Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Solid Dispersion as an Approach for Dissolution Enhancement and Delivery of Trandolapril, a Poorly Water-soluble ACE Inhibitor

OFOKANSI KC[1], KENECHUKWU FC[1,*], ISAH AB[2] AND OGBONNA JDN[1]

[1]Drug Delivery Research Unit, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka
[2]Department of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University, Zaria, Kaduna State.

ARTICLE DETAILS

Article history:
Received on 19 August 2012
Modified on 28 November 2012
Accepted on 07 December 2012

Keywords:
Trandolapril,
Solid dispersion,
Urea, PEG 8000,
Dissolution,
Eudragit RL 100,
Moisture sorption.

ABSTRACT

This study was designed to formulate and evaluate solid dispersions as novel carrier system for the delivery of trandolapril. Trandolapril-loaded solid dispersions (SDs) were prepared by fusion method using varying combination ratios of Eudragit RL 100 and polyethylene glycol (PEG) 8000 with or without urea as a hydrophilic carrier. Characterization based on surface morphology, particle size, absolute drug content and moisture sorption properties were carried out on the SDs. The *in vitro* release of trandolapril from the SDs was performed in 0.1 N HCl (pH 1.2) and phosphate buffered saline (PBS, pH 7.4). To evaluate the mechanism of release of trandolapril from the SDs, the *in vitro* release data from different batches of the SDs were fitted into different kinetic models. Results indicate that discrete and irregular SDs of mean particle size range 3.87 ± 0.15 to 22.14 ± 1.09 µm, which were stable over 3 months, were obtained. SDs containing urea entrapped greater amounts of drug in comparison with SDs containing only Eudragit RL 100 and PEG 8000. The moisture sorption studies indicate that both amorphous and microcrystalline state of trandolapril are present in the SDs **.** *In vitro* release studies revealed that there was marked increase in the dissolution rate of trandolapril from the solid dispersions when compared to pure trandolapril. The improved dissolution, which was better in PBS than in 0.1 N HCl, was highest in the SDs containing Eudragit RL 100, PEG 8000 and urea. The increased dissolution rate of trandolapril may be due to the formation of microcrystals, increased wettability and dispersibility in systems containing Eudragit RL 100, PEG 8000 and urea. The release pattern of the drug was found to follow predominantly the Higuchi square root model. This study has shown that a formulation of trandolapril SDs could offer a better and more effective approach of increasing the dissolution rate of the poorly water-soluble prodrug, trandolapril.

INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Most of the newly discovered chemical entities, in spite of high therapeutic activity, have low aqueous solubility and poor bioavailability, leading to poor absorption in the gastrointestinal tracts [1]. Several approaches including particle size reduction, salt formation, solubilization, and complexation with β-cyclodextrins, have been employed to tackle this challenge. However, all these methods suffer from drawbacks. SDs have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs.

Author for Correspondence:
Email: chimafrankduff@yahoo.com

Thus, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs[2, 3].The term solid dispersion is the dispersion of one or more active ingredients in a hydrophilic inert carrier matrix at molecular level, prepared by fusion, solvent or solvent fusion methods[4]. SDs have several advantages in terms of improved wettability (and hence enhanced solubility) and amorphosity, higher porosity and lower sizes of the drug particles (hence a higher specific surface area), resulting in an increased dissolution rate and consequently, improved bioavailability of poorly water-soluble crystalline drugs[5 - 7].

