form and process design to improve both efficacy and patient compliance (2). The purpose of this paper is to examine the practical applications of some published techniques used or intended to improve bioavailability of solid dosage forms with particular emphasis on the problems associated with the reduction of particle size and the use of solid dispersions. It is suggested that the optimism sometimes shown for the new systems and the criticism directed towards solid dosage forms prepared by conventional processes are not entirely justified.

Novel dosage forms

About 50 years after the invention of tablets, the Pharmaceutical Journal of 1895, published the Alumni Report of the Philadelphia College of Pharmacy (3) which said:- "Tablets have had their day and like every form of drug preparation which has preceded them, will pass away, in part at least to make room for something else". Similar optimism is often detected in the statements of some scientists, who feel that oral solid dosage forms are unreliable delivery systems for administering drugs and should ideally, be replaced by programmed delivery devices. Many problems have yet to be overcome before targetted delivery systems become widely acceptable. There is no doubt that considerable skill has been shown in designing precise and reliable therapeutic delivery systems, but similar expertise will have to be demonstrated in developing suitable processing technology so that these devices can be manufactured economically. Apart from manufacturing, the quality control of therapeutic systems is both difficult and complicated (4). For example, as Michaels *etal* (4) point out, a standard dosage form (tablet capsule or injectable) will usually be identified by the active substance(s) it contains, and the quality thereof in a unit dose. A therapeutic system, on the

other hand, is characterised by the substance(s) it administers and its "functionality", that is:, the time dependent rate at which the substance is released and the length of the time of the delivery process. Conformity of a therapeutic system with specified functionality tests calls upon numerous and complicated quality control methods and requirements than does conformity with the compendial standards of quantity and purity (4). This will, inevitably, add to the cost of the product. It should be remembered that while dosage form design is a scientific exercise, it is also a compromise between costs and benefits. The cost of development required to meet the higher standards of quality and performance is also likely to be higher. As the standards of regulatory requirements and quality increase, the task of balancing various factors eg. patient acceptability, efficacy, stability, large scale manufacture etc. will become more difficult. A significant change in marketing and medical opinion is also required and until that happens, the use of the sophisticated drug delivery systems will be limited to special cases (5). In contrast, conventional solid dosage forms appear far simpler to manufacture, to control and to administer.

Standard dosage forms

Solid dosage forms are usually designed for oral ingestion and this mode of administration can often result in inefficient and erratic drug therapy (6). Although tablets and capsules have often been termed as inefficient drug delivery systems, there have not been many examples, apart from digoxin, which unfortunately showed both brand to brand and batch to batch variability, where properly designed solid dosage forms failed to meet performance requirements. The clinical problems encountered with prednisolone, warfarin, tolbutamide and a few other drugs were of different types and were also associated with poor tablet formulations (5).

Since absorption normally occurs only after the drug is in solution, solid dosage forms must first dissolve in the gastro-

intestinal tract. After ingestion of a tablet or capsule, dissolution occurs from three structures, i.e. intact dosage form, disintegrated granules, fine particles. Dissolution will be fastest from fine particles, followed by granules and tablets or a capsule slug. Since dissolution is the primary step which affects drug absorption the prime object of a formulation is to ensure that the formulation ingredients or processing do not inhibit the intrinsic dissolution rate of the drug. In a few cases a product may be formulated with the object of enhancing dissolution. This may apply particularly to insoluble and hydrophobic drugs especially if they are converted to their insoluble free acid form at stomach pH.

However before attempting to improve the dissolution rate of a relatively insoluble drug, a formulator must determine whether dissolution is a rate limiting step using a properly designed in vitro test. It is also important to determine a minimum acceptable level of dissolution rate which will serve as a base line during product development and lower dissolution specification for the quality control of the manufactured product.

The efficiency and reproducibility of clinical response can generally be improved by designing products which release the drug rapidly in the gastro intestinal tract so that the drug is absorbed into the blood stream rapidly and completely (6). Some of the methods which can be used to enhance dissolution are listed below.

Methods for increasing dissolution rates

1. Reduction in particle size (7, 8).
2. Reduction in hydrophobicity (e.g. coating and granulation with a hydrophilic material or surfactants, (9, 10, 11).
3. Increase in solubility and dissolution rates (e.g. salt formulation, pH effect, polymorphism, complexation, solid dispersion, (10).

1. Reduction in particle size

Reduction of particle size to expose larger surface areas to the dissolution medium is perhaps the most obvious choice for improving dissolution. The literature contains several examples where bioavailability was increased following particle size reduction (7). Ridolfo et al (8) have recently shown that the bioavailability of benaxoprofen, a new anti-inflammatory agent, was increased by reducing particle size. The mean peak serum level concentration for crystals smaller than 150μ was found to be 12μg/ml, which was twice that observed (5.5μg/ml) for crystals larger than 250μ. Although particle size seems 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 tableting, effect on disintegration.
d. Increased rate of degradation of relatively unstable drugs.

