ELSEVIER

International Journal of Pharmaceutics 143 (1996) 113–118

international journal of pharmaceutics

Preliminary study of different omeprazole-γ-CD co-grinded systems

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Received 12 May 1996; revised 10 July 1996; accepted 29 July 1996

Abstract

In this work, we illustrate the usefulness of co-grinding as a resourceful procedure for preparing OME-γ-CD inclusion complexes with faster and higher dissolution characteristics than the drug alone. Different modified variants of the co-grinding processing method have been checked, and DRX, SEM and dissolution rate studies have been employed to characterize the final products. The main conclusion arising from the former studies has been the obtention of a new solid phase, the OME-γ-CD inclusion compound, after buffer-wetted co-grinding of both components during 4 h. Such complex presented a 170-folded DE_{15} respecting the pure OME.

Keywords: Omeprazole; γ-cyclodextrin; Co-grinding; XRD; SEM; Dissolution rate

1. Introduction

Omeprazole (OME), is a gastric proton-pump (H^+/K^+-ATP_{asa}) inhibitor widely used as antiulcerative for regulation of gastric acid secretion in the prophylaxis of stomach or intestinal diseases. This acid-labile benzimidazole is presented as a scarcely water-soluble powder, with slow and erratic dissolution rate and hence, wide interindividual variations in its absorption from the gut. These characteristics makes OME a good candidate for formulation with cyclodextrins (CDs).

As is well known, CDs are cyclic oligosaccharides which can incorporate small organic (and several inorganic) compounds into their hydrophobic cavity. This remarkable complexing ability and its effect on the solubility, bioavailability and stability of drugs have promoted many investigations into their usefulness in pharmaceutical formulation (Duchêne and Wouessidjewe, 1990; Moyano et al., 1995; Pitha and Pitha, 1985; Szejtli, 1994).

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PII S0378-5173(96)04684-4

Many methods of preparing CD inclusion complexes have been tried. Among them, the co-grinding of CDs and drugs has been the starting point for increasing the dissolution rate and bioavailability of many drugs (Ahmed et al., 1990; Çelebi and Erden, 1992; El-Gendy et al., 1986; Ginés et al., 1995; Lin et al., 1988). In this way, the present work reports on the effect of different co-grinding conditions of OME with γ-CD on the dissolution behaviour of the new solid phases formed.

2. Experimental

Micronized OME was a gift from Tedec-Meiji Farma S.A. (E-Madrid) and commercial γ-CD was provided by Cyclolab (H-Budapest). All other reagents were of analytical reagent grade.

Co-grinding has been carried out in a semi-industrial mill (*Fritsch pulverisette, type 02102*) at 1:1 OME-γ-CD ratio during 4 h. The grinding was been carried out under different conditions: dry grinding, to yield the dry grinded mixture (DGM), and wetted grinding with absolute EtOH (EWGM), 1:1 EtOH:phosphate buffer (EBWGM) and phosphate buffer (BWGM). Phosphate buffer was used to wet the systems during the grinding instead of water due to the instability of OME at low pH. Final products were pulverised and sieved between 50 and 200 μm mesh. Physical mixture (PM) and dry grinded OME, were used as references.

X-ray diagrams were obtained in a Siemens Kristalloflex D-500 diffractometer with Ni-filtered Cu Kα radiation at a goniometer speed of 1Θ (2°/min) and a chart speed of 1 cm/min.

Philips XL30 SEM equipment was used to study the morphology of the OME-γ-CD co-grinded systems. Previously, the samples were coated with Au in order to make them conductors.

The dissolution performance of OME from the PM and the co-grinded mixtures was investigated adopting the USP XXII rotating basket apparatus (Turu Grau D-6) with 1000 mL dissolution medium (buffered at pH 9), regulated at 50 rpm and 37°C. Amounts of product equivalent to 25 mg drug were packed into hard gelatin capsules. The capsules were placed in the dissolution basket and, at settled times, samples of 3 mL were withdrawn and measured spectrophotometrically (Hitachi U-2000) at 303.5 nm.

