New binary solid dispersion of indomethacin and croscarmellose sodium: physical characterization and *in vitro* dissolution enhancement.

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Original Article

ABSTRACT

Solid dispersions (SD_x) containing Indomethacin (IND), a poorly water-soluble drug, and the disintegrant excipient sodium croscarmellose (SC) were prepared by a co-drying method and characterized by Infrared spectroscopy (FT-IR), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). An FT-IR analysis performed on IND-SC solid dispersion and their physical mixtures indicated that IND does not interact with SC in the solid state. An analysis of the information produced by DSC, XRD, and SEM confirmed that the crystalline α-form of IND was homogeneously incorporated into SD_x. IND release from SD_x was significantly greater than that from its corresponding physical mixtures with the high homogeneous molecular dispersion and the crystalline modification of IND appearing to be the cause. This behavior may have a beneficial effect on the biopharmaceutical performance of this drug.

KEY WORDS: Solid dispersions, croscarmellose sodium, indomethacin, dissolution rate, solid state characterization, co-processed material

INTRODUCTION

The bioavailability of poorly water-soluble drugs that undergo dissolution rate-limited gastrointestinal absorption can generally be improved by innovative formulation strategies such as the preparation of solid dispersions (1). The resulting increase in the dissolution rate is especially useful for Class II compounds (Biopharmaceutical Classification System, BCS), which have low gastrointestinal solubility and high permeability (2).

Solids dispersions (SD_x), defined as molecular mixtures of poorly water-soluble drugs and hydrophilic carriers, have been proposed as an alternative for the improvement of the dissolution rate of this class of drugs. These systems can be prepared by fusion, dissolution or a combination of fusion-dissolution (3). Numerous reports about solid dispersions comprising a great variety of carriers, drug/carrier ratios and methods of preparation

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have already been published (4), with explanations for the probable mechanism of dissolution enhancement (5, 6).

According to the BCS, Indomethacin (IND) is a class II compound, a hydrophobic and poorly water soluble antirheumatic agent used in many pharmaceutical preparations (7, 8). Different polymorphic forms of IND exist (9). Several methods for increasing the dissolution rate of IND have been investigated, such as increase of wettability (incorporation of a surfactant) (10, 11), the use of a higher energy crystalline form (appropriate selection of the polymorph) (12, 13) and the increase of the particle surface exposed to the medium (14). An, as yet unexplored strategy, is the incorporation of the drug in an SD_x based on a material that facilitates water intake, granule disruption and the spread of fine particles into the dissolution medium. Among these types of materials, disintegrating excipients are usually included in the tablet composition in order to produce a quick rupture of the compact, thus facilitating exposure of a greater surface area available for drug dissolution.

One of the most commonly used disintegrating excipients is sodium croscarmellose (SC), which is a crosslinked polymer of sodium carboxymethylcellulose used in oral pharmaceutical formulations as a disintegrant in capsules, tablets and granules, in concentrations from about 0.5% to 25% (15).

The objective of this study was to develop a process aimed at preparing binary solid dispersions using croscarmellose sodium as the carrier. This study also includes the physicochemical characterization of SD_x and an *in vitro* evaluation of the influence of this material on the IND dissolution rate.

MATERIALS AND METHODS

Materials

The following substances were used for the solid dispersion preparations: γ or I form of IND (Pharmaceutical grade, Parafarm, Buenos Aires, Argentina) and SC (AcDiSol®, FMC Biopolymer, Montevideo, Uruguay). Other chemicals used in this study were of analytical grade. All the materials were used as received.

Methods

Preparation of solid dispersions by the solvent evaporation method

Solid dispersions with different concentrations of IND and SC (SD_x, Table 1) were prepared as follows: different amounts of SC were suspended in 50 ml of ethanol and different amounts of IND were dissolved in 100 ml of ethanol. Then, the suspension and the solution were thoroughly mixed. The solvent was evaporated under reduced pressure using a rotary evaporator at 60°C and the resulting solid materials were stored in closed screw-cap vials at 8°C until used.

Preparation of physical mixtures

Physical mixtures containing different concentrations of the drug and SC (PM_x in Table 1) were prepared by mixing IND with the carrier in a mortar until homogenous mixtures were obtained by visual examination. The powders were stored in screw-cap vials at (8°C) until used.

Table 1 Compositions of the solid dispersions and physical mixtures.

