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Hydrophilic matrices for the extended release of a model drug exhibiting pH-dependent solubility

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Summary

After oral administration of basic drugs, the different pH values of the gastrointestinal tract can result in drastic changes in drug solubility, which can be very high at acidic pH values and dramatically low at neutral/basic pH, with consequent problems for the design of oral extended release formulations. In this paper, the preparation of an oral extended release formulation containing a basic drug is proposed, using dipyridamole as model. Three-component modified release granules capable of moderating the drastic dissolution behavior of dipyridamole were prepared by loading a swellable polymer (cross-linked sodium carboxymethylcellulose) with both the drug and an enteric polymer (cellulose acetate phthalate or cellulose acetate trimellitate). In vitro dissolution tests of modified release granules in USP gastric fluid showed a modulation of the high dissolution rate of dipyridamole at the acidic pH values, while in USP intestinal fluid a very marked improvement in drug dissolution was observed. Hydrophilic matrices containing the drug with the smoothed dissolution rate characteristics were prepared via mixing the granules with a gelling polymer (cellulose ether) and then tabletting the resulting mixture. In vitro release tests performed both at constant pH and with pH variation showed that the matrices are capable of providing extended drug release in both acidic and neutral/basic media.

Introduction

The in vivo efficacy of oral extended release formulations containing a basic drug may be limited by the variability in the solubility and dissolution rate of the drug at the different pH values of the gastrointestinal tract (Serajuddin and Rodoff, 1984). These parameters can be too high in the gastric (acidic) pH, with consequent possible problems in controlling drug release in the stomach, and can dramatically decrease when the formulation reaches the neutral/basic pH values of the intestine, with the consequence that drug release can be considerably reduced.

The problem of ensuring pharmaceutical availability of basic drugs could be solved by the specific localization of the drug delivery system in the gastric environment, for example through the incorporation of excipients delaying the gastric empting rate, such as fatty acids (Palin et al., 1982), or preparing bioadhesive (Park and Robinson, 1984), or floating (Sheth and Tossounian, 1984; Ingani et al., 1987) dosage forms, even if it

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has not been possible thus far to locate effectively a drug formulation in a selected region of the gastrointestinal tract (Bridges et al., 1988).

The pharmaceutical availability of these drugs can be also achieved by adding internal buffer systems to the tabletting mass (Doherty and York, 1989; Thoma and Zimmer, 1990); however, in this case possible formulation and stability problems can arise.

The aim of this work was the preparation of oral extended release formulations able to release basic drugs in a manner sufficiently independent of the pH of the gastrointestinal tract, choosing dipyridamole as a model.

This drug is an antithrombotic and vasodilator agent, used in the long-term therapy of chronic angina pectoris, of the usual doses of 50 mg three times daily (Martindale, 1989). It is characterized by a dissolution rate which is very high at acidic pH, but very low at neutral/basic pH, and to date very few formulations able to provide its extended release are available (Gruber et al., 1980).

We considered that the preparation of an oral extended release formulation of a basic drug should be carried out in two consecutive steps:

(1) Smoothing of the drastic dissolution behaviour of the drug at the different physiological pH values (very high dissolution rate in acidic pH and dramatically low in neutral/basic pH), in such a way as to render its dissolution behaviour 'uniform'.

(2) Preparation of a dosage form containing the drug with the 'smoothed' dissolution characteristics and allowing regulation of its extended release.

Previous studies carried out in our laboratory demonstrated clearly that the loading of a water insoluble drug (without problems due to pH-dependent solubility), such as nifedipine or carbamazepine, on a so-called superdisintegrant (swellable polymer) leads to a marked improvement in the rate of drug dissolution (Sangalli et al., 1989; Giunchedi et al., 1990). This improvement can be ascribed to the rapid interaction water/superdisintegrant, that occurs after contact with the dissolution medium and leads to the swelling of polymer and the development of a swelling force, which was characterized as formulation parameter and measured in our laboratory (Caramella et al., 1984; Colombo et al., 1984).

