Drug Information Journal, Vol. 30, pp. 1039–1044, 1996
Printed in the USA.
0092-8615/96

THE ROLE OF DISSOLUTION TESTING IN THE DESIGN OF IMMEDIATE RELEASE DOSAGE FORMS

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Dissolution testing is an invaluable tool for the formulation team to use in the design of oral dosage forms. This paper covers dissolution tests for high solubility/high bioavailability compounds, low solubility compounds, and apparently insoluble compounds, as well as accelerated stability testing.

Key Words: Dissolution testing; Immediate release dosage forms; Design; Formulation team

INTRODUCTION

A FORMULATION TEAM'S objectives in designing oral solid dosage forms can be summarized as follows:

1. To develop a composition and process for Phase I clinical studies which are consistent with the intended market composition (qualitative and quantitative),
2. To develop a highly discriminating dissolution test; not as a quality control tool but as an aid to optimization of a formulation,
3. To develop a dosage form with a consistently high performance throughout its shelf life, and
4. To develop a dissolution test to serve as a quality control tool.

The formulation team may not always be entirely successful in achieving the third objective, but significant progress prior to Phase I certainly provides a jump start to the final design and development of the dosage form and the manufacturing process.

A wide variety of factors need to be considered at the early design stage, in relation to both the dosage form and the dissolution test. These include the human dose/drug solubility relationship (dose prediction being based upon preclinical *in vivo* and *in vitro* data); with influencing physical factors such as salt form, polymorphic form and hydrate/solvate; the intrinsic dissolution rate over the pH range 1–7, which covers the predominant range of pH in the upper gastrointestinal (GI) tract where a significant proportion of absorption normally occurs; and the crystal surface energy, quantified by moisture sorption thermodynamics, wetting thermodynamics and modeling of surface free energies by reference to molecular structure. Also of importance are absorption rate data from animal studies together with information on region-specific absorption. These data provide an indication of potential problems if one is interested in achieving rapid absorption/onset of action in man.

There is a considerable body of data in the literature supporting the use of drug permeability coefficients in cell cultures as a

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predictor of drug bioavailability. It has been Merck's experience, however, that such *in vitro* data can often be misleading, and the preferred approach is to measure bioavailability in at least three preclinical animal models, with supporting metabolism data or portal plasma level data to clearly resolve membrane permeability/metabolism and bioavailability issues.

There has recently been renewed interest in measuring drug permeability coefficients directly in animal models and using permeability/solubility relationships to predict potential bioavailability problems in man. There is currently an inadequate database, however, to support the general application of this approach.

There are a number of warning signals, "soft triggers," which alert the formulation team to potential absorption/bioavailability problems and which may necessitate control of certain physicochemical properties of the bulk drug. For example, when the quotient of the predicted human dose divided the drug's aqueous solubility (minimum solubility value in the pH range 1–7) exceeds ca 100 mL, or the intrinsic dissolution rate is less than 0.1 mg/sq. cm/minute or the percentage of the oral dose which is absorbed does not exceed about 60% in any one preclinical animal species (excluding presystemic metabolism effects).

HIGH SOLUBILITY/HIGH BIOAVAILABILITY COMPOUNDS

If none of these soft triggers are met, then one would expect very rapid dissolution *in vitro* and *in vivo*. The dissolution test for formulation design could simply be water, but instead of using the standard 900–1000 mL, one should consider reducing the volume of dissolution medium to achieve less than three-fold sink conditions to challenge the design of the dosage form. Other ways of challenging the dissolution rate of the dosage form include reducing the stirring speed or adjusting the pH to reduce the solubility.

For compounds with aqueous solubilities in excess of 1 mg/mL (in the pH range 1–7), ultimately a dissolution specification in the region of Q = 80 at 15 minutes in 900 mL would not be unreasonable. For a compound at the limit of the dose/solubility quotient which has a solubility less than 0.1 mg/mL, however, ultimately a dissolution specification of Q = 75 in 30 minutes may well be more appropriate.

Potential pitfalls in interpreting dissolution data for this class of compounds (high solubility/high bioavailability) include the entrapment of drug particles in loosely packed water insoluble excipients (starches, cellulosics, calcium phosphate) if the formulation disintegrates too rapidly during dissolution testing (eg, paddle at 50 rpm). The enigma in this situation is whether to slow down the rate of disintegration merely to satisfy the artificial conditions of the dissolution test and enhance dissolution rate purely to satisfy a perceived need for a rapid *in vitro* dissolution or to maintain the rapid disintegration rate which may be more important for *in vivo* behavior and provide an explanation of the slower dissolution profile in the regulatory submission.

