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RESEARCH PAPER

Inclusion of Methoxybutropate in β- and Hydroxypropyl β-Cyclodextrins: Comparison of Preparation Methods

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ABSTRACT

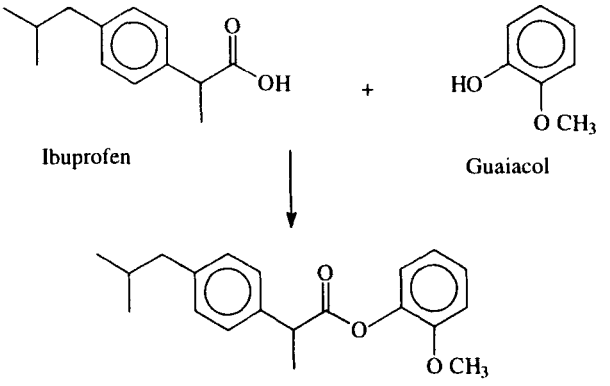
Interactions between methoxybutropate and β-cyclodextrin or hydroxypropyl β-cyclodextrin and the possibility of obtaining inclusion complexes have been evaluated by phase solubility diagram, HPLC, DSC, and x-ray diffractometry. Solid inclusion complexes were prepared by spray drying, kneading, and solid dispersion. The dissolution profiles of the obtained powders were studied in order to define the most appropriate cyclodextrin preparation method and molar ratio to use in the production of methoxybutropate inclusion complexes.

INTRODUCTION

Methoxybutropate is an analgesic, nonsteroidal, anti-inflammatory drug derived from the esterification reaction between ibuprofen and guaiacol. This molecule presents a very good stability, being insensible to oxygen and UV radiations; it undergoes hydrolysis only at very low or very high pH values and it is also thermally stable. Unfortunately, the drug must be administered in a relatively high dosage (600 mg); it possesses a low melting point (35.5°-36.5°C) and a very unpleasant bitter taste, and what is more, its water solubility is less than 10^{-6} M. The inclusion complexation of the drug with cyclodextrins should surely be taken into account in efforts to overcome these drawbacks.

Actually, besides natural cyclodextrins (α, β, γ), there are a great many derivatives such as acylated, nitrogen-containing, halogenated, carboxylic group containing, glucosyl-cyclodextrins, expanded ring (crown-ether-like), or the well-known alkylated derivatives (1). Most of them are not considered for industrial purposes because of their toxicity or their cost.

For this reason the authors chose β-cyclodextrin (2-12) and hydroxypropyl β-cyclodextrin (13-23) to study the possibility of including methoxybutropate in a host molecule. The first one (the least expensive cyclodex-



Methoxybutropate

trin) is indicated in the realization of an oral dosage form because of its acute nephrotoxicity if administered parenterally. The second one possesses a much higher water solubility, which allows parenteral administration without toxicity problems, and for this reason is more often used in parenteral formulations.

So, solid dispersion, kneading, and spray-drying processes were used to obtain an inclusion complex between methoxybutropate and β-cyclodextrin or hydroxypropyl β-cyclodextrin. The powders of the complexes were successively evaluated by dissolution studies.

MATERIALS AND METHODS

Solubility Studies

Phase solubility diagrams of the systems drug–cyclodextrin were carried out according to the method of Higuchi–Connors (24). Excess amounts of methoxybutropate (ACRAF, Ancona, Italy) were added to aqueous solutions containing different concentrations of β-cyclodextrin or of hydroxypropyl β-cyclodextrin (Aldrich) and stirred for 5 days. Then, the filtered solutions were analyzed spectrophotometrically to define the solubility characteristics.

Physical Mixture Preparation

Fine powdered physical mixtures of methoxybutropate and β- or hydroxypropyl β-cyclodextrin with host–guest molar ratios of 1:1, 2:1, and 4:1 were prepared by blending in a mortar for 5 min. These mixtures were next compared with the corresponding solid complex powders.

Inclusion Complex Preparation by Solid Dispersion

β-Cyclodextrin

Methoxybutropate and an equimolar or double molar or 4 times molar quantity of β-cyclodextrin were dissolved at 40°C in the lowest volume of 59% ethanol necessary to obtain a solution, and maintained under stirring for 30 min. Then, the solutions were evaporated under vacuum at 40°C with a rotary evaporator. The collected powders were stored under vacuum in a dessicator 3 days and then analyzed.

Hydroxypropyl β-Cyclodextrin

Methoxybutropate and an equimolar or double molar or 4 times molar quantity of β-cyclodextrin were dissolved at 20°C in the lowest volume of 80% ethanol necessary to obtain a solution, and maintained under stirring for 30 min. Then, the solutions were evaporated under vacuum at 40°C with a rotary evaporator. The collected powders were stored under vacuum in a dessiccator 3 days before analysis.

Inclusion Complex Preparation by Kneading

Methoxybutropate and an equimolar or double molar or 4 times molar quantity of β-cyclodextrin or hydroxypropyl β-cyclodextrin were wetted in a mortar with 50% ethanol until a paste was obtained and mixed for 30 min. Then, these pastes were left to air dry for one night and finally mildly ground and stored under vacuum in a dessiccator 3 days before analysis.

Inclusion Complex Preparation by Spray Drying

β-Cyclodextrin

Methoxybutropate and an equimolar or double molar or 4 times molar quantity of β-cyclodextrin were dissolved at 40°C in the lowest volume of 59% ethanol necessary to obtain a solution, and maintained under stirring for 30 min. After that, the solutions were spray dried (Büchi Mini Spray Dryer B-191, Switzerland) under the following conditions: feed rate 10 ml/min, inlet temperature 95°C, outlet temperature 65°C, pressure 5 bar, and throughput of drying air 35 m^3/hr. The collected powders were stored under vacuum in a dessiccator 3 days and then analyzed.

