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In vitro dissolution medium with supramicellar surfactant concentration and its relevance for in vivo absorption

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Summary

Use of a dissolution medium with supramicellar surfactant concentration is proposed for the in vitro testing of practically insoluble drugs (less than 0.01%). Based on the fact that the model drug tested—palmitoylcatechin—is absorbed in the intestine, a pH 6.8 phosphate buffer (Pharm. Eur.) with the addition of 50 mmol/l sodium laurylsulfate was used in our work. At that concentration, this surfactive agent had similar solubilizing properties toward the drug as the natural bile salts sodium cholate and sodium taurocholate. Five experimental and commercial palmitoylcatechin preparations, namely four tablet and one capsule formulations, were tested. A preliminary disintegration stage in simulated gastric fluid (a 30-min period was adopted here) was sometimes necessary in order to better correlate dissolution and in vivo absorption data.

Introduction

Drugs that are practically insoluble (less than 0.01%) are of increasing therapeutic interest but it is well recognized that they may present particular problems of

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bioavailability when administered orally. Since their dissolution rate can be the rate-limiting step in the in vivo absorption process, there is a definite need for the development of an appropriate dissolution test. Because of the low solubility of such drugs, various dissolution methods have been suggested in the pharmaceutical literature: (i) use of sufficiently large liquid volumes (Symchowicz et al., 1968; Chiou and Riegelman, 1970); (ii) testing under non-sink conditions and/or incomplete drug dissolution (Gibaldi and Feldman, 1967); (iii) removal of dissolved drug from the dissolution medium by the use of an upper or lower organic phase (Gibaldi and Feldman, 1967) or by the addition of adsorbents to the aqueous medium (Wurster and Polli, 1961); and (iv) mixtures of water and water-miscible solvents (Walkling et al., 1979).

All these media are either of poor physiological significance (ii, iii, iv) or not easy to use (i).

In the past, little attention has been focused on the use of dissolution media with supramicellar surfactant concentration in order to enhance the solubility of the drug (Bates et al., 1975). Such a test liquid can match quite closely the properties of the intestinal fluid in which mixed micelles of bile salts and lecithin are capable of solubilizing insoluble substances. The increase in drug solubility by surfactant micelles has been demonstrated in vitro for a large number of poorly water-soluble compounds, using synthetic (Vaution et al., 1981) as well as natural surface-active agents (Miyazaki et al., 1981). A bile salt, sodium deoxycholate, was used for instance by Bates et al. (1975) to study the dissolution of griseofulvin. In this work, we used the less expensive synthetic sodium laurylsulfate (CMC = 1.5 mmol/l) since it has been shown in a recent investigation (Buri and Humbert-Droz, 1983) that natural surfactants (sodium cholate and sodium taurocholate) can be interchanged with this synthetic compound for solubilizing purpose.

To illustrate this concept, palmitoylcatechin was used as a practically insoluble model drug. Its solubility in a phosphate buffer of pH 6.8 at 37°C was found to be only 0.0006% (Buri and Humbert-Droz, 1983).

In a first part, the in vitro and in vivo availabilities of three experimental tablet formulations with distinct disintegration characteristics and of a 1% reference suspension of the micronized drug were investigated. Based on the fact that palmitoylcatechin is absorbed in the intestine, a pH 6.8 phosphate buffer was used. A comparison was made with a mixed organic aqueous dissolution medium. A biphasic dissolution medium (phosphate buffer with octanol) was also considered, but this system did not permit dissolution of a significant amount of drug in 24 h because of the very low rate of transfer from the aqueous to the organic phase.

In this part, the tablet was placed directly into the solubilizing dissolution medium (e.g. intestinal fluid), but it is well recognized that the disintegration process of a given dosage form may be affected by the composition of the aqueous environmental liquid. Therefore, the effect of a preliminary stage in simulated gastric juice, prior to adding intestinal fluid with a surfactant, will be examined in a second part of our work. This effect will be investigated for the three experimental tablet formulations and for two industry dosage forms, one hard gelatin capsule and one film-coated tablet, in order to validate the dissolution test proposed.

Materials and Methods

Materials

The O-palmitoyl-3(+)catechin powder (Zyma, Nyon, Switzerland) used to prepare all formulations had a mean particle diameter of 4 μm (Coulter Counter) and a contact angle with water of 45.4°.

The three experimental tablet formulations tested contained 400 mg palmitoylcatechin. These formulations varied, depending on the binding and disintegrating agent used. Their exact compositions and disintegration characteristics (particle size distribution of the disintegrated tablets) can be found elsewhere (Gander et al., 1985).

The two commercial preparations (Zyma) are under clinical investigation. The hard gelatin capsule contained 250 mg palmitoylcatechin and the plain film-coated tablet (external soluble coating) had 400 mg active substance.

Additionally, a 1% drug suspension in water (ultrasonically homogenized) was used as reference for in vivo absorption testing.

All reagents used were of analytical grade.

Dissolution studies

The in vitro dissolution rates of the three experimental tablet preparations were determined at 37°C using the USP paddle method at 60 rpm. Samples were withdrawn periodically for spectrophotometric assay at 279 nm.