Another, less common, pitfall in interpreting dissolution rate for high solubility/high bioavailability compounds has been a slowing in dissolution rate due to adherence of film coated tablets to the dissolution vessel wall. Small changes in the radius of curvature of a tablet surface following redesign of tablet tooling may lead to this effect. This emphasizes the need for careful observation during dissolution testing. A video camera may prove an invaluable resource. Additionally, polar compounds have been found to bind reversibly to certain water insoluble excipients such as cellulosics and starches. During dissolution testing, complete dissolution of the active dose may not be achieved, with the dissolution curve reaching an asymptote significantly below 100%. Screening of drug-excipient binding at the preformulation stage can help to eliminate or reduce such binding phenomena. Again one must treat the interpretation of such data with care,

however, since *in vivo* this reversible binding may have little or no impact on drug absorption as it is a dynamic equilibrium.

Other parameters which can be optimized during the design phase through appropriate dissolution testing are tablet crushing strength specifications, tamping force specifications during capsule filling, influence of lubricant level and mixing time ranges, processing conditions to avoid unwanted changes in drug form during manufacturing/stability testing, and the influence of compression speed on powder/granule/tablet performance. It is at this early stage when only small quantities of compound are available that use of a compaction simulator can enable the gathering of a significant amount of important information.

Even for high solubility/high bioavailability compounds, some control over drug particle size is still appropriate for compounds which do not meet any of the soft triggers. For example, one may wish to ensure adequate content uniformity for a low dose, potent compound or to ensure that the quality of the bulk drug is reproducible and hence maintain close control of the manufacturing process of the dosage form for higher dose drugs.

If any of the soft trigger criteria are met, this is a strong indication that dissolution rate and/or solubility may influence drug absorption/bioavailability. If such data are available early enough, consideration can be given to enhancing solubility through choice of salt form or polymorph or by reducing particle size appropriately. When the dose/solubility quotient exceeds 100 mL but is less than ca 500 mL, use of the standard 900–1000 mL dissolution medium volume should be adequate to challenge the dissolution performance and aid optimization of the formulation composition.

LOW SOLUBILITY COMPOUNDS

A series of "hard triggers" will indicate that special formulation technologies may be required to achieve an adequate absorption rate/bioavailability. Such hard triggers include a dose/solubility quotient greater than 1000 mL, an intrinsic dissolution rate less than 0.01 mg/sq. cm/minute, and an oral bioavailability (excluding presystemic metabolism) in all preclinical animal species of less than 20%.

For such compounds, if enhancements in solubility cannot be achieved through salt formation (eg, acidic or basic functions too weak or absent), the first approach is usually to reduce particle size to below about 20 microns or less. Dissolution testing of tablet and capsule dosage forms incorporating such compounds can be problematic. Nonetheless, use of surfactants, such as sodium dodecyl sulphate, at concentrations up to several percent, has usually been found adequate to achieve the required level of solubility to allow monitoring of dissolution rate and hence optimize product performance.

For hydrophobic compounds which wet poorly, studies of crystal surface free energies and the interfacial free energy between the wetting liquid and the crystal surface have proven to be of benefit in selecting appropriate wetting agents to include in capsule and tablet dosage forms. Wetting agents commonly employed include hydrophilic polymers such as PVP, HPMC, and HPC and surface active agents such as docusate sodium and sodium dodecyl sulphate. In general, it has been found that for poorly wetting/low solubility (below 10 mcg/mL) compounds, the disintegration rate of the solid dosage form has a more profound effect on the dissolution profile than for high solubility compounds. Hence, besides employing an appropriate wetting agent, maximization of the disintegration rate of the dosage form is essential.

Many of the bioavailability problems associated with compounds which meet the hard trigger criteria have arguably arisen because of a poor understanding of the formulation requirements and the emergence of generic formulations of such compounds. There is an enormous amount of information in the literature on the design of sustained release

formulations; if one examines the theories behind these different technologies, it is readily apparent that by a design fault one can develop a poorly dissolving immediate release formulation and thereby influence a drug's pharmacokinetics. For background information, refer to Murthy and Ghebre-Sellassie (1). Nevertheless, simply because a drug displays a dissolution profile which is apparently related to the rate of disintegration/erosion of the dosage form during dissolution testing, it should not be assumed that this will result in a slower absorption rate *in vivo* because the forces exerted upon the dosage form in the gastrointestinal tract are unrelated to those it experiences using standard paddle or basket methodologies. This is exemplified by the frequent failure to demonstrate *in vivo/in vitro* correlations for sustained release dosage forms relying solely on erosion of a tablet matrix for release control. Even so, there are a number, albeit limited, of examples in the literature where *in vivo/in vitro* correlations have been found for immediate release, low solubility compounds. See, for example, Simmons et al. (2). This particular example, however, perhaps serves more effectively to demonstrate the role of animal studies in formulation optimization and selection of the final Phase I clinical formulation.

If the rate of drug dissolution from an immediate release oral dosage form is controlled by the properties of the drug, however, then there is a possibility that *in vivo/in vitro* correlations may be found. This was recognized as dissolution rate limited absorption by Hersey back in 1969 (3).