Hydroxypropyl β-Cyclodextrin

Methoxybutropate and an equimolar or double molar or 4 times molar quantity of hydroxypropyl β-cyclodextrin were dissolved at 20°C in the lowest volume of 59% ethanol necessary to obtain a solution, and maintained under stirring for 30 min. After that, the solutions were spray dried (Büchi Mini Spray Dryer B-191, Switzerland) under nitrogen at the following conditions: feed rate 10 ml/min, inlet temperature 95°C, outlet temperature 65°C, pressure 5 bar, and throughput of drying air 35 m^3/hr. The collected powders were stored under vacuum in a dessiccator 3 days before analysis.

Inclusion Complex Investigation

UV Measurements

After 3 days of storage, all the powders obtained were assayed spectrophotometrically (Cary 1E UV-Vis spectrophotometer, Varian) at 271 nm in ethanol-dimethylsulfoxide 85:15 (analytical grade, Carlo Erba, Milan, Italy) to be sure that no loss or decomposition of drug occurred during their preparation.

High-Pressure Liquid Chromatography

HPLC analyses of the powders were performed with a Hewlett-Packard 1090/II set at 20 μl injection volume and 1 ml/min flow rate using a Micro Porasil 0.39 × 30 cm (Waters) column. The UV detector was set at 271 nm and the mobile phase used was *n*-hexane:chloroform:ethyl acetate 55:30:15. A weighted amount of each powder was put in a flask with 25 ml of chloroform and stirred for 1 hr; the suspension was filtered with 0.45 μm membrane filters and the resulting solution diluted with chloroform in order to obtain theoretical methoxybutropate concentrations of 30 mg/liter. This final solution was injected and the results compared with those of a solution containing the same methoxybutropate concentration without cyclodextrins.

Differential Scanning Calorimetry

The DSC patterns were determined by a Perkin-Elmer DSC-2C differential scanning calorimeter (Perkin-Elmer Corporation, Norwalk, USA) connected to a data station. Each sample (10 mg of powder in aluminum pans) was heated at a heating rate of 5°C/min from 22° to 102°C (295° and 375°K).

X-ray Diffractometry

X-ray diffractograms of the prepared powders and of pure drug and cyclodextrins were carried out with a Philips PW 1730 x-ray generator using CuK_α radiation, at a scanning speed of 1 degree/min between 2 and 40 theta.

Dissolution Studies

The dissolution studies were performed in triplicate with an Erweka DT6 dissolution test, in distilled water at 37°C using the paddle method at a rotation speed of 75 rpm (USP XXIII Apparatus 2). A certain amount of each powder, containing 40 mg of methoxybutropate, was put into a vessel with 1000 ml of water. After 2.5-5-7.5-10-15-20-25 min and so on, 3 ml of water were withdrawn, passed through a 0.45 μm membrane filter (Millipore), and assayed spectrophotometrically with a Cary 1E UV-Vis spectrophotometer at 271 nm to measure the concentration of methoxybutropate present in the solution. The initial volume of the vessel was maintained by adding 3 ml of distilled water after each sampling.

RESULTS AND DISCUSSION

Inclusion Complex in Aqueous Solution

Figures 1 and 2 show the phase solubility diagrams of the drug/β-cyclodextrin and drug/hydroxypropyl β-cyclodextrin systems, respectively. In the first case (Fig. 1), the B_s-type curve suggests a molar ratio for the solid complex different from 1:1. In fact, the calculated

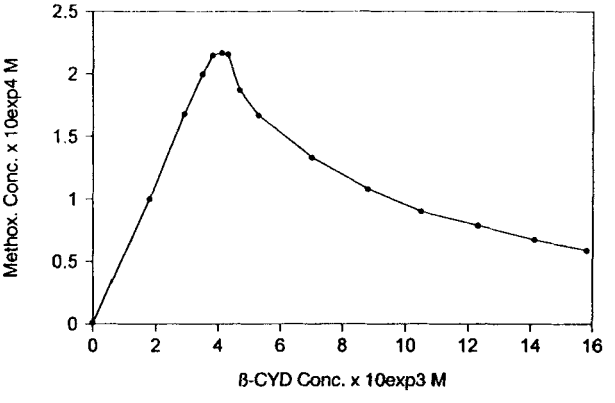


Figure 1. Methoxybutropate-β-cyclodextrin phase solubility diagram.

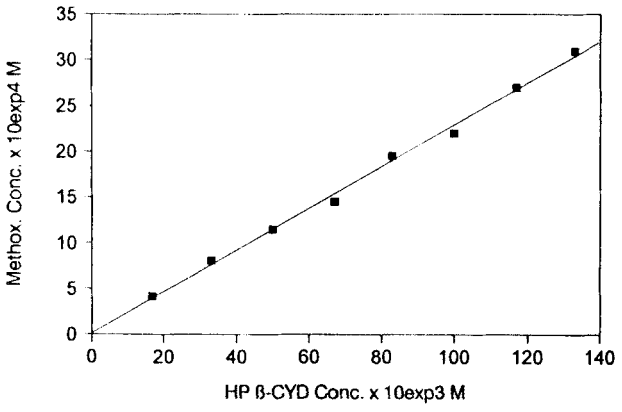


Figure 2. Methoxybutropate–hydroxypropyl β-cyclodextrin phase solubility diagram.

guest–host ratio from the data of the plateau region of the curve is 1:2 and the theoretical stability constant, calculated from the initial right portion of the curve, is $4.35 \times 10^4\ M^{-1}$.

In the second case (Fig. 2), an A_L-type curve is obtained; this means that there is a linear host–guest correlation and a complex of constant composition is formed until high hydroxypropyl β-cyclodextrin concentrations. The stability constant, calculated from all data of the curve, is $2.37 \times 10^3\ M^{-1}$.

Solid Complex Characterization

UV and HPLC Analysis

The UV analyses performed on the prepared powders show in all cases a 100% drug content according to the theoretical composition.

