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Original Article

Enhancing Dissolution Rate of Carbamazepine via Cogrinding with Crospovidone and Hydroxypropylmethylcellulose

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Abstract

Carbamazepine belongs to the class II biopharmaceutical classification system (BCS) which is characterized by a high per-oral dose, a low aqueous solubility and a high membrane permeability. The bioavailability of such a drug is limited by the dissolution rate. In order to increase the drug dissolution, its solid dispersions were prepared by the cogrinding technique using an insoluble but highly hydrophilic crospovidone and soluble hydroxypropylmethylcellulose (HPMC) as the carriers. The ratios of drug to carrier were 1:1, 1:5 and 1:10. Comparison of the dissolution of the drug from its cogrounds with that of the unground drug, its ground form and the corresponding physical mixtures revealed considerable differences. The percentage of drug dissolved during the first 30 min, ($\%D_{30}$), for the ground and coground drug was 75-95, whereas the $\%D_{30}$ for unground drug and its physical mixtures ranged from 41-62. FT-IR spectra indicated no intraction between the drug and the carriers in the cogrounds. But reduced crystallinity of the drug in the ground and cogrounds was evident in the x-ray diffraction patterns. The decreased crystallinity together with a reduced particle size, enhanced deaggregation and increased wettability of the drug. This could be accounted for the increased dissolution from the cogrounds. From the dissolution point of view, the physical mixtures of HPMC were inferior to the cogrounds, but were slightly superior to the physical mixtures of crospovidone due to the solubilization effect of HPMC.

Keywords: Carbamazepine; HPMC; Crospovidone; Cogrinding; Solid dispersion; Dissolution rate.

Introduction

Carbamazepine, an effective anti-epileptic drug, belongs to the class II biopharmaceutical classification system (BCS), the characteristics of which are low aqueous solubility, slow dissolution rate and high membrane permeability (1, 2). Thus, the main problem associated with class II drugs is generally their low bioavailability, due

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to a slow dissolution rate. Several attempts have been made to increase the dissolution rate or bioavailability of carbamazepine (3-8). Different methods have been exploited to enhance the dissolution of poorly water soluble drugs among which solid dispersion (SD) techniques, because of their simplicity and effectiveness have received considerable attentions and have been discussed in a recent review article (9). Cogrinding is one of the solid dispersion techniques which is superior to other approaches from economical as well as environmental stand points in that unlike similar methods it does not require any toxic organic solvents (10). Such a technique has already been employed for phenytoin (11), frusemide (12), glibenclamide (13) and nifedipine (10). However, the method of cogrinding for the preparation of carbamazepine solid dispersion has not been reported in the literature. The present investigation focused on the formulation of carbamazepine cogrounds using crospovidone and hydroxypropylmethylcellulose (HPMC) as carriers at different drug: carrier ratios, in an attempt to alter the drug dissolution rate. These carriers have already been used to improve the dissolution rate of other drugs (12, 14). Drug solubility measurement, FT-IR spectroscopy and x-ray diffraction were performed in order to elucidate the mechanisms involved in dissolution rate changes of the drug from solid dispersions.

Experimental

Materials

For the preparation of solid dispersions, the following materials were used:

Carbamazepine powder was from Sigma-Aldrich Chemie Gmbh (Steinheim، Germany), crospovidone (Kollidon CL-M, viscosity of a 2% w/v sample being 40 mPa s) was supplied by BASF Company (Ulm, Germany) hydroxypropylmethylcellulose (HPMC K100LV, viscosity of a 2% w/v sample being 100 mPa s) was from Colorcon (Kent, England). All the other materials used were analytical or HPLC grade.

Methods

Preparation of solid dispersions and physical mixtures

Solid dispersions (cogrounds) with 1:1, 1:5 and 1:10 ratios of carbamazepine to the carriers (either crospovidone or HPMC) were prepared using the cogrinding method. It should be mentioned that for a relatively high dose drug such as carbamazepine, the use of higher amounts of polymer is not unusual. Indeed, in previous reports 12 and 15 parts of polymer per unit part of carbamazepine were used in the formulation of the drug solid dispersions (4, 5). The cogrinding was carried out by means of a ball mill (Fritsch Gmbh, Germany) containing balls of different diameters ranging from 8 to 20mm that occupied nearly 1/3 of the mill chamber. The rate of vibration was 360 rpm for 3 h. A sample of about 10 g ground drug powder was prepared using a similar milling process used for the coground systems. The tumbling bottle method was employed to prepare the corresponding physical mixtures (PMs). The tumbling time was 15 min and the bottle volume was 100 ml. All the preparations were stored in screw-cap vials at room temperature until use.

