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CHARACTERIZATION AND DISSOLUTION STUDY OF OXODIPINE FROM SOLID BINARY SYSTEMS

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ABSTRACT

Thermomicroscopy and differential scanning calorimetry were employed to characterize solid binary systems prepared with oxodipine and PEG 6000, 2-hydroxypropyl-ß-cyclodextrin or mannitol. DSC curves did not allow to diferentiate physical mixtures from solid dispersions. Thermomicroscopy revealed the interactions that can be produced between drug and each carrier, due to heat contribution, when the physical mixtures were observed; also this thermal technique permited us to ascertain the composition of particles that constitute the solid dispersions. Dissolution studies showed that the amelioration obtained in oxodipine dissolution from physical mixtures was due to the dessagregant action of the carriers, which obtained an increase of the drug surface in contact with the dissolution medium. The proportions and carrier nature influence the oxodipine dissolution, fundamentally from solid dispersions, where the interaction drug/carrier is stronger than in physical mixtures.

INTRODUCTION

Oxodipine is a new drug with calcium channel blocking properties; its chemical structure is: 1,4-dihydro-2,6-dimethyl-4-(2',3'-methylenedioxyphenyl)pyridin-3,5-dicarboxylic acid, methyl ethyl ester. Like other 1,4 dihydropiridines is very slightly water soluble, which can cause bioavailability problems when incorporated in a solid oral dosage form. As a consequence, when designing a formulation which contains this drug it is necessary to add some substances capable for enhancing its dissolution characteristics in aqueous fluids.

Sekiguchi and Obi (1) proposed the using of solid dispersions to improve the dissolution and the bioavailability of poorly water-soluble drugs. Polyethylene glycols of molecular weight in the range 1500-8000 can be used, with success, as carriers to prepare these systems, as the numerous scientific articles published on solid dispersions prepared with these water-soluble polymers demonstrate (2-6). But on the market there are few products using these combinations; the explanation can be the difficulties of scaling up, the incorporation of the solid dispersions in a classic solid dosage form, or the modification of the dissolution process observed after storage (7, 8).

Mannitol is a very useful substance in the pharmaceutical field as a tonicity agent, sweetening agent, filler for tablets, especially chewable tablets and as a bulking agent for

lyophilized preparations (9). But mannitol can also be used to prepare solid dispersions because it is freely water soluble and the results obtained on ibuprofen and chloramphenicol dissolution enhancement are satisfactory (10, 11).

Cyclodextrins are substances capable of giving rise to inclusion compounds with many drugs. The complexes obtained allow the improvement of chemical stability, aqueous solubility and bioavailability of drugs. Of the different existing cyclodextrins those which provide the best results are the branched ß-cyclodextrins (glucosyl-ß-cyclodextrin, maltosyl-ß-cyclodextrin or di-maltosyl-ß-cyclodextrin) and the hydroxyalkylated ß-cyclodextrins (2-hydroxypropyl-ß-cyclodextrin) because of their higher water solubility, lower hemolytic activity and lower local tissue irritancy compared to parent ß-cyclodextrin (12, 13). The ability of ß-cyclodextrin as a direct compression excipient, either singly or in blends with other vehicles, to prepare tablets has been also evaluated; and the results show that this dextrin allows the obtention of tablets with good mechanical properties and dissolution characteristics (14).

The aim of this work is to enhance the oxodipine dissolution process by means of its incorporation in binary systems prepared with poliethylene glycol 6000 (PEG 6000), mannitol or 2-hydroxypropyl-ß-cyclodextrin. Carrier nature and binary system obtention process condition the interaction between drug and mannitol, PEG 6000 or 2-hydroxypropyl-ß-cyclodextrin molecules, and the nature, and the strength of those bonds will be the reponsible factors for the dissolution of the drug in the aqueous medium. Therefore, the characterisation of the binary systems is also included in this paper, to ascertain the interactions existing between drug and carrier in each system prepared.