The HPLC analysis shows only a partial chloroform extraction of the methoxybutropate (Table 1), despite the very high drug solubility in this solvent. The quantity of methoxybutropate extracted—which is rather low particularly in the case of β-cyclodextrin inclusion in complexes—is more relevant for the powders with a drug–cyclodextrin 1:1 molar ratio and gradually decreases going towards the 1:2 and 1:4 molar ratio. The 100% of drug is extracted only from the physical mixtures. This is a proof that inclusion complexes between methoxybutropate and β-cyclodextrin or hydroxypropyl β-cyclodextrin are formed, and that they possess a good stability.

DSC Data

Figure 3 shows the DSC curves of powders prepared with β-cyclodextrin compared with those of the pure methoxybutropate, β-cyclodextrin, and their physical mixtures. In agreement with data of phase solubility diagrams (Fig. 1), the powders with drug–cyclodextrin molar ratio 1:1 present a small melting peak located in

Table 1

HPLC Data

	% Drug Extracted	
	β-Cyclodextrin	HP β-Cyclodextrin
Physical mixture		
1:1	100	100
1:2	100	100
1:4	100	100
Solid dispersion		
1:1	41	92
1:2	28	85
1:4	10	55
Kneading		
1:1	32	90
1:2	21	86
1:4	7	61
Spray drying		
1:1	34	86
1:2	18	74
1:4	8	58

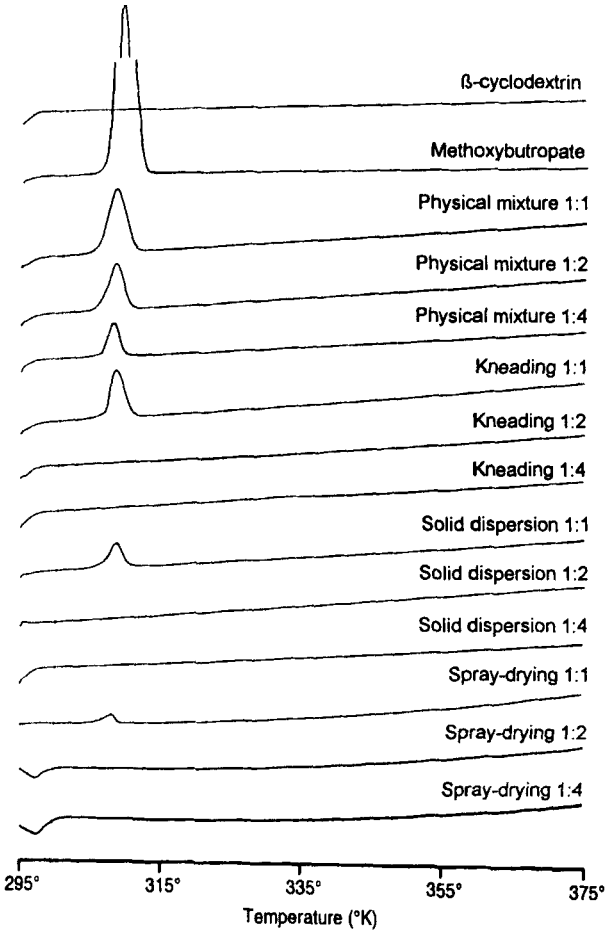


Figure 3. DSC curves of methoxybutropate–β-cyclodextrin powders.

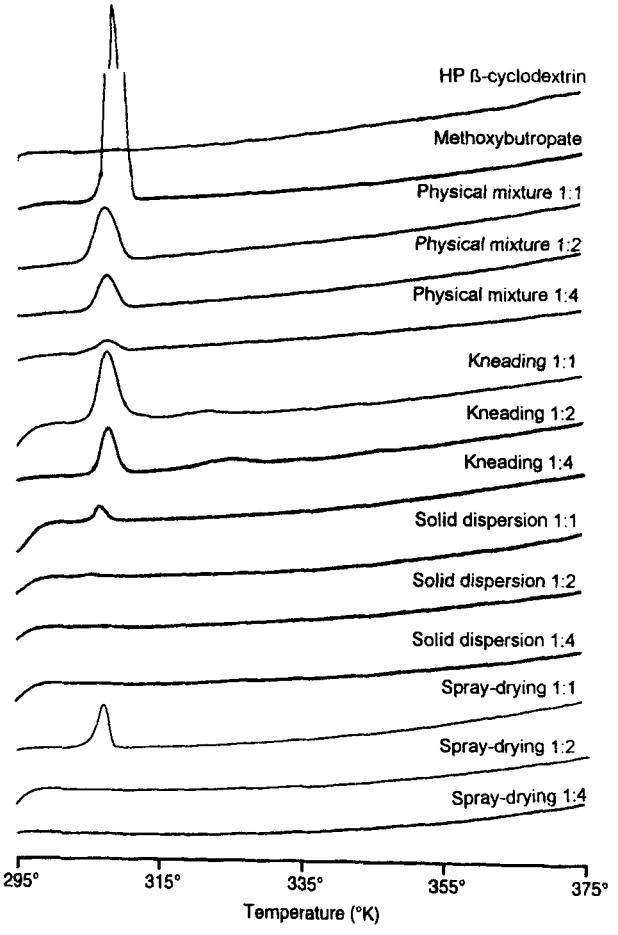


Figure 4. DSC curves of methoxybutropate–hydroxypropyl β-cyclodextrin powders.

nearly the same position of pure methoxybutropate melting peak. The presence of these peaks indicates a partial complexation of drug. On the other hand, powders with drug–cyclodextrin molar ratio 1:2 and 1:4 do not show melting peaks independently from the complexation method used, and their thermograms are practically identical to that of cyclodextrin. This suggests a total complexation of drug in these powders.