The following two dissolution media (1000 ml) were used: (i) mixed organic aqueous medium made of 20% (v/v) isopropanol and 80% pH 6.8 phosphate buffer (Pharm. Eur.); and (ii) pH 6.8 phosphate buffer medium with a supramicellar surfactant concentration of 50 mmol/l sodium laurylsulfate.

The palmitoylcatechin solubilities in these two media are 6 and 17 g/l, respectively.

The two commercial formulations were tested only in the second medium in view of the results obtained with the experimental forms.

In a second part, the dissolution behaviours of all preparations were further examined by placing the dosage forms first for 30 min in simulated gastric juice (Pharm. Eur.) and then in the pH 6.8 phosphate buffer with surfactant added. For practical reasons, the preparation was placed in 500 ml gastric fluid to which 500 ml pH 6.8 phosphate buffer (with double concentration of sodium laurylsulfate) were added. The pH value of the dissolution medium was finally adjusted to 6.8 using concentrated sodium hydroxide solution. Because of good reproductibility, results are the mean of only three replicates.

Disintegration studies

The disintegration times of the preparations were determined using the USP apparatus without discs. The same test media as before were used. Average data of three runs varying by less than about 10% are presented in Table 1.

TABLE 1

DISINTEGRATION TIMES * (min) OF THE PALMITOYLCATECHIN PREPARATIONS TESTED (USP METHOD WITHOUT DISCS)

Medium	Experimental forms			Commercial forms	
	Tablet 1	Tablet 2	Tablet 3	Tablet	Capsule
Simulated gastric fluid	1	2	63	5	5
Hydro-alcoholic medium	10	18	>180	–	–
pH 6.8 phosphate buffer with 50 mmol/l sodium laurylsulfate	4	20	>180	18	32

* Average data of three runs varying by less than 10%.

In vivo absorption studies

The apparent bioavailabilities of the 3 experimental tablet formulations with reference to that of the 1% suspension were determined through urinary excretion. Six fasted male volunteers (age 27–47 years, weight 65–82 kg) ingested 1600 mg doses of palmitoylcatechin as 4 tablets (with 200 ml water) or as 160 ml of 1% suspension (with 40 ml water), administered at intervals of at least one week. Urine specimens were collected periodically over a 24 h period and the excreted metabolites with intact phloroglucinol group were assayed colorimetrically (Balant et al., 1979). Appropriate ethical approval was obtained for this study.

Results and Discussion

Dissolution of the experimental tablet formulations

Both solubilizing media allowed complete dissolution under perfect sink conditions (Figs. 1 and 2). The dissolution rates were very high for the two rapidly disintegrating formulations (tablets 1 and 2) and were close to that of the standard suspension. Tablet 3, which was intentionally designed to disintegrate in more than 1 h, dissolved very slowly. It is to be noted that the rank order of dissolution rates was consistent with that of the corresponding disintegration values only in the case of the purely aqueous medium. It seems that the addition of the organic solvent changes the tablet breakdown process.

In vivo absorption of the experimental tablet formulations

The mean cumulative plots of urinary excretion are shown in Fig. 3. For all three tablet formulae and for the suspension, a plateau was reached between 6 and 9 h after drug administration. No statistical differences in absorption and elimination rate constants were found between the four formulations, as determined by paired *t*-tests. In contrast, analysis of the mean total amounts of excreted metabolites showed that the extent of absorption of palmitoylcatechin was significantly decreased for tablet formulation 3, which already exhibited prolonged in vitro release behaviour. Thus, in the case of this model drug, both dissolution methods using

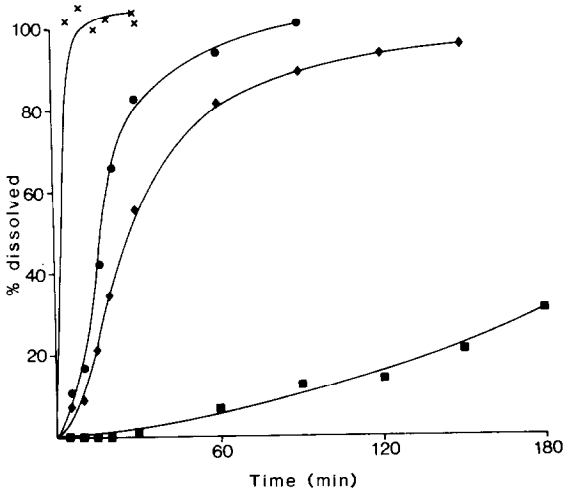

Fig. 1. Dissolution profiles of the experimental palmitoylcatechin formulations in an isopropanol–pH 6.8 phosphate buffer (20 + 80 v/v) medium. Key: ×, suspension; ◆, tablet 1; ●, tablet 2; ■, tablet 3.

solubilizing agents made it possible to differentiate dosage forms with different bioavailability characteristics. The surfactant medium, however, affected tablet disintegration less than the hydro-alcoholic fluid.

