ELSEVIER

International Journal of Pharmaceutics 140 (1996) 131–143

international journal of pharmaceutics

Invited review

Dissolution testing for sustained or controlled release oral dosage forms and correlation with in vivo data: challenges and opportunities

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Abstract

Despite the fact that dissolution tests were first introduced to characterise the release profile of low solubility (< 1%) drugs in aqueous media, the emphasis is now to adopt dissolution tests in monographs of almost all oral solid dosage forms in most pharmacopoeias. This is attributable mainly to the growing demand by both regulatory authorities and pharmaceutical industries of more in vivo predictability of the release and absorption behaviours of drug(s) from the dosage form by means of in vitro tests, i.e. in vitro-in vivo correlation. Dissolution testing is also essential in various stages of formulation development for screening and proper assessment of different formulations. Although dissolution tests have been successfully implemented on conventional dosage forms, there are enormous difficulties in establishing proper dissolution test conditions and parameters for testing sustained or controlled release oral dosage forms because of prolonged gastrointestinal residence of the dosage form and variabilities in physiological conditions of the gastrointestinal tract. This review focuses on the challenges faced by formulation scientists and regulatory authorities in generalising the dissolution test conditions and parameters for testing sustained or controlled release dosage forms, and describes some recent trends and progress in overcoming some of these challenges.

Keywords: Dissolution testing; Dissolution media; In vitro-in vivo correlation; Controlled release; Sustained release; Extended release; Food effect; Dissolution review

1. Introduction

Prior to the emergence of dissolution tests as being official in the United States Pharmacopeia (USP) in the early 1960s, disintegration tests were the only official in vitro tests used by major pharmacopoeias throughout the world as means of in vivo release predictability and product performance. Although the disintegration test is only indirectly related to drug bioavailability (Cohen et al., 1990), this test has been the number one choice for the pharmaceutical industry in assess-

PII S0378-5173(96)04561-9

ing the quality and performance of any conventional oral solid dosage form. This is perhaps due to the fact that this test is inexpensive, quick and does not require skilled personnel.

With modernisation of technology, advancement in research in drug delivery and more emphasis on in vivo predictability of therapeutic effect by means of in vitro tests, dissolution tests have been gaining more and more popularity. Initially, dissolution tests were introduced to characterise the release profiles of low solubility (< 1%) drugs in aqueous media. But now the emphasis is to adopt dissolution tests in monographs of all oral solid dosage forms with minor exceptions (e.g. nonabsorbed drugs). Not surprisingly, any report in literature on formulation and development of any solid dosage form starts with dissolution testing.

The dissolution tests have been successfully implemented on conventional dosage forms, and generalised monographs described in pharmacopoeias are usually sufficient to test any such new formulation. Unfortunately, this is not the case with sustained or controlled release dosage forms. Formal guidelines to evaluate sustained or controlled release products do not exist. The current trend is to evaluate each and every sustained or controlled release dosage form on individual basis. The formulation scientists and regulatory authorities face an enormous challenge of generalising the test conditions for dissolution testing because most individual drug candidates for sustained or controlled release dosage forms and their delivery design possess diverse physicochemical and pharmacokinetic properties requiring specific considerations. The difficulties are also in simulating in vivo conditions in in vitro. Since most sustained or controlled release preparations are designed for prolonged release and therapeutic effect, variabilities in in vivo conditions (such as presence and nature of food in the gastrointestinal tract, time of the day the dosage form is administered) which can substantially affect the release profile of the drug are bound to happen.

The formulation aspects of sustained or controlled release oral dosage forms for some water soluble drugs were addressed in a recent review (Khan, 1995). The overall design aspects of sustained/controlled release dosage forms were also addressed by other reviewers (Caramella et al., 1995). But despite significant emphasis given on dissolution testing of sustained or controlled release dosage forms by regulatory authorities (Skelley et al., 1990; AAPS/FDA Workshop Committee, 1995) the difficulties faced by formulation scientists and regulatory authorities in generalising the test conditions have not been addressed in recent years. Almost a decade ago, Thoma (1987) discussed dissolution testing and bioavailability of various dosage forms covering sustained/controlled release preparations briefly, but ever since, the sustained/controlled release technology has progressed substantially. The main objective of this review is to focus on various factors that deserve consideration during dissolution testing of sustained or controlled release oral dosage forms and to summarise the recent trends and progress in overcoming these difficulties with an emphasis on in vivo predictability. This review would be helpful in selecting dissolution test conditions for sustained or controlled release oral dosage forms in early stages of development and during quality control and performance checks. The term 'extended release' has been used throughout this review in place of both 'sustained release' and 'controlled release' terminologies.