Figure 4 shows the DSC curves of powders prepared with hydroxypropyl β-cyclodextrin compared with those of the pure methoxybutropate, hydroxypropyl β-cyclodextrin, and their physical mixtures. In this case there is a difference between the three preparation methods. All the powders prepared by kneading present the methoxybutropate melting peak, even that with drug–cyclodextrin molar ratio 1:4, and their thermograms are very similar to those of the physical mixtures. Hence, kneading is not an appropriate preparation method to obtain inclusion complexes between methoxybutropate and hydroxypropyl β-cyclodextrin. On the contrary, the powders obtained by the solid dispersion method do not show any peaks, even with the drug–cyclodextrin molar ratio 1:1. This suggests a total complexation of drug in these powders and a methoxybutropate–hydroxypropyl β-cyclodextrin complex molar ratio of 1:1, in agreement with the phase solubility data (Fig. 2). Finally, thermograms of spray-dried powders show lack of melting peaks only for 1:2 and 1:4 drug–cyclodextrin molar ratio but not for the 1:1, and this is in contrast with results obtained by the solid dispersion method. Table 2 summarizes the values of the methoxybutropate melting enthalpy/gram expressed in joules for the dif-

Table 2

DSC Data

	β-Cyclodextrin		HP β-Cyclodextrin	
	J/g	% Complex	J/g	% Complex
Methoxybutropate	95.4	0	95.4	0
Solid dispersion				
1:1	7.53	63.5	0	100
1:2	0	100	0	100
1:4	0	100	0	100
Kneading				
1:1	10.46	49	11.42	28.8
1:2	0	100	5.14	41.5
1:4	0	100	1.42	69.2
Spray drying				
1:1	2.51	87.5	12.55	22
1:2	0	100	0	100
1:4	0	100	0	100

ferent powders prepared. From these values the theoretical complexation percentages have been calculated comparing the melting enthalpy of pure drug with peaks enthalpies of processed powders (if a peak is present) and, at the same time, taking into account the real quantity of drug in the powder.

X-ray Diffractometry

Figure 5 shows the diffraction patterns of pure methoxybutropate, β-cyclodextrin, and their physical mixtures. Diffractograms of solid complexes obtained by the solid dispersion, kneading, and spray-drying methods, with methoxybutropate–β cyclodextrin molar ratio 1:1, 1:2, and 1:4, are presented in Figs. 6, 7, and 8, respectively. First of all, comparing diffractograms of solid complex powders with those of pure drug, β-cyclodextrin, and of their physical mixtures, a crystallinity reduction in all processed powders can be observed, due to the particular preparation method. The crystallinity reduction is complete in the spray-dried powders, which are completely amorphous. In agreement with all other data suggesting a solid complex molar ratio of 1:2, solid dispersed and kneaded powders with a 1:1 molar ratio show a low complexation percentage because even if their diffractograms show new peaks which are not present in the physical mixtures, at the same time, they also confirm the presence of all old peaks. This is due to the insufficient amount of β-cyclodextrin in the composition of these powders. In fact, with a double quantity of β-cyclodextrin (powders with a 1:2 molar ratio) the complexation is practically total as deducible by the disappearance of most of the methoxybutropate and β-cyclodextrin peaks, and the appearance of new ones confirming the existence of a crystalline inclusion complex. The situation of the spray-dried powders is different. As the spray-drying process makes the β-cyclodextrin amorphous, the presence of drug peaks, indicating only a partial complexation, is easier to see. In fact, with 1:1 molar ratio a total complexation is not obtained, while diffractograms of spray-dried powders with 1:2 and 1:4 molar ratios show amorphous inclusion complexes. Finally, diffractograms of powders, prepared by solid dispersion and kneading with a 1:4 drug–β-cyclodextrin molar ratio, show at the same time peaks of the crystalline complex and of the β-cyclodextrin excess.

Figure 9 shows the diffraction patterns of pure methoxybutropate, hydroxypropyl β-cyclodextrin, and their physical mixtures. Diffractograms of solid complexes obtained by solid dispersion, kneading, and spray drying, with methoxybutropate–hydroxypropyl β-cyclodextrin molar ratio 1:1, 1:2, and 1:4, are presented in

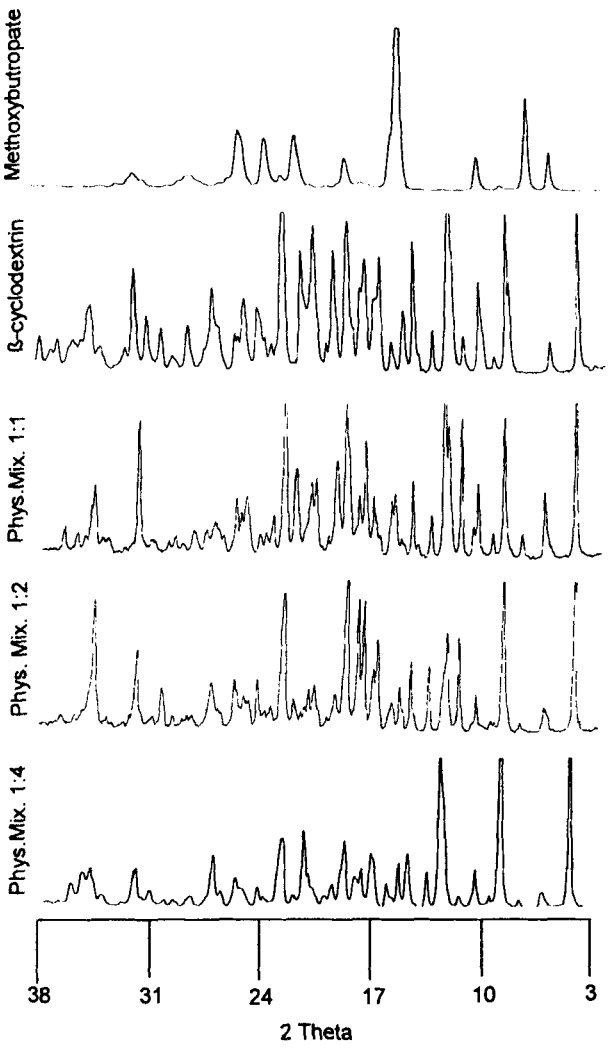


Figure 5. X-ray diffractograms of methoxybutropate, β-cyclodextrin, and their physical mixtures.

