Enhancement of Dissolution Profile of Poorly Water Soluble Loratadine by Solid Dispersion Technique

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ABSTRACT: This study was carried out to improve the dissolution properties of loratadine by solid dispersion technique. A series of solid dispersions of loratadine in PVP K-30 (1:1, 1:3 and 1:5) were prepared by kneading technique. The prepared solid dispersions were characterized by various physicochemical properties (fourier transform infrared spectroscopy, X-ray diffraction and scanning electron microscopy) and the dissolution characteristics were compared with loratadine and the physical mixtures of loratadine. It was revealed from the physicochemical analyses that there was a good compatibility between drug and carrier. On the other hand, the drug release from the prepared binary solid dispersions was significantly enhanced in comparison to both drug alone and the physical mixtures. Finally solid dispersion of loratadine: PVP K-30 prepared as 1:5 ratio was found to be described by non-Fickian release mechanism and was selected as the best formulation in this study.

Key words: Solid dispersion, hydrophilic carrier, loratadine, kneading technique

INTRODUCTION

Oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion.[1] The therapeutic efficacy of an orally administered drug depends mainly on its absorption by the gastrointestinal tract.[2] However, for a drug substance to be absorbed and transported to the site of action, the absorbable form of the active compound must first be in solution in the gastrointestinal tract, preferentially at a site where absorption is greatest. Therefore, the dissolution rate of a drug, or rate in which the drug goes into solution, is an important parameter for determining how much drug is available for absorption.[3] If a drug is difficult to get into solution, then the amount of drug available for absorption may be small and thereby present difficulties in achieving the desired therapeutic effect.[4] Numerous works have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. Among them solid dispersion technology was mostly used.[5-10] Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion.[11] Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers.[12] The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing.[13,14] Various hydrophilic carriers such as polyethylene,[15] polyvinylpyrrolidone[16] and sugars[17] have been investigated for improvement of dissolution characteristics and bioavailability of poorly water soluble drugs. Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersion of loratadine using rotary evaporation and spray-drying solvent evaporation techniques.[18] The objective of the present study was to improve the dissolution profile of loratadine by preparing solid

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dispersion employing kneading technique using polyvinylpyrrolidone as hydrophilic carrier.

MATERIALS AND METHODS

Materials. Loratadine and polyvinylpyrrolidone (PVP K-30) were obtained as a gift samples from Beximco Pharmaceuticals Ltd., Dhaka, Bangladesh. All other reagents and solvents used in the study were of analytical grade.

Preparation of physical mixtures. Physical mixtures (PM) of loratadine at three different mass ratios (1:1, 1:3 & 1:5 by weight of loratadine and PVP K-30, respectively) were prepared by pulverizing in a glass mortar. The mixtures were passed through sieve no. 60.

Preparation of solid dispersions by kneading technique.[19] Solid dispersions (SD) of loratadine at three different mass ratios (1:1, 1:3 & 1:5 by weight of loratadine and PVP K-30 respectively) were prepared by wetting with water-ethanol (1:1 ratio) till the slurry was formed and kneaded thoroughly for 30 minutes in a glass mortar. The pastes formed were then dried in oven at 45^0 C for 24 hours. The solid masses were triturated in glass mortar. The resulting powders were passed through sieve no. 40. Finally solid dispersions were stored in a desiccator until further evaluation. The formulations of physical mixtures and solid dispersions are listed in Table 1.

Table 1. Composition of physical mixtures and solid dispersions of loratadine.

Formulation	Composition of physical mixtures			Composition of solid dispersions		
	PM-1	PM-2	PM-3	SD-1	SD-2	SD-3
Loratadine	10 g	10 g	10 g	10 g	10 g	10 g
PVP K-30	10 g	30 g	50 g	10 g	30 g	50 g

Fourier transform infrared (FTIR) spectroscopy. FTIR spectroscopic study was conducted using a Shimadzu FTIR IR Prestige- 21 spectrophotometer (Japan) and the spectrum was recorded in the wavelength region of 4400 to 500 cm^{-1}. The procedure consisted of dispersing a sample (Pure loratadine, PM-3 & SD-3) in KBr and compressing into disc by applying a pressure of 5 tons for 5 minutes in a hydraulic press. Spectrum was obtained by placing the disc in the light path.

