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Linear extended release of a water-insoluble drug, carbamazepine, from erodible matrices

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Summary

The preparation and in vitro characterization of extended release erodible hydrophilic matrices containing a water insoluble drug (carbamazepine) are described. The matrices are obtained by tabletting mixtures of the drug with a water swellable polymer (cross-linked sodium carboxymethylcellulose) and a water gelling polymer (hydroxypropylmethylcellulose). These matrices appear to be subject, during in vitro tests, both to a gelation and to an erosion process and they are capable of releasing the drug at a nearly constant rate, until almost the entire drug content is released. The influence of the technological parameters of the formulation (weight ratios of polymers used, compression forces, etc.) and of the gelation and erosion processes of the matrices during the in vitro tests, on drug release are investigated.

Introduction

The administration of water insoluble drugs in solid dosage forms by the oral route is usually characterized by problems of low bioavailability due to the adsorption of drug being dissolution rate limited (Fincher, 1968), and consequently slow and irregular.

Therefore, there is the need of improving the water dissolution properties of these drugs, to ensure their good oral bioavailability.

In order to enhance the low dissolution rate of water insoluble drugs, model drugs were previously loaded (by using a solvent method), on cross-linked sodium carboxymethylcellulose (CMC-XL), a water swellable polymer, which showed itself to be a good enhancer of the drug dissolution rate (Sangalli et al., 1989; Giunchedi et al., 1990).

This polymer is a modified (by cross-linking) cellulose, known in the pharmaceutical field as a tablet disintegrating agent (Shangraw et al., 1980); it is able to interact actively with water, developing a swelling force (Caramella et al., 1984) and its properties of being a drug dissolution rate enhancer seem to be connected with this active interaction.

Furthermore, some of these drugs are also characterized by a short half life, and for this reason oral extended release formulations could be required for them. However their water insol-

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ubility can also lead to problems in the design, preparation and efficacy of oral dosage forms capable of providing extended drug release.

In the field of controlled drug delivery by the oral route, it is commonly believed that zero-order drug release from the dosage form is the optimal choice. Moreover, hydrophilic gel-forming matrices obtained by compression are a kind of solid oral dosage form which is very important, since it is easy to prepare and has numerous possible applications. However, in this case, since diffusion is a more important mechanism governing the drug release, their main disadvantages are firstly that water-soluble drugs, rather than drugs of poor water solubility, are usually formulated in this kind of dosage form, and secondly that the drug release rate usually declined continuously with time owing to the corresponding lengthening of the diffusional pathway of the drug from the matrix.

Recently, zero-order release hydrophilic matrices containing drugs which are very soluble in water (such as alprenolol hydrochloride and metoprolol tartrate) were prepared by using a combination af anionic sodium carboxymethylcellulose and hydroxypropylmethylcellulose (Ranga Rao et al., 1988).

Taking into account all of these considerations, the aim of this work was the design and preparation of oral extended release dosage forms containing a water-insoluble drug capable of releasing the drug at a nearly constant rate for a programmable period of time.

Starting from our previous experiences, the design of the dosage form was set up in the following two sequential steps:

(1) Enhancement of the dissolution rate of the insoluble drug, by using cross-linked sodium carboxymethylcellulose (CMC-XL) as a dissolution rate enhancer.

(2) Incorporation of the drug with the enhanced dissolution rate characteristics in a gel-forming hydrophilic matrix obtained by direct compression and made of hydroxypropylmethylcellulose (HPMC).

Carbamazepine (Cb), chosen as the model drug, is one of the most important antiepileptic agents, used in the therapy of psychomotor seizures and trigeminal neuralgia (Martindale, 1989). It is characterized by slow and irregular gastrointestinal absorption due to its low water solubility (about 170 mg/l at 24°C), and by a short half-life (less than 8 h), on chronic dosing or in multitherapy, owing to the enzymatic auto-induction of its metabolism (Eichelbaum et al., 1975; Larkin et al., 1989).