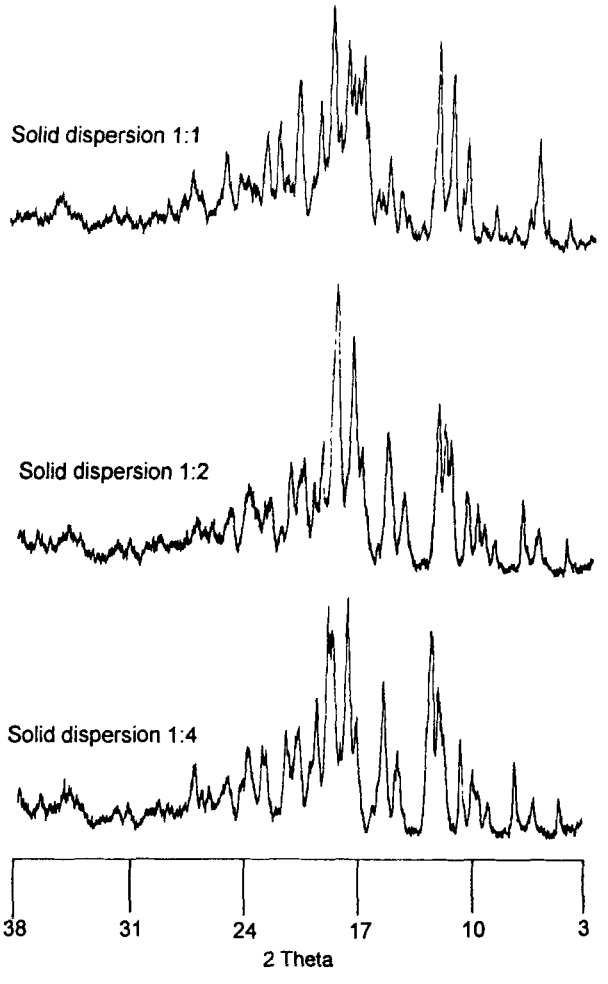


Figure 6. X-ray diffractograms of methoxybutropate–β-cyclodextrin solid dispersed powders.

Figs. 10, 11, and 12, respectively. Because the hydroxypropyl β-cyclodextrin is amorphous in the solid state, an eventual complexation is easily verified. In fact, in agreement with DSC data, kneaded powders present diffractograms similar to those of the corresponding physical mixtures, giving proof of the uselessness of the kneading method in this case. On the contrary, diffractograms of solid dispersed powders show no peak of drug and are practically identical to that of the amorphous cyclodextrin. Thus, it can be deduced that an equimolar amount of hydroxypropyl β-cyclodextrin is sufficient to complex all the drug using the solid dispersion method. Unexpectedly the same results are not obtained by spray drying. In this case, diffractograms not only confirm the partial complexation already pointed out by the DSC for 1:1 molar ratio powders but, in disagreement with DSC data, they show an incomplete complexation also for 1:2 drug–cyclodextrin molar ratio. Only with 1:4 molar ratio there is a total complexation.

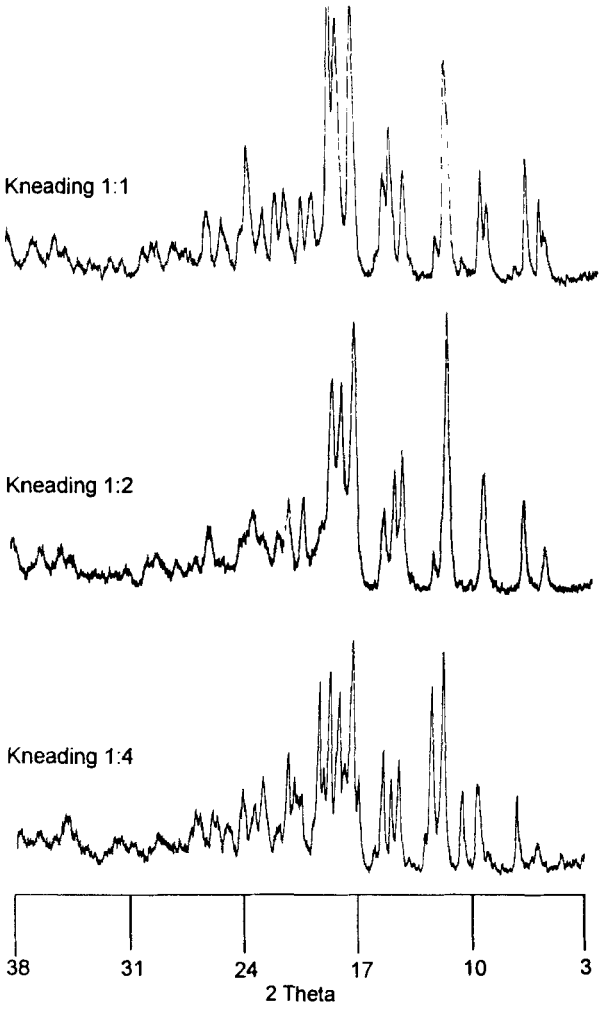


Figure 7. X-ray diffractograms of methoxybutropate–β-cyclodextrin kneaded powders.