Differential scanning calorimetry (DSC). The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The important components of the instrument are calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60) and operating software (TA 60). The samples (Pure loratadine, PM-3 & SD-3) were heated in sealed aluminum pans under nitrogen flow (10 ml/min) at a scanning rate of 10 °C/min from 30 to 300 °C. Empty aluminum pan was used as a reference. The heat flow was also recorded as a function of temperature for each sample.

X-ray diffraction (XRD). X-ray powder diffraction patterns were obtained at room temperature using a PW 1710 X-ray diffractometer (Philips, Holland) with Cu as anode material and graphite monochromator, operated at a voltage of 35 kV and 20 mA current. The samples (Pure loratadine, PM-3 & SD-3) were analyzed in the 2θ angle range of 0°–70° and the process parameters were set as: scan step size of 0.02° (2θ), and scan step time of 0.5s.

Scanning electron microscopy (SEM). The morphology of pure loratadine, physical mixture (PM-3) and solid dispersion (SD-3) were investigated by scanning electron microscopy (SEM), Hitachi S 3400 N, Japan. The samples were placed in aluminum stubs and then were mounted on double-sided adhesive tape for analysis by SEM. The accelerating voltage was 15 kV. The samples were analyzed at magnification of 2000. The analysis utilized 11100 μm working distance and 57000 nA emission current in this study.

***In vitro* dissolution studies.**[20] *In vitro* dissolution studies were performed in 0.1N hydrochloric acid at 37 ± 0.5 °C, using 6-station USP Type II apparatus (Erweka DT 600, Germany) with paddle rotating at 50 ± 2 rpm. Samples of both solid dispersion and physical mixtures for dissolution study were taken in such a way that each containing 10 mg of drug. At fixed time intervals, samples withdrawn were filtered (pore size 0.45 µm) and spectrophotometrically assayed for drug content at 280 nm. Each test was performed in triplicate.

Data treatment. Different release kinetics is assumed to reflect different release kinetics mechanism. Therefore four kinetics models including zero order release equation Eq. (I), first order equation Eq. (II), Higuchi Eq. (III)[21] and Korsmeyer-Peppas Eq. (IV)[22] equations were applied to process *in-vitro* data.

$$Q = K_1 t \quad \text{(I)}$$

$$Q = 100(1 - e^{-K_2 t}) \quad \text{(II)}$$

$$Q = K_3 t^{1/2} \quad \text{(III)}$$

$$\text{Log}\left(\frac{M_t}{M_\infty}\right) = \text{Log}\, k_4 + n\, \text{Log}\, t \quad \text{(IV)}$$

Where Q is the release percentage at time t. K_1, K_2 K_3 and K_4 are the rate constant of zero order, first order, Higuchi and Korsmeyer-Peppas model respectively. The Mt/M∝ is the fractional drug release at time t and the n is a kinetic constant. The n values give us an idea about the drug release mechanism from different formulations.

The MDT (Mean dissolution time) of different formulations were calculated using dissolution data according to Mockel and Lippold (1993) Eq. (V).[23]

$$MDT = \left(\frac{n}{n+1}\right) k^{-1/n} \quad \text{(V)}$$

RESULTS AND DISCUSSION

Fourier transform infrared (FTIR) spectroscopy. Figure 1 showed the IR spectra of loratadine, its physical mixture (PM-3) and solid dispersion (SD-3). Pure loratadine spectra showed sharp characteristic peaks at 3440 (N-H stretching), 3000 (C-H stretching of methyl group), 1700 (C=O), 1440 and 1220 cm^{-1}. It is concluded from the spectra that there is no interaction between the drug and the carrier as the most characteristic peaks appeared in the spectra of the physical mixture (PM-3) and solid dispersion (SD-3) at the same wave numbers.