The resulting two-component systems (water-insoluble drug/swellable polymer) were also used for the preparation of extended release formulations (Giunchedi et al., 1991). Moreover, enteric coating agents were previously used to prevent the degradation of drugs in the stomach (Abd El-Fattah et al., 1984), or to prepare delayed release solid dispersions of drugs such as nifedipine, dipyridamole and griseofulvin at drug/polymer weight ratios ranging from 1:3 to 1:10 (Hasegawa et al., 1985a,b, 1986). However, these solid dispersions are characterized by their extreme dissolution behaviour: no drug dissolution at all occurs at acidic pH, whereas a certain extent of drug dissolution occurs at neutral/basic pH, which is high in the case of nifedipine, but relatively low for dipyridamole.

Taking into account all these considerations and on the basis of our previous observations, we believed that the combination of a dissolution rate enhancer, such as a water-swellable polymer with a dissolution rate decreaser, such as an enteric polymer, could lead to a effective means of moderating the drastic dissolution behaviour of the basic drug at the different pH values.

Therefore, dipyridamole extended release formulations were prepared via the following two consecutive steps:

(1) Preparation of three-component modified release granules, constituted by a swellable polymer loaded with dipyridamole and an enteric polymer. As swellable polymer, cross-linked sodium carboxymethylcellulose was employed, while as enteric polymer, cellulose acetate trimellitate and cellulose acetate phthalate were used.

The drug/enteric polymer/swellable polymer weight ratio used was 1:2:1.

(2) Preparation of extended release formulations constituted by hydrophilic matrices, resulting from tabletting mixtures of the modified release granules with a gelling polymer (cellulose ether).

In vitro tests were carried out both at constant (acidic or neutral/basic) pH, and with pH variation during the test.

Materials and Methods

Materials

The following materials were obtained from the indicated sources.

Dipyridamole (Recordati, Milano, Italy; Mol. Wt = 504.6, m.p. = 163°C, dvs = 5.16 μm; Coulter Counter model TA II, Coulter Electronics, Ltd, Luton, U.K.). Cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, U.S.A.). Cellulose acetate trimellitate (Eastman® C-A-T; soluble from pH 5.5) and cellulose acetate phthalate (Eastman® C-A-P; soluble from pH 6.5) (both from Eastman Chemical Products Inc., Kingsport, TN, U.S.A.). Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, U.K.). Mannitol (USPXXII grade, Carlo Erba, Milano, Italy).

Preparation of modified release granules

The compositions of the modified release granules are listed in Table 1. Their preparation was carried out using a solvent method. The enteric polymer and drug were dissolved in a suitable volume of an acetone : 95° ethyl alcohol 2 : 1 mixture, cross-linked sodium carboxymethylcellulose was then added to the organic solution and the resulting suspension was stirred for about 10 min.

The solvent was evaporated under reduced pressure (rotavapor Buchi R110, Flawil, CH), at about 45°C, yielding a yellow residue which was dried in a circulating hot air oven (about 60°C) for 12 h, and then stored in a desiccator, under reduced pressure, at room temperature for 48 h.

TABLE 1

Composition of modified release granules

Modified release granules	% DIP	% CAT	% CAP	% CM-XL
DIPCAT	25	50	–	25
DIPCAP	25	–	50	25

DIP, dipyridamole; CAT, cellulose acetate trimellitate; CAP, cellulose acetate phthalate; CM-XL, cross-linked sodium carboxymethylcellulose.

TABLE 2

Composition of extended release matrices

Matrix [Tablet]	DIPCAT [a] [DIPCAP] [a] (%)	Methocel® K4M (%)	Mannitol (%)
T1[P1]	80	20	–
T2[P2]	75	20	5
T3[P3]	75	15	10

[a] 63–250 μm particle size fraction of modified release granules.

The resulting dry material was ground using a blade miller, and for each preparation the particle size fractions of 63–250 and 250–500 μm were collected by sieving (ASTM series, Endecotts, London, U.K.).