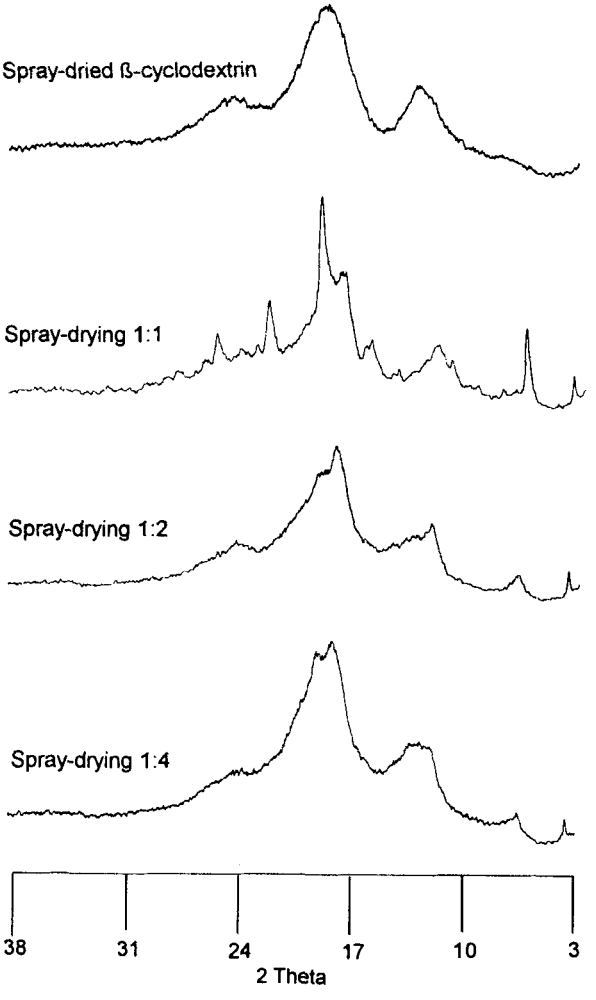


Figure 8. X-ray diffractograms of methoxybutropate–β-cyclodextrin spray-dried powders.

Dissolution Studies

The reported values are obtained by calculating the arithmetical mean of three measurements, and standard deviation bars are omitted to avoid overlapping.

Figure 13 shows the dissolution profiles of powders prepared with methoxybutropate and β-cyclodextrin by solid dispersion, kneading, and spray drying, of pure drug and of the physical mixture 1:4. While the physical mixture is practically insoluble, like the pure drug, all other processed powders improve drug solubility. The extent of this improvement varies according to the applied complexation method and the host–guest molar ratio, in perfect agreement with DSC and x-ray data.

The most effective complexation method is surely spray drying. In fact, with the 1:2 and 1:4 drug–cyclodextrin molar ratios, all methoxybutropate present in the initial powder is dissolved, giving a concentration of nearly 1.3×10^{-4} M. Spray-dried powder with 1:1 molar ratio gives a little lower drug concentration, and this is probably due to the partial complexation which has been found out in this powder. Anyway, all spray-dried powders possess the capability to give a "plateau"

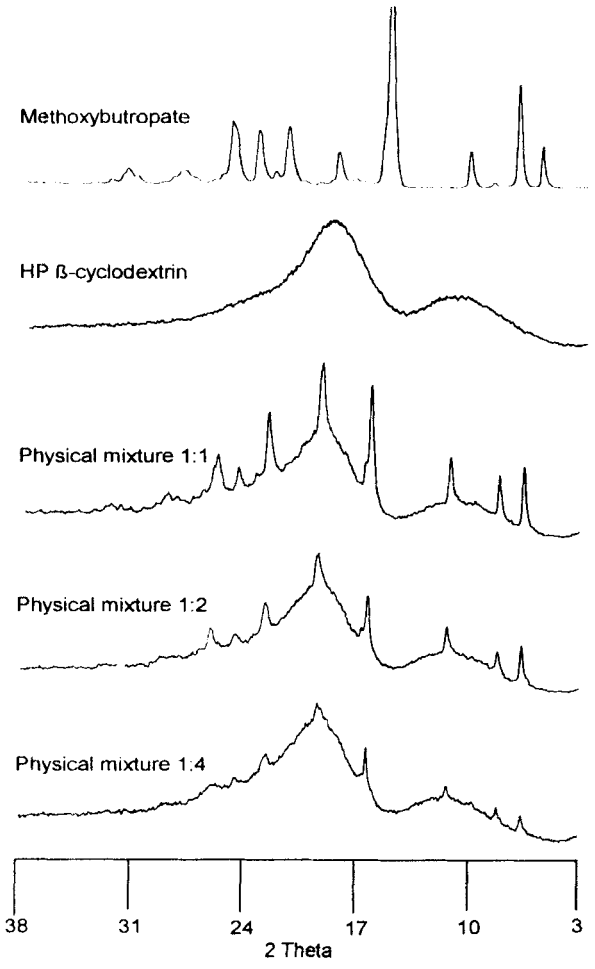


Figure 9. X-ray diffractograms of methoxybutropate, hydroxypropyl β-cyclodextrin, and their physical mixtures.

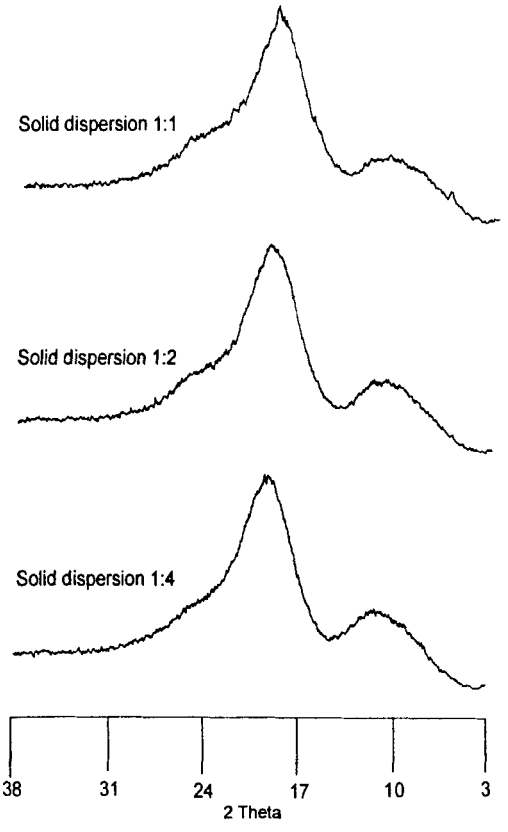


Figure 10. X-ray diffractograms of methoxybutropate–hydroxypropyl β-cyclodextrin solid dispersed powders.

after having reached the maximum of solubility, while powders differently processed are not able to conserve this highest reached value. In fact, their dissolution curves present a descending portion before forming a common "plateau."

Among these last mentioned powders, the solid dispersed ones give better results, particularly when the drug–cyclodextrin molar ratio is 1:2 or 1:4. Finally, the less efficient complexation method is the kneading one because it gives an improvement of drug solubility lower than the other two tested methods, especially for 1:1 molar ratio.