Drug content

Three samples from each preparations, equivalent to 5 mg drug, were chosen randomly and their carbamazepine contents determined spectrophotometrically (Shimadzu UV-160 spectrophotometer, Kyoto, Japan) at a wavelength of 286 nm after dissolving in water, and appropriate dilution with water using the Beer's plot. The drug contents were between 97.03 and 102.50% of the theoretical value. Preliminary studies showed no interference of the carriers with the drug at the utilized wavelength.

Dissolution studies

Samples the of preparations equivalent to 10 mg of carbamazepine which assured the presence of sink conditions were added to 900 ml of distilled water as the dissolution medium, within a USP 28 apparatus II. The temperature of the test medium was 37±0.2 °C and the paddle speed was adjusted to 100 rpm. Five ml aliquots were withdrawn at predetermined time intervals of 5, 10, 15, 20, 30, 45, 60 and 90 min and the same volume of 37 °C distilled water was added to the medium to compensate for each sample taken. Samples were filtered through a filter

paper and the dissolved drug was assayed by a spectrophotometer at 286 nm. Three replicates of each dissolution test were carried out.

Solubility measurements

The solubility of carbamazepine was measured in the presence of 0, 0.1, 0.25, 0.5, 1 and 1.5% w/v HPMC in distilled water. An excess amount of drug was then added to approximately 20 ml of either distilled water or the HPMC solutions in glass tubes. The tubes were sonicated in the ultra-sound apparatus (Starsonic35, Bologna, Italy) for 20 min and then shaken in a water bath (Memmert, Germany) set at 25 °C for 3 days. Preliminary experiments showed that this period was sufficient to assure saturation. After reaching the equilibrium status, the saturated solutions were filtered through a 0.45 µm membrane filter, diluted with water and then assayed spectrophotometrically. Crospovidone, due to its insolubility in water, was not included in the solubility studies.

Powder x-ray diffraction

The powder x-ray diffraction, (PXRD), pattern of all ingredients, cogrounds and physical mixtures were recorded using an automated x-ray diffractometer (Siemens D5000, Germany). Cross-section of the samples were taken and held in place on a quartz plate for exposure to Cu K α radiation of wavelength 1.5406 Å. The samples were then analyzed at room temperature over a 2θ range of 0-60, with sampling intervals of 0.02° 2θ and a scanning rate of 6 °/min (15, 16).

Fourier Transform Infrared Spectroscopy (FT – IR)

Fourier Transform Infrared, (FT-IR), spectroscopy (Bomem, Quebec, Canada) was performed using the KBr disk method. Samples were mixed with KBr powder and compressed into 10mm discs, using a hydraulic press at a pressure of 10 tons for 30 seconds. The scanning range was 450-4000 cm^{-1} and the resolution was 2 cm^{-1} (15, 16).

Statistical methods

Statistical analyses of the dissolution parameters were performed by means of the One-Way ANOVA and Scheffe multiple range test, using the SPSS version 11.5, in order to detect possible differences between the mean values of the dissolution parameters. The accepted probability level for significancy between any two mean values of dissolution parameters was less than 0.05 ($P<0.05$).

Results and Discussion

The X-ray pattern of the unground carbamazepine powder used in this study is shown in Figure 3 and found to be identical to that reported for β (III) polymorph, with characteristic diffraction peaks at 2θ° values of 14.9, 15.2, 15.8, 27.2, 27.5, and 32.0°. The corresponding IR spectrum (Figure 4) also matched that of the mentioned polymorph and the characteristic absorption bands were noted at 3464 cm^{-1} (-N-H stretching), 1677 cm^{-1} (-C=O stretching), 1605 and 1593 cm^{-1} (range of -C=C- and –C=O vibration and -NH deformation), 1383 cm^{-1}, 1271 cm^{-1} (-C≡N bond), 1245 cm^{-1} and 1019 cm^{-1}(15, 16).