MATERIALS

Oxodipine was kindly supplied by the Instituto para el Desarrollo Químico Biológico, Madrid (Spain). The 2-hydroxypropyl-ß-cyclodextrin (2-HP-ß-CD) was a gift from Rhône-Poulenc, Madrid (Spain). Mannitol, PEG 6000 and methanol were purchased from Panreac, Madrid (Spain). All materials were used without further purification.

METHODS

Phase solubility study

This study was carried out as described by Higuchi and Connors (15). Aqueous solutions of 2-hydroxypropyl-ß-cyclodextrin with concentrations between 0.928 and 36.3 mM were prepared. These solutions were introduced in glass ampoules of 5 ml capacity and oxodipine in excess was added into. The closed ampoules were agitated for 7 days at 25°C. Then, the suspensions were filtered through 0.45 μm membrane filters (Millipore, Millex HA) and dissolved oxodipine concentration was measured spectrophotometrically using a Beckman DU 6 spectrophotometer at the UV maximum of the drug (233 nm). Six replicates were made. The stability constant was calculated from the linear portion of the phase solubility diagram.

Preparation of physical mixtures

The drug and the three water-soluble carriers were previously sieved and the particle size below 100 μm was selected. Oxodipine/2-hydroxypropyl-ß-cyclodextrin physical mixtures were prepared in 1:1 and 1:2 molar proportions, that correspond to 20.65/79.35 and 11.52/88.48 w/w proportions because of the molecular weights of oxodipine and 2-hydroxypropyl-ß-cyclodextrin are 359 and 1379 respectively. The oxodipine/PEG 6000 and oxodipine/mannitol physical mixtures were prepared in identical proportions that with cyclodextrin: 11.52/88.48 and 20.65-/79.35 w/w proportions. The mixtures were prepared by simple agitation in a recipient of adequate size.

Preparation of solid dispersions

The solid dispersions between oxodipine and PEG 6000, 2-hydroxypropyl-ß-cyclodextrin or mannitol were obtained in the same proportions as the physical mixtures above mentioned (11.52/88.48 and 20.65/79.35 w/w drug/carrier). The methods used to prepare these binary systems are different and they have been chosen according to the carrier nature.

Solid dispersions of oxodipine/2-hydroxypropyl-ß-cyclodextrin were prepared by kneading method. The substances with particle size below 100 μm were weighed, mixed and placed in a mortar. The mixture was then kneaded with a small amount of water. When the water was almost completely evaporated and the interposition was difficultous, the system was dessicated in an oven at 35°C for 24 hours. Then the product was sieved and the fraction below 100 μm selected for further studies.

Oxodipine/PEG 6000 solid dispersions were obtained by the fusion method. PEG 6000 was melted at 70°C, the drug (particle size smaller than 100 μm) was added in the solid state and mixed until a homogeneous system was obtained. It was then left to solidify at room temperature. The system obtained was ground and sieved. The fraction with a size smaller than 100 μm was collected to carry out later studies.

Solid dispersions of oxodipine and mannitol were prepared by the evaporation method. Suitable amounts of oxodipine and mannitol were dissolved in methanol and water respectively. Both dissolutions were mixed and the whole was placed in a water bath (70°C) until total evaporation of the solvent. After grinding and sieving the fraction below 100 μm was chosen.

Characterisation of the binary systems

Differential scanning calorimetry (DSC): This technique was performed using a Mettler modular system with an FP-80 HT control unit and an FP-85 furnace. The sample size was about 10 mg, and the scanning rate used 10°C/min between 30 and 350°C.

Hot stage microscopy (HSM): A Reichert microscope with Kofler stage was used to carry out the thermomicroscopic study. Sample behaviour was observed between 30 and 350°C. The heating rate was the same in every case.

Dissolution study

Dissolution process of pure oxodipine and all the binary systems prepared was studied. Sotax AT-7 dissolution apparatus with paddles was used. An agitation rate of 100 r.p.m., 1000 ml of distilled water as dissolution medium and 37 $\pm$ 0.1°C of temperature were the experimental conditions. All samples containing an amount equivalent to 40 mg of drug were added to the medium in a powdered form (size less than 100 μm). The duration of assay was 3 hours and at measured time intervals, samples were withdrawn and filtered with a porous filter of 0.45 μm pore diameter (Millipore, Millex HA). The analysis of dissolved oxodipine was according the spectrophotometric method above mentioned. Three replicates were made from each assay.