SAMPLES		COMPOSITION (% w/w)	
SOLID DISPERSION (SD_x)	PHYSICAL MIXTURE (PM_x)	IND	SC
SD_1	PM_1	5	95
SD_2	PM_2	10	90
SD_3	PM_3	25	75
SD_4	PM_4	50	50

Solid product characterization

Fourier-transform infrared spectroscopy (FT-IR)

KBr disks containing the solid dispersions or the physical mixtures in a concentration of 1%

were evaluated using a Nicolet 5SXC FT-IR Spectrometer (Thermo Scientific, USA).

Powder X-ray Diffraction (PXRD)

The XRD patterns were recorded using a Rigaku Miniflex 2000 diffractomer (Rigaku, Japan) (Δ: 1.5418 Å using a Bragg-Brentano geometry) and the radiation was generated by a Cu K_α lamp. The instrument was operated in the continuous scan mode with a scanning speed of 2°/min. The scan range was 5-70°, 2θ/θ, with a scan speed of 0.066°, 2θ/s.

Differential scanning calorimetry (DSC)

A differential scanning calorimeter (Modulated-DSC 2920 model, TA-instruments, USA) was used under a nitrogen gas flow of 60 ml/min. at a heating rate of 20°C/min from 25 to 250°C. The samples with weights of ~1 to 2 mg were sealed in open aluminum pans. The temperature was calibrated using pure indium with a melting point of 156.60°C. Results were expressed as maximum temperature (°C) and ΔH (J/g). Melting enthalpy values of the drug in each binary mixture or SD_x, in particular, are reported as functions of the IND proportion in the sample.

Scanning Electron Microscopy (SEM)

The samples were coated with gold in a PELCO 91000 sputter coater (Ted Pella, Canada). Particle morphology was assessed in an EVO 40-XVP, LEO Scanning Electron Microscope (LEO, United Kingdom).

Dissolution experiment

A dissolution test was performed using a SOTAX AT 7 Smart (USP30 dissolution apparatus 2) (Sotax, Switzerland) with the rotational paddle speed kept constant at 100 rpm and water bath equilibrated to 37.0 ± 0.5°C. The amount of the sample material used was equivalent to 75 mg of the drug.

The dissolution medium was 1 volume of pH 7.2 phosphate buffer mixed with 4 volumes of water to a total amount of 750 ml. 5 ml aliquots were withdrawn at predetermined intervals over a period of 2 hours. The same amount of fresh medium was used to keep the volume constant throughout the test. The samples were filtered and IND was assayed at 320 nm using a UV-Vis spectrophotometer (Termo Evolution 300, Thermo Scientific, USA). Three replicates of each dissolution test were assayed. The Similarity Factor f_2 was calculated for comparison with *in vitro* dissolution of solid dispersions of drug alone and in physical mixtures. A model-independent mathematical approach proposed by Moore and Flanner (16) for calculating a Similarity Factor (f_2) was used to compare the dissolution profiles of different samples. The f_2 value was calculated using Equation 1.

$$f_2 = 50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} 100\right\} \quad \text{Eq. 1}$$

Where,

R_t and T_t represent the cumulative percent dissolved for the reference (physical mixture) and the test (solid dispersion) samples at each time point to be compared and "n" is the number of dissolution time points. An f_2 value between 50 and 100 suggests similarity between the two release profiles, whereas an f_2 value below 50 suggests dissimilarity between the release profiles.

RESULTS AND DISCUSSION

Indomethacin can arrange its crystalline structure into four different polymorphic forms, (17,18) although the α and γ-forms are the most reported (9). The α-form is kinetically stable (metastable), whereas the γ-form is thermodynamically stable (stable). At room temperature, both forms grow concomitantly from ethanol solutions in glass containers (19).