The percentage of dissolved carbamazepine against time profiles of the unground powder, ground powder, cogrounds with different amounts of HPMC and crospovidone as well as the corresponding physical mixtures (altogether fourteen preparations) are shown in Figure 1. The dissolution curves of the cogrounds rise more quickly than those of the unground powder, ground drug powder and the physical

Table 1. Percentage of carbamazepine dissolved in the first 30 min ($\%D_{30}$), from different preparations and the corresponding percentage coefficient of variation (CV[a]).

	Drug powder		Physical mixture						Solid dispersion					
	Unground	*Ground*	*Drug:HPMC*			*Drug: Crospovidone*			*Drug:HPMC*			*Drug: Crospovidone*		
			1:1	1:5	1:10	1:1	1:5	1:10	1:1	1:5	1:10	1:1	1:5	1:10
$\%D_{30}$	51.8	75.2	56.0	61.8	57.6	41.0	45.0	48.9	93.4	94.3	75.5	95.4	92	90.6
%CV	7.4	8.4	6.2	7.9	4.8	9.2	8.2	4.7	1.0	4.7	2.8	3.8	6.4	2.3

[a] Values of $\%D_{30}$ are mean of three determinations.

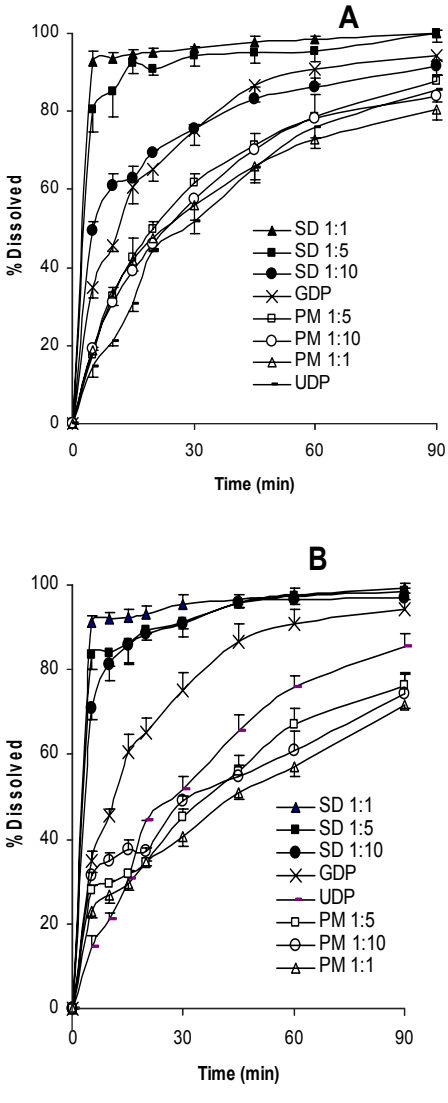

Figure 1. Dissolution profiles of carbamazepine from physical mixtures (PM) and solid dispersions (SD) prepared with (A) HPMC and (B) crospovidone. Each point is the average of 3 determinations and vertical bars represent the standard deviation. GDP and UDP stand for "ground drug powder " and " unground drug powder".

mixtures. As a model independent metric, the mean percentage of drug dissolved in the first 30 min ($\%D_{30}$) was used to represent the dissolution rate from various preparations (Table 1). The reason for choosing $\%D_{30}$ was that with the exception of 1:10 drug coground HPMC ratio, other cogrounds released more than 90% of their drug content during this period. The statistical analyses of $\%D_{30}$ values revealed that while all solid dispersions (possessing higher $\%D_{30}$), with the exception of SD 1:10 containing

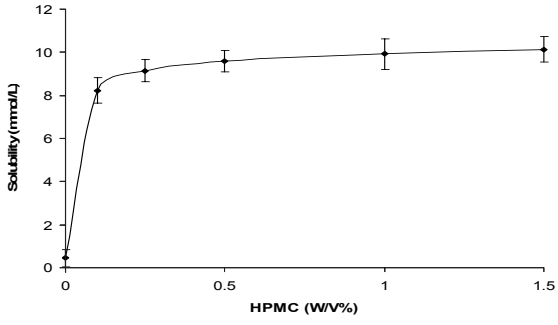

Figure 2. Solubility of carbamazepine vs. HPMC concentration in aqueous solutions at 25 C°. Each point is average of three determinations. Vertical lines represent standard diviations.