Preparation of extended release matrices

The compositions of the extended release hydrophilic matrices (tablets) are given in Table 2. Hydroxypropylmethylcellulose and mannitol were mixed with the corresponding quantity of modified release granules (63–250 μm particle size fraction) in a Turbula apparatus (type T2A, W.A. Bachofen, Basel, Switzerland). The mixing time was of 20 min duration. Tablets containing 100 mg of drug were prepared by direct compression using a reciprocating tablet press machine (Korsch EKO, Berlin, Germany), equipped with 12 mm convex punches (compression force about 25 kN).

The choice of the 63–250 μm sieve fraction of granules for the preparation of all the matrices was made on the basis of the better mixing and compression properties of this fraction as compared with the other (250–500 μm).

In vitro dissolution / release tests

Using the USPXXII dissolution test apparatus no. 2 (paddle, 100 rpm, 37°C), two kinds of in vitro dissolution/release tests were carried out: (a) At constant pH: 1000 ml of USP gastric simulated fluid (pH 1.2) and 1000 ml of USP intestinal simulated fluid (pH 7.5), both without enzymes. (b) With pH variation: 750 ml of HCl 0.1 N (pH 1) from 0 to 2 h of the test, and then addition of 250 ml of 0.2 M tribasic sodium phosphate solu-

tion, to give a final pH of 6.8 in a total volume of 1000 ml (USPXXII drug release test, method A for enteric coated articles).

The in vitro tests at constant pH were performed on samples of 100 mg of dipyridamole as powder (dvs = 5.16 μm), samples of modified release granules containing the equivalent of 100 mg of drug, and tablets. The tests with pH variation were performed only on the tablets. Six replicates were used in each test (in the figures only mean values are reported).

Due to the variations in the UV absorbance of the drug in the different dissolution media, dipyridamole was spectrophotometrically determined (Spectracomp 602, Advanced Products, Milano, Italy) at 283 nm for the tests in gastric medium or in 0.1 N HCl and 294 nm for the tests in intestinal medium or in the final phosphate buffer (pH 6.8).

Results and Discussion

Figs 1 and 2 illustrate the respective dissolution profiles of the modified release granules (63–250 and 250–500 μm particle size fractions) in gastric (pH 1.2) and intestinal (pH 7.5) fluids, in both cases compared with that of the pure drug as powder (dvs = 5.16 μm).

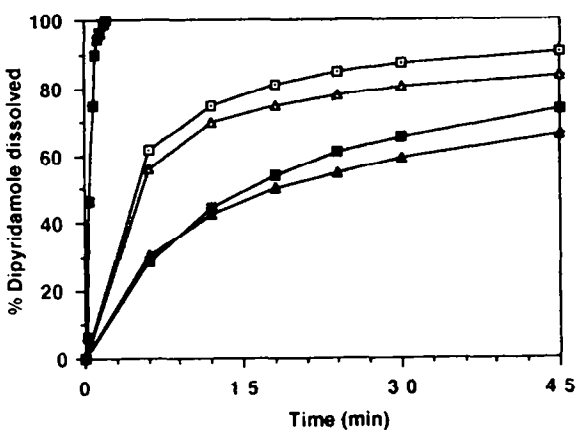

Fig. 1. Dissolution profiles in USP gastric fluid (pH 1.2) of modified release granules: (⊡) DIPCAT (63–250 μm), (■) DIPCAT (250–500 μm), (△) DIPCAP (63–250 μm), (▲) DIPCAP (250–500 μm), (■) dipyridamole (dvs = 5.16 μm).