The γ-form has a melting temperature (T_m) of 161°C, whereas the α- form has a T_m of 155°C

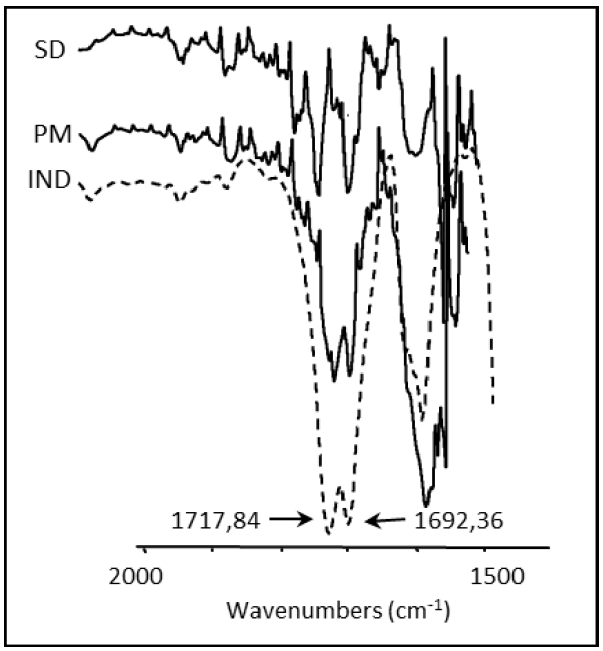

Figure 1 The FT-IR spectra of SD_4, PM_4 and IND.

and a greater rate of dissolution (intrinsic solubility of a given molecule in a given solvent is constant regardless of the thermodynamic state of its crystalline solid form as well as particle size) than the γ-form. In the γ-form, the dominating feature is the crystal packing within the hydrogen bonding of carboxylic acid groups, in order to form molecular dimers. In contrast, in the α-form, the asymmetric unit consists of three molecules with the third hydrogen molecule bonded to the molecular dimer being formed by the remaining two molecules (20).

To detect any possible IND crystalline changes in the SD_x samples due to its processing, the FT-IR, DSC and the X-ray powder diffraction data of SD_1 and SD_4 were compared with PM_1 and PM_4. In the FT-IR, the 1700 cm^{-1} region of the each spectrum was analyzed (21). Figure 1 shows examples of the IND, SD_4 and PM_4 peaks. The signals appearing at 1717 and 1692 cm^{-1} in the IND and PM_4 spectra may be attributed to the asymmetric stretching of carboxylic acid in the dimer structure. This arrangement is characteristic for the γ-form, because of the presence of the anhydride groups formed as a consequence of the interaction of the acidic hydrogen with the amide-carbonyl group of a second molecule of IND (20).

The SD_4 spectrum presented a peak at 1730 cm^{-1}, suggesting that the carbonyl group of COOH was involved in a different type of hydrogen bond in the crystal lattice, which might be attributed to a change in the polymorphic form of IND. Andronis and Zografi (22) found that the maximun nucleation rate for α-indomethacin occurred at 60°C, corresponding to the temperature utilized for the SD_x preparation. It is therefore probable that IND was present as the α-form in the SD_x. No other changes in the FT-IR pattern were identified between SD_x and PM_x indicating that the drug did not interact with the polymer in the SD_x.

The X-Ray diffraction patterns of these substances were also determined as shown in Figure 2. The IND diffractogram revealed the characteristic crystalline pattern of the γ-form, whereas, for SC, a pattern corresponding to an amorphous solid was observed. In the case of physical mixtures, a superimposed diffractrogram reflecting the additive behavior of both components could be observed. Regarding SD_x, the crystalline diffraction

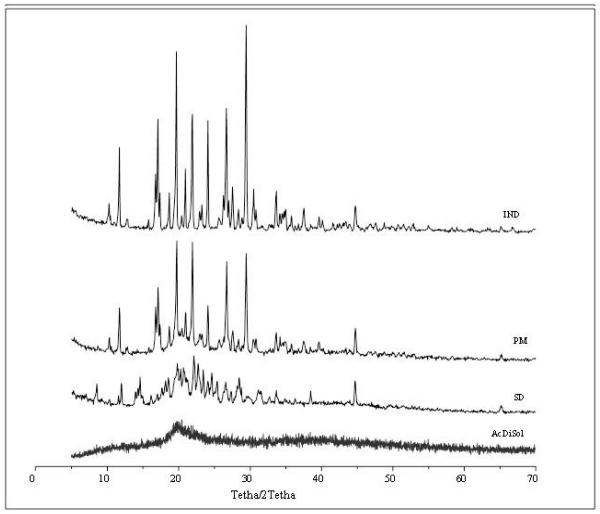

Figure 2 XRD patterns of SD_4, their precursors and the physical mixture.

