DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(13), 1753-1764 (1991)

CARBAMAZEPINE MODIFIED RELEASE DOSAGE FORMS.

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ABSTRACT

The preparation of sustained release dosage forms of Carbamazepine (anti-epileptic drug characterized by a very low water solubility and by a short half life on chronique dosing) was carried out.

These formulations were obtained in two different steps :

a) modified release granules were prepared by the loading of cross-linked sodium carboxymethylcellulose (swellable polymer), with the drug and an enteric polymer. Cellulose acetate phthalate, methacrylic acid - methacrylic acid methyl ester copolymer (usually employed as enteric coating agents) and cellulose acetate trimellitate (a new enteric polymer) were used in different weight ratios.

b) some sustained release dosage forms were prepared tabletting physical mixtures of the modified release granules with different weight ratios of hydroxypropylmethylcellulose.

In vitro dissolution tests of modified release granules in gastric fluid (USP XXI) showed a modulation of the drug release, while in intestinal fluid (USP XXI) a quick drug dissolution was observed.

In vitro dissolution tests of sustained release dosage forms, performed varying during the test, the pH of the dissolution medium, (hydrochloric acid pH 1 from 0 to 2 hours and phosphate buffer pH 6.8 from 2 to 18 hours) showed that the

determining factors in the controlling release of the drug are: the type and amount of enteric polymer constituting the granules and the amount of hydroxypropylmethylcellulose mixed with them.

INTRODUCTION

Carbamazepine is one of the most important drugs for the therapy of psychomotor epilepsy, used to control grand mal, and also in the treatment of trigeminal neuralgia (1). This drug is characterized by a slow and irregular gastro-intestinal absorption, due to its low water solubility (about 170 mg/l at 24°C) (2).

In order to enhance the dissolution rate of this drug, we previously prepared (3) systems in which Carbamazepine was mixed with or loaded onto cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®, swellable polymer).

These systems were characterized by an enhanced drug dissolution rate, owing to the active interaction between the swellable polymer (Ac-Di-Sol®) and the aqueous dissolution medium.

Carbamazepine is also characterized by a short half-life on chronique dosing, due to the auto-induction of its epatic metabolism; the initial half-life is of about 24 hours, while on chronique dosing it lowers to approximately 12 hours with monotherapy, and 8 hours in those patients who take other enzyme - inducing drugs (4,5). Consequently, the daily Carbamazepine dose very often must be divided into three or four doses, that reduce patient compliance and that could be the cause of plasma fluctuations and side effects.

It is, therefore, important and advisable to dispose of drug formulations able to give a prolonged release of Carbamazepine.

So, the purpose of the present study was the design and the preparation of modified release dosage forms of Carbamazepine, able to smooth out plasma fluctuations and side effects.

Starting from our previous experience (3), we considered that the first step to obtain a formulation able to give a sustained release of a water insoluble drug like Carbamazepine, could be to prepare drug / swellable polymer systems in which the water / swellable polymer interaction would be modulated.

Besides, to produce sustained release dosage forms, recently Hasegawa et al. prepared solid dispersions using water insoluble materials (enteric coating agents) (6,7,8).

Taking all these considerations into account, the preparation of Carbamazepine sustained release dosage forms was carried out in the following two different steps:

a) preparation of modified release granules, constituted by a swellable polymer (cross-linked sodium carboxymethylcellulose) loaded with Carbamazepine and an enteric polymer, this acting as modulating agent of the water / swellable polymer interaction.

Three kinds of enteric polymers, cellulose acetate trimellitate (Eastman® C-A-T), cellulose acetate phthalate (Eastman® C-A-P™) and methacrilic acid - methacrilic acid methyl ester copolymer (Eudragit® S 100), were chosen and were used in two different weight ratios (20% and 25% w/w).

b) the second step was the preparation of some sustained release dosage forms (tablets), obtained tabletting physical mixtures of the modified release granules, with hydroxypropylmethylcellulose (Methocel® K4M).

MATERIALS

Carbamazepine (Fermion, Orion Corporation Ltd., Espoo - SF); Mw = 236.26; mp = 189-93°C; dvs = 4.58 μm (Coulter Counter mod. TA II + PCA, Coulter Electr. Ltd., Harpenden - UK) ; surface area = 1.81 m^2/g (Flow Sorb 2300 Surface area analyzer - Micromeritics Instrument Corp., Norcross, GA - USA).

Cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA - USA).

Cellulose Acetate Trimellitate (Eastman® C-A-T; Eastman Chemical Products, Inc., Kingsport, TN - USA); soluble from pH 5.5.

Cellulose Acetate Phthalate (Eastman® C-A-P™; Eastman Chemical Products Inc., Kingsport, TN - USA); soluble from pH 6.5.

Methacrylic acid - methacrylic acid methyl ester copolymer (Eudragit® S 100, Rohm Pharma, GmbH, Darmstadt - FRG); soluble from pH 7.

Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington - UK).

METHODS

a) Preparation of Modified Release Granules.

The composition of the prepared modified release granules and the weight ratios of their components are given in table 1.

TABLE 1

Composition of Modified Release Granules

Code	Weight ratio
Carb50 CAT20 ACD30	5.0 : 2.0 : 3.0
Carb50 CAT25 ACD25	5.0 : 2.5 : 2.5
Carb50 CAP20 ACD30	5.0 : 2.0 : 3.0
Carb50 CAP25 ACD25	5.0 : 2.5 : 2.5
Carb50 EudS20 ACD30	5.0 : 2.0 : 3.0
Carb50 EudS25 ACD25	5.0 : 2.5 : 2.5

Keys : Carb (Carbamazepine) ; ACD (Ac-Di-Sol®) ; CAT (Eastman® C-A-T) ; CAP (Eastman® C-A-P™) ; EudS (Eudragit® S 100).

Carbamazepine (25 g) and the corresponding quantity of enteric polymer were dissolved in 400 ml of acetone : 95° ethyl alcohol 3:1. Cross-linked sodium carboxymethylcellulose was added to the organic solution, and the suspension obtained was magnetically stirred for 10 minutes, to obtain uniform wetting of the polymer.

The solvent was evaporated off using a rotavapor (Buchi R110, Flawil - CH), under reduced pressure, at about 45°C, to obtain a slurry, which was kept in a desiccator, under reduced pressure, at room temperature, for 48 hours.

The resultant dry material was powdered in a mortar and for each preparation the 300 - 600 μm particle size fraction was collected by sieving (ASTM series, Endecotts, London - UK).

b) Preparation of Tablets.

The composition of prepared sustained release formulations and the weight ratios of their components are given in table 2.

All the tablets were prepared using the sieved fraction of modified release granules.

TABLE 2

Composition of Sustained Release Formulations*

Formulation	Mod. Rel. Granule	%	% Methocel® K4M	Tablet weight
T1	Carb50 CAT25 ACD25	80	20	250mg
T2	Carb50 CAT25 ACD25	73	27	275mg
T3	Carb50 CAT20 ACD30	80	20	250mg
T4	Carb50 CAT20 ACD30	73	27	275mg
P1	Carb50 CAP25 ACD25	80	20	250mg
P2	Carb50 CAP25 ACD25	73	27	275mg
P3	Carb50 CAP20 ACD30	80	20	250mg
P4	Carb50 CAP20 ACD30	73	27	275mg
S1	Carb50 EudS25 ACD25	80	20	250mg
S2	Carb50 EudS25 ACD25	73	27	275mg
S3	Carb50 EudS20 ACD30	80	20	250mg
S4	Carb50 EudS20 ACD30	73	27	275mg

Keys : Carb (Carbamazepine) ; ACD (Ac-Di-Sol®) ; CAT (Eastman® C-A-T) CAP (Eastman® C-A-P™) ; EudS (Eudragit® S 100).

*All tablets have a drug content of 100 mg.

Twenty percent or 27% w/w of hydroxypropylmethylcellulose (Methocel® K4M) was mixed in a Turbula apparatus (type T2A, W.A. Bachofen, Basel - CH) with the corresponding quantity of modified release granules. Mixing time was 20 minutes.

The tablets were prepared by direct compression using a reciprocating tablet press (Korsch, Berlin - FRG), equipped with 9 mm convex punches.

c) *In Vitro* Dissolution Tests.

Owing to the low water solubility of Carbamazepine (about 170 mg/l at 24°C), and in order to carry out the dissolution test "in sink" conditions, a modified USP

XXI no. 2 dissolution test apparatus was used, in which the cylindrical vessel was of nominal capacity of 5000 ml.

The distance between the blade of the paddle and the inside of the bottom of the vessel was of 50 mm.