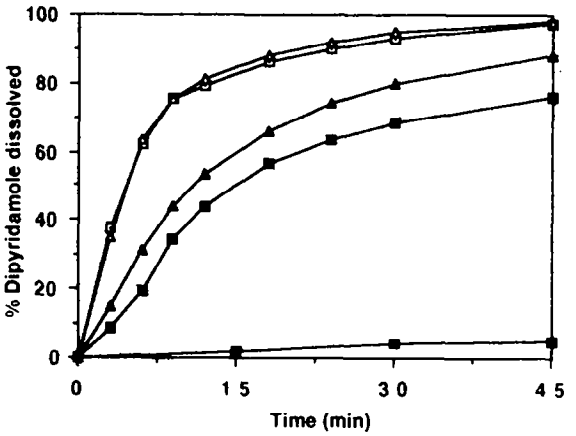

Fig. 2. Dissolution profiles in USP intestinal fluid (pH 7.5) of modified release granules: (⊡) DIPCAT (63–250 μm), (■) DIPCAT (250-500 μm), (△) DIPCAP (63–250 μm), (▲) DIPCAP (250–500 μm), (■) dipyridamole (dvs = 5.16 μm).

The behaviour of drug dissolution from the modified release granules was profoundly altered in comparison with the pure drug; the result of this change is the modulation of the high rate of dissolution of the pure drug, which was completely dissolved in acidic medium within 2 min (Fig. 1), while a considerable enhancement in dissolution rate was achieved in intestinal medium (Fig. 2), particularly in the case of the 63–250 μm particle size fraction (about 80% of drug dissolved within 10 min).

Comparison between Figs 1 and 2 shows that the more moderate dissolution behaviour is also uniform at the two different pH values. In fact, complete depression of the drug dissolution does not occur at acidic pH, as in the case of dipyridamole/enteric polymer solid dispersions, however, at both pH 1.2 and 7.5, within 30 min 60–90% dissolution of drug is achieved, in contrast with the two extremes of dissolution behaviour of pure drug.

As far as the kind of enteric polymer is concerned, the granules containing cellulose acetate trimellitate yield similar dissolution profiles with respect to the corresponding systems containing cellulose acetate phthalate.

In both cases, the 63–250 μm particle size fraction, as expected, is characterized by a higher

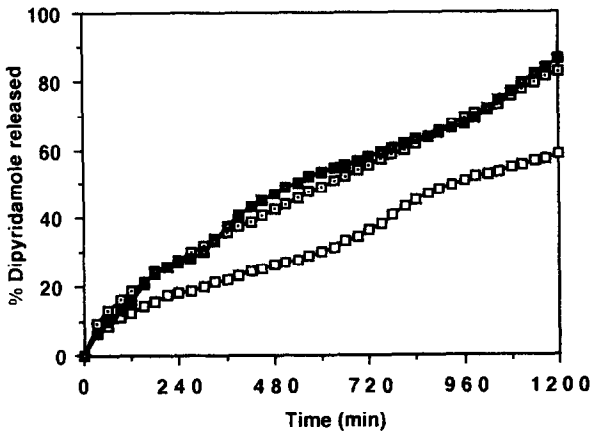

Fig. 3. Release profiles of T1 matrices in: (⊡) USP gastric fluid (pH 1.2), (□) USP intestinal fluid (pH 7.5) and in (■) hydrochloric acid (pH 1) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 20 h.

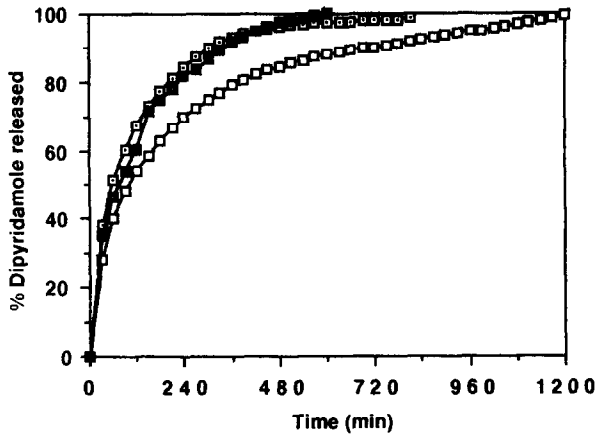

Fig. 5. Release profiles of T3 matrices in: (⊡) USP gastric fluid (pH 1.2), (□) USP intestinal fluid (pH 7.5) and in (■) hydrochloric acid (pH 1) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 20 h.

rate of drug dissolution than the corresponding 250–500 μm fraction.