Figure 14 shows the dissolution profiles of powders prepared with methoxybutropate and hydroxypropyl β-cyclodextrin by solid dispersion, kneading, and spray drying, of pure drug and of the physical mixture 1:4. In this case, the most effective technique is solid dispersion rather than spray drying. As expected, solid dispersed powder with drug–cyclodextrin molar ratio 1:4 gives the highest drug solubility improvement, while powder with 1:1 molar ratio shows a lower, but always remarkable, capability to increase this solubility. Powder with 1:2 molar ratio is in an intermediate position. Anyway, dissolution curves of all the three preparations present a descending portion before becoming stable. This is the same phenomenon observed for β-cyclodextrin solid dispersed powders and is probably due to a partial dissociation of the complex with formation of an equilibrium in water solution.

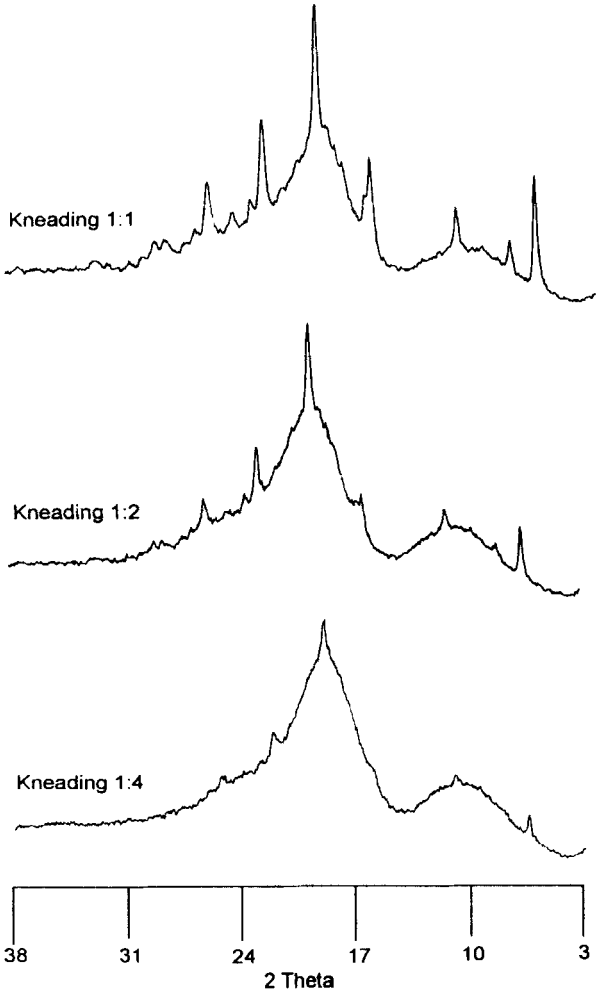


Figure 11. X-ray diffractograms of methoxybutropate-hydroxypropyl β-cyclodextrin kneaded powders.

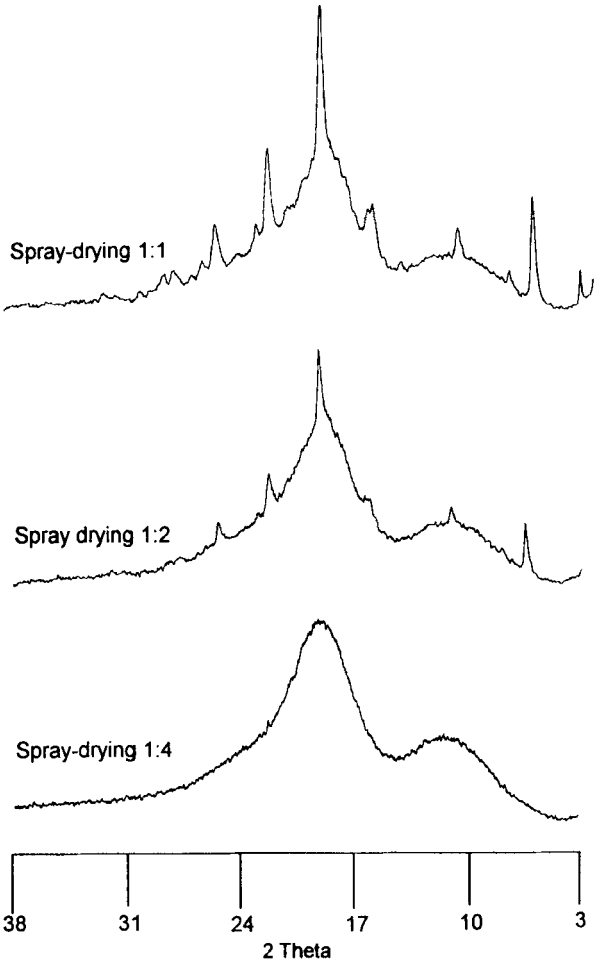


Figure 12. X-ray diffractograms of methoxybutropate-hydroxypropyl β-cyclodextrin spray-dried powders.

Among spray-dried powders, the only one which considerably improves drug solubility is that with 1:4 drug–cyclodextrin molar ratio, in agreement with x-ray diffractometry data. The dissolution profile of this powder is practically identical to that of 1:1 solid dispersion. The other two spray-dried powders, containing a certain amount of uncomplexed methoxybutropate, show lower dissolution curves.

Finally, also in this case, the less effective complexation method is kneading.

CONCLUSION

Both cyclodextrins tested can be used to prepare methoxybutropate inclusion complexes even if differ-

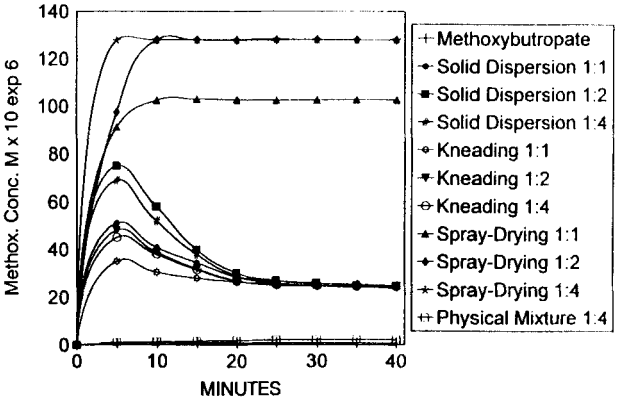


Figure 13. Dissolution profiles of methoxybutropate–β-cyclodextrin powders.

