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SUSTAINED-RELEASE TABLET CONTAINING OXAZEPAM: STUDY AND DESIGN

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ABSTRACT

Sustained-release tablets containing oxazepam were prepared and dissolution profiles were investigated. The total dose of oxazepam is constituted of initial and maintenance dosage. A method for the preparation of hydrophilic matrix tablets is presented. The study of the dissolution rate of these preparations in artificial gastric (in the first two hours) and enteric juices (in the following ten hours) was experimented. No significant differences in oxazepam release rate were found between the formulations containing lactose, zinc sulfate, calcium sulfate or calcium phosphate added intragranularly to the maintenance dosage. The dissolutions studies of oxazepam preparations demonstrated differences in drug release properties depending on the content of extragranular croscarmellose sodium.

INTRODUCTION

Benzodiazepines have been used clinically to reduce anxiety (in non-sedative doses), agitation and muscular tension and in the treatment of convulsive disorders (1).

Oxazepam is a benzodiazepine drug with unique pharmacokinetic properties as it is active *per se* and does not form metabolites with clinical effects. In the metabolic elimination of other benzodiazepines, oxazepam is a final congener with pharmacological activity (2).

Oxazepam is well absorbed, passes the blood-brain barrier readily and has a short half-life.

It is pratically insoluble in water and the usual adult oral dose is 10-15 mg 3-4 times daily (3).

The hydrophilic matrix carbomer used in the preparation of oxazepam sustained-release tablets is a synthetic cross-linked polymer of acrylic acid copolymerized with approximately 0,75-2% w/w of polyalkylsucrose. The end product contains 56-68% carboxylic acid groups arranged in the Carbomer group, and is commercialized under the name of Carbopol. The most-used variety is termed 934 (4-9). The ionic nature of these polymers means that the gelifying process is dependent on pH (10-15). The polymer is the substance responsible for the formation, by hydration, of a diffusion and erosion-resistant gel layer. It is the fundamental component of the hydrophilic matrix system (16-20).

The release of an active principle by a matrix system is produced by two simultaneous mechanisms: erosion or attrition of the outermost, least consistent gel layers; dissolution of the active principle in the liquid medium and diffusion through the gel barrier formed (11,12,21,22).

The development of technologically acceptable formulations requires, in addition to the active principle and the gelifying agent, the presence of other excipients, in particular diluents and lubrificants, whose presence can markedly

affect release. The purpose of this study was to evaluate the influence of various diluents (lactose, zinc sulfate, calcium sulfate or calcium phosphate) on the dissolution rate of the drug.

For many drugs, dissolution must be preceded by disintegration of the tablet matrix. To improve the rate and extent of tablet disintegration, and thereby increase the rate of drug dissolution, "superdisintegrants" are now commonly used in tablet formulations. The effect of different percentages of croscarmellose sodium (added extragranulary) on the dissolution rate of oxazepam from sustained-release tablets was investigated.

The dissolution rate in artificial gastric and enteric juices was studied in tablets containig 15 mg of oxazepam as the initial dosage (to be released in the first two hours of the experiment) and 15,6 mg as the maintenance dosage (to be slowly released in the next ten hours).

MATERIALS

Oxazepam was kindly supplied by Wyeth/Instituto Pasteur de Lisboa, Portugal.

Carbopol 934 and lactose were obtained from J.V.P., Portugal. Zinc sulfate heptahydrate, calcium sulfate dihydrate, calcium phosphate dibasic anhydrous, talc and magnesium stearate were obtained from Merck. Croscarmellose sodium was kindly supplied by Wyeth Laboratories, Inc., Philadelphia.

The buffer solutions were USP XXII gastric and enteric juices without pepsine and pancreatin.

EXPERIMENTAL

Dose determination

Nelson's method was used to calculate the oxazepam dose in matrix tablets (23-26). The usual dose (15 mg) was used as the initial dose. The maintenance

dose (15,6 mg) was determinated from the wanted therapeutic concentration (2 μg/ml), oxazepam pharmacokinetic data and the action time (12 h) (27-30). The total dose of oxazepam for tablet is 30,6 mg.

Preparation of tablets

The tablets were prepared by dry granulation. The powder submitted to the first compression was constituted of the maintenance dosage oxazepam, the gelifying agent (Carbopol 934) and the remaining excipients. Before compression, the granule was mixed with the initial dosage oxazepam and the others excipients.

All formulations used are tabulated in Tables 1, 2 and 3. The tablets weight was 200 mg, the die's diameter was 8 mm and the punches were concave.