Finholt (11) for example has shown that dissolution rate of phenacetin powder increases with increasing particle size and decreasing surface area in direct contradiction to the effect seen for benaxoprofen (8). In fact, the smaller phenacetin particles had more air adsorbed on their surfaces and actually floated on the dissolution medium. Levy (12) has also shown that in some cases a reduction in particle size may decrease efficacy. It is probable that for some hydrophobic drugs a reduction in particle size also reduces the effective surface area because the resulting agglomeration reduces the portion of the surface actually in contact with the dissolving fluid. The effective surface area of hydrophobic drug particles may be increased by the addition of wetting or surface

active agents (11). Formulators must be aware that particle size reduction, on its own, may not improve dissolution rate of some hydrophobic systems, and further treatment with hydrophilic materials as well as some processing and formulation adjustments may be required.

Reduction of particle size increases dustiness and problems of handling bulk drugs. The environmental risk has to be reduced by taking extra precautions (wearing of masks etc.) which inevitably places constraints on both operators and production. The problems associated with the poor flow of fine powders are also well known (13).

The compaction process can significantly modify the particle size distribution of a starting material (14). If the material compacts by plastic deformation we might expect a reduction in the surface area. However, if the material consolidates by the process of fragmentation, the particle size may be reduced (11). The changes in particle size distribution will also depend upon the concentration and effectiveness of the tablet disintegrant and the compaction pressure used (15,16). Therefore, during the preformulation phase a study carried out to investigate the effect of particle size on bioavailability, using two size fractions, may be of limited value if ultimately a tablet formulation is required. The effect of particle size reduction during processing should be examined therefore as early as possible. For example, Chalmers and Elworthy (17) showed that for oxytetracycline tablets, a reduction in the particle size of the drug increased the drug/disintegrant particle ratio which resulted in an increase in disintegration time.

Particle size reduction may increase the rate of moisture uptake by hygroscopic and moisture sensitive drugs. Since materials are exposed only for a brief period to the atmosphere

during processing excessive moisture absorption by fine powders can be detrimental to the long term stability of some moisture sensitive compounds. Therefore, extra care and humidity control might be required for the processing of fine powders of relatively unstable drugs.

When a drug is unstable in the gastric fluid, then rapid dissolution may enhance degradation and the net effect, may be reduced availability (7). It has been said that the particle size reduction of acid unstable drugs such as penicillin G and erythromycin may, in fact, reduce their bioavailability (7). This, of course, assumes that the rate of degradation is faster than the rate of absorption. Since both absorption and degradation will occur only after dissolution the extent and rate of availability will depend upon the overall balance between the rates of absorption and degradation and the respective kinetics of the two processes.

2. Reduction in hydrophobicity

As described above, a major problem of traditional particle size reduction is that it results in a very cohesive powder and the high surface energy results in the formation of aggregates and agglomerates. These particle aggregates tend to be hydrophobic and are, thus, difficult to wet. This problem was overcome by Yamamoto et al (18,19), who showed that a reduction in particle size of poorly water soluble griseofulvin and phenytoin by grinding with microcrystalline cellulose resulted in a significant improvement in dissolution rate and bioavailability. The exact physical nature of the ground mixture was not determined. However it was proposed that the drug molecules in the ground mixture were probably dispersed on the surface of the cellulose and were present in an amorphous state. Their energy level was expected to be higher than that of the original crystals. In addition, the

hydrophilic nature of the cellulose, reduced hydrophobicity of the drug in the ground mixture and improved its wettability.

Lerk et al (9) have successfully used a technique for reducing the hydrophobicity of drugs with a hydrophilic polymer (hydroxyethyl cellulose). The method appears similar to a conventional granulation technique and simply relies on improving the wettability and solubilisation of a hydrophobic drug partically coated with a hydrophilic polymer. Finholt et al (11) have previously shown that the dissolution of phenacetin can be improved by granulating phenacetin powder with a hydrophilic binder (gelatin). When these hydrophilic granules were compressed into tablets the dissolution rate of phenacetin decreased but remained greater than the rate of dissolution for the hydrophobic drug.

3. Increasing solubility and dissolution rates

If dissolution is the rate limiting step in absorption, then the rate of availability will increase as solubility increases. Since the salt form of a drug is more soluble in an aqueous medium than its unionised form, the bioavailability can be improved by making readily soluble salts (10). In practice however, the selection of the preferred 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 availability.

The chemical modification of the salt to render it more readily soluble and a reduction in the particle size (discussed earlier) are the most widely used and successful methods for improving dissolution rate and availability. Hersey (20) has recently reviewed the effect of milling on particle size reduction and has proposed that milling can also induce mechanical activation which in turn could lead to an increase in solubility and dissolution rate.