Angiotensin converting enzyme (ACE) [the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII), a key

component of the renin-angiotensin-aldosterone system (RAAS) which also regulates blood pressure] inhibitor therapy is a valuable treatment option for patients with hypertension, effectively lowering blood pressure without influencing cardiovascular reflexes [8]. Trandolapril, one of the newer drugs in this class, is a non-sulfhydryl prodrug which, after oral administration, is readily hydrolysed in the liver to its biologically active diacid, trandolaprilat, which is a more potent and longer-acting inhibitor of plasma and tissue ACE than quinaprilat, enalaprilat and captopril [9].Trandolapril 2 to 4 mg once daily effectively controls blood pressure for at least 24 h in patients with mild to moderate hypertension [10]. The tolerability profile of trandolapril is similar to that of other ACE inhibitors, most adverse events being generally mild and transient in nature, and trandolapril lacks adverse effects of carbohydrate and lipid metabolism [11]. Thus, trandolapril, with its favourable pharmacological profile (high lipophilicity, high enzyme affinity and long duration of action) and antihypertensive activity similar to that of other agents currently used to treat patients with mild to moderate hypertension, is likely to provide a well tolerated option for treatment of this disease. However, trandolapril exhibits inter-individual bioavailability variations probably due to its poor aqueous solubility and unsatisfactory dissolution rate[11 -13]. Improvement in its solubility and dissolution rate is the primary reason for this study, as this improvement could be achieved by the use of water soluble polymers based on solid dispersion technology [2, 3]. Eudragit RL and polyethylene glycol 8000 have been employed in previous studies to improve the dissolution rate of a wide range of drugs via SDs [14 - 17]. Similarly, although without surface activity, urea has been utilized successfully as a carrier for improving the wettability of a good number of drugs via SDs [14, 15, 18]. A review of the literature has not revealed any study on trandolapril solid dispersions.

Consequently, the purpose of this research was to evaluate, *in vitro*, trandolapril solid dispersions based on Eudragit RL 100, PEG 8000 and urea prepared using the fusion method for the controlled delivery of trandolapril. The SDs were also characterized in terms of particle size and morphology, entrapment efficiency, moisture sorption and drug delivery properties.

MATERIALS AND METHODS

Materials

Trandolapril (Dr. Reddy's Laboratories Ltd., Hyderabad, India), Poly (ethylene glycol) 8000 (Clariant, Germany), methanol (Sigma Aldrich, Germany), urea of Pharmacopoeial grade (SD Fine Chemicals Ltd., Mumbai, India), concentrated hydrochloric acid, potassium chloride, potassium thiocynate and calcium chloride (BDH Chemicals, UK), sodium hydroxide (Merck, Germany), monobasic potassium phosphate (Sigma Chemical Co., USA) and Eudragit RL 100 (Rohm, Germany) were used as procured from the manufacturers without further purification. All other reagents were analytical grade and used as such. Distilled water was obtained from an all-glass still.

Formulation of solid dispersions

Trandolapril-loaded solid dispersions (SD) were prepared using varying ratios of Eudragit RL 100, PEG 8000 and urea, as shown in Table 1, by the fusion method [19]. Briefly, appropriate amount of trandolapril was dissolved in methanol. The required amount of Eudragit RL 100 was melted in a beaker on a thermostatically controlled water bath maintained at 70 – 80°C, followed by addition of appropriate amount of PEG 8000 to the molten Eudragit RL 100. An accurately weighed amount of trandolapril was incorporated into the melted carriers and mixed thoroughly with a glass rod for 5 min to ensure homogeneity. The mixture was cooled rapidly by placing the beaker in an ice bath for 5 min to solidify, then powdered in a mortar, sieved through a 100-mesh screen, and stored in a screw-cap vial at room temperature pending further use. The SDs were coded F-1 to F-5.

By following the above procedure the batch that contains urea (F-6) was similarly prepared except that the required quantity of urea was introduced into the polymer admixture as an additional carrier before the addition of the drug solution.

Determination of percentage yield

The SDs from each batch were weighed to obtain the yield of SDs formulated per batch. The percentage (%) yield was calculated using the formula:

$$\text{Percentage (\%) recovery} = \frac{W_1}{W_2 + W_3} \times 100 \quad \text{..... (1)}$$

Where:
W_1= Weight of the SDs formulated (mg)
W_2= Weight of the drug (mg)
W_3= Weight of Eudragit RL 100, PEG 8000 and urea (mg).