The underlying message to the formulation team designing a dosage form for low solubility compounds is that optimization of the rate of drug dissolution through appropriate control of the drug form (polymorph, salt, solvate, hydrate, particle size, surface energy) and through challenging the ability of the dosage form to provide rapid dissolution, makes it possible to design into a formulation the greatest flexibility for processing changes on scale-up and postapproval. There will always be certain "insoluble" compounds for which this may not be possible using conventional tablet/capsule technologies and more specialized technologies are needed to assure adequate and reproducible bioavailability, as discussed in the following section.

APPARENTLY "INSOLUBLE" COMPOUNDS

For compounds with aqueous solubilities of less than 1 mcg/mL, rationally it would seem impossible to achieve adequate bioavailability, particularly in cases where the human dose/solubility quotient is in excess of 3000 mL and intrinsic dissolution rate is immeasurably slow. For such compounds, particle size control is essential and surfactant solutions (SDS, Tweens) are screened as suitable dissolution media, followed by hydroalcoholic solutions and lastly flow through cell type dissolution apparatus; for further details, refer to Dakkuri and Shah (4). To obtain complete dissolution within a reasonable time period (less than one hour), increased stirring speeds are employed. The role of any wetting agent in the formulation may be masked by the surfactant in the dissolution medium. Hence, design of the optimal formulation is aided by animal (primate, dog) bioavailability studies using an appropriate pharmaceutically acceptable solution formulation, if feasible, as a "best case" control.

With only a limited number of animals ($n = 6$), the power to discriminate between formulations is not very high. At this stage, however, the formulation team should be looking for significant differences in bioavailability (eg, <20%–>50%) between what is predicted from physical measurements to be an optimal conventional dosage form and the solution formulation. One might also compare at this stage two conventional formulations with markedly different dissolution profiles to see how predictive the current dissolution method is.

It has not been too difficult to demonstrate significant differences in bioavailability in animals for these apparently insoluble compounds in comparing conventional dosage

forms with soft gelatin capsule solution formulations (or for that matter other well-known technologies for enhacing the bioavailability of low solubility compounds, such as extending a solution of the drug over a high surface area substrate, nano-meter sized drug particles, nonaqueous microemulsions). Experience to date, however, indicates that such differences are minimized in man. Nonetheless, it is essential to demonstrate as early as possible in the clinical program that the alternative technologies really have no advantages in man. To discover this during clinical dose range finding studies and to attempt switching between formulations will almost certainly mean a restart of the range finding studies.

ACCELERATED STABILITY TESTING

It has been claimed that performing dissolution testing on dosage forms subjected to accelerated stress conditions (temperature and humidity) is without meaning. Some formulation teams believe that such testing can provide a useful guide to potential problems and provides the opportunity to select excipients/manufacturing processes which minimize these effects. Taking this approach provides an extra margin of safety, knowing that performance of the dosage form after storage at the International Conference on Harmonization (ICH) recommended stress conditions will be unaffected or that special packaging considerations are required. It also provides assurance that the dosage form is no more temperature- or humidity-sensitive than the bulk drug itself. After all, having carefully selected an appropriate form of the bulk drug for development, whenever possible the formulation team's objective should be to build on these physiochemical properties and not to design a formulation with greater sensitivity to heat and moisture than the bulk drug itself.

A wide variety of factors affect dissolution stability, including processing factors, formulation variables, drug and excipient solubility/hygroscopicity/thermal behavior, changes in tablet tensile strength and/or porosity, and the product packaging itself in terms of its moisture barrier properties. To fully understand and predict potential dissolution stability problems, a database on moisture sorption isotherms of bulk drug excipients and finished dosage form over the range of expected storage conditions (ICH recommended conditions of 40°C/75% RH, 30°C/60% RH, and 25%°C/60% RH) is invaluable. Further insight can be gained from the thermodynamics of the moisture sorption process, for example, for exothermic moisture sorption processes, 25°C/60% RH may be more detrimental than 40°C/75% RH. The question remains, however, on what constitutes a significant change in the dissolution profile.

CONCLUSIONS

Dissolution testing is an invaluable tool for the formulation team to use in the correct design of oral dosage forms. The dissolution test itself should be designed to challenge the dissolution performance of the dosage form during the early design stage and should later be modified to yield the standard quality control tool. For highly water soluble compounds, one might question the need for a dissolution test at all, both in design and routine manufacturing, provided certain disintegration criteria are met. *In vivo* and *in vitro* correlations for most drugs and their formulations are unlikely provided the formulations have been correctly designed and the drug solubilities are in general above about 100 mcg/mL. Poorly formulated products of drugs with very low water solubilities whose rate of dissolution/rate of absorption is controlled by the physiochemical properties of the bulk drug are more likely to demonstrate *in vivo–in vitro* correlations. Hence, one would not expect to see *in vivo–in vitro* correlations for well-designed formulations of even very low solubility compounds.

For compounds of extremely low water solubility which necessitate either very high surfactant levels or organic solvents in the dissolution medium, one has to question

whether a better quality control tool is needed/remains to be developed to ensure lot to lot consistency. This needs to be determined on a case-by-case basis.

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