Dissolution study

The dissolution test was carried out using USP XXII rotating basket method. The stirring rate was 50 r.p.m. The pH 1,2 (first 2 h) and pH 7,4 (2-12 h) solutions were used as dissolution media (900 ml) and were maintained at 37±0,5°C. Samples (9 ml) were removed at prescribed intervals, filtered, diluted and assayed spectrophotometrically. An equal volume of fresh medium was immediately added to maintain the dissolution volume. The samples were filtered through a 0,45 μm filter and were analyzed spectrophotometrically at 230 nm to assay the amount of oxazepam dissolved at eachtime interval. A cumulative correction factor was applied to account for previously withdraw samples. Dissolution studies were performed in quintuplicate.

Statistical analysis

Percentage of oxazepam dissolved in 2, 4, 6, 8, 10 and 12 hour were reported. The area under the dissolution curve (AUC) was evaluated by the

TABLE 1

Tablets Formulations (mg/tablet)

	A	A1	A2	B	B1	B2	C	D	D1	D2	D3	D4	D5
INITIAL DOSAGE													
Oxazepam	15,0	15,0	15,0	15,0	15,0	15,0	15,0	15,0	15,0	15,0	15,0	15,0	15,0
Lactose	15,0	15,0	15,0	—	—	—	—	—	—	—	—	—	—
Zinc sulfate	—	—	—	15,0	52,8	—	—	—	—	—	—	—	—
Calcium sulfate	—	—	—	—	—	—	15,0	—	—	—	—	—	—
Calcium phosphate	—	—	—	—	—	—	—	11,9	25,0	20,0	17,0	15,0	—
Croscarmellose sodium	—	—	—	—	—	—	—	—	—	5,0	8,0	10,0	25,0
Talc	2,0	2,0	2,0	2,0	2,0	2,0	2,0	2,0	2,0	2,0	2,0	2,0	2,0
MAINTENANCE DOSAGE													
Oxazepam	15,6	15,6	15,6	15,6	15,6	15,6	15,6	15,6	15,6	15,6	15,6	15,6	15,6
Lactose	—	75,7	106,0	—	—	—	—	—	—	—	—	—	—
Zinc sulfate	—	—	—	75,7	37,9	90,7	—	—	—	—	—	—	—
Calcium sulfate	—	—	—	—	—	—	75,7	—	—	—	—	—	—
Calcium phosphate	—	—	—	—	—	—	—	59,8	56,6	56,6	56,6	56,6	56,6
Carbopol 934	151,4	75,7	45,4	75,7	75,7	75,7	75,7	75,7	84,8	84,8	84,8	84,8	84,8
Magnesium stearate	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0

TABLE 2

Oxazepam Dissolution Data (Percentage)

pH	Time (h)	A	A 1	A 2
1,2	2	5,1±0,5	7,0±0,5	7,1±0,4
7,5	4	10,0±1,5	12,1±1,0	14,0±1,3
7,5	6	16,9±1,1	19,5±2,0	21,0±2,2
7,5	8	21,7±2,6	24,1±2,2	28,6±4,4
7,5	10	27,5±3,5	29,4±3,3	34,7±3,8
7,5	12	32,1±3,1	33,6±4,1	39,5±4,1
AUC (t=12h)		194,9±21,1	220,0±25,5	252,1±28,4
E% (t=12h)		16,2±1,8	18,3±1,9	21,0±2,4

TABLE 3

Oxazepam dissolution data (Percentage)

pH	Time (h)	B	B 1	B 2	C	D
1,2	2	11,4±1,1	10,4±1,0	11,4±1,4	6,5±0,5	8,3±1,0
7,5	4	27,3±4,1	24,0±3,7	23,2±3,4	14,2±0,9	18,2±0,9
7,5	6	53,0±3,3	36,9±5,3	29,8±4,1	20,0±1,3	29,4±1,7
7,5	8	68,9±4,4	48,7±8,7	38,1±4,7	26,0±2,6	39,7±2,3
7,5	10	72,4±4,8	57,0±11,1	47,7±5,1	32,9±1,4	47,5±4,0
7,5	12	77,4±5,7	68,9±8,5	58,5±7,8	40,6±4,0	57,5±5,6
AUC (t=12h)		544,5±42,6	427,7±68,6	362,6±50,3	243,8±16,2	346,1±23,6
E% (t=12h)		45,4±3,6	35,6±5,7	30,2±4,2	20,3±1,4	28,8±2,0

trapezoidal method. The dissolution efficiency (E%) was calculated according to Khan (31).

