Journal of Thermal Analysis and Calorimetry, Vol. 82 (2005) 167–170

CHARACTERIZATION OF SOLID DISPERSIONS OF ROFECOXIB USING DIFFERENTIAL SCANNING CALORIMETER

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Solid dispersions were prepared to enhance the dissolution rate of rofecoxib. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were used for the characterization of solid dispersions of polyvinyl pyrrolidone (PVP):talc:drug (3:1:1) and hydroxypropyl methylcellulose (HPMC):talc:drug (4:1:1). The DSC study indicated that PVP solid dispersion showed formation of fusion solution while HPMC solid dispersion showed no intermolecular fusion during the preparation of solid dispersions by spray dry process. The dissolution profiles and the calculated times for 75 and 90% drug release showed that dissolution rate of rofecoxib was improved in solid dispersions as compared to pure drug and physical mixtures. The DSC and XRD were successfully employed to find out the crystalline state of drug in the both solid dispersions. PVP solid dispersion gave better dissolution rate than HPMC solid dispersion. The drug was transformed from crystalline to amorphous form in PVP solid dispersion which was further conformed by XRD and DSC. The PVP:talc:drug solid dispersion can be used for the dissolution enhancement and thereby bioavailability of rofecoxib.

Keywords: *DSC, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, rofecoxib, solid dispersion, talc*

Introduction

The use of solid dispersions of drugs in water-soluble carriers to increase their solubility and dissolution rate, and therefore bioavailability, has been widely studied and reviewed [1–3]. Several researchers have used solid dispersion technique for the improvisation of dissolution of many drugs including anti-inflammatory agents [4–8].

Rofecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenyl -2-(5 H)furanone, is a non-steroidal anti-inflammatory drug (NSAID), which is a specific cyclooxygenase-2 (COX-2) inhibitor for pain and inflammation. Rofecoxib offers the unique therapeutic prospect in arthritis, pain and fever without untoward gastric tract, renal and platelet effects associated with conventional NSAIDs. Because, rofecoxib is a COX-2-specific inhibiting agent, it inhibits the conversion of arachidonic acid to the prostaglandins that mediate pain and inflammation, while having no effect on the formation of the prostaglandins that mediate normal homeostasis in the gastrointestinal tract, kidney and platelets and that are formed under the control of cyclooxygenase-1 [9, 10]. It has comparable efficacy and superior gastric tolerability and it is safer, when compared to the conventional NSAIDs. The major drawback with rofecoxib therapy is its poor aqueous solubility and dissolution in gastric fluid. It is practically insoluble in water (0.0086 mg mL^{-1}) and its oral absorption is dissolution rate limited [11–14]. The poor dissolution characteristics of relatively insoluble drug have long been a problem to pharmaceutical industries. The poor aqueous solubility of the drug causes difficulties in formulation of dosage forms and may lead to a variable bioavailability, therefore the attempt was made to enhance the aqueous solubility of rofecoxib by using solid dispersion technique.

The amorphous form of the drug particles gives more dissolution rate than the crystalline form. Therefore, it was necessary to find out the state of the drug particles in the solid dispersion which was characterized by thermal techniques like differential scanning calorimeter (DSC) and X-ray diffraction (XRD) spectroscopy.

The techniques such as DSC and XRD spectroscopy can be used to characterize the thermal behavior of solid dispersion [15, 16]. The aim of the present work is to investigate the crystallinity of drug in solid dispersion, the effects of solid dispersions on the dissolution rate using DSC.

Experimental

Materials

Rofecoxib (Alembic Ltd., Vadodara, India) was received as a gift sample. Polyvinyl pyrrolidone (PVP) (S.D. Fine Chem. Ltd., Mumbai, India) was used without further purification. Hydroxy propyl methylcellulose (HPMC), talc and methylene chloride were obtained from Loba Chemical. Ltd., Vadodara, India.

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1388–6150/$20.00

Akadémiai Kiadó, Budapest, Hungary
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Preparation of solid dispersions by spray drying method

Spray drying process was used to prepare the solid dispersions of PVP:talc:drug and HPMC:talc:drug in the ratio of 3:1:1 and 4:1:1, respectively. The above-mentioned ratios of drug to carriers were dissolved in common solvent (methylene chloride) and spray dried using laboratory spray dryer (LSD-48, JISL, Japan). The process parameters were as follow: inlet temp: 45±1°C, outlet temp: 28±1°C, aspirator: 75±5 rpm, pump speed: 20±2 rpm, process time: 30±5 min. The solvent was dried immediately and subsequently solid dispersions were collected at the bottom of cyclone separator.