The modified release granules were tested in 5000 ml of gastric simulated fluid (USP XXI, pH 1.2) and intestinal simulated fluid (USP XXI, pH 7.5).

Samples containing the equivalent of 100 mg of Carbamazepine were placed directly into the dissolution medium, mantained at 37±1°C and with a stirring rate of 100 rpm.

The drug content was spectrophotometrically determined at 285 nm, (SPECTRACOMP 602, Advanced Products, Milano - I).

As regards the tablets, in the modified USP XXI apparatus, a modified USP XXI drug release test (method A for enteric coated articles) was carried out.

The tablets (each containing the equivalent of 100 mg of Carbamazepine), were placed into 3750 ml of 0.1 N hydrochloric acid, and after 2 hours 1250 ml of 0.20 M tribasic sodium phosphate solution were added in order to obtain a pH of 6.8 in a total volume of 5000 ml.

RESULTS

a) *In Vitro* Dissolution Behaviour of Modified Release Granules.

The dissolution profiles of the modified release granules in gastric fluid are shown in figure 1 and are compared to the dissolution profile of a system Carbamazepine / Ac-Di-Sol® (1:3, physical mixture), the preparation of which was previously reported (3)

All the systems loaded with enteric polymers present a lower drug dissolution rate compared to the physical mixture Carbamazepine / Ac-Di-Sol® (90% of dissolved drug after 20 minutes): within 2 hours the rank order of the dissolution profiles for these systems is the following: Carb50 CAP20 ACD30 (≃ 90%), Carb50 CAT20 ACD30 (≃ 85%), Carb50 CAP25 ACD25 and Carb50 CAT25 ACD 25 (70%).

The systems containing Eudragit® S 100 are characterized by the two lowest dissolution profiles: after 2 hours Carb50 EudS20 ACD30 ≃ 65% of dissolved drug and Carb50 EudS25 ACD25 ≃ 55%.

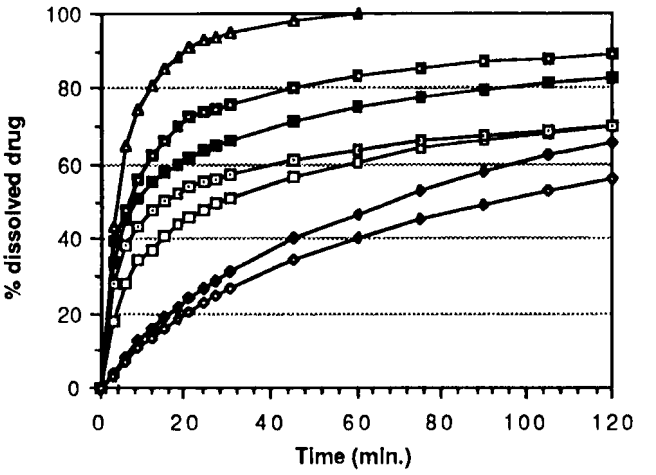

FIGURE 1
Dissolution Profile in Gastric Fluid (USP XXI, pH 1.2) of:
■ Carb50 CAP20 ACD30; ⊡ Carb50 CAP25 ACD25;
■ Carb50 CAT20 ACD30; □ Carb50 CAT25 ACD25;
◆ Carb50 EudS20 ACD30; ◇ Carb50 EudS25 ACD25;
▲ Carbamazepine / Ac-Di-Sol® 1:3 physical mixture

In all cases, each system containing 25% w/w of enteric polymer presents a lower dissolution profile compared to the corresponding 20% enteric polymer system.

In intestinal fluid (fig. 2) all modified release granules are characterized by a very high drug dissolution rate: within 12 minutes all the systems reach 100% of dissolved drug (the system containing 20% w/w of C-A-P™ after only 6 minutes).

b) *In Vitro* Dissolution Behaviour of Sustained Release Formulations.

Figures 3, 4 and 5 show the dissolution profiles of respectively the formulations T1, T2, T3 and T4 (fig. 3 - prepared with C-A-T granules), of the formulations P1, P2, P3 and P4 (fig. 4 - prepared with C-A-P™ granules) and of the formulations S1, S2, S3 and S4 (fig. 5 - prepared with Eudragit® S 100 granules); the tests were performed varying the pH of the dissolution medium.