A more stable serum concentration of Cb can be achieved by using oral slow-release preparations (Sivenius et al., 1988).

Extended release matrices containing 100 mg of drug were prepared at different levels of compression forces and in vitro release tests and erosion studies were carried out on them.

Materials and Methods

Carbamazepine (Cb), Fermion, Orion Corp. Ltd, Espoo, SF; Mol. wt 236.3; m.p. 189–193°C; dvs = 4.58 μm (Coulter Counter model TA II, Coulter Electronics Ltd, Luton, U.K.); surface area 1.81 m^2/g (FlowSorb 2300 Surface Area Analyzer, Micromeritics Instrument Corp., Norcross, GA, U.S.A.); cross-linked sodium carboxymethylcellulose (CMC-XL); Croscarmellose sodium, type A NF (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, U.S.A.); viscosity 25 cP s (aqueous dispersion 2% w/w); and hydroxypropylmethylcellulose (HPMC); (Methocel® K4M, Colorcon, Orpington, U.K.); viscosity 4000 cP s (aqueous solution 2% w/v) were obtained from the indicated sources.

Enhancement of the drug dissolution rate

Enhancement of the drug dissolution rate was achieved by using cross-linked sodium carboxymethylcellulose (CMC-XL), water swellable polymer, as dissolution rate enhancer; two techniques of preparation of drug/swellable polymer systems were employed: mixing (for Mx systems) and ball milling (for BM systems).

The compositions of the drug/swellable polymer systems are given in Table 1.

Mixing technique (Mx systems) Cb and CMC-XL were placed in a mixing jar (1 l capacity). Mixing was performed in a Turbula apparatus

TABLE 1

Composition of drug / swellable polymer systems

System	% Cb	% CMC-XL	Preparation technique
Mx1/2	33.3	66.6	mixing
Mx1/4	20.0	80.0	mixing
BM1/2	33.3	66.6	ball Milling
BM1/4	20.0	80.0	ball Milling

Cb, carbamazepine; CMC-XL, cross-linked sodium carboxymethylcellulose.

(W.A. Bachofen, Basel, Switzerland), at a speed of 90 rpm for 2 h.

Ball milling technique (BM systems) Cb and CMC-XL were placed in a ball mill made of stoneware material, whose jar has a capacity of 1 l and a cylindrical size of 12 cm. Milling was carried out for 2 h at a speed of 70 rpm.

In both cases, the weight of each batch of drug/swellable polymer system prepared was 100 g and the powders obtained showed good flow properties.

Preparation of hydrophilic matrices

The compositions of the hydrophilic matrices prepared from the drug/swellable polymer systems obtained with mixing and ball milling techniques are listed in Tables 2 and 3, respectively.

In order to evaluate the influence of the polymeric materials used on the release rate of the water insoluble drug, the hydrophilic matrices were prepared with particularly simple compositions (only the drug/swellable polymer system and HPMC, without lubricants, glidants, etc.), and were used as model formulations.

TABLE 2

Composition of matrices prepared from drug / swellable polymer systems obtained with the mixing technique

Matrix	% Cb	% CMC-XL	% HPMC
Mx1/2K20	26.7	53.3	20.0
Mx1/2K30	23.3	46.7	30.0
Mx1/4K20	16.0	64.0	20.0
Mx1/4K30	14.0	56.0	30.0

TABLE 3

Composition of matrices prepared from drug / swellable polymer systems obtained with the ball milling technique

Matrix	% Cb	% CMC-XL	% HPMC
BM1/2K20	26.7	53.3	20.0
BM1/2K30	23.3	46.7	30.0
BM1/4K20	16.0	64.0	20.0
BM1/4K30	14.0	56.0	30.0

HPMC and the corresponding quantity of drug/swellable polymer system were mixed in a Turbula apparatus for 20 min.