The shapes of the dissolution curves have been examined using the following parameters: the times employed in dissolving the 20, 50 and 80% of the drug (t_{20}, t_{50} and t_{80}), the dissolution percentage over the first 15, 30 and 60 min (DP_{15}, DP_{30} and DP_{60}) and the dissolution efficiency over the first 15, 30 and 60 min (DE_{15}, DE_{30} and DE_{60}).

3. Results and discussion

The X-ray-diffraction patterns of the binary systems are shown in Fig. 1. Since the diffraction peaks of OME (Fig. 1a) and γ-CD (Fig. 1c) are quite coincident, we have selected the peak situated at 26° (2Θ) as the OME characteristic one. It is clearly observed that whereas the diffraction pattern of the PM (Fig. 1b) consists on the simple superposition of the patterns of each component, in the case of the DGM (Fig. 1e), the diffraction peaks of OME and γ-CD exhibit a dramatic reduction, showing an halo diffraction pattern. This fact may be explained on the basis of the CD amorphization reached by the co-grinding treatment, that masks the decreased crystallinity of the drug (Fig. 1d). This behaviour has been already described in the literature by Lin and Lee (1989). For the EWGM (Fig. 1f), only a slight amorphization of the CD is presented, appearing as the main peaks of the dry grinded OME in the pattern. On the other hand, both the EBWGM and the BWGM displayed the appearance of a new crystalline solid phase, more complete in the second case (Fig. 1g and 1h, respectively). These results may suggest the formation of a true inclusion compound in these two systems, partial in the EBWGM and total in the BWGM. The formation of the complex seems to be favoured by the wetting-process of drug and CD with water during the co-grinding, because the water that is indispersable for complex formation. In contrast, the dry or the ethanolic treatment of the samples

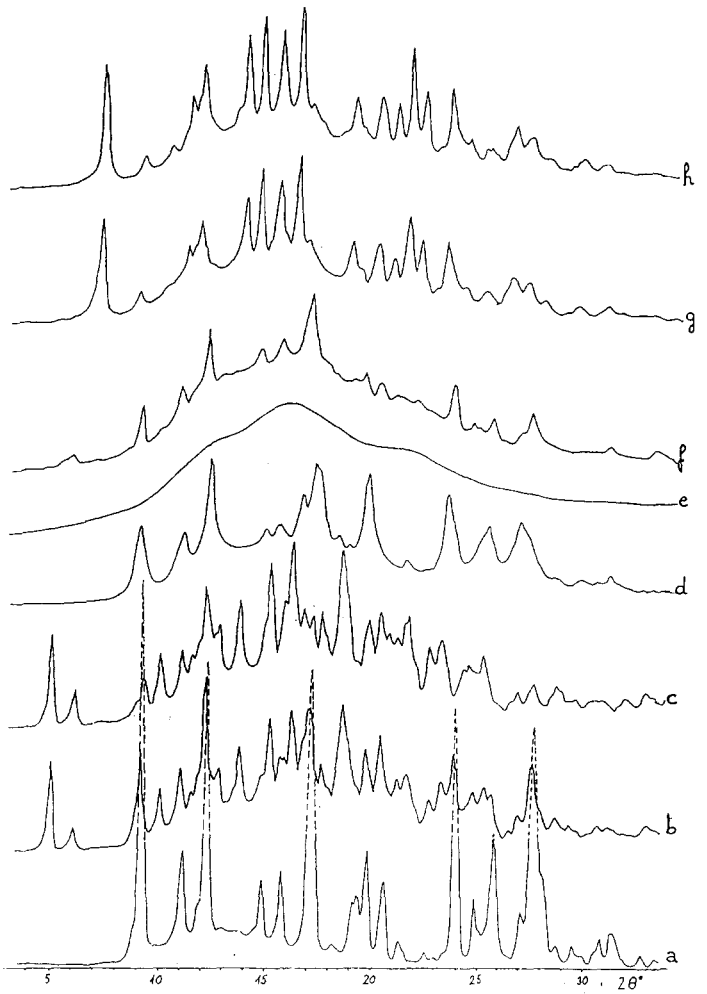

Fig. 1. XRD patterns corresponding to OME-γ-CD binary systems treated by different co-grinding variants: (a) OME, (b) PM, (c) γ-CD, (d) Dry Grinded OME, (e) DGM, (f) EWGM, (g) EBWGM and (h) BWGM.

during grinding lead to a simple reduction crystallinity of the final products.