RESULTS AND DISCUSSION

Figure 1 shows the oxodipine/2-hydroxypropil-ß-cyclodextrin phase solubility diagram. To increase dissolved cyclodextrin concentration into the medium, solubility of oxodipine is also increased. This sketched line indicates that the phase solubility diagram between oxodipine and 2-hydroxypropyl-ß-cyclodextrin is A_L type. The $K_{1:1}$ value calculated from Higuchi and Connors's method (15) is 83.22 M^{-1} for the oxodipine/2-hydroxypropyl-ß-cyclodextrin complex, but it is lower than 100 M^{-1}, which is considered as the inferior limit for the formation of a stable

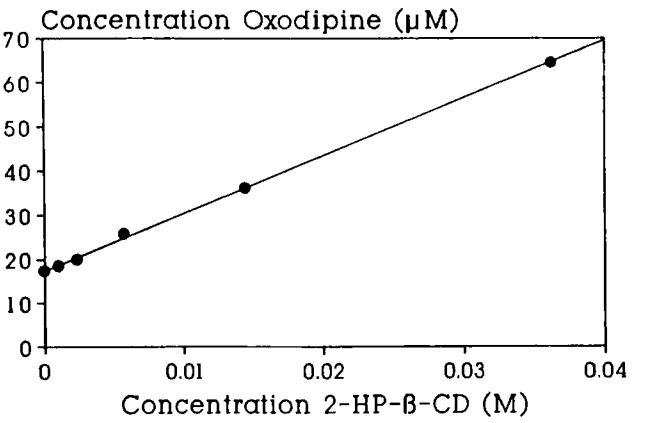

Figure 1.- Phase solubility diagram of oxodipine/2-hydroxypropyl-ß-cyclodextrin in water at 25 ± 0.1 °C.

inclusion complex (16). This indicates that the molecular structure of oxodipine is not too adequate to form a stable complex with 2-hydroxypropyl-ß-cyclodextrin.

Figure 2 shows the DSC for PEG 6000, oxodipine and the binary systems prepared with them. PEG 6000 shows an endothermic peak at 58-60°C (melting point), and oxodipine exhibits also an unique endothermic peak (167°C) that corresponds to its fusion. The DSC curves for the physical mixtures are similar to those which belong to solid dispersions, and they display DSC with only one peak that shows PEG 6000 fusion; the drug is not detected in those curves.

Figure 3 shows DSC curves for mannitol, oxodipine and their binary systems. The six DSC curves included in this figure are similar, because of mannitol melting range (164-166°C) practically coincides with that of oxodipine. The DSC curves of these binary systems are similar to those displayed by oxodipine/PEG 6000 systems, only one endothermic peak that does not allow the differentiation of physical mixtures from solid dispersions.

Figure 4 shows the DSC curves for 2-hydroxypropyl-ß-cyclodextrin, oxodipine and their binary systems prepared. The cyclodextrin DSC curve exhibits two endothermic peaks: the first at 100°C due to water loss and the latter (300-350°C) that corresponds to fusion process. Because of 2-hydroxypropyl-ß-cyclodextrin is an amorphous substance, its melting peak is not as clear as the one of a crystalline substance (17). The oxodipine/2-hydroxypropil-ß-cyclodextrin binary systems display DSC curves that clearly show the endothermic peak (fusion process) of oxodipine, and also the fusion of the cyclodextrin can be noted. As in the previous figures there are no differences between DSC curves from physical mixtures and solid dispersions either.

The observation of samples through hot stage microscope allows us to see directly the modifications that occur during the heating process, as well as the diferentiation of pure substances from impurities, and amorphous materials from crystalline ones.