The matrices (containing 100 mg of drug) were prepared by direct compression of the mixtures obtained at three different levels of compression force (1000, 2000 and 3000 kg), by using a Kilian single punch reciprocating tablet machine (Kilian, Berlin, Germany), equipped with 11.28 mm flat punches, and instrumented with two piezoelectric load-washers (Model Kistler 903 A) (Conte et al., 1972).

In vitro dissolution / release tests

The in vitro dissolution/release tests were carried out using a modified USP XXII dissolution test apparatus. Owing to the low solubility in water of the drug and in order to maintain the sink conditions throughout the duration of the test, a cylindrical vessel with a nominal capacity of 5000 ml (instead of 1000 ml) was used. The distance between the blade of the paddle and the bottom of the vessel was 50 mm.

All the dissolution/release tests were carried out in 5000 ml of distilled water, at 37°C and at a stirring rate of 100 rpm.

Samples of drug/swellable polymer systems corresponding to 100 mg of drug and samples of 100 mg of drug as powder (dvs = 4.58 μm) were placed directly in the dissolution medium.

Concerning the in vitro release tests of the hydrophilic matrices, in order to reduce the variability due to the hydrodynamic conditions of the test and to overcome the problem due to sticking of the gelled matrix on the wall of the dissolution container, the matrices were placed in a stationary basket in the vessel. This basket was located

above the blade of the paddle and at a distance of 140 mm from the bottom of the vessel and 30 mm from the paddle.

The drug content was spectrophotometrically determined at 285 nm (Spectracomp 602, Advanced Products, Milano, Italy).

Dissolution/release tests were made in triplicate for each batch of systems and matrices (mean values with standard deviations are reported).

Erosion / release studies

Erosion/release studies of the hydrophilic matrices were carried out by using the modified USP dissolution test apparatus above described.

In vitro release tests were performed under the conditions above described and, after different intervals of time, the content of drug released in the dissolution medium was spectrophotometrically determined and at the same time each basket containing the gelled/eroded matrix was taken out of the dissolution medium and placed in a circulating hot air oven (about 70°C) until the residual matrix reached complete dryness (determined based its constant weight).

For each matrix, mean values ($n = 3$) of percent of residual matrix weight and corresponding percent of drug released vs time (h) are reported with the corresponding standard deviations.

Results and Discussion

Fig. 1 shows the dissolution profiles of the drug/swellable polymer systems compared to the drug.

The enhancement of the dissolution rate of Cb from the systems prepared is in every case considerably greater as compared with the dissolution rate of the pure drug.

Within 9 min about 100% drug dissolution is achieved in the case of the systems characterized by the highest (80%) content of swellable polymer (Mx1/4 and BM1/4), and about 90% for with the lower (66.6%) content (Mx1/2 and BM1/2); in this case, the drug is completely dissolved within 15 min.

As far as the comparison of the two techniques of preparation (mixing and ball milling) is concerned, almost superimposed dissolution profiles are obtained from the systems with the corresponding weight ratios of drug/swellable polymer.

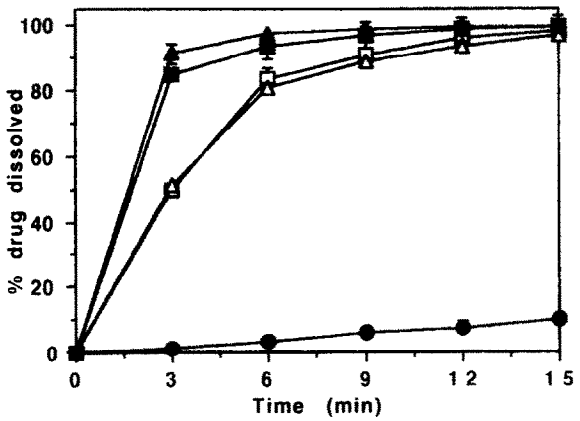

Fig. 1. Dissolution profiles ($n = 3 \pm$ S.D.) of the drug/swellable polymer systems: (□) Mx1/2; (■) Mx1/4; (△) BM1/2; (▲) BM1/4, compared to (●) pure drug (dvs = 4.58 μm).