T1, T2 (fig. 3) and P1, P2 (fig. 4) formulations (tablets made of 25% C-A-T granules or 25% C-A-P™ granules), exibit a prolonged drug release throughout 14

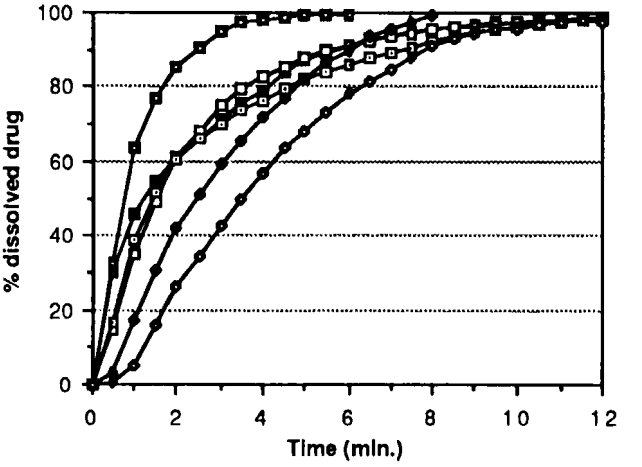

FIGURE 2
Dissolution Profiles in Intestinal Fluid (USP XXI, pH 7.5) of:
■ Carb50 CAP20 ACD30; ⊡ Carb50 CAP25 ACD25;
■ Carb50 CAT20 ACD30; □ Carb50 CAT25 ACD25;
◆ Carb50 EudS20 ACD30; ◈ Carb50 EudS25 ACD25.

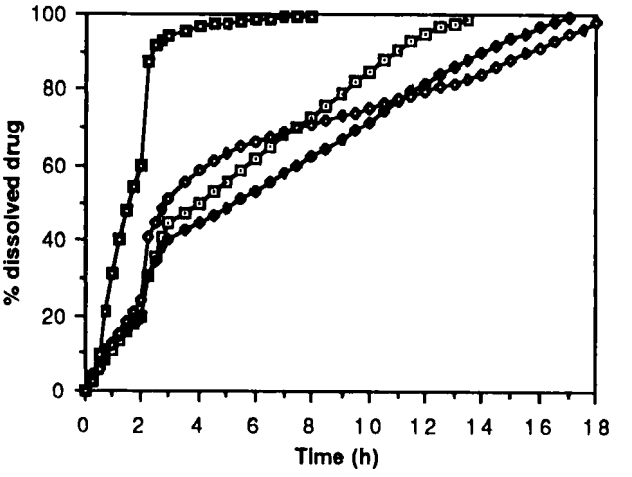

FIGURE 3
Dissolution Profiles in Hydrochloric Acid pH 1 (0-2 hours) and Phosphate Buffer pH 6.8 (2-18 hours) of: ⊡ T1; ● T2; ◘ T3; ◆ T4.

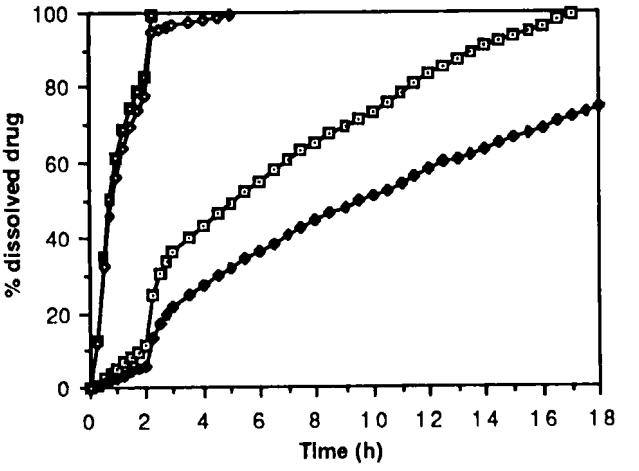

FIGURE 4
Dissolution Profiles in Hydrochloric Acid pH 1 (0-2 hours) and Phosphate Buffer pH 6.8 (2-18 hours) of: ▫ P1; ◆ P2; ▪ P3; ◆ P4