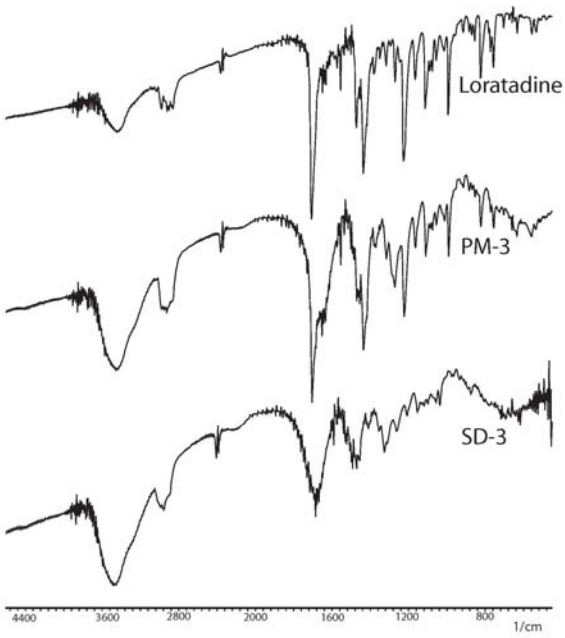

Figure 1. IR spectra of loratadine, PM-3 and SD-3.

Differential scanning calorimetry (DSC). DSC thermograms of loratadine, its physical mixture (PM-3) and solid dispersion (SD-3) prepared by kneading method are shown in figure 2. Loratadine gave a characteristic and sharp endothermic peak at 138 ^{o}C which is close to its melting point. Thus it indicates the crystalline nature of the drug. The same peak in PM-3 at 135.42 ^{o}C also indicating the presence of crystalline form. However, the characteristic endothermic peak with reduced intensity at 133.50 ^{o}C, corresponding to drug melting point, was observed in SD-3 indicating reduced crystallinity of the drug. This may be happened due to dispersion of the drug molecules in the PVP K-30.

X-ray diffraction (XRD). X-ray diffraction spectra are depicted in figure 3. The diffraction spectra of pure loratadine showed numerous distinct peaks indicating presence of high crystalline state.

The characteristic loratadine peaks with high intensity were found to be at 7.61, 12.75, 15.19, 16.35, 16.57, 19.60, 21.13 and 23.83 at 2θ degrees. On the other hand, it showed less intensity peaks of loratidine in the XRD pattern of physical mixture (PM-3). Moreover, much lowered intensity peaks of loratidine was observed in case of solid dispersion (SD-3). It is revealed from the study that the crystallinity of loratadine was reduced to a certain extent by making a solid dispersion of loratidine in PVP K-30.

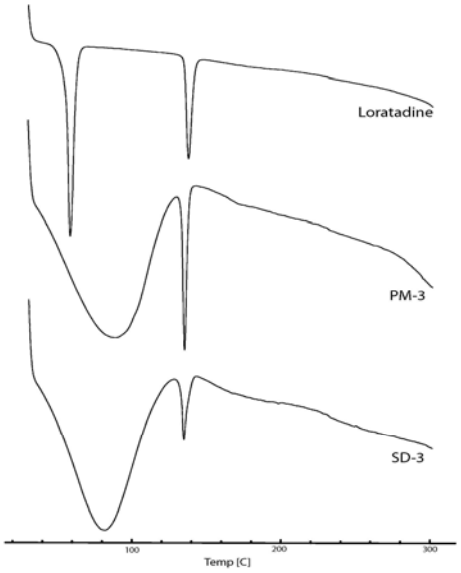

Figure 2. DSC thermogram of loratadine, PM-3 and SD-3.

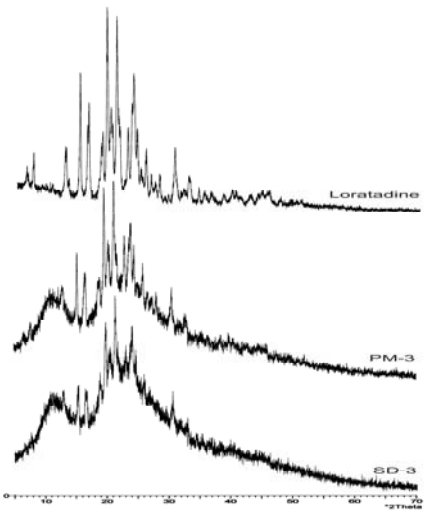

Figure 3. Powder X-ray diffraction spectra of loratadine, PM-3 and SD-3.