HPMC, were not different with each other, but were significantly different from the rest of preparations including SD 1:10 HPMC. There was no significant difference between the mean $\%D_{30}$ values of ground drug powder and SD 1:10 HPMC. However, both the latter samples produced significantly higher dissolution rates than those of the unground powder as well as the physical mixtures. The dissolution rates of the physical mixtures containing crospovidone and the unground drug powder were statistically the same, but were statistically inferior to those of HPMC physical mixtures. Also, it should be mentioned that there was no significant difference among the HPMC physical mixtures. The reason for the slightly higher dissolution rates of HPMC physical mixtures with respect to those of crospovidone physical mixtures and the unground drug powder may be due to the fact that HPMC is soluble in water and hence could increase the aqueous solubility of carbamazepine (Figure 2) In contrary, crospovidone is insoluble in water, and does not influence drug solubility. There are two mechanisms involved in the increased aqueous solubility of carbamazepine in the presence of HPMC firstly, the hydroxyl and ether groups of the polymer can interact via H-bonding with the amide group of the drug in the solution. However, such an interaction in the case of crospovidone cogrounds cannot enhance drug solubility, because of aqueous insolubility of the polymer. Secondly, HPMC is a surface active agent with a critical polymer concentration (CPC, which is similar to CMC or critical micelle concentration of low molecular weight surfactants) of approximately above

0.01 %w/v or higher (17) and the aggregate can solubilize the drug. On the other hand, HPMC is more hydrophilic than crospovidone, therefore, it confers more hydrophilicity upon the hydrophobic carbamazepine particles, enhancing wettability of carbamazepine particles and consequently increases particles dissolution. In addition to the solubilizing effect and high hydrophilicity of HPMC, the other possible mechanisms accounted for a lower mean $\%D_{30}$ of crospovidone physical mixture is aqueous insolubility and lower hydrophilicity of the latter. The cogrounds containing 5 parts of HPMC as well as 5 and 10 parts of crospovidone showed no difference in dissolution rate, as compared with the corresponding cogrounds containing 1 part of the carriers (Table 1). This is probably due to the embedment of drug particles deep inside the carrier mass, which opposes their dissolution enhancement attribute. The reason for the lower dissolution of 1:10 HPMC coground in comparison with other cogrounds is probably due to a high microenvironmental viscosity around the drug particles, brought about by a higher concentration of HPMC (18, 19). Such a phenomenon is not seen in the case of 1:10 crospovidone coground, because of its lower viscosity. In order to explain the differences observed in the dissolution rates, x-ray diffraction and FT-IR spectroscopy measurements were performed on the preparations. The results are shown in Figures 3 and 4. The ground drug and its cogrounds exhibited x-ray diffraction patterns consisting of characteristic peaks, with lessened intensity or complete disappearance of the peaks as compared to the unground drug and its physical mixtures. These phenomena imply the loss of crystallinity of the drug, which in turn increases the free energy with subsequent enhancement of the dissolution. In Figure 3 some representative PXRD patterns are depicted. The IR spectra indicated no intraction between the drug and the carriers in the solid dispersions (Figure 4). Thus, the dominant factors affecting

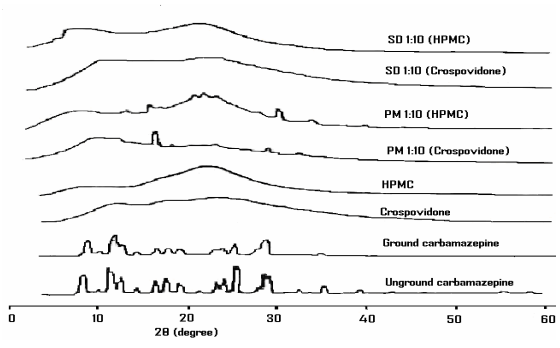

Figure 3. PXRD of unground carbamazepine, ground carbamazepine, physical mixture (PM) and solid dispersion (SD) of carbamazepine with HPMC and crospovidone at a ratio of 1:10. The ordinate (not shown) represents the counts which are between 0 and 2700.