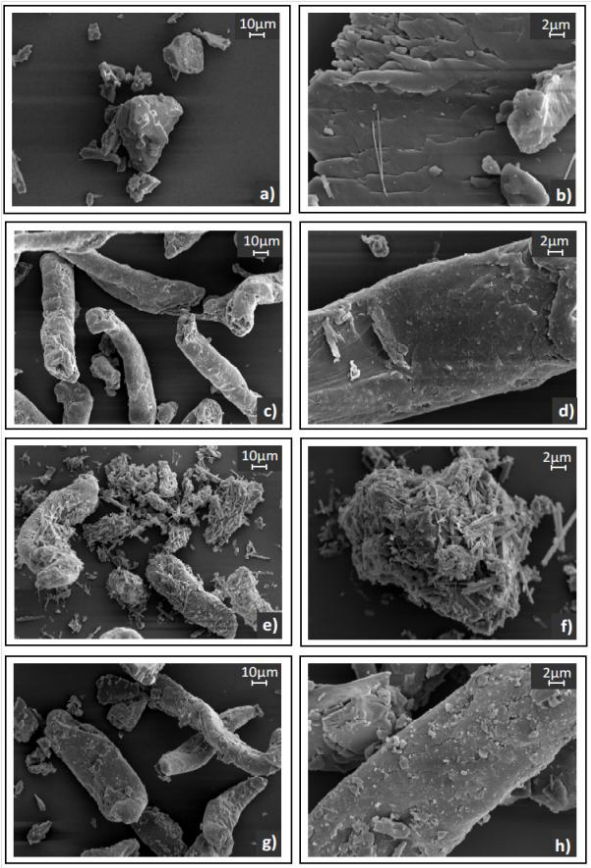

Figure 3 Comparative SEM photographs of IND: (a) 2000x and (b) 6000x, SC: (c) 2000x and (d) 6000x, SD_4: (e) 2000x and (f) 6000x, PM_4: (g) 2000x and (h) 6000x.

pattern corresponding to IND was quite different, with, the signal observed at 8.6°, 2θ corresponding to the α-form of IND and suggesting that the crystalline arrangement of IND changed as a consequence of its inclusion in SD_x (23).

The thermal events associated to probable phase transitions were also studied. The DSC curve of γ-IND exhibited a sharp endothermic peak at 160.5 °C (ΔH 120 J/g), which corresponded to its melting point. The temperature at which this transition occurred also remained unchanged for PM_1 (160.5°C, ΔH 97 J/g) and PM_4 (161.0ΔC, ΔH 128 J/g). The melting enthalpy of γ-IND measured in PM_1 was lower than that of the pure drug. This result could be attributed non-homogeneity associated with the low proportion of the drug in this particular blend. On the other hand, the solid dispersions SD_1 and SD_4 showed endothermic peaks at 155.1°C (ΔH 107 J/g) and 155.2°C (ΔH 109 J/g), respectively, corresponding to the fusion of the α-IND crystals. The measured enthalpy values for SD_x are in conformity with previously published data (24).

Figure 3 shows SEM photographs of SD_4, PM_4 and their precursors. The pure drug image of SEM showed crystalline particles of irregular shape, while the SC pictures revealed the fibrous nature of the excipient. In the physical mixture, the SC existed as individual particles with IND dispersed in its native crystalline form. Comparatively, the morphology of the