Pure oxodipine is a crystalline substance; during heating, it remains unchanged until its melting range is reached (164-165°C). PEG 6000 is also a crystalline substance that melts to

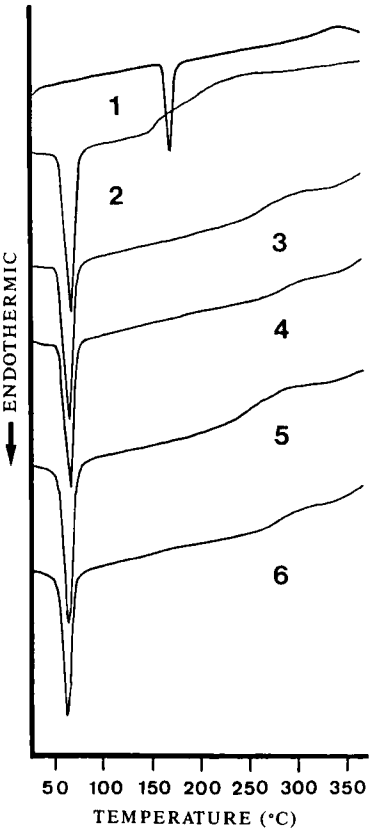

Figure 2.- DSC curves from oxodipine/PEG 6000 binary systems: (1) oxodipine, (2) PEG 6000, (3) 11.52/88.48 w/w physical mixture, (4) 20.65/79.35 w/w physical mixture, (5) 11.52/88.48 w/w solid dispersion, and (6) 20.65/79.35 w/w solid dispersion.

58°C. Mannitol (crystalline particles) shows a fusion process at about 165°C. The sample of 2-hydroxypropyl-ß-cyclodextrin is constituted by amorphous particles of varied form: filamentous, spherical, etc.; during the heating the darkening of the particles about 100°C (water loss) can be observed, and when the temperature reaches the range 285-288°C we see the fusion of the particles.

The behaviour of the two physical mixtures of oxodipine/PEG 6000 is similar. At 58-60°C carrier fusion is observed and subsequently dissolution of oxodipine into melted PEG 6000. Only the oxodipine particles that are near to melted PEG are dissolved, the rest of drug particles remaining unchanged until its fusion (160-165°C).

The oxodipine/PEG 6000 solid dispersions behave in different ways from their respective physical mixtures, because in the solid dispersions an intimate union between drug and carrier was produced during the process of preparation.

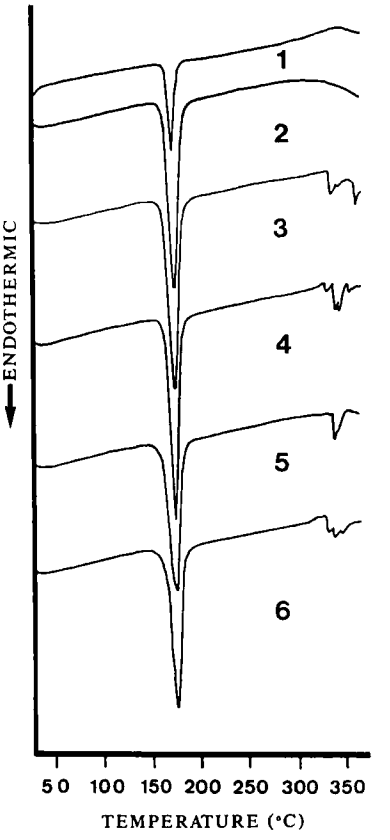

Figure 3.- DSC curves from oxodipine/mannitol binary systems: (1) oxodipine, (2) mannitol, (3) 11.52/88.48 w/w physical mixture, (4) 20.65/79.35 w/w physical mixture, (5) 11.52/88.48 w/w solid dispersion and (6) 20.65/79.35 w/w solid dispersion.

The observation to hot stage microscope of oxodipine/PEG 6000 11.52/88.48 w/w solid dispersion revealed that this sample was constituted by aparentely homogeneous and crystalline particles, but during the heating we saw that they were formed of mixed crystals of PEG 6000 and oxodipine. To reach 56°C of temperature, the PEG 6000 of the particles melted, and then oxodipine dissolution was initiated. Total dissolution of oxodipine into melted PEG 6000 appeared at 65°C. During the elaboration of this solid dispersion we directly observed the drug dissolution into melted carrier, and the system appeared at 70°C as a transparent liquid (true dissolution). To cool at room temperature solidification of carrier was produced, and solidification of drug also was produced into the crystals of PEG 6000, originating mixed crystals.