Table 1: Formulation compositions of the solid dispersions

Formulation code	Ratio of Drug, PEG 8000, Eudragit RS 100 and Urea	Trandolapril (g)	PEG 8000 (g)	Eudragit RS 100 (g)	Urea (g)
F-1	0.2:1:1:0	0.2	1.0	1.0	-
F-2	0.4:1:2:0	0.2	0.5	1.0	-
F-3	0.4:1:3:0	0.2	0.5	1.5	-
F-4	0.4:2:1:0	0.2	1.0	0.5	-
F-5	0.4:3:1:0	0.2	1.5	0.5	-
F-6	0.2:1:1:0.25	0.2	1.0	1.0	0.25

Estimation of drug content and encapsulation efficiency

A known amount of the SDs (50 mg) was weighed out accurately and dissolved in 100 ml of methanol. The solution was shaken vigorously and filtered, and the filtrate was spectrophotometrically (Unico 2102 PC UV/Vis Spectrophotometer, USA) analyzed at 230 nm for trandolapril content. The amount of drug encapsulated in the SDs was calculated with reference to a standard Beer's plot for trandolapril to obtain the encapsulation efficiency using the formula below [5, 6]:

$$EE\ \% = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \ldots. (2)$$

The above procedure was repeated to obtain the encapsulation efficiency from the mean of triplicate determinations.

Particle size analysis and morphological characteristics

The particle size of the SDs was determined by computerized image analysis on a photomicroscope (Lieca, Germany). Samples from each of the batches were dispersed in methanol and mounted on a slide and observed under a light microscope. With the aid of software in the microscope, the projected diameters of the particles corresponding to the particle sizes of the SDs were determined and the mean calculated. The particle morphologies were also observed and captured by the photomicroscope.

Moisture sorption characteristics

Quantities of the SDs were placed in a Petri dish and stored in an activated desiccating chamber at 10 °C for one week to remove residual moisture from the materials. The moisture sorption isotherms of the SDs were determined by gravimetric method [20]. One gram of each dry SD was placed in an aluminum foil and put in a desiccator with a guaze holding tray containing either distilled water or saturated solution of different salts to provide the required relative humidity (RH) (water 100 %, potassium chloride 84 %, sodium chloride 75 %, potassium thiocynate 47 % and calcium chloride 31 %). The SDs were weighed at 12 h intervals until equilibrium was attained. The equilibrium moisture sorption (EMS) was determined using the equation:

$$EMS = M_e / M_d \times 100 \ldots\ldots (3)$$

where M_e is the amount of moisture sorped at equilibrium and M_d is the dry weight of the material [21]. The profile of percentage weight gain vs RH was then evaluated for each batch.

***In vitro* drug release studies**

In vitro release profile for each solid dispersion as well as pure drug was performed using USP XXII rotating paddle apparatus (Erweka, Germany). Beer's plot for trandolapril at different concentrations was made at a wavelength of 241 nm in 0.1 N HCl (pH 1.2) and at a wavelength of 258 nm in phosphate buffered saline (PBS, pH 7.4).The dissolution medium consisted of 250 ml of freshly prepared 0.1 N HCl (pH 1.2) maintained at 37 ± 1ºC. The polycarbonate dialysis membrane used was pretreated by soaking it in the dissolution medium for 24 h prior to the commencement of each release experiment. In each case, 100 mg of the formulated SDs was placed in the dialysis membrane containing 5 ml of the dissolution medium, securely tied with a thermo-resistant thread and then immersed in the dissolution medium under agitation provided by the paddle at 50 rpm. At predetermined time intervals (15 min), 2 ml portions of the dissolution medium were withdrawn, filtered and analyzed spectrophotometrically (Unico 2102 PC UV/Vis

Spectrophotometer, USA) at 241 nm. For each sample withdrawn, an equivalent volume (2 ml) of 0.1 N HCl maintained at the same temperature was added to the contents of the dissolution medium to maintain sink conditions throughout the release period. The amount of drug released at each time interval was determined with reference to the standard Beer's plot for trandolapril in 0.1 N HCl**.** A positive control was set up for each batch by similarly weighing amounts of pure trandolapril equivalent to that in the SDs. The release study was repeated using freshly prepared PBS (pH 7.4) as the release medium. Three replicate release studies were carried out in each case.