The solubility of the drug and the dissolution properties of dosage form can also be improved by modifying the pH of the dissolution medium and/or of the microenvironment of the stagnant diffusion layer (10,21). The later method has been used for Aspirin (10) and some penicillin salts (21) which are converted to their free acid form at the stomach pH.

The mode of tablet disintegration (i.e. gradual erosion or rapid deaggregation) has also been found to be important for products whose solubility changes with the pH of the dissolution medium. For example, Bates et al (22) have shown that for nitrofurantoin, a weak acid with a pKa of 7.2, the tablet disintegration rate was more important than the pH of the dissolution medium. Their study showed that for both the suspension and capsules containing nitrofurantoin, dissolution rate increases with an increase in the pH of the dissolution medium. However for the tablet which did not disintegrate at the higher pH 7.2 the dissolution rate decreased. Arnold et al (23), on the other hand, have shown that a rapidly disintegrating capsule of sodium phenytoin, in fact dissolved slowly at lower pH, as compared to a capsule which gradually eroded from its outer surfaces. It was suggested that the fine particles generated after the disintegration of the former preparation, precipitated as the poorly soluble acid form of phenytoin and retarded dissolution. Since, the slowly dissolving capsule preparation did not disintegrate, most of the sodium phenytoin was not exposed to the lower pH medium and as a result only a small proportion of the material on the capsule surface got converted to its very slowly dissolving acid form. These particles were gradually removed by the dissolution medium exposing fresh surfaces.

Solvate formation is also claimed to influence the solubility and bioavailability of some compounds (10) but the

evidence is not very convincing. For example Poole et al (24) showed that the solubilities of the anhydrous and the trihydrate forms of ampicillin in water were 10 and 8mg/ml respectively. These results were correlated with the bioavailability of the products containing the anhydrate and the trihydrate of ampicillin. The results showed that the anhydrous ampicillin gave slightly higher blood serum levels than the fromulations containing ampicillin trihydrate. Hill et al (25) subsequently criticised these results on the grounds that the comparisons made by Poole et al (24) were with formulated products from different manufacturers and the results were therefore subject to processing and formulations factors. Hill and his colleagues (25) pointed out that since both forms of ampicillin are highly soluble in acidic gastric environments, dissolution rate is unlikely to be a rate limiting factor. They showed that if the formulations containing the two form of ampicillin were prepared in as simple a manner as possible, by milling the drug to the same particle size and filling into identical capsule shells loosly, by hand, with no added excipients, both the dissolution rates in the acidic solution and the bioavailability of both products were virtually identical.

Although polymorphism is known to affect the solubility of drugs, in practice it is often difficult to produce the desired polymorphic form which is both physically and chemically stable. In general the more soluble polymorph is the least stable thermodynamically and ageing, therefore, can significantly affect the bioavailability of drugs exhibiting polymorphism (10).

The advantages of solid solution and solid dispersion systems in solubility and dissolution rate enhancement have, of course, been well documented. A number of publications have shown that urea, polyethylene glycol and polyvinyl-

pyrrolidone are capable of improving the solubility and rate of dissolution of various drugs (26,27,28). However, most of these systems have been of limited application to manufacturing because of the processing problem of solid dispersions, which tend to be wax like sticky masses (29). Their poor processing properties result from the use of hydrophilic compounds such as polyethylene glycol and polyvinylpyrrolidone, which impart stickiness to the system. In view of these problems, very few conventional dosage forms have exploited the advantages offered by these systems. Recently Walker et al (30) have described a technique for filling molten or thixotropic liquids into hard gelatin capsules, which appears to offer a simple answer to some of the manufacturing difficulties associated with the use of solid dispersions (29). The filling material is based on water soluble hot melt of polyethylene glycol or water dispersible thixotropic systems of pharmaceutical oils with thixotropic additives. A. Zanasi LZ64 capsule filling machine was adapted to fill liquids using a liquid filling pump. It is claimed that the technique can be used to both promote solubility and dissolution using the appropriate carriers and for producing slow release formulation by using suitable retarding excipients (30). Although the aforementioned method certainly provides an answer to some of the practical difficulties linked with solid dispersions, a number of problems have not yet been solved and some of them are listed below:

a. The use of solid dispersions is limited to low dose drugs. A large amount of carrier is often required to improve the dissolution of the drug and this limits the use of solid dispersions to low and in a few cases medium dose drugs (31). For systems containing urea, less than 30% drug has been used and polyethlene glycol has, generally, been used above 70% to improve dissolution properties of

various drugs (31). The examples quoted by Walker et al (30) in their paper discussing the filling of liquid dispersion systems into capsules, also include carriers above 80% level.