Under the SEM, micronized OME (Fig. 2a) appears as polyhedral crystals presenting a large amount of small microcrystals—produced during the micronization process—adhered to the surface of the larger crystals. γ-CD is presented as well-formed crystals with a lamellar structure containing small fragments of crystals deposited on the smooth surface of the larger ones. The DGM and EWGM occurred in the form of amorphous particles of irregular shapes. On the contrary, EBWGM appeared as crystalline particles of uneven surface, where OME microparticles are already adhered. Fig. 2b shows the BWGM, presenting irregular-size crystals with rough and porous surface and characterized by only one type of granules. Although SEM technique is inadequate to conclude in genuine complex formation, the obtained micrographs support the idea of the consecution of a new single component (surely the inclusion compound) in this co-grinding variant.

Table 1 summarizes all the in vitro dissolution parameters corresponding to the systems under study. The only one which has significantly improved the OME dissolution rate is the BWGM.

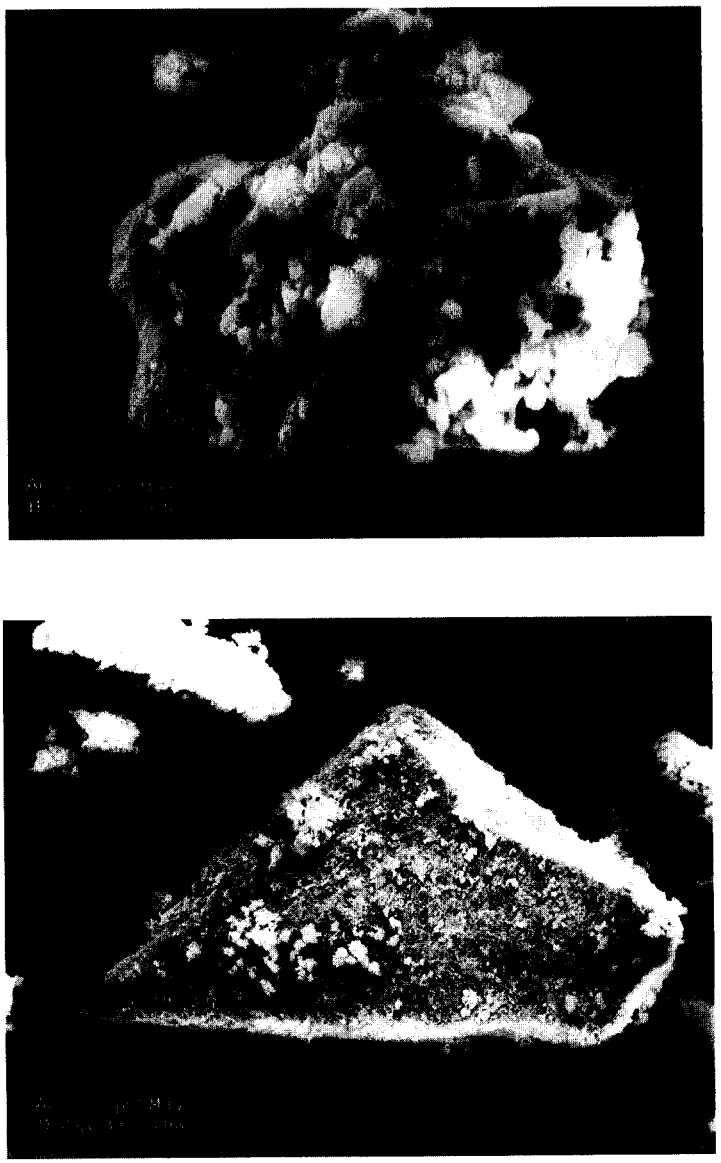

Fig. 2. SEM micrographs corresponding to: (a) Micronized drug (b) OME-γ-CD BWGM.