Stability study on the formulation

Stability study was carried out on batch F-6 at 40°C in a humidity chamber having 75 % RH for 3 months. The formulation was packed in amber-colored bottle, which was tightly plugged with cotton and capped with aluminium. After 3 months, samples were withdrawn and evaluated for physicochemical properties and dissolution study in phosphate buffer (pH 7.4).

Statistical analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± SD. ANOVA and Student's t-test were performed on the data sets generated using SPSS. Differences were considered significant for p-values < 0.05.

RESULTS AND DISCUSSION

The percentage of the SDs recovered from the formulations (Table 2) shows that there were high percentage recoveries for the formulated trandolapril-loaded SDs. The percentage recovery increased with increasing amounts of Eudragit RL for the ternary systems consisting of trandolapril, PEG 8000 and Eudragit RL 100; however, the highest percentage recovery was observed in the formulation containing urea in addition to Eudragit RL 1000, PEG 8000 and trandolapril. High values of the SDs recovered from the formulations are a strong indication that the formulation technique adopted is reliable and amenable to validation.

The various amounts of trandolapril entrapped in each batch of the solid dispersions are also presented in Table 2. It is evident from Table 2 that the drug contents were dependent on the composition of the solid dispersions. The higher values of the encapsulation efficiency observed may be due to increase in core material in the SDs. Batch F-5 containing three parts of PEG 8000 and one part of Eudragit RL 100 entrapped the greatest amount of trandolapril (91.35 ± 2.00 %) in comparison with other batches of the SDs. The drug entrapment efficiency is an important variable for assessing the drug loading capacity of solid dispersions and their drug release profiles, thus providing an insight into the amount of drug that would be available at the absorption site. This parameter is dependent on the preparation method, physicochemical properties of the drug, and the formulation variables [5 – 7]. Relatively higher entrapment efficiency of the drug in batch F-5 may be due to the enhanced solubilizing effect of higher quantity of PEG 8000.

Table 2: Some physical properties of trandolapril-loaded solid dispersions

Formulation code	Size (μm)[a,b]	Yield (%)	EE (%)[a,c]
F-1	5.95 ± 0.42	81.8	79.12 ± 0.15
F-2	6.82 ± 0.91	65.3	86.10 ± 0.27
F-3	7.35 ± 0.68	93.8	81.78 ± 1.06
F-4	3.87 ± 0.15	65.3	81.17 ± 0.93
F-5	3.49 ± 0.20	82.1	91.35 ± 2.00
F-6	22.17 ± 1.09	97.1	74.67 ± 0.84

[a]Mean ± SD, [b]n =30, [c]n=3.

The mean particle diameters of the solid dispersions formulated are presented in Table 2 and ranged from 3.87 ± 0.15 to 22.14 ± 1.09 μm. This range of particle diameter for SDs would be useful in oral, intramuscular and intravenous delivery of various classes of drugs since the size of SDs is known to play a critical role in determining the route of delivery of various drugs [22 - 24]. The SDs formulated in this study might be suitable for all purpose delivery of various classes of drugs. The photomicrographs of the different batches of the SDs are depicted in Fig 1. The SDs showed different surface characteristics that varied with the compositions of the SDs. A discreet, irregular-shaped brownish-amber coloured SDs were obtained with the ternary systems (batches F-1 to F-5), whereas the quarternary system (batch F-6) yielded a sticky, irregular-shaped, brownish-amber coloured SDs, which may be attributed to partial hydration of the SDs.