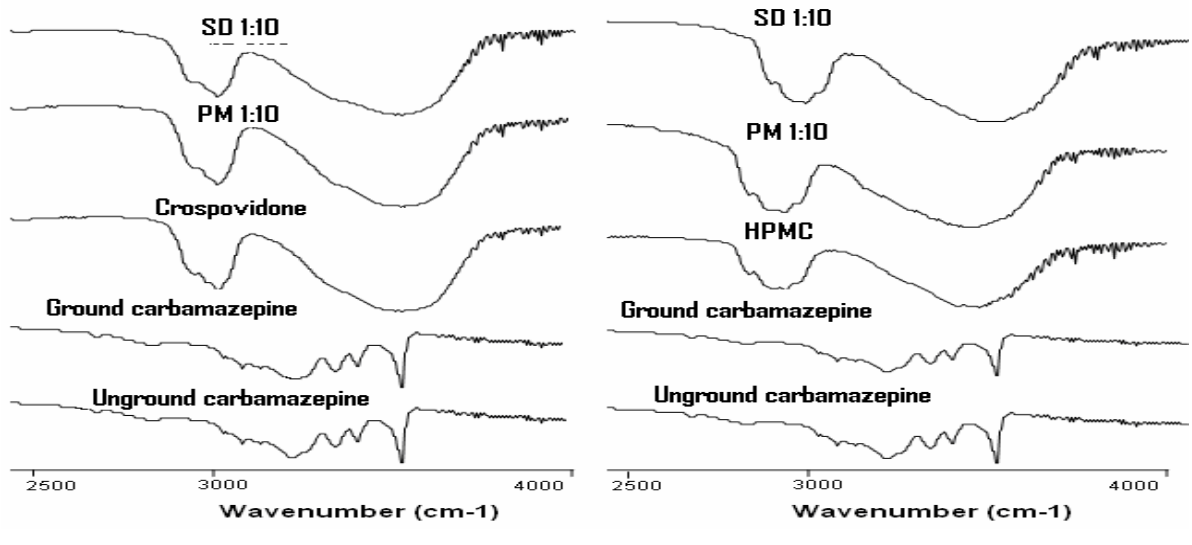

Figure 4. FT-IR spectra of unground carbamazepine, ground carbamazepine, HPMC, crospovidone, physical mixture (PM) and solid dispersion (SD) of carbamazepine with HPMC and crospovidone at a ratio of 1:10.

drug dissolution from the cogrounds are the reduction of drug cristallinity (Figure 3), a probable decrease in drug particle size, an increase in the deaggregation and wettability of hydrophobic drug particles (10,18-21).

Among various methods of preparing solid dispersions the cogrinding technique is superior from the environmental and economical points of view, since unlike other techniques it dose not require sophisticated equipments (5, 7) and toxic solvents (18, 19). The cogrinding technique has been successfully employed to increase the both dissolution rate and bioavailability of glibenclamide (18) and carbamazepine (21). In the latter studies, different grades of microcrystalline cellulose were used as the carrier materials.

Conclusion

The results indicate that the dissolution rate of the water insoluble drug carbamazepine can be enhanced significantly via the simple cogrinding technique, using the hydrophilic carriers HPMC and crospovidone at different drug: carrier ratios. Among the cogrounds (i.e the solid dispersions), the 1:1 ratio of both carriers may be an ideal form for the formulation of rapid release dosage forms (e.g. capsule and tablet of the drug). Considering the high dose of carbamazepine (200mg), limitations in the size of the dosage forms and comparability of the dissolution rate of the 1:1 ratio with higher ratios are the reasons for its suitability. Such a rapid release form can be beneficial in immediate relief of acute neuralgia as a single administration, because due of its quick and complete absorption. In chronic regimen, the complete absorption may enhance the effectiveness of the drug. It is also possible to reduce the usual dose of the drug, which could be economically desirable.

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