To microscope the sample of oxodipine/PEG 6000 20.65/79.35 w/w solid dispersion appeared to be formed by apparently homogeneous particles, but they were heterogeneous as can be deduced from its thermal behaviour. Firstly when the temperature reached 56°C the fusion

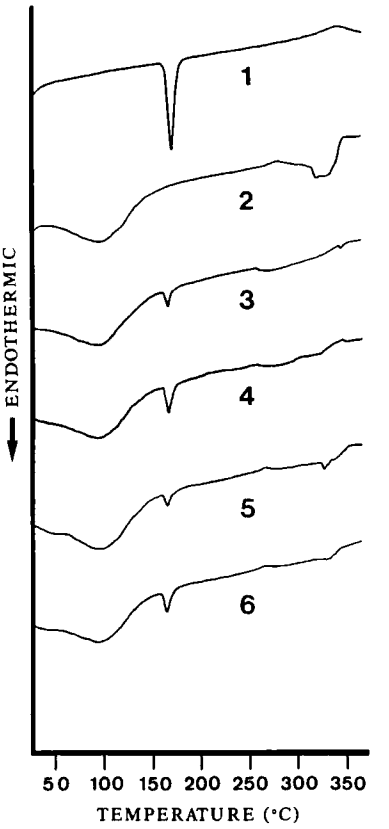

Figure 4.- DSC curves from oxodipine/2-hydroxypropyl-ß-cyclodextrin binary systems: (1) oxodipine, (2) 2-hydroxypropyl-ß-cyclodextrin, (3) 1:2 mol/mol physical mixture, (4) 1:1 mol/mol physical mixture, (5) 1:2 mol/mol solid dispersion, and (6) 1:1 mol/mol solid dispersion.

of particles' PEG 6000 and beginning of the dissolution of particles' oxodipine into PEG 6000 melted was observed; proceeding the heating continued oxodipine dissolution, and the dissolution of drug into melted PEG 6000 was total at 110-120°C. In this solid dispersion, in contrast with the solid dispersion mentioned above (with a smaller proportion of drug), it is necessary to increase temperature more to obtain total drug dissolution, because there is a larger proportion of drug in the system. When this solid dispersion was prepared we did not manage to completely dissolve the drug into the carrier at 70°C, and at this temperature the system was a true suspension: the drug was partially dissolved into the melted carrier, and the rest remained suspended as solid particles. During cooling, at room temperature, mixed crystals from melted PEG 6000 and dissolved oxodipine were formed, and in the system appeared together with the solid particles of pure oxodipine that did not change during the process of elaboration of the solid dispersion.

Hot stage microscopy does not permit the diferentiation of physical mixtures from solid dispersions prepared with oxodipine and mannitol because both substances melt in the same temperature range (160-165°C), and it is not possible to check with this technique the interaction obtained between drug and carrier during solid dispersion obtention process. During heating only the total fusion of all the particles that constitute the sample can be observed at 165°C.

The examination of oxodipine/2-hydroxypropyl-ß-cyclodextrin physical mixtures by microscope allows us to diferentiate the drug particles from the carrier particles because of their different morphologic characteristics. The thermal behaviour of both physical mixtures is the same and independent of drug/cyclodextrin proportions. When the system reaches the temperature 165°C the oxodipine particles fusion can be observed; to continue heating the decomposition of melted drug is detected. This decomposition finishes at 270-280°C. When the temperature is 285°C the fusion of cyclodextrin particles is observed. It can be clearly observed, that at no point interaction between melted oxodipine and 2-hydroxypropyl-ß-cyclodextrin solid particles is produced. This indicates that any obtention method based only on heating of the components is not useful to prepare inclusion compounds with oxodipine and 2-hydroxypropyl-ß-cyclodextrin, because at temperatures below melting point of cyclodextrin this substance is not soluble in melted oxodipine, and at temperatures above cyclodextrin fusion, oxodipine has disappeared by decomposition.