One way analysis of variance with a Student test was used to determine significant differences ($p<0,05$) among values of the different preparations (32).

RESULTS AND DISCUSSION

In hydrophilic matrix sustained-release tablets, the drug release occurs in a two-step way that takes place simultaneously and consecutively. Just after the ingestion, the first drug portions are released before the macromolecules gelification is complete. During this step, the drug release depends on the penetration capacity of the dissolution medium and on the gelifying characteristics of the matrix.

When the macromolecule hydration is concluded, the drug release depends mainly on the drug diffusion rate through the tablet core, i.e., on the physico-chemical properties of the viscous layer. During both steps, the drug solubility and the particle size play a major role.

According to the oxazepam biological half-life (8 hours) and the total release time choosed (12 hours), the relationship between the initial and the maintenance doses was 1:1. The theoretical drug release profile was the following (23):

- after 2 hours - 35 to 55% of the total amount of drug;
- after 4 hours - 60 to 70% of the total amount of drug;
- after 8 hours - 80 to 90% of the total amount of drug and
- after 12 hours - 95 to 100% of the total amount of drug.

Lactose - Carbopol 934

Lactose is widely used as a tablet soluble diluent (33-35). To study its effect on the oxazepam release, we mixed it with the hydrophilic matrix (intragranular lactose) and with the granules and the initial dose (extragranular dose).

Table 1 contains the formulations assayed. The analysis of the oxazepam dissolution data (Table 2) shows that there is a significative difference only when the amount of intragranular lactose exceeds 70% of the total weight of the granules. Besides, the dissolution profile differs from what was established previously.

Zinc sulfate, calcium sulfate, calcium phosphate-Carbopol 934

Zinc sulfate, calcium sulfate and calcium phosphate are used as diluents in tablet formulation (36-38). Its effect on oxazepam release was studied by using them, separately, as intra and extragranular diluents. Table 1 contains the tablet formulations tested.

The dissolution profile of the zinc sulfate tablets (Table 3) did not also comply with the previously established specifications, as the total amount of the drug release in the gastric juice was only about 11%. But the results obtained in the enteric juice show significative differences, varying from 58,4% (formulation B2) to 77,4% (formulation B) after 12 hours. According to the results, there is an ideal proportion of intra and extragranular zinc sulfate (50% intragranular and 50% extragranular), and extragranular zinc sulfate plays a major role on oxazepam release.

Oxazepam gastric release is not improved by calcium sulfate (Table 3), but the enteric release is affected in a significative way, as the amount of drug released after 12 hours is only half of those obtained with zinc sulfate. As equimolecular amounts of zinc and calcium were used, these results suggest that the Carbopol neutralizing effect of Zn ion is greater than the Ca ion.

The gastric dissolution profiles of the calcium phosphate tablets (Table 3) are identical to those containing calcium sulfate. But the enteric profiles are quite surprising, as the total amount of drug released with the insoluble diluent (calcium

phosphate) is greater than the total amount obtained with the soluble diluent (calcium sulfate). Besides, to keep the amount of calcium ion constant in both formulations, the relative proportion of the diluent/Carbopol is greater when calcium sulfate is used (50% of calcium sulfate and 50% of Carbopol 934) than when calcium phosphate is used (44% calcium phosphate and 66% of Carbopol 934). These results suggest that the use of a soluble diluent delays the drug release, as the hydrophilic macromolecules come closer, occupying the empty spaces resulting from the dissolved calcium sulfate. Thus, the matrix porosity gets lower as the hydration proceeds, opposing the water circulation and the drug diffusion. On the contrary, the presence of insoluble diluent particules forms a mechanical structure that opposes the formation of a compact struture of the gelifying agent, originating a more porous matrix.

Calcium phosphate-croscarmellose sodium-Carbopol 934

The gastric dissolution profiles of the tablets mentioned before (Figure 1) did not comply with the theoretical requirements previously stated. This results can be explained as the hydration capacity of Carbopol 934 at pH values below 3 is very small and the tablets porosity is also very small. Some of the enteric dissolution profiles comply with the stated percents, specially when calcium phosphate was used as diluent.