Figs 3–5 and Figs 6–8 show the respective release profiles of matrices T1–T3 (prepared from granules containing cellulose acetate trimellate) and P1–P3 (prepared from granules containing cellulose acetate phthalate). These figures provide a comparison of the release profiles, for each type of matrix, as constructed using the data obtained from the tests at constant pH (gastric fluid, pH 1.2; intestinal fluid, pH 7.5) and with pH variation (pH 1 and 6.8).

The results demonstrate that extended release of dipyridamole is achieved under different pH conditions, for periods of time from 8 to 20 h or longer.

The major element determining the duration of drug release appears to be the composition of the matrices rather than the pH of the dissolution medium. In fact, irrespective of the pH, matrices with the highest content of hydroxypropylmethyl-

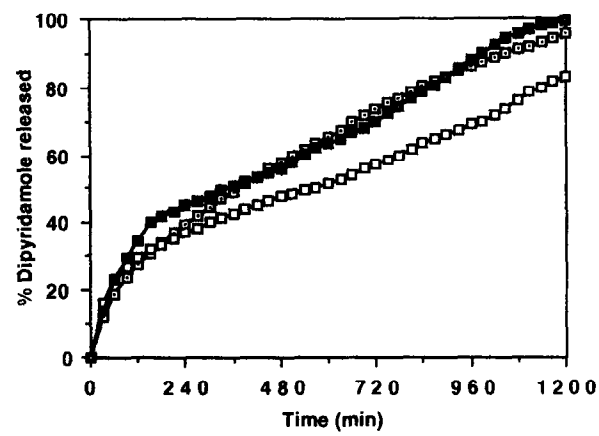

Fig. 4. Release profiles of T2 matrices in: (⊡) USP gastric fluid (pH 1.2), (□) USP intestinal fluid (pH 7.5) and in (■) hydrochloric acid (pH 1) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 20 h.

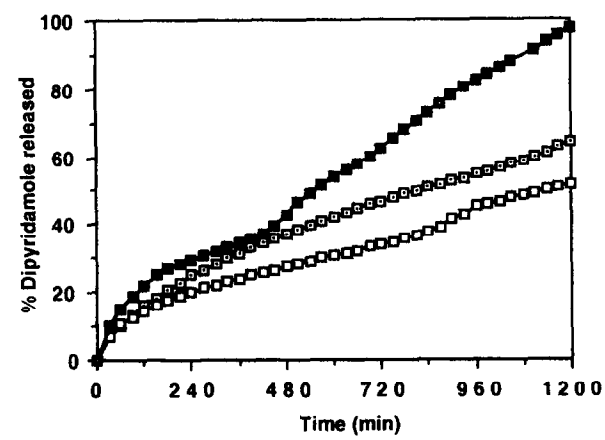

Fig. 6. Release profiles of P1 matrices in: (⊡) USP gastric fluid (pH 1.2), (□) USP intestinal fluid (pH 7.5) and in (■) hydrochloric acid (pH 1) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 20 h.

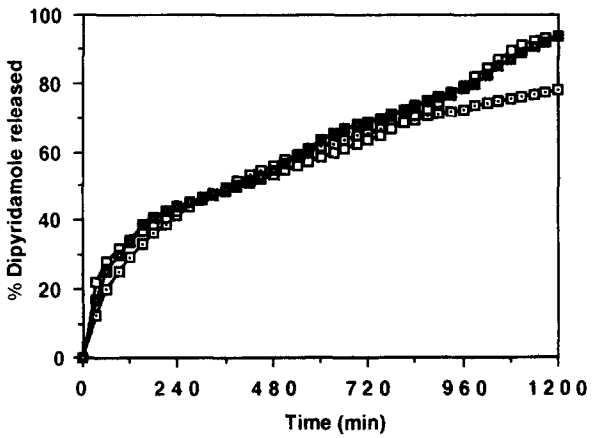

Fig. 7. Release profiles of P2 matrices in: (⊡) USP gastric fluid (pH 1.2), (□) USP intestinal fluid (pH 7.5) and in (■) hydrochloric acid (pH 1) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 20 h.