Both oxodipine/2-hydroxypropyl-ß-cyclodextrin solid dispersions display similar thermal behaviours. The samples are constituted by aparently homogeneous particles. During heating it can be observed modification in the sample (steaming over and between the particles) when temperature reaches 165°C (oxodipine melting point), but the size and shape of the particles remain unmodified until its fusion: 285°C. To explain this behaviour we can analyze the obtention method of these solid dispersions. The kneading method is done by adding a small water amount on the physical mixture, thus cyclodextrin (water soluble) is dissolved, but it is not possible to dissolve oxodipine (not water soluble); during the kneading water evaporation is produced, and the dissolved cyclodextrin crystallizes on oxodipine particles that act as crystalline nuclei, thus mixed particles: oxodipine particles coated by 2-hydroxypropyl-ß-cyclodextrin are formed. The results of DSC and HSM obtained from oxodipine/2-hydroxypropyl-ß-cyclodextrin solid dispersions seem to indicate that a true inclusion compound has not been formed, given that the fusion of the drug is detected.

The results obtained with both thermal analysis techniques show that the exclusive use of DSC to explain thermal behaviour of the binary systems in this work studied is not enough to find out the interactions that exist between the drug and each carrier, because it does not show the differences that exist between physical mixtures and solid dispersions nor does it detect processes that take place with very low energetic changes as drug dissolution into melted carrier (oxodipine/PEG 6000 binary systems). On the other hand, HSM has proven to be a very useful technique in the characterisation of binary systems, provided that the components of the system have different and distinguishable thermal behaviours.

Figure 5 shows the dissolution profiles of oxodipine from physical mixtures with PEG 6000, 2-hydroxypropyl-ß-cyclodextrin, and mannitol. Also the dissolution curve of pure oxodipine can be seen. In the physical mixtures only a superficial interaction exists between drug particles and carrier particles, but this is enough to enhance drug dissolution with regard to pure drug. On the elaboration of physical mixtures the hydrophilic carrier is interposed with the drug, thus the electrostatic forces that maintain the oxodipine particles united together are decreased; in this way the drug solid surface in contact with the dissolution medium is increased and an amelioration on dissolution rate is obtained.

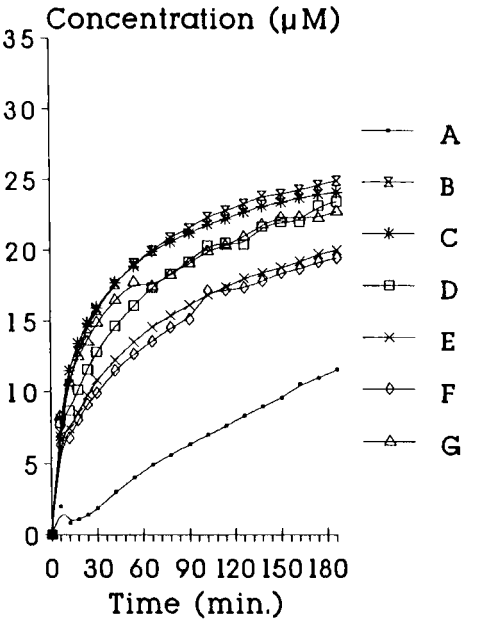

Figure 5.- Dissolution profiles of oxodipine from physical mixtures and pure oxodipine: (A) pure oxodipine, (B) 20.65/79.35 w/w oxodipine/PEG 6000, (C) 11.52/88.48 w/w oxodipine/PEG 6000, (D) 1:1 mol/mol oxodipine/2-HP-ß-CD, (E) 1:2 mol/mol oxodipine/2-HP-ß-CD, (F) 20.65/79.35 w/w oxodipine/mannitol, and (G) 11.52/88.48 w/w oxodipine/mannitol.