Scanning electron microscopy (SEM). The SEM results are shown in figure 4. Loratadine existed in lamellar-like crystals, consisted of large crystalline particles of rather irregular size, partially agglomerated in bundles. In case of physicals mixture (PM-3), the particle size and shape of loratadine was approximately the same. The original morphology of the components in solid dispersion was disappeared by forming an irregular appeared particle. It indicates that loratadine in solid dispersions was homogeneously dispersed into PVP K30 at the molecular level.

***In vitro* dissolution studies.** Dissolution profiles data of loratadine are presented in figure 5. It is clear from the figure that the solid dispersion of loratadine has enhanced dissolution rate than those of physical mixture of loratadine. The zero order drug release rates (K_1 in % release/time) of different formulations as well as their corresponding binary systems with carriers are summarized in table 2. Only 32.12% of the drug was released from pure loratadine powder after first 30 minutes. However, the drug release from PM-1, PM-2 and PM-3 after first 30 minutes were 32.94%, 37.86% and 40.67% respectively. Whereas, in case of SD-1, SD-2 and SD-3 the cumulative percent of drug released after first 30 minutes were 60.82%, 65.41% and 69.39% respectively. Incorporation of drug with a hydrophilic carrier system offered an increased wetting and reduction in interfacial tension between hydrophobic drug and dissolution medium.[24] It was observed during the dissolution studies that drug release from the solid dispersion was found to be faster. At the same time, the dissolution rate was also increased with the increase of proportion of PVP K-30 in solid dispersion. The SD-3 formulation of solid dispersion prepared using 1:5 drug carrier ratios showed the maximum dissolution rate of drug. It was almost 2.06 fold increased dissolution rate compared to the pure drug.

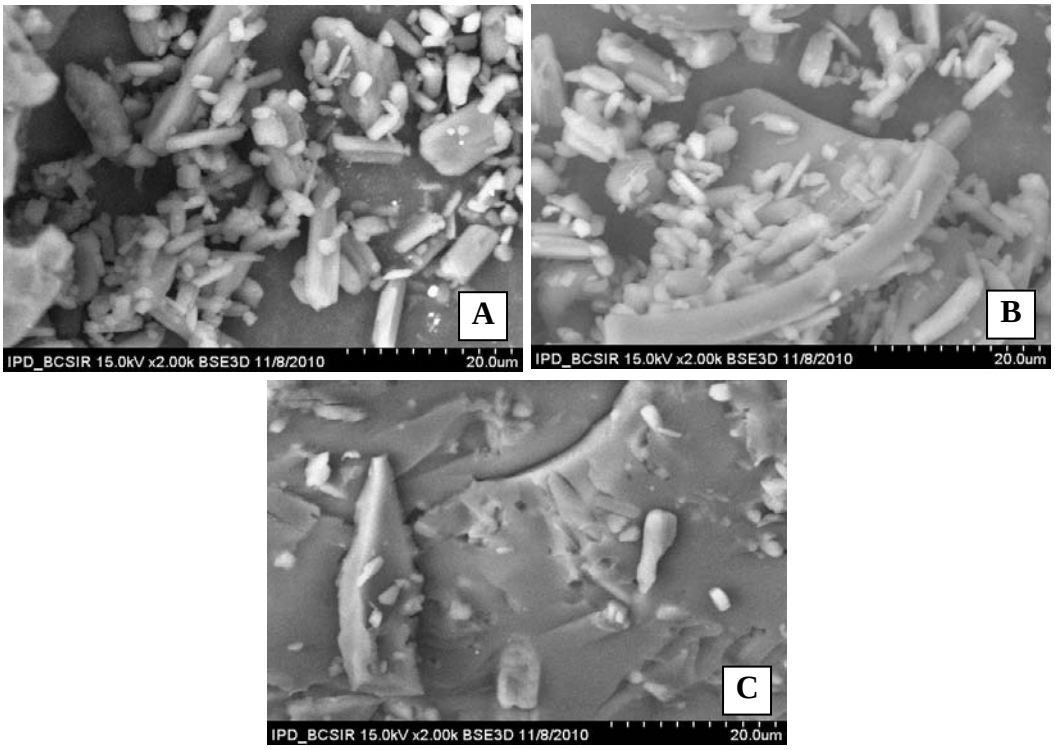

Figure 4. Scanning electron micrographs of (A) loratadine at X-2000, (B) PM-3 at X-2000 and (C) SD-3 at X-2000.