Preparation of solid dispersions by physical mixture method

PVP:drug (3:1) and HPMC:drug (4:1) were mixed together (with trituration in a pestle–mortar) by simple geometric ratios to prepare the physical mixtures and stored in a desiccated environment.

Dissolution study

The dissolution studies of pure drug (50 mg rofecoxib), physical mixtures with both polymers and above prepared solid dispersions were carried out using USP26 apparatus-II (Model TDT-06P, Electrolab, Mumbai, India) using 900 mL 0.1 N hydrochloric acid containing 0.5% sodium lauryl sulfate as a dissolution medium kept at 37±0.5°C. Samples were withdrawn at intervals of 5, 10, 15, 30, 45, 60, 90, 120 min with replacement of the dissolution medium therein. The collected samples were suitably diluted and absorbance measured at 260.5 nm using UV–spectrophotometer (Model UV-1601 UV, Visible spectrophotometer, Shimadzu, Japan).

Differential scanning calorimeter

DSC study was performed using DSC (TA 4000, Mettler, Japan) apparatus with a DSC-25 cell. The instrument was calibrated with indium standard. Samples (5–10 mg) were weighed and sealed into the aluminum pan. DSC runs were conducted over a temperature range of 40 to 240°C at a rate of 5°C min^{-1}.

X-ray diffraction study

X-ray diffraction studies of pure drug, PVP:talc:drug (3:1:1) and HPMC:talc:drug (4:1:1) solid dispersions were carried out using X-ray diffractometer (DMAX-III 3KVA, Rigaku Co. Ltd., Japan) with Geigerflex horizontal goniometer, CuK_α as target, Ni as filter and scanned between 5–45° angle with a scanning speed of 3° min^{-1}.

Stability study

The intimate mixing of polymeric carriers with the drug may affect the storage stability of rofecoxib. Stability of rofecoxib in the solid dispersions systems was, therefore, evaluated by analyzing the assay and dissolution characteristics of the systems after storage at different temperatures and the data were compared with the initial samples. Stability study of the prepared solid dispersions were carried out at three different temperatures 8, 25 and 50°C for a duration of 45 days and samples were analyzed periodically at the interval of 15, 30 and 45 days and the percentage of the drug present in each sample was calculated.

Results and discussion

The results of the dissolution study of pure drug, the physical mixtures and the solid dispersions are given in the Table 1. The time required for 75 and 90% drug release ($t_{75\%}$ and $t_{90\%}$) of both the solid dispersions was below 5 min. The values of $t_{75\%}$ for PVP physical mixture and HPMC physical mixture both were below 30 min while the value for $t_{90\%}$ of PVP physical mixture was below 60 min and that of HPMC physical mixture was below 90 min. The better dissolution rate of solid dispersions prepared by spray drying process than that of physical mixtures and pure drug indicated the better dissolution enhancement of drug in both the solid dispersions. This may be due to an improved wettability of the drug particles, a significant reduction in particle size during the formation of solid dispersion, and the intrinsically higher rate of dissolution of the soluble polymer component of the solid dispersion, which would pull along the more insoluble but finely mixed drug into the dissolution medium.

The dissolution profiles of pure rofecoxib, the physical mixtures and the solid dispersions are given in Fig. 1. The physical mixtures and the solid dispersions showed more dissolution rate than that of pure drug due to an improved wettability of the drug particles. The PVP:talc:drug solid dispersion showed more dissolution rate than that of HPMC:talc:drug solid dispersion and both physical mixtures. The

Table 1 Results of the dissolution study of pure drug, physical mixtures and solid dispersions

Sr. No.	Sample	$t_{75\%}$	$t_{90\%}$
1	pure drug	<45 min	<90 min
2	physical mixture of PVP:drug (3:1)	<30 min	<60 min
3	physical mixture of HPMC:drug (4:1)	<30 min	<90 min
4	PVP:talc:drug (3:1:1)	<5 min	<5 min
5	HPMC:talc:drug (4:1:1)	<5 min	<5 min