2. Dissolution media and test conditions

2.1. Challenges in selecting dissolution media

The dissolution test plays an important role both in the development process of a new formulation and as a means of production control. Perhaps for regular performance check and production control it is not so important for the dissolution method to produce a dissolution profile which is superimposable to the in vivo release profile of the drug, provided the method is discriminatory enough to differentiate formulations which would have different in vivo performance. But from the formulation view point it is extremely important that at various stages of development the formulator is able to test the re-

lease profile of the drug in an environment which would closely relate to the actual in vivo conditions, particularly for dosage forms which would have different release/absorption profiles at various physiological conditions of the gastrointestinal (GI) tract. This justifies a critical assessment of the physiological conditions an extended release dosage form passes throughout its total residence time in the body.

Therefore, in an ideal situation, an extended release oral dosage form should be tested in vitro throughout the entire physiological pH (1–7.8) of the GI tract in order to simulate the in vivo conditions. But the difficulties are in determining the time interval which should closely relate to a particular pH segment of the in vivo condition. Even the type of buffer species in the dissolution medium (at a particular pH) was reported to influence significantly the release profile of diltiazem hydrochloride from extended release dosage forms coated with Eudragit RS and RL (Bodmeier et al., 1996). The physico-chemical and physiological properties of the GI fluid where release of the drug from the administered dosage form occurs are determined by many factors (particularly for extended release dosage forms); notably: (a) the state of the stomach when the dosage form is taken, i.e. whether it is taken in an empty stomach or after meal, (b) the nature of food and build up of mucus, and (c) excipients of the dosage form itself and co-current administration of other drugs.

On an empty stomach an oral dosage form is known to reach the intestine in as little as 10 min (Vidgren et al., 1991), whereas in a fed stomach an extended release pellet formulation had gastric emptying times of 119–285 min depending on the size of food administered (light vs. heavy) (Davis et al., 1984). The presence of food in the stomach also influenced the integrity of orally administered pellets; from empty stomachs the pellets came out as boluses, but from fed stomachs, spreading of the pellets occurred (Hunter et al., 1982; Davis et al., 1987; Fischer et al., 1987). There are also contradicting reports in literature about food induced changes in absorption and bioavailability of drugs from the dosage forms indicating no changes (Davis et al., 1990; Wilding et al., 1992), enhanced absorption (Marvola et al., 1987, 1989) or reduced bioavailability (Digenis et al., 1990; Ogiso et al., 1994; Nazareno et al., 1995) compared to fasting conditions. The enhanced plasma levels or bioabsorption of verapamil from extended release dosage forms due to the presence of food was explained as due to increased GI residence time of the dosage forms in the stomach where absorption of the drug is favoured (Marvola et al., 1987, 1989). 'The interaction of the gastrointestinal tract with sustained release dosage forms is highly complex and dynamic and controlled, in part, by transit of the product through the stomach and intestine' (Liaw et al., 1990).