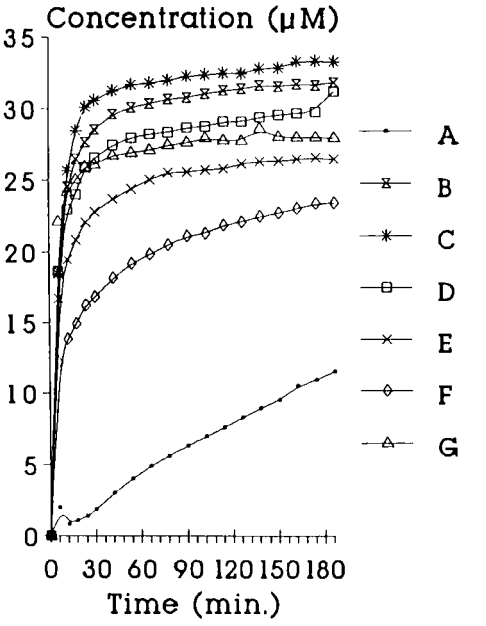

Figure 6.- Dissolution profiles of oxodipine from solid dispersions and pure oxodipine: (A) pure oxodipine, (B) 20.65/79.35 w/w oxodipine/PEG 6000, (C) 11.52/88.48 w/w oxodipine/PEG 6000, (D) 1:1 mol/mol oxodipine/2-HP-ß-CD, (E) 1:2 mol/mol oxodipine/2-HP-ß-CD, (F) 20.65/79.35 w/w oxodipine/mannitol, and (G) 11.52/88.48 w/w oxodipine/mannitol.

TABLE 1

Variation Coefficient Values from Dissolution Profiles of: (A) Pure Oxodipine, (B) Oxodipine/2-HP-ß-CD 1:1 mol/mol Physical Mixture, (C) Oxodipine/2-HP-ß-CD 1:2 mol/mol Physical Mixture, (D) Oxodipine/Mannitol 11.52/88.48 w/w Physical Mixture, (E) Oxodipine/Mannitol 20.65/79.35 w/w Physical Mixture, (F) Oxodipine/PEG 6000 11.52/88.48 w/w Physical Mixture and (G) Oxodipine/PEG 6000 20.65/79.35 w/w Physical Mixture.

Time (min.)	A	B	C	D	E	F	G
6	3.66	21.13	9.04	13.46	11.38	6.49	6.60
12	11.87	5.22	4.11	5.02	6.25	4.46	4.18
18	54.84	2.17	1.95	7.48	3.90	4.21	3.89
24	53.17	2.51	2.25	3.51	1.04	3.99	4.54
30	44.74	2.48	3.84	2.22	2.72	3.46	3.85
42	37.24	4.64	7.41	2.52	2.83	3.82	2.85
54	32.51	4.67	5.85	3.34	2.13	3.54	3.50
66	24.74	4.35	7.87	3.15	2.14	3.37	2.65
78	24.68	6.70	6.84	4.30	1.79	2.44	2.36
90	21.45	6.11	6.64	2.14	0.84	2.25	2.31
102	21.64	5.25	7.27	1.82	1.20	2.09	2.26
114	17.10	5.82	7.65	2.32	4.85	1.85	2.08
126	18.09	6.80	7.81	2.06	4.27	1.16	2.55
138	16.66	4.59	5.57	1.08	1.46	1.85	2.39
150	14.92	4.27	7.65	0.64	3.10	1.93	1.85
162	11.00	5.83	5.71	1.54	2.30	2.00	2.00
174	9.49	4.40	5.75	1.50	3.16	1.73	2.47
186	8.62	4.91	4.94	2.36	2.22	2.00	2.35

TABLE 2

Variation Coefficient Values from Dissolution Profiles of: (A) Oxodipine/2-HP-ß-CD 1:1 mol/mol Solid Dispersion, (B) Oxodipine/2-HP-ß-CD 1:2 mol/mol Solid Dispersion, (C) Oxodipine/Mannitol 11.52/88.48 w/w Solid Dispersion, (D) Oxodipine/Mannitol 20.65/79.35 w/w Solid Dispersion, (E) Oxodipine/PEG 6000 11.52/88.48 w/w Solid Dispersion and (F) Oxodipine/PEG 6000 20.65/79.35 w/w Solid Dispersion.