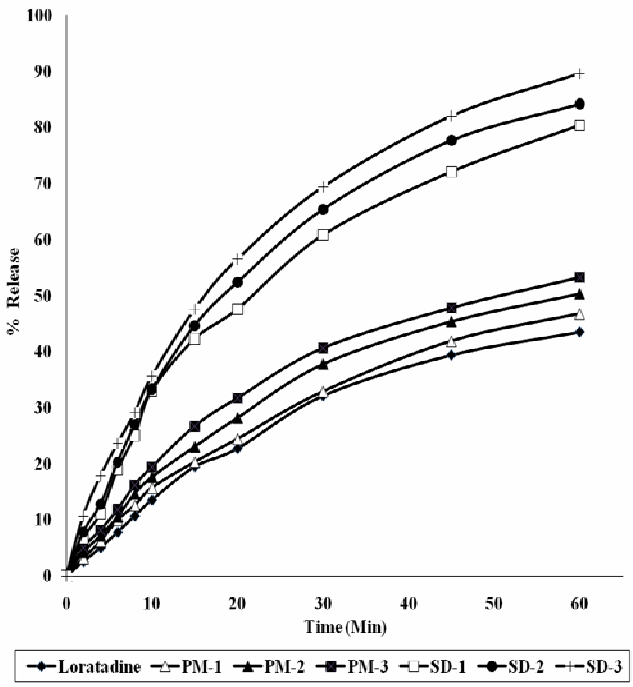

Figure 5. Dissolution profiles of loratadine and its binary systems.

Table 2. Zero order drug release rate constant (K_1), first order drug release rate constant (K_2), rate constant of Higuchi model (K_3), kinetic constant (n) of Korsmeyer-Peppas model (K_4), coefficient of determination (R^2) for different model which indicates the goodness of fit of a model, mean dissolution time (MDT), time to release 50% of drug ($T_{50\%}$).

System	Zero Order		First Order		Higuchi		Korsmeyer		MDT (min)	$T_{50\%}$ (min)
	K_1	R^2	K_2	R^2	K_3	R^2	n	R^2		
Loratadine	0.751	0.942	-0.004	0.970	6.378	0.974	0.848	0.981	56.031	53.920
PM-1	0.786	0.947	-0.005	0.978	6.679	0.981	0.787	0.982	56.240	52.929
PM-2	0.846	0.931	-0.005	0.969	7.253	0.982	0.747	0.984	51.262	47.401
PM-3	0.883	0.914	-0.006	0.961	7.638	0.981	0.715	0.982	47.197	42.939
SD-1	1.324	0.902	-0.012	0.989	11.51	0.980	0.740	0.963	25.751	23.731
SD-2	1.400	0.897	-0.014	0.991	12.20	0.979	0.719	0.971	23.626	21.540
SD-3	1.451	0.900	-0.016	0.998	12.67	0.986	0.639	0.985	21.998	19.071

Release kinetics. The release kinetics of loratadine from different binary systems and the mean dissolution time (MDT) are depicted in table 2. Pure loratadine and the physical mixtures (PM-1, PM-2 & PM-3) were best fitted with Korsmeyer model; while the solid dispersions (SD-1, SD-2 & SD-3) were best fitted with first order model. The value of release exponent (n) of all the samples were in the range of 0.715- 0.848 which indicates non-Fickian release, that is combination of diffusion of drug through the carrier with erosion of carrier.

MDT value is used to characterize the drug release rate. A lower value of MDT indicates a higher drug release rate and vice versa. From table 2 it can be observed that MDT decreased with increased carrier load which means if the carrier load was increased, drug dissolution was also increased in a step wise fashion.

CONCLUSION

The study shows that the dissolution rate of loratadine can be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method. The solid dispersion complex of drug displayed better dissolution profile as compared to pure drug. This, in turn, can result in reduced doses of drug, reduction in dose related adverse effects and improved bioavailability.

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