Not only the presence of food but also its extent (i.e. heavy or light, single or succession of meals) and nature (fatty or fibrous) determine the degree of effect on drug absorption or bioavailability. Single meal or succession of meals taken before dosage form administration made enormous differences in GI residence times of bilayer floating capsules of misoprostol (Oth et al., 1992). The capsules took 199 min to pass the stomach after a single meal compared to 618 min after a succession of meals. Wilson et al. (1991) reported a gastric emptying time of 2.2 h following oral administration of an extended release buflomedil HCl formulation in healthy humans after a light breakfast compared to 6.2 h after a heavy breakfast, although small intestinal transit time was unaffected by the meal size. The difference in gastric emptying time was also reflected in the time to reach peak plasma concentration (T_{max}) of the drug showing 4 and 6 h following light and heavy meals. The presence of a heavy breakfast caused extended GI transit time and greater spreading within the small intestine of extended release pellet formulations than caused by light breakfasts (Davis et al., 1984, 1987). Dietary fibre modified small intestinal transit of pellet and tablet dosage forms causing slower overall transit in vegetarians than in omnivores (Price et al., 1991). The bioavailability of theophylline in healthy humans from various extended release formulations were significantly influenced by the presence of 'high fat' breakfast compared to fasting condition causing either increased or decreased rate and extent of absorption depending on the type of formulation (Karim et al., 1985).

Even the type of oily food (emulsion) present in the stomach made a difference in bioavailability (T_{max}) of propranolol when studied in rats (Ogiso et al., 1994). The peak plasma concentration (C_{max}) of propranolol administered orally to rats having 20% soybean oil emulsion was delayed compared with rats having a 20% lauric acid-oleic acid emulsion. For obvious reasons, the presence of fatty food in the stomach can have a substantial effect on release profiles of lipophilic drugs or from dosage forms that control the release process on the basis of hydrophilicity. Other notable factors related to the presence of food in stomach include changes in pH of the gastric fluid that occur as a result of food consumption, and secretion of various enzymes (e.g. pepsin in the stomach) and chemicals (e.g. bile salts in the intestine). The pH of gastric fluid of an empty normal human stomach is between 1.2 and 2.5 which rises to about 4.5 after ingestion of food.

Another parameter of the dissolution medium which plays a significant role in the dissolution process is its ionic strength (Bodmeier et al., 1996). Dissolution behaviours of extended release formulations which use hydrophilic gel forming polymers, such as hydroxypropyl methylcellulose (HPMC), are known to be significantly affected by any changes in ionic strength of the dissolution media. Certain ionic salts and drugs were reported to cause failure to some HPMC-based extended release products (Fagan et al., 1989). Extended release diclofenac sodium tablets prepared in the form of HPMC matrices had significantly different release profiles in dissolution media of different ionic strength but same pH (6.8), and the changes in dissolution rates as a function of ionic strength of the dissolution media did not have any direct relationship (Chetty et al., 1994). Some commercially available diclofenac sodium extended release tablets (Voltaren® SR, Ciba-Geigy Canada Ltd., Mississauga, Canada), showed significantly different release profiles in phosphate buffers (pH 6.8) of various ionic strength (Fig. 1). But this contradicts a report by Chetty et al. (1994) who found that similar tablets (Voltarol Retard) manufactured also by Ciba (Basle, Switzerland), known to be wax matrix tablets, had identical dissolution profiles in phosphate buffers (pH 6.8) of different ionic strengths. Jalil and Ferdous (1993) reported the dissolution variability of theophylline extended release granules prepared using HPMC as a retarding agent as a function of ionic strength of the dissolution media. They found an exponential increase in the dissolution rate of theophylline from these granules against increasing ionic strengths of the dissolution media; whereas, in an earlier study, Li Wan Po et al. (1990) found an initial decrease followed by an increase in dissolution rate of theophylline from a commercially available extended release matrix tablet formulation (Lasma®) with increases in ionic strength of the dissolution media. The presence of ions (e.g. Na^+) in the dosage form itself was reported to cause a rapid disintegration of extended release HPMC matrix tablets (Rajabi-Siahboomi et al., 1994). The mechanism of action of ions in dissolution profiles of HPMC and other cellulose ether-based extended release dosage forms has been explained as due to changes in thermal gelation point (TGP) of these polymers that occur due to dehydrating effect of electrolytes on these polymers. The TGP, which is a critical temperature point, determines the sol to gel transition of the polymers in aqueous media, and is depressed by ions causing failure to the system (Fagan et al., 1989; Rajabi-Siahboomi et al.,