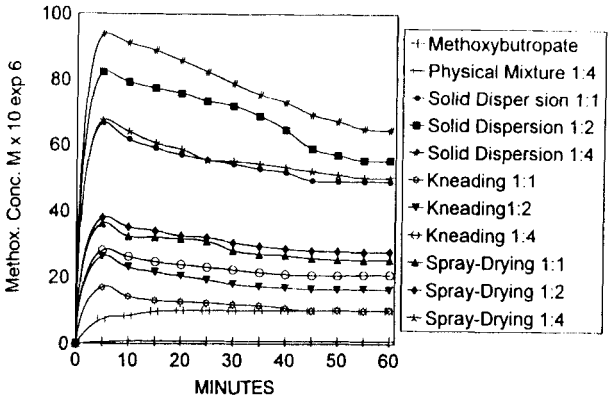


Figure 14. Dissolution profiles of methoxybutropate–β-cyclodextrin powders.

ences in the complexation effectiveness and in increasing water drug solubility are remarkable, depending on the drug–cyclodextrin molar ratio in the processed powder, on the applied complexation method, and the type of cyclodextrin used. In fact, with increased quantity of cyclodextrin in the powder, an increase in the percentage of complexation and in water drug solubility is obtained. Generally, β-cyclodextrin gives better results than hydroxypropyl β-cyclodextrin in the complexation of this specific drug. Spray drying is by far the best method, particularly if combined with the use of β-cyclodextrin. On the other hand, solid dispersion is more indicated for the preparation of methoxybutropate–hydroxypropyl β-cyclodextrin complexes.

On the basis of these results and considering the dosage needed to obtain the required pharmacological response, the preparation of this inclusion complex on an industrial scale should be carried out by spray drying a solution of drug and β-cyclodextrin with 1:2 molar ratio. In fact with this method an excess of β-cyclodextrin does not give any improvement to the already effective formulation.

In any case, production of tablets as a final pharmaceutical dosage form cannot be taken into account because of the high mass of powder necessary for a single dose. More realistic is an approach to the realization of a powder single-unit dosage from such as strip packaging.

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REFERENCES

1. J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988.
2. S. Y. Lin and Y. H. Kao, Int. J. Pharm., 56, 249–259 (1989).
3. F. Kedzierewicz, M. Hoffmann, and P. Maincent, Int. J. Pharm., 58, 221–227 (1990).
4. G. Puglisi, N. A. Santagati, R. Pignatello, C. Ventura, F. A. Bottino, S. Mangiafico, and G. Mazzone, Drug Dev. Ind. Pharm., 16, 395–413 (1990).
5. M. A. Hassan, M. S. Suleiman, and N. M. Najib, Int. J. Pharm., 58, 19–24 (1990).
6. S. Z. Lin, D. Wouessidjewe, M. C. Poelman, and D. Duchêne, Int. J. Pharm., 69, 211–219 (1991).
7. C. Torricelli, A. Martini, L. Muggetti, and R. De Ponti, Int. J. Pharm., 71, 19–24 (1991).
8. X. Tan and S. Lindenbaum, Int. J. Pharm., 74, 127–135 (1991).
9. M. G. Fucile, G. Mazzitelli D. Ratti, and F. Pozzi, Eur. J. Pharm. Biopharm., 38, 140–144 (1992).
10. S. Anguiano-Igea, F. J. Otero-Espinar, J. L. Vila-Jato, and J. Blanco-Méndez, STP Pharma Sci., 2, 325–331 (1992).
11. G. F. Palmieri, P. Wehrlé, G. Duportail, and A. Stamm, Drug Dev. Ind. Pharm., 18, 2117–2121 (1992).
12. G. F. Palmieri, P. Wehrlé, and A. Stamm, Drug Dev. Ind. Pharm., 19, 875–885 (1993).
13. J. Pitha, J. Milecki, H. Fales, L. Pannel, and K. Uekama, Int. J. Pharm., 29, 73–82 (1986).
14. T. Loftsson, S. Björnsdóttir, G. Pálsdóttir, and N. Bodor, Int. J. Pharm., 57, 63–72 (1989).
15. R. T. Darrington, T. X. Xiang, and B. D. Anderson, Int. J. Pharm., 59, 35–44 (1990).
16. T. X. Xiang and B. D. Anderson, Int. J. Pharm., 59, 45–55 (1990).
17. K. Dietzel, K. S. Ester, M. E. Brewster, N. S. Bodor, and H. Derendorf, Int. J. Pharm., 59, 225–230 (1990).
18. K. S. Estes, M. E. Brewster, A. I. Webb, and N. Bodor, Int. J. Pharm., 65, 101–107 (1990).
19. T. Loftsson and B. Ólafsdóttir, Int. J. Pharm., 66, 289–292 (1990).
20. A. Yoshida, M. Yamamoto, T. Itoh, T. Irie, F. Hirayama, and K. Uekama, Chem. Pharm. Bull., 38, 176–179 (1990).
21. M. Krenn, M. P. Gamcsik, G. B. Vogelsang, O. M. Colvin, and K. W. Leong, J. Pharm. Sci., 81, 685–689 (1992).
22. C. J. Betlach, M. A. Gonzalez, B. C. McKiernan, C. Neff-Davis, and N. Bodor, J. Pharm. Sci., 82, 1058–1060 (1993).
23. T. Järvinen, K. Järvinen, N. Schwarting, and V. J. Stella, J. Pharm. Sci., 84, 295–299 (1995).
24. T. Higuchi and K. A. Connors, Adv. Chem. Instr., 4, 117 (1965).