Figs 2 and 3 demonstrate the release profiles of the hydrophilic matrices prepared from the drug/swellable polymer systems obtained with the mixing technique (Fig. 2) and with the ball mill technique (Fig. 3) and at a compression force of 2000 kg.

The in vitro results demonstrate that the release rate is (as expected) dependent on the content of HPMC; in fact, the matrices contain-

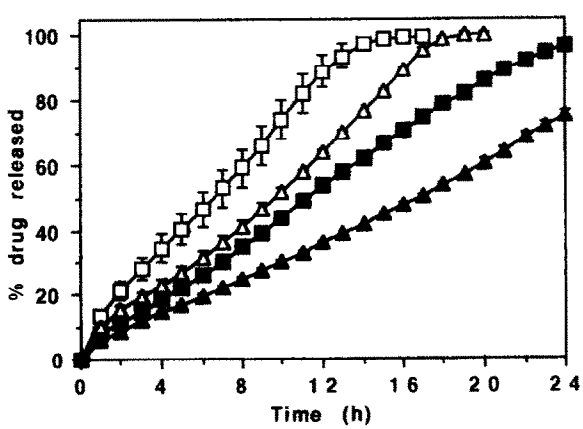

Fig. 2. Release profiles ($n = 3 \pm$ S.D.) of matrices: (□) Mx1/2K20; (■) Mx1/2K30; (△) Mx1/4K20; (▲) Mx1/4K30, prepared at 2000 kg compression force.

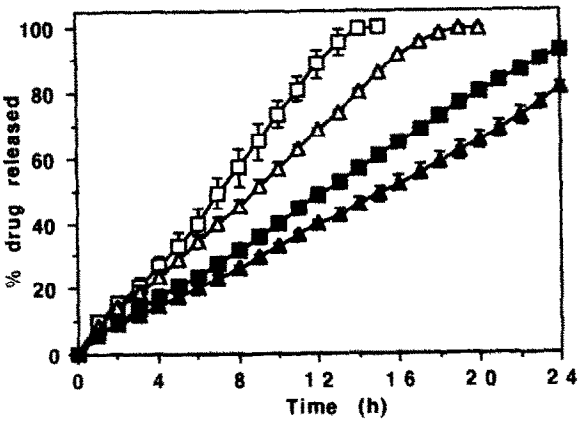

Fig. 3. Release profiles ($n = 3 \pm$ S.D.) of matrices: (□) BM1/2K20; (■) BM1/2K30; (△) BM1/4K20; (▲) BM1/4K30, prepared at 2000 kg compression force.

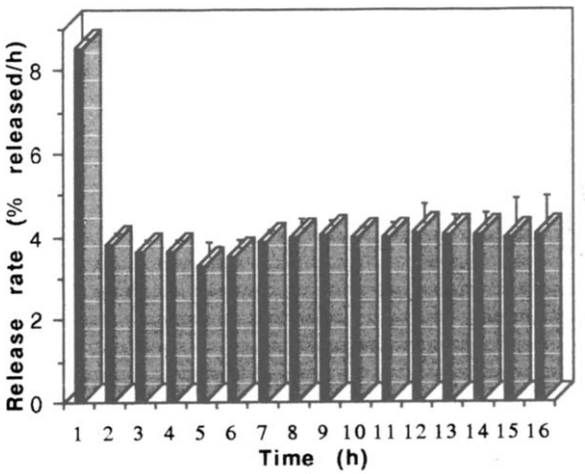

Fig. 4. Rate of drug release (% of drug released/h) from Mx1/2K30 matrix as a function of time ($n = 3 \pm$ S.D.).

ing 30% of HPMC are in all cases characterized by a slower release rate with respect to those containing 20% of HPMC. However, the drug release rate also appears to be influenced by the CMC-XL content. In fact, if we consider the two matrices with 20% of HPMC and prepared from the drug/swellable polymer system obtained with the mixing technique (Fig. 2), the one containing 53% of CMC-XL (Mx1/2K20) releases the entire drug content within about 12 h, while that containing 64% of CMC-XL (Mx1/4K20) required about 16 h for 100% drug release.