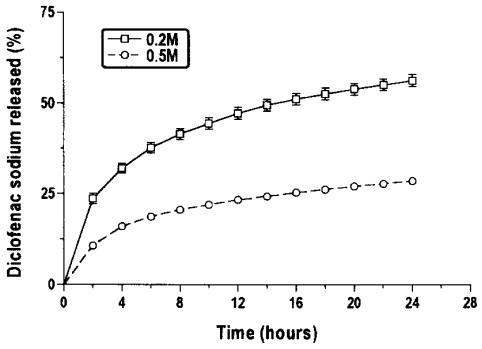

Fig. 1. Dissolution profiles of a commercially available diclofenac sodium (Voltaren® SR) extended release tablet in phosphate buffers (pH 6.8) of two different ionic strengths. Vertical bars representing standard errors of the means ($n = 6$) are within the points where not visible.

1994). Jalil and Ferdous (1993) further linked this effect of electrolytes to factors like (i) increased surface erosion and dissolution of polymer chains and (ii) increased osmotic pressure created due to higher ionic strength in the dissolution media.

In another study, Hamaguchi et al. (1995) reported that an increase in ionic strength (to a certain extent) of dissolution media (pH 5.0–5.8) resulted in an increase in dissolution rate of sulpiride from tablets film-coated with a polyelectrolyte, polyvinylacetal diethylaminoacetate. The increased dissolution rate was explained as due to increased solubility of the film-coating polymer in the dissolution media with higher ionic strength.

As previously stated, presence of food in the stomach can induce secretion of various chemicals in the GI tract causing changes in ionic strength of the GI fluid. The presence of ions in food itself is also not unique making it difficult to generalise the ionic strength of dissolution media used to test extended release dosage forms. This emphasises the importance of screening extended release formulations during development stages in dissolution media with various ionic strengths so that a proper judgement of the developed formulation(s) can be made during in vitro studies in order to avoid any possible in vivo failures.

As is the case with conventional dosage forms for poorly water-soluble drugs, the selection of appropriate dissolution medium for extended release dosage forms containing poorly water-soluble drugs is also complicated due to the difficulties in achieving sink conditions during the dissolution test. Among other methods, addition of a solubiliser to the test medium to improve the solubility of the drug has been tried successfully to overcome this problem (Wingstrand et al., 1990; Abrahamsson et al., 1994; Shah et al., 1995).

2.2. Challenges in selecting dissolution test parameters

The difference in GI residence times of administered dosage forms in fed and fasted objects is mainly caused by a physiological factor, motility pattern of the GI tract, which is completely different in fed and fasted humans and animals that consume food on a discrete basis (Liaw et al., 1990). Most extended release products are not disintegrating; hence, it is important that in vivo hydrodynamic conditions are properly simulated during dissolution testing. But the variability in motility patterns of the GI tract in fasted and fed objects complicates the task of setting a unique agitation condition during in vitro testing. Dissolution studies performed on TA-5707F wax matrix extended release tablets by the JP (XII) disintegration method (30 strokes/min, no disk) were found to correlate with the physiological state of GI tract of fasted beagle dogs better than when the studies were performed by the JP (XII) paddle method (100 rev./min) due to stronger frictional forces generated by the disintegration method (Yamakita et al., 1995).

Since the human body temperature is about 37°C, standard dissolution testing is carried out at this temperature with an allowable variation of ± 0.5°C in most pharmacopoeias. But a report exists about significant differences in dissolution profiles of some commercially available extended release solid dosage forms containing isosorbide dinitrite tested at various temperatures within this specified range of 36.5–37.5°C (Kaniwa et al., 1995).

3. Dissolution apparatuses

An ideal dissolution apparatus for extended release product should be able to tackle at least some of the challenges (as stated above) that the formulation scientists face in simulating in vivo conditions. The apparatus would be capable of simulating (i) the entire pH range of the GI tract according to the desire of the formulation scientist, (ii) food induced physiological changes (at least in part) that occur in the GI tract, and (iii) the motility pattern and other mechanical forces encountered by the dosage form in the GI tract.

Currently available dissolution apparatuses are based on two distinct methodologies, either a closed or an open system (Möller and Wirbitzki, 1993). The majority of studies focusing on dissolution profiles of extended release products use USP dissolution apparatus with either paddle or basket method which is designed as a closed

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