b. The process of preparing solid solution or dispersion might cause degradation of drugs or excipients used. Thermolabile drugs may break down during the preparation of solid dispersions. Melts containing more than 80%w/w sulphathiazole dispersed in urea were discoloured, soft and sticky after fusion because of thermal decomposition (26). The decomposition of urea to biuret when fused with salicylic acid was predicted by Collet et al (33). Allen (33) showed that an amber discolouration of solid dispersions of steroid in sugar was caused by decomposition of the dextrose and sucrose. Chiou and Riegleman (34) suggested that decomposition of digitoxin dispersed in polyethylene glycol 6000 may be reduced by lowering the fusion temperature, decreasing the proportion of digitoxin in the solid dispersion or by using the solvent method. A composition dependent decomposition of primidone/citric acid melts had similarly been shown (35).

c. The physico chemical stability of solid dispersions is, generally poor.
Ford and Rubinstein (36) found that although tablets freshly made from the solid dispersion had superior disintegration and dissolution properties to tablets made by traditional methods, they became harder on ageing and tended to have decreased dissolution rates. Solid dispersion tablets were moisture sensitive and less stable than conventional tablets, when stored at 35 and 45°C.

d. For tabletting, other excipients are required to aid the flow compaction and disintegration of solid solution.

These materials increase the tablet size and may make high dose compounds difficult to swallow.

To improve the handling properties of the sticky and waxy materials flow aids (e.g. silica) and antiadherants (e.g. cellulose and talc) are required (31). Since some of these carriers (polyethylene glycol and polyvinylpyrrolidone) also act as binders on tabletting, a disintegrant is often necessary to counter the effect of binding. The presence of the disintegrant, in addition to the large amount of dispersion carrier make the tablet larger.

e. The compaction process often destroys the improved dissolution achieved by solid dispersion.

As stated above, some of the hydrophilic carriers also act as tablet binders, and the improvement in dissolution achieved by solid dispersion may therefore be destroyed if tablet disintegration is delayed. Ford (31) has shown that there was a significant reduction in the release of drugs from solid dispersion after tabletting.

4. Other Processing Factors

Although the effect of various processing factors on disintegration and dissolution has been examined (10) little work has been carried out in relating bioavailability with the processes used during the manufacture of solid dosage forms. Compression force has been shown to both increase and decrease dissolution rates, depending upon the physical properties of the tablet constituents (37). It has been said that the direct compression process for making tablets produces fast disintegrating and dissolving tablets (38) as compared to those prepared by moist granulation. However practical evidence showing differences in the disintegration properties of tablets prepared by direct compression and moist granulation

using identical or at least similar formulations is lacking. For example in a paper published by Marlow and Shangraw (39), directly compressed spray dried lactose containing sodium salicylate was shown to have superior dissolution properties compared to sodium salicylate tablets prepared by moist granulation using crystalline lactose as the diluent and ethyl cellulose plus acacia mucilage as the granulating agents. Although these results have been interpreted by some readers suggesting that directly compressed formulation are likely to disintegrate faster, the obvious conclusion is that some viscous binding agents are capable of retarding tablet disintegration by forming a physical barrier around drug particles.

Schwartz (40), on the other hand, reported that when granulated and direct compression mixtures of the same ingredients were prepared, the granulated mixtures showed superior processing and dissolution properties. In this case, the differences in the dissolution can be attributed to the differences in the bonding mechanisms of the wet granulation and directly compressed systems. The former is expected to produce a more porous compact which would allow faster penetration of the dissolution medium into the tablet structure. However, if large proportions of the "self disintegrating diluents" (e.g. microcrystalline cellulose or directly compressible starch) are used both in the direct compression and the wet massed systems, then the differences in the disintegration properties of tablets are expected to be minimal. For hydrophobic drugs used in medium or high dose ranges, wet granulation may be more appropriate. This is because, surfactants and other hydrophilic materials (e.g. polyvinylpyrrolidone, and hydroxymethyl cellulose) tend to give better results when incorporated either in solution, as granulating agents, or activated by solvents during processing.

CONCLUSIONS

Of all the methods discussed so far, the use of suitable tablet excipients and tablet disintegrants at their optimum level is still the most effective and convenient method of improving dissolution properties of solid dosage forms.

It should also be stressed that as the formulator modifies the design of the product or process to improve dissolution, other quality and performance features may also be altered. For example it is not uncommon for the tablet size, geometry, hardness and gloss parameters to compete with tablet disintegration and dissolution.

A formulation is often developed under a large number of constraints; marketing, packaging, economics, regulatory requirements and patient acceptability. The design of a product cannot therefore be considered in isolation since in practice a compromise between factors having the best possible combination, has to be achieved.

In conclusion, it is suggested that although considerable progress has been made in improving efficacy by maximising drug dissolution, further research should be directed towards improving stability of products made by these processes and examining feasibility of using these processes in large scale manufacture.

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