Analogously, for the two matrices with 30% of HPMC, the one containing 47% of CMC-XL (Mx1/2K30) releases the entire drug content within about 24 h, while within the same time the matrix containing 56% of CMC-XL (Mx1/4K30) releases only about 70% of drug. In the latter case, 100% drug release is achieved within about 30 h (data not shown).

The release profiles shown in Fig. 3 present the same rank order.

In all cases, no time lag characterizes the release of the drug from these matrices and extended release at a fairly constant rate is achieved in a range of time between 12 and 24 h, with good linearity, until almost the entire drug content is released from the matrix.

In all cases, the release data demonstrate good reproducibility. In fact, all the standard deviation values are negligible: they are within about 1%, except for the case of Mx1/2K20 (Fig. 2) and BM1/2K20 (Fig. 3) matrices, which present standard deviation values only slightly higher (within about 6%). This is probably because both matrices are characterized by the presence in their composition of the lower percentual content of cellulosic polymers and higher percentual content of Cb (Tables 2 and 3), and consequently have a lower capacity for controlling drug release (faster release rates).

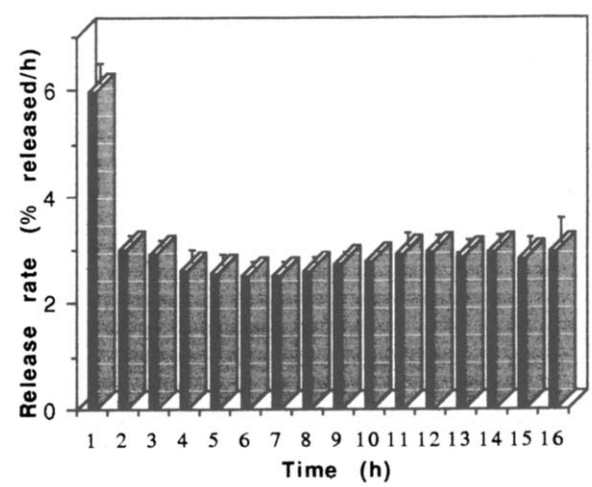

Fig. 5. Rate of drug release (% of drug released/h) from Mx1/4K30 matrix as a function of time ($n = 3 \pm$ S.D.).

The bar graphs shown in Figs 4 and 5 illustrate, respectively for the Mx1/2K30 matrix (30% of HPMC and 47% of CMC-XL) and Mx1/4K30 matrix (30% of HPMC and 56% of CMC-XL), chosen as examples, the release data presented as the rate of drug release (percent dissolved per h) vs time (h); in both cases, the values presented here are only for the first 16 h of the test.

The bar graphs clearly show a small burst effect, followed by fairly constant drug release, which corresponds to about 4% of the total drug content per h in the case of the Mx1/2K30 matrix, and about 3% per h in the case of the Mx1/4K30 matrix.

During the in vitro tests, the matrices appear to be subject both to the formation of a gel layer, and to a slow and progressive erosion process; in fact, at the end of the tests the matrices appear to be completely eroded.

In order to evaluate the mechanism connected with the linear drug release, erosion/release studies (Ranga Rao et al., 1988) were carried out. The results obtained are presented for the first 16 h of the test in Fig. 6 for the Mx1/2K30 matrix and in Fig. 7 for the Mx1/4K30 matrix, as percent residual (w/w) of eroded matrix and percent of drug released at the corresponding times, vs time (h).