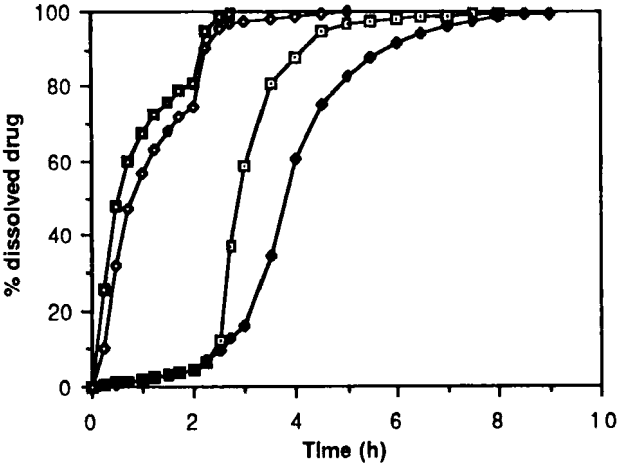

FIGURE 5
Dissolution Profiles in Hydrochloric Acid pH 1 (0-2 hours) and Phosphate Buffer pH 6.8 (2-18 hours) of: ▫ S1; ◆ S2; ▪ S3; ◆ S4

/ 18 hours and more. In all cases the pH change at the second hour of dissolution determines a modification of the slope of the curve.

The formulations T3 (fig. 3), P3 and P4 (fig. 4), made of 20% C-A-T granules or 20% C-A-P™ granules, disintegrate during the first two hours of test in acidic medium, leading to a dissolution of most drug present in the formulation (60% of dissolved drug after 2 hours for T3 tablet and ≃80% after the same time for P3 and P4 tablets). The remaining part of the drug dissolves rapidly after the pH change.

T4 formulation (fig. 3) is the only one, constitued by 20% enteric polymer (C-A-T) granules, whose behaviour is similar to the formulations containing 25% of enteric polymer granules. This formulation exhibits a prolonged drug release throughout 18 hours.

The formulations containing Eudragit® S 100 as enteric polymer (fig. 5), are characterized by the following behaviour : S3 and S4 formulations (20% enteric polymer granules), like the corresponding ones made of 20% of C-A-T and C-A-P™ granules, disaggregate in gastric fluid, and most drug present in the formulation dissolves within 2 hours; the systems constitued by 25% enteric polymer granules (S1 and S2) are characterized by an "off / on switch" drug release (fig. 5): a very low drug release is present during the first 2 hours in acidic environment (less than 5% of dissolved drug for either formulations), while getting the pH to 6.8, a quick drug release is achieved with the following order: S1 formulation ≃ 85% of dissolved drug after the fourth hour of dissolution and S2 formulation 60% of dissolved drug after the same time.

DISCUSSION

The dissolution tests of the modified release granules show that the loading of the enteric polymers onto the swellable polymer leads to:

a) in gastric fluid a modulation of the drug release rate, compared to the dissolution rate enhancement obtained from the Carbamazepine / Ac-Di-Sol® system, in which after the immersion of the system into the dissolution medium, an active and immediate interaction between water and the swellable polymer occurs.

b) in intestinal fluid a very high drug dissolution rate enhancement, even higher than that of the Carbamazepine / Ac-Di-Sol® system in gastric fluid.

As can be seen from their *in vitro* dissolution test results, the sustained release formulations work through two different steps:

1) in the first step, during the contact with the acidic environment, the determining factor in the controlling release of the drug is the amount of enteric polymer: if the enteric polymer is able to modulate the interaction between the swellable polymer and the dissolution medium, a first, gradual drug release can occur (very low in the case of Eudragit® S 100) and the gelling of hydroxypropylmethylcellulose has time to take place.

2) when the pH of the environment changes (from 1 to 6.8) the dissolution rate of the drug from the enteric polymer granules is high, but the gelling of the hydroxypropylmethylcellulose brings on a prolonged release from the formulation.

If the modulation of the enteric polymer in the first acidic phase, fails, the swellable polymer interacts with water and the tablet disaggregates, leading to a rapid drug dissolution.

CONCLUSIONS

The preparation of three component granules (drug / enteric polymer / swellable polymer) mixed with a gelling polymer can be a way of obtaining sustained release dosage forms of water insoluble drugs.

The prepared formulations have a double control release mechanism: the modulated swelling of cross-linked sodium carboxymethylcellulose, due to the enteric polymer, and the gelling of hydroxypropylmethylcellulose.

In particular, the results show that the employment of the new enteric polymer cellulose acetate trimellitate (C-A-T) is comparable with that of the well-known cellulose acetate phthalate (C-A-P™), and both are suitable for the preparation of the described systems.

ACKNOWLEDGMENTS

The authors wish to acknowledge Mrs. M.C. Sacchi for her assistance in text and figure preparation.

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