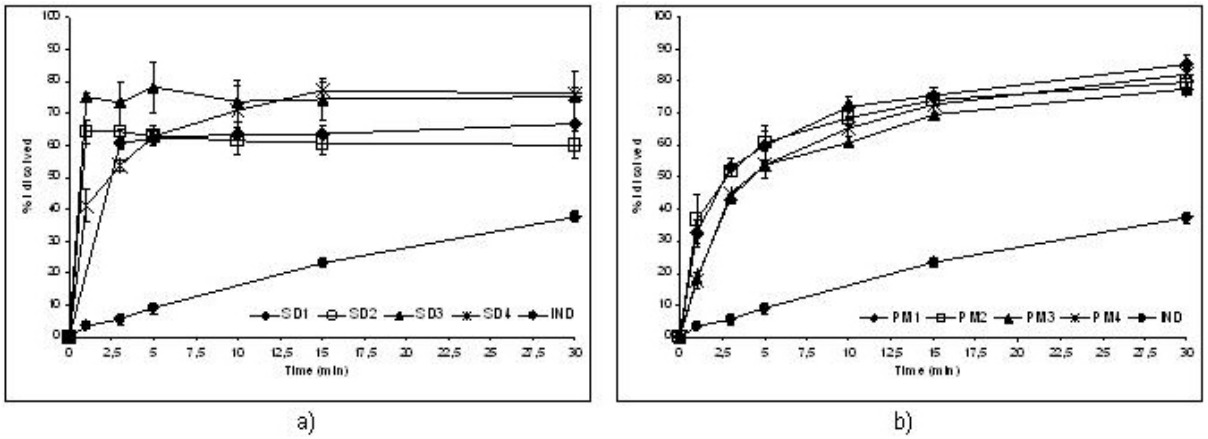

Figure 4 Dissolution profile of IND, solid dispersions and physical mixtures of IND and SC in buffer pH 7.2 solution.

SD_4 was quite different to the corresponding physical mixture, the drug being present in the latter as needles on the surface of the SC particle, thereby losing the original size and shape of the IND (21).

In order to evaluate the drug dissolution kinetics of IND from SD_x, these results were compared with those of the corresponding physical mixture and IND alone. As shown in Figure 4 and Tables 2 and 3, SD_x and PM_x exhibited faster dissolution rates than IND alone in all cases. This may be mainly attributed to the improvement of wetting properties of the drug mixed or co-processed with the hydrophilic carrier, as the high swelling and hydration capacity of SC increases the water uptake of the powder (25).

The incorporation of IND as a solid dispersion seems to be important for a very fast dissolution at an early stage of the process, since a greater burst effect of SD_x was not observed in the case of PM_x. In addition, the change in the crystalline arrangement of IND could also have an additional effect on the

On the other hand, similar dissolution rates (f_2>50) were observed for different SD_x (SD_1, SD_2, SD_3 and SD_4) as well as for different PM_x (PM_1, PM_2, PM_3 and PM_4). Although the tendency for the dissolution rate to increase was related to the increase of SC in SD_x, it was noted than SD_3 showed a faster dissolution rate at the beginning of the process (<5 min), whereas SD_1 and SD_2 (with higher SC proportions) were less effective as dissolution rate enhancers. Although further studies are necessary to explain this behavior, the diluting effect of SC may be the reason why IND is less exposed to the aqueous environment, thus leading to a delay in the dissolution. This hypothesis would infer that in the case of SD_4, the maximum increase in the dissolution rate would be expected since, IND is present at the highest proportion.

However as shown in Figure 4, SD_4 was not able to release IND any faster than SD_3. Based on this fact, it is suggested that the amount of SC was not enough to the able to produce a noticeable dissolution effect and consequently an increase in the drug dissolution rate.

Table 2 Percentage of Indomethacin dissolved in the dissolution medium.

% of IND dissolved								
SD_x	**1 min**	**3 min**	**5 min**	**15 min**	**PM_x**	**1 min**	**3 min**	**5 min**
1	70.8	60.5	62.3	63.5	1	32.4	53.2	59.8
2	64.4	64.1	62.9	60.7	2	36.7	51.7	60.7
3	75.2	73.3	78.8	74.4	3	18.7	43.9	53.9
4	41.0	53.7	63.0	77.3	4	17.8	44.8	53.8
IND	3.43	5.52	9.04	23.3	IND	3.43	5.52	9.04

Table 3 Similarity factor values of dissolution profiles.

SAMPLES CONTAINING DIFFERENT % of IND	SIMILARITY FACTOr (f_2)		
	SD_x- PM_x	**SD_x- IND**	**PM_x- IND**
5	41.63	20.78	16.96
10	40.83	21.20	18.19
25	39.97	15.28	20.11
50	55.28	18.37	18.86

CONCLUSION

A new binary material of IND and a disintegrant excipient (SC) was obtained by a simple method. The SC favorably influenced *in vitro* IND dissolution by means of two principal effects: first, the process by which SD_x was obtained produced a γ→α transition, leading to an IND polymorph that exhibited a greater rate of dissolution and, second, the very efficient water uptake properties of SC made the rapid wetting of SD_x possible, thus facilitating the drug dissolution. It was observed that this effect was strongly related to the percentage of SC present in SD_x. Therefore, according to these results, an improvement of IND bioavailability when administered as SD_x would be expected. Nevertheless, further studies are necessary in order to confirm this hypothesis, including those that observe the effect of dissolution rates when such PM_xs and SD_xs are compressed into tablets.

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DECLARATION OF INTEREST

The authors report no declarations of interest.

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