These results in both cases show that the matrix erosion process follows a linear profile, which corresponds with the linear release profile of the drug.

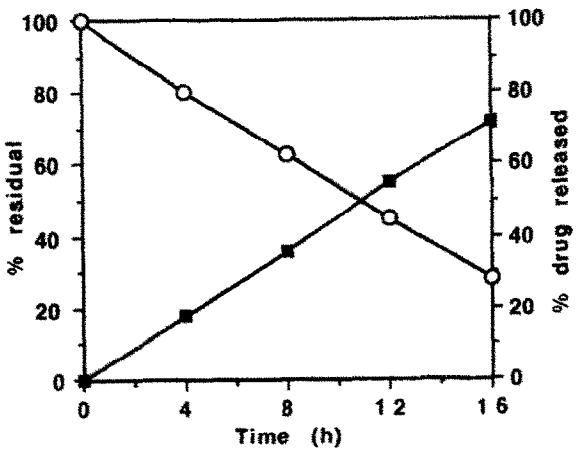

Fig. 6. Erosion/release studies of Mx1/2K30 matrix: (○) % matrix residual; (■) % drug released ($n = 3 \pm$ S.D.).

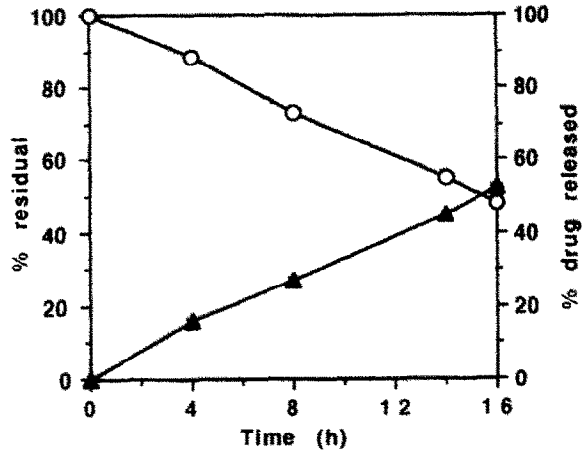

Fig. 7. Erosion/release studies of Mx1/4K30 matrix: (○) % matrix residual; (▲) % drug released ($n = 3 \pm$ S.D.).

The influence of the compression force on the drug release rate from the hydrophilic matrices is negligible.

In fact, as shown in Fig. 8 (for Mx1/2K20 and Mx1/2K30 matrices) and Fig. 9 (for Mx1/4K20 and Mx1/4K30 matrices), the release profiles achieved for each kind of matrix (all obtained from drug/swellable polymer systems prepared via the mixing technique), at the three different levels of compression force (1000, 2000 and 3000 kg) are almost superimposed. The same results

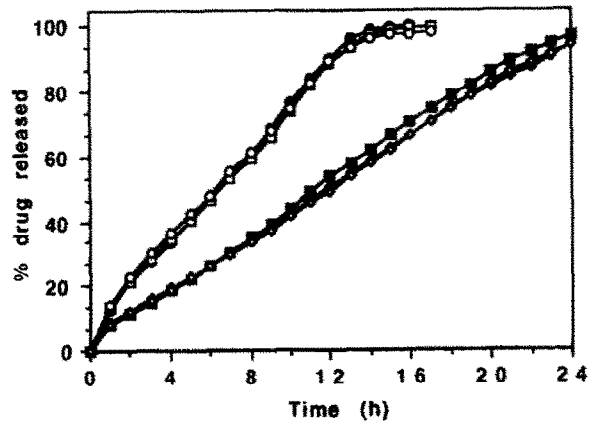

Fig. 8. Influence of compression force on drug release: release profiles of Mx1/2K20 matrices prepared at (●) 1000 kg; (□) 2000kg; (○) 3000 kg; and of Mx1/2K30 matrices prepared at (♦) 1000 kg; (■) 2000 kg; (◇) 3000 kg.