Effect of a preliminary stage in simulated gastric fluid on dissolution behaviour

In view of the much shorter disintegration times observed in simulated gastric

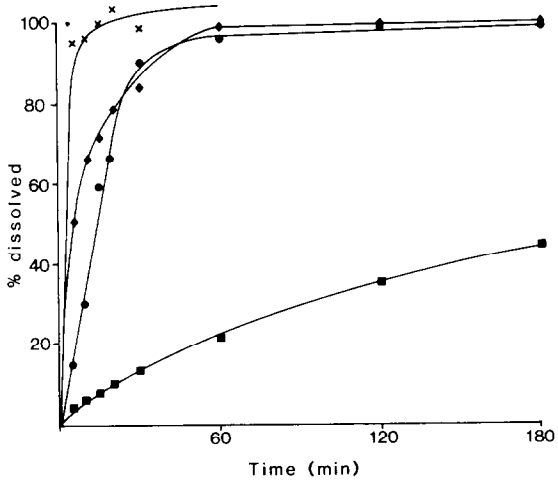

Fig. 2. Dissolution profiles of the experimental palmitoylcatechin formulations in a pH 6.8 phosphate buffer medium with 50 mmol/l sodium laurylsulfate. Key: ×, suspension; ◆, tablet 1; ●, tablet 2; ■, tablet 3.

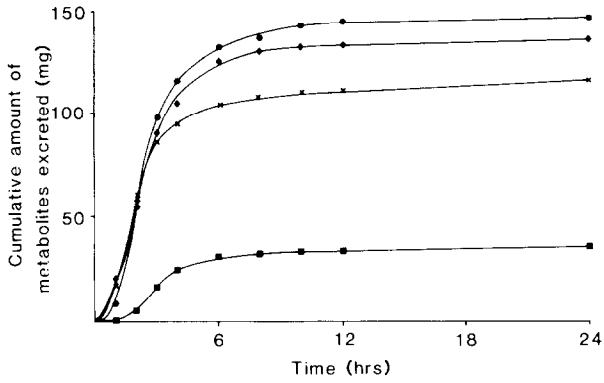

Fig. 3. Mean cumulative excretion amounts of palmitoylcatechin metabolites as a function of time after oral administration of 1600 mg palmitoylcatechin. Key: ×, suspension; ◆, tablet 1; ●, tablet 2; ■, tablet 3.

juice (Table 1), the effect of a 30-min stage in this medium on dissolution behaviour was examined with the 3 experimental tablets. No significant differences in the release patterns were observed with any of the three formulations, even the slow dissolving tablet 3 with which poor in vivo availability was noted.

More information was obtained by comparing the behaviours of the commercial preparations under both dissolution testing conditions (Fig. 4). These two formulations had very short disintegration times both in gastric fluid and in surfactant medium (Table 1) but were very differently affected in their release patterns by a preliminary stage in simulated gastric fluid. A simple 30-min shift in the dissolution profile (due to very low solubility in an acid medium) was noted for the coated

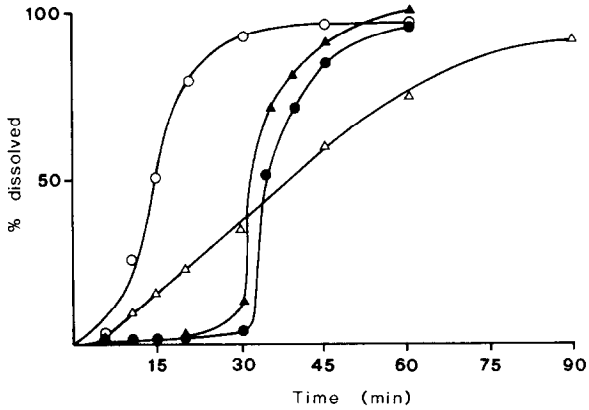

Fig. 4. Effect of a preliminary stage (30 min) in simulated gastric fluid (sgf) on the dissolution behaviour of the two industry palmitoylcatechin formulations in a pH 6.8 phosphate buffer medium with 50 mmol/l sodium laurylsulfate. Key: capsules with (▲) and without (△) preliminary stage in sgf, tablets with (●) and without (○) preliminary stage in sgf.

tablet. In contrast, a much higher dissolution rate of the capsule in the surfactant medium was apparent when it first disintegrated in gastric fluid. This can probably be ascribed to the effect of the additives (diluent, lubricant) used in the capsule.

With this preliminary treatment, both preparations showed similar dissolution behaviours. This was to be expected because of the biological equivalence of the two forms in man (unpublished results).

Conclusion

These results show that a supramicellar surfactant concentration medium is a realistic alternative to other dissolution techniques used for very poorly soluble drugs. In our work, sodium laurylsulfate was added at 50 mmol/l to the Pharm. Eur. pH 6.8 phosphate buffer because its solubilizing properties toward the model drug palmitoylcatechin were very similar to those of the natural bile salts. Of course, other concentrations or types of surfactant may be convenient.

Finally, when examining tablets and capsules, a preliminary stage in simulated gastric fluid (i.e. a 30-min period was used in this study) may be appropriate in order to simulate better their in vivo disintegration behaviours. For routine work assaying of drug in gastric fluid may generally be omitted because of the low solubility of the drug in this medium.

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