After 15 min, the DE of the complex was 170-folded respecting the one corresponding to micronized OME. The dramatic difference in the dissolution rates of the complex and the free OME highlights the solubility improvement brought about by complexation of the drug into the γ-CD. Additionally, since OME is surrounded by γ-CD, the possibility of aggregation and agglomeration taking place is virtually non-existent, whilst the dispersion and wettability of OME increase. In this way, the superior dissolution rate of BWGM respecting the EBWGM may be explained on the basis of a minor ratio of complex formation for this last system.

On the other hand, the great reduction of crystallinity from the DGM and EWGM slightly con-

Table 1
In vitro dissolution parameters for the indicated systems

	t_{20}	t_{50}	t_{80}	DP_{15}	DP_{30}	DP_{60}	DE_{15}	DE_{30}	DE_{60}
OME	48.7	—	—	1.06	6.35	25.44	0.40	1.49	8.76
Dry grinded OME	25.0	—	—	13.49	22.64	34.69	6.48	12.42	20.91
PM	16.6	25.1	50.0	12.72	54.44	81.86	2.47	22.88	49.68
DGM	12.5	48.8	—	22.11	37.00	62.44	10.89	20.36	34.50
EWGM	31.2	58.6	—	3.47	18.98	52.61	1.28	6.20	21.02
EBWGM	18..9	40.0	56.7	15.51	32.47	84.90	5.64	15.04	37.15
BWGM	3.6	4.9	6.8	99.49	100.00	100.00	69.97	84.94	92.47

OME, micronized drug; PM, physical mixture; DGM, dry co-grinded mixture; EWGM, EtOH-wetted co-grinded mixture; EBWGM, EtOH-buffer-wetted co-grinded mixture; BWGM, buffer-wetted co-grinded mixture; —, >60.

tributes to the improvement of the drug dissolution rate. The low dissolution rate from these systems may be attributed to the sum of various factors. First, the complexation in solution from these intimate mixtures of drug and CD is limited because of the low stability constant between OME and γ-CD. Moreover, the partial amorphization of the drug reached in these systems scarcely helps the drug release, as corroborated by the dissolution profile shown by the dry grinded OME. Finally, a third factor must be taken into account: the CDs present surfactant-like properties which can reduce the interfacial tension between water-insoluble drugs and the dissolution medium, thus leading to a higher dissolution rate. This ability may explain the increase in the dissolution rate of OME from the PM, where in a moment all the CD is dissolved and its solubilizing ability helps to go dissolving the relatively large drug particles. However, this same ability may be attenuated by the consecution of particles where similarly the CD encircles the drug and the drug encircles the CD, but where we have not a complex, i.e. in the case of DGM and EWGM. In these cases a rapid local solubilization of the CD is produced, thus improving the wettability and hence dissolution of the OME particles. However, only when these drug particles are totally dissolved the water can accede to the deeper layers of CD, which again rapidly dissolves to help the dissolution of the most interior particles of the drug. From these results, it is shown the utility of the co-grinding method, under suite conditions, in order to obtain a true inclusion compound with increased solubility and dissolution rate. The impact of this appreciable improvement on the in vivo availability of OME from solid dosage forms is currently under investigation.

4. Conclusions

Our studies demonstrated that carrying out the co-grinding of OME with γ-CD under suite conditions may lead to the consecution of a crystalline inclusion compound. This system will present considerably improved dissolution characteristics with respect to the drug alone, surely due to the increase in the solubility and wettability of OME in the complexed form. This enhancement in solubility brought about by complexation may be of potential use in developing suitable oral dosage forms of OME, more sure, safe and stable, and containing less doses of the drug to reach the same pharmacologic effect.

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