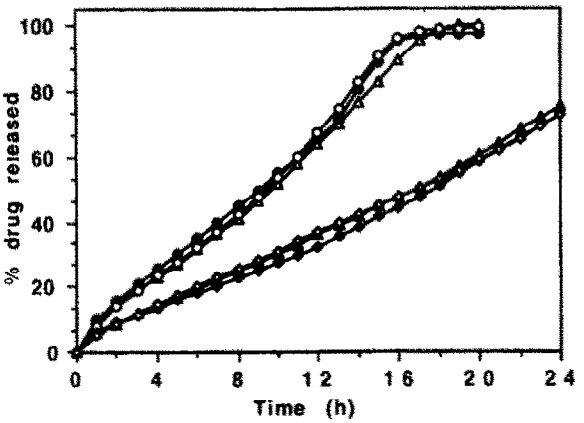

Fig. 9. Influence of compression force on drug release: release profiles of Mx1/4K20 matrices prepared at: (●) 1000 kg; (△) 2000 kg; (○) 3000 kg; and of Mx1/4K30 matrices prepared at (♦) 1000 kg; (▲) 2000 kg; (◇) 3000 kg.

were observed for the release profiles of the matrices obtained from the drug/swellable polymer systems prepared using the ball milling technique (data not reported).

These data confirm previous results (Salomon et al., 1979) concerning hydrophilic matrices made only of HPMC; it is interesting to note that the influence of the compression force is also negligible in the case of the matrices that we prepared, even those containing not only a gel-forming polymer (HPMC), but also a swellable polymer (CMC-XL).

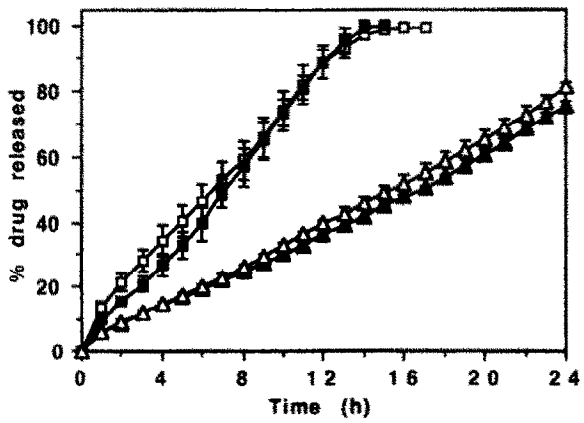

Fig. 10. Release profiles ($n = 3 \pm$ S.D.) of matrices: (□) Mx1/2K20; (■) BM1/2K20; (▲) Mx1/4K30; (△) BM1/4K30.

Fig. 10 shows a comparison between the release profiles obtained from matrices with the corresponding composition, but prepared from drug/swellable polymer systems obtained via different techniques.

The comparison of matrices with corresponding compositions shows no significant differences (release profiles almost superimposed).

Conclusions

Ball milling and mixing of carbamazepine with cross-linked sodium carboxymethylcellulose are feasible and effective dry techniques wich are useful to achieve marked enhancement in the rate of drug dissolution.

These systems, containing a drug with improved dissolution rate characteristics, can be formulated in a hydrophilic matrix made with hydroxypropylmethylcellulose (gel-forming polymer), and are capable of providing in vitro extended drug release characterized by good linearity that lasts until almost their entire drug content has been released.

During the in vitro test, the matrices are subject to both gelation and erosion and the linearity of in vitro drug release appears to be mainly correlated with the linearity of the corresponding in vitro matrix erosion.

Cross-linked sodium carboxymethylcellulose (the main component of the matrices prepared) is known in the pharmaceutical field as as a superdisintegrant; in fact, it swells in water while maintaining the integrity of cellulose fibers, thus reducing gelling (Shangraw et al., 1980).