cellulose (T1, Fig. 3; P1, Fig. 6) are characterized by the slowest release rates (at least 24 h of drug release), those containing 5% mannitol (T2, Fig. 4; P2, Fig. 7) are a little faster (about 20 h of release), while the presence in the matrices of 10% mannitol (T3, Fig. 5; P3, Fig. 8) does not lead to efficient control of drug release (about 70% dissolution of the drug after only 3–4 h), with the exception of P3 tablets in intestinal fluid (about 85% dissolution of drug after 18 h).

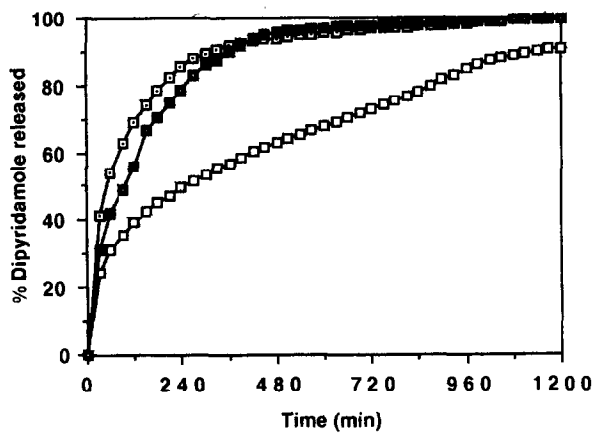

Fig. 8. Release profiles of P3 matrices in: (⊡) USP gastric fluid (pH 1.2), (□) USP intestinal fluid (pH 7.5) and in (■) hydrochloric acid (pH 1) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 20 h.

The comparison of the release profiles for each kind of matrix in the three different release tests demonstrated that the results obtained from the dissolution tests in gastric fluid and those with variation of pH are very similar, while drug release is always less in intestinal fluid.

In particular, P2 tablets display three almost superimposable release profiles (Fig. 7), irrespective of the pH value of the release test.

The presence of cellulose acetate trimellitate instead of the enteric polymer cellulose acetate phthalate as a component of the granules does not lead to unequivocal variability of drug release in the final matrices.

Conclusions

The preparation of three-component granules (drug/enteric polymer/swellable polymer), is proposed as a suitable procedure for moderating the drastic dissolution behaviour at different physiological pH values of a basic drug such as dipyridamole. The result of this preparative procedure is a greater uniformity in dissolution behaviour.

The compounding of a swellable polymer with an enteric polymer permits its utilization to overcome the drawback due to the low solubility not only of water-insoluble drugs that do not show pH-dependent solubility, but also of basic drugs.

The granules containing the drug with the modified dissolution characteristics can be incorporated in a hydrophilic matrix constituted by a gelling polymer, in order to obtain the desired drug release profile at different pH values.

The composition of the matrices, rather than the pH values of the dissolution media, appears to be the main factor influencing the release of the modified drug, as in the case of matrices containing drugs without the drawbacks of (pH-dependent or -independent) solubility problems.

P2 tablets (containing granules made with cellulose acetate phthalate) are the most promising among all the systems prepared, since their release profiles were almost superimposable in all the release tests, independently of the pH.

In addition, the results show that the new enteric polymer cellulose acetate trimellitate (Eastman® C-A-T) has characteristics comparable to those of the well-known cellulose acetate phthalate (Eastman® C-A-P™) and both are appropriate for preparation of the dipyridamole modified release granules described here.

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