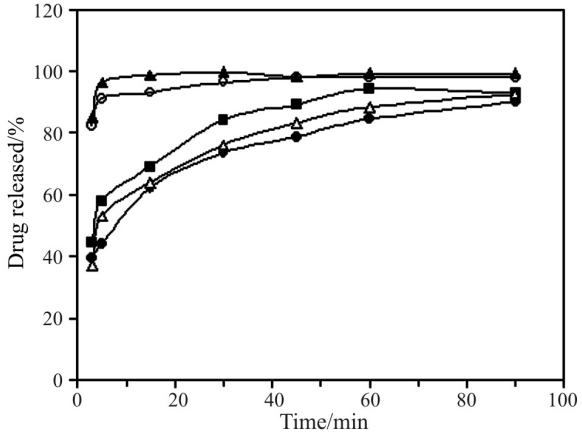

Fig. 1 Dissolution profiles of ● – pure drug, physical mixture of ■ – PVP:drug, △ – HPMC:drug, ▲ – PVP:talc:drug and ○ – HPMC:talc:drug solid dispersion

higher dissolution rate observed with PVP solid dispersion is due to the presence of rofecoxib in amorphous form in this solid dispersion. Since the amorphous form is the highest energy form of a pure compound, it produces faster dissolution rate.

To find out the crystalline state of drug in both solid dispersions, the DSC and XRD analysis were carried out. The DSC curves of pure rofecoxib, pure PVP and both solid dispersions are given in Fig. 2. DSC curve of pure drug (rofecoxib) gives an endothermic peak corresponding to its melting point at 213°C with an enthalpy value (ΔH) of 107.07 J g^{-1}. DSC curve of pure PVP shows an endothermic peak corresponding to its melting point at 139.6°C with an enthalpy value (ΔH) of 27.422 J g^{-1}.

DSC curve of PVP:talc:drug solid dispersion (3:1:1) has an endothermic peak at near 136.2°C. Here, endothermic peak corresponding to the melting point of the drug at 213°C disappeared. The transition very close to the PVP melting temperature indicated that sharp endothermic peak of melting point disappeared (since the drug loading was very low compared to the polymer) and the DSC curve showed only endothermic peak corresponding to that of polymer with a shoulder peak at its base which indicated that system showed fusion temperature and formation of solid solution. The increased intermolecular bonding between solute and the solvent results in a common endothermic peak that confirms the interstitial solid solution formation.

DSC curve of HPMC:talc:drug solid dispersion (4:1:1) gave a peak at 70.5°C with an enthalpy (ΔH) of 4.59 J g^{-1} corresponding to HPMC and an endothermic peak corresponding to the drug at 211.3°C with an enthalpy (ΔH) of 43.34 J g^{-1}. This shows that the fusion or intermolecular bonding has not occurred to a greater extent and there is little hope to form an interstitial solid solution.

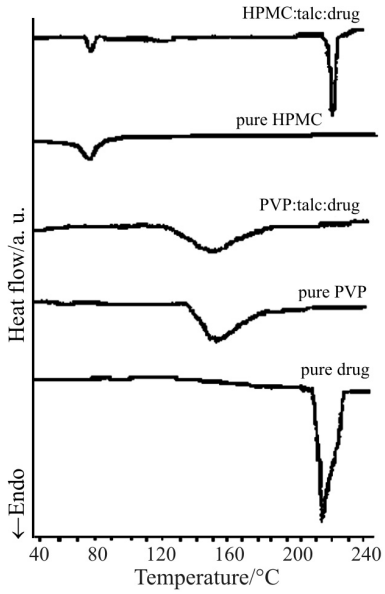

Fig. 2 DSC curves of pure drug, pure PVP, PVP:talc:drug and HPMC:talc:drug solid dispersion

X-ray diffraction analysis can be used to judge any changes in crystallinity of the drug when formulated into a solid dispersion. Rofecoxib is a crystalline drug and gives characteristic XRD peaks. Thus, XRD could be used to study any changes in crystallinity of the drug or its precipitation in an amorphous form, which could be one of the mechanisms responsible for improved dissolution. The X-ray diffraction patterns for pure rofecoxib, PVP solid dispersion and HPMC solid dispersion is given in Fig. 3. While no significant difference was observed in the crystallinity of HPMC solid dispersion, PVP solid dispersion showed a change in intensity as well as number of peaks compared to those of pure rofecoxib. In PVP solid dispersion, the absence of characteristics peaks of the drug indicated the formation of solid solution with PVP by spray drying process and transformation of drug from crystalline to amorphous form (characteristic property of PVP is to form amorphous solid complexes with the drug rofecoxib). This reduction of crystallinity may explain the higher drug release profile of PVP solid dispersion as compared to HPMC solid dispersion. The most XRD peaks of both the solid dispersions resembled to those of talcum indicating the deposition of talcum in these products.