Time (min.)	A	B	C	D	E	F
6	2.09	1.80	3.44	4.50	16.45	8.75
12	2.58	0.65	2.57	1.00	6.93	3.52
18	7.83	1.60	1.98	0.34	2.09	1.12
24	0.85	2.14	1.80	1.60	2.02	1.64
30	1.00	1.18	1.10	0.43	2.41	0.54
42	1.73	0.96	0.09	0.70	0.99	1.07
54	1.79	0.78	0.58	1.08	1.59	0.33
66	1.78	0.77	1.17	0.51	1.60	0.56
78	2.73	2.95	2.02	0.51	1.50	0.62
90	1.84	1.20	3.35	0.27	1.68	0.55
102	2.40	1.57	1.90	0.58	1.82	0.23
114	3.70	2.04	2.15	0.37	1.36	0.14
126	3.22	1.56	2.31	0.45	1.20	0.18
138	3.36	1.20	0.76	1.10	1.35	0.33
150	3.96	0.75	2.95	0.84	1.74	0.41
162	3.59	0.41	1.39	1.41	1.41	0.68
174	4.20	1.38	0.94	1.52	2.39	0.09
186	0.44	1.71	2.22	1.11	2.67	0.44

Dissolution curves of oxodipine from solid dispersions are showed in figure 6. A considerable improvement compared with physical mixtures is observed when oxodipine is formulated as a solid dispersion, because during the elaboration of all solid dispersions interaction between drug and carrier was obtained; mixed crystals from oxodipine and PEG 6000; and mixed particles from oxodipine and 2-hydroxypropyl-ß-cyclodextrin were formed, as was commented above. The method used to prepare solid dispersions from oxodipine and mannitol has also allowed the obtention of mixed crystals, but in this case the crystals are different from the obtained with PEG 6000. To evaporate the mixture of oxodipine in ethanolic solution with mannitol in aqueous solution, the first solvent evaporated is the ethanol, and oxodipine in solution begins to precipitate; proceed with the evaporation process, simultaneous precipitation of mannitol and oxodipine producing mixed crystals is obtained.

The results of oxodipine dissolution obtained from each solid dispersion with the same drug/carrier proportions are different because of solid particles composition, as above mentioned, and because of carrier nature. This latter characteristic conditions carrier dissolution, which constitutes the preceeding step to drug dissolution. Thus, it has been observed that solid dispersions prepared with PEG 6000 or mannitol showed similar dissolution behaviours; increasing carrier proportion in the system also increased the dissolution rate of drug included. However, in solid dispersions and physical mixtures prepared with 2-hydroxypropyl-ß-cyclodextrin the carrier proportions had different influence over oxodipine dissolution. The presence of cyclodextrin improves the drug dissolution, but above a determined proportion, it decreases oxodipine dissolution rate although without reaching values obtained from pure drug. A possible explanation would be that the drug and 2-hydroxypropyl-ß-cyclodextrin compete for water to dissolve and as this cyclodextrin is more water soluble that oxodipine, the carrier dissolution process retards the drug dissolution process when cyclodextrin is in excess. This hypothesis does not contradict the results obtained on the phase solubility diagram, since to carry out this study we already start from cyclodextrin aqueous dissolutions and the increase obtained in oxodipine solubility is due to inclusion of drug molecules into the hydrophobic cavity of cyclodextrin molecules.

The variation coefficients obtained to compare the dissolution mean values with its corresponding individual values show that the incorporation of oxodipine to a binary system (solid dispersion or physical mixture) not only produces an amelioration in drug dissolution, but we also make the dissolution process more homogeneous.

From the observation of variation coefficient values showed on Table 1 and Table 2 we can also deduce that to increase the interaction between drug and each carrier (pass from physical mixture to solid dispersion) decreases the variation coefficients. Therefore the system that allows the obtention of more homogeneous dissolution profiles are the solid dispersions, and of all those systems those which include PEG 6000 are those which permit the optimization of the dissolution of oxodipine, due to the fact that this carrier annuls the interaction forces between drug molecules during the perparation of the systems, as could be observed with hot stage microscopy.

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