The effect of croscarmellose sodium, a superdesintegrant widely used in tablet formulation (39-42), was then evoluated, the used amounts varied from 2,5 to 12,5% of the total weight of the tablet (Table 1) and it was mixed with the granule, the lubrificant and the extragranular calcium phosphate. The dissolution profiles are presented on Table 4 and Figure 2. The effect of 2,5 % of croscarmellose sodium is insufficient and the presence of 12,5% of desintegrant accelerates too much the release rate. But the dissolution profiles obtained with the tablets containing 5 and

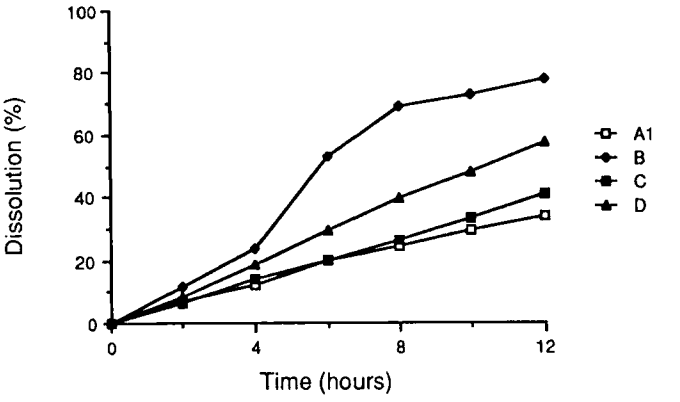

FIGURE 1

Dissolution of oxazepam from tablets containing different excipientes. Tablets containing intragranular lactose (A1-75,7 mg), zinc sulfate (B-75,7 mg), calcium sulfate (C-75,7 mg) and calcium phosphate (D-59,8 mg).

TABLE 4

Oxazepam dissolution data (Percentage)

pH	Time (h)	D1	D2	D3	D4	D5
1,2	2	11,3±1,4	12,9±2,0	36,8±5,9	52,3±3,7	80,6±6,3
7,5	4	24,1±1,5	49,6±2,6	57,3±4,2	67,1±4,9	92,3±5,9
7,5	6	38,8±5,6	63,9±1,0	73,9±2,1	80,1±5,2	97,4±3,6
7,5	8	54,6±6,7	75,9±2,2	80,9±2,3	87,7±5,1	99,3±2,8
7,5	10	63,1±8,5	80,3±1,6	89,1±6,4	93,2±5,2	100,3±1,4
7,5	12	72,7±8,1	85,8±2,9	93,4±5,3	99,5±0,9	100,8±1,1
AUC (t=12h)		459,0±55,3	651,5±21,2	773,8±52,5	868,3±51,8	1066,0±43,4
E% (t=12h)		38,3±4,6	54,3±1,8	64,5±4,4	72,4±4,3	88,8±3,6

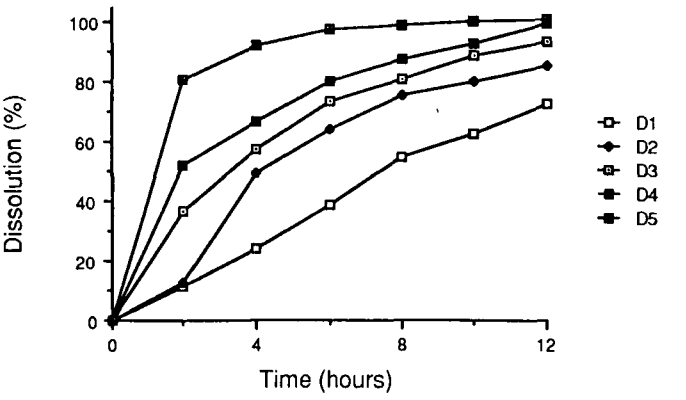

FIGURE 2

Dissolution of oxazepam from tablets containing different amounts of extragranular croscarmellose sodium (D1- 0 mg; D2- 5 mg; D3- 8 mg; D4- 10 mg; D5- 25 mg).

7,5% of croscarmellose sodium are quite different, as all the values obtained are within the previously stated limits.

CONCLUSIONS

According to the results of this study it is possible to conclude that the various diluents play an important role in the oxazepam release rate in hydrophilic matrix. In equal proportions, the positive effect of zinc sulfate on the oxazepam release rate is greaty than the effect obtained with lactose, calcium sulfate and calcium phosphate. There is an ideal proportion between intra and extragranular zinc sulfate (1:1) in order to promote the oxazepam release rate.(Table 1). However, calcium phosphate (insoluble diluent) originates a higher oxazepam release rate than calcium sulfate (soluble diluent).

The amount of extragranular croscarmellose sodium in hydrophilic matrix to be included is 4-5%, while the relationship in calcium phosphate/Carbopol 934 is, respectively, 60% and 40%.

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