The results of stability study of pure drug, physical mixtures and both the solid dispersions stored at 50°C are given in Table 2. The results of stability indicated that the drug was degraded up to 10–12% when stored at 50°C for 45 days while it was stable in both the physical mixtures and solid dispersions when stored at 8 and 25°C for 45 days. The HPMC:talc:drug dispersion has better stability after 45 days when stored at 50°C than pure drug and other dispersion and the

physical mixtures. The dissolution profiles after storage at 8 and 25°C for 45 days showed no significant difference confirming drug present did not revert from the amorphous to crystalline form.

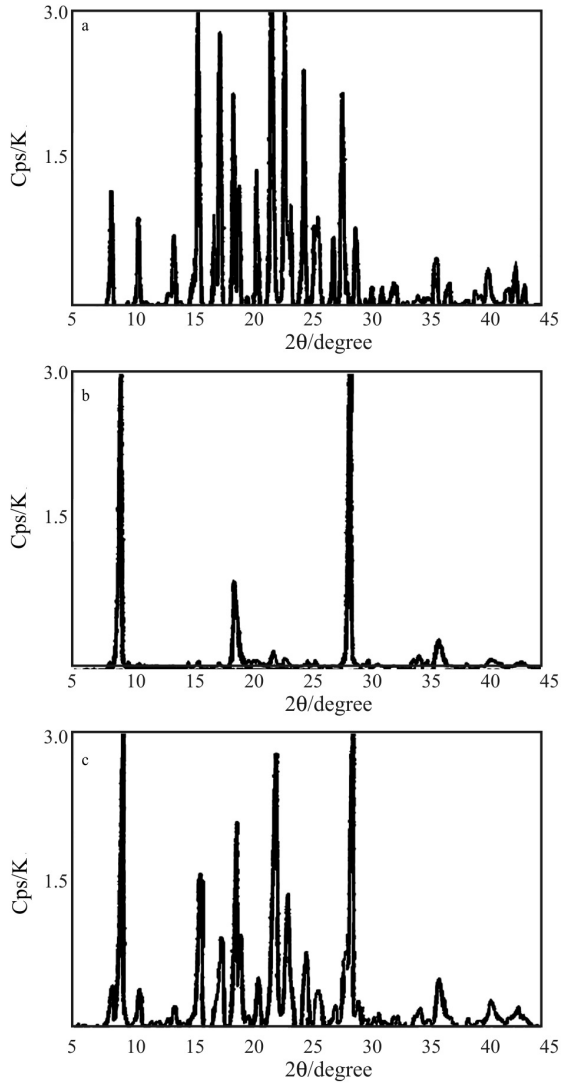

Fig. 3 Power X-ray diffraction patterns for a – pure rofecoxib, b – PVP:talc:drug solid dispersion and c – HPMC:talc:drug solid dispersion

Table 2 Results of the stability study of pure drug, physical mixtures and solid dispersions stored at 50°C

Sr. No.	Samples	Drug released/% after		
		15 days	30 days	45 days
1	pure drug	90.71	88.42	74.39
2	physical mixture of PVP:drug (3:1)	92.64	90.33	78.01
3	physical mixture of HPMC:drug (4:1)	90.89	81.72	79.84
4	PVP:talc:drug (3:1:1)	94.30	90.60	82.00

Conclusions

Improving the dissolution characteristics of insoluble drugs is important to achieve better bioavailability and reduced side-effects. The solid dispersion technique is an important tool in this direction. The present work shows that the dissolution rate of rofecoxib improved markedly. Further, both the solid dispersions performed better than the corresponding physical mixtures. PVP solid dispersion showed better dissolution rate than HPMC solid dispersion. The DSC was employed for the characterization of pure drug, pure PVP and prepared solid dispersions. The solid dispersion of PVP showed formation of solid solution during spray drying process while there was no formation of intermolecular bonding or fusion during the spray drying process of HPMC solid dispersion. The data of dissolution, thermal analysis, XRD, and stability study revealed that PVP:talc:drug solid dispersion can be used for the dissolution enhancement and thereby bioavailability of rofecoxib. The drug was transformed from crystalline to amorphous form in PVP solid dispersion which was further conformed by XRD and DSC. It was concluded that solid-dispersion formulations of PVP can be used to design a solid dosage form of the drug, which would have significant advantages over the currently marketed tablets dosage form.

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Received: January 21, 2005

DOI: 10.1007/s10973-005-6804-7