The presence of this polymer in the matrix plays a dual role in controlling drug release. Its properties of water swelling exert an important influence on the erosion process of the matrix.

However, the fact that the duration of the linear in vitro drug release (from 12 to 24 h) is strictly connected not only to the presence of hydroxypropylmethylcellulose, but also to the content of cross-linked sodium carboxymethylcellulose, means that this polymer plays an important role in the gelling process as well.

This can be explained by the fact that the presence of hydroxypropylmethylcellulose leads

to an improvement in the gelling process of cross-linked sodium carboxymethylcellulose, which remains entrapped in the gelled layer of hydroxypropylmethylcellulose, itself becoming gelled and able to control drug release, but in the meantime without losing its swelling/eroding properties towards the 'guest' matrix.

Furthermore, the in vitro behaviour of the matrices is almost independent of variations in the compression force.

The combination of hydroxypropylmethylcellulose with cross-linked sodium carboxymethylcellulose as mixtures with a water insoluble drug such as carbamazepine can therefore be proposed for the preparation of erodible hydrophilic matrices which provide linear drug release and whose in vitro characteristics are not significantly affected the processing variables.

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References

Caramella, C., Colombo, P., Bettinetti, G.P., Giordano, F., Conte, U. and La Manna, A., Swelling properties of disintegrants. *Acta Pharm. Technol.*, 30 (1984) 132–139.

Conte, U., Colombo, P., Caramella, C. and La Manna, A., The effect of magnesium stearate and polytetrafluoroethylene as lubricants in direct compression of acetylsalicylic acid. *Il Farm. Ed. Prat.*, 8 (1972) 440–452.

Eichelbaum, M., Ekbom, K., Bertilson, L., Ringenberger, V.A. and Rane, A., Plasma kinetics of carbamazepine and its epoxide metabolite in man after single and multiple doses. *Eur. J. Clin. Pharmacol.*, 8 (1975) 377–341.

Fincher, J.H., Particle size of drugs and its relationship to absorption and activity. *J. Pharm. Sci.*, (1968) 1825–1835.

Giunchedi, P., Conte, U. and La Manna, A., A swellable polymer as carbamazepine dissolution rate enhancer. *Boll. Chim. Farm.*, 129 (1990) 17–20.

Larkin, J.G., McLellan, A., Munday, A., Sutherland, M., Butler, E. and Brodie, M.J., A double-blind comparison of conventional and controlled-release carbamazepine in healthy subjects. *Br. J. Clin. Pharmacol.*, 27 (1989) 313–322.

Martindale, The Extra Pharmacopoeia, 29th Edn, Reynolds, J.E.F. (Ed.), The Pharmaceutical Press, London, 1989, pp. 400–402.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P., Cellulose matrices for zero-order release of soluble drugs. *Drug Dev. Ind. Pharm.*, 14 (1988) 2299–2320.

Salomon, J.L., Vuagnat, P., Doelker, E. and Buri, P., Importance de la technologie et de la formulation pour le mécanisme de libération du chlorure de potassium contenu dans des matrices hydrophiles. *Pharm. Acta Helv.*, 54 (1979) 86–89.

Sangalli, M.E., Giunchedi, P., Colombo, P., Conte, U., Gazzaniga, A. and La Manna, A., Cross-linked sodium carboxymethylcellulose as a carrier for dissolution rate improvement of drugs. *Boll. Chim. Farm.*, 128 (1989) 242–247.

Shangraw, R., Mitrevej, A. and Shah, M., A new era of tablet disintegrants. *Pharm. Technol.*, 4 (1980) 49–57.

Sivenius, J., Heinonen, E., Lehto, H., Järvensivu, P., Anttila, M., Ylinen, A. and Riekkinen, P., Reduction of dosing frequency of carbamazepine with a slow release preparation. *Epilepsy Res.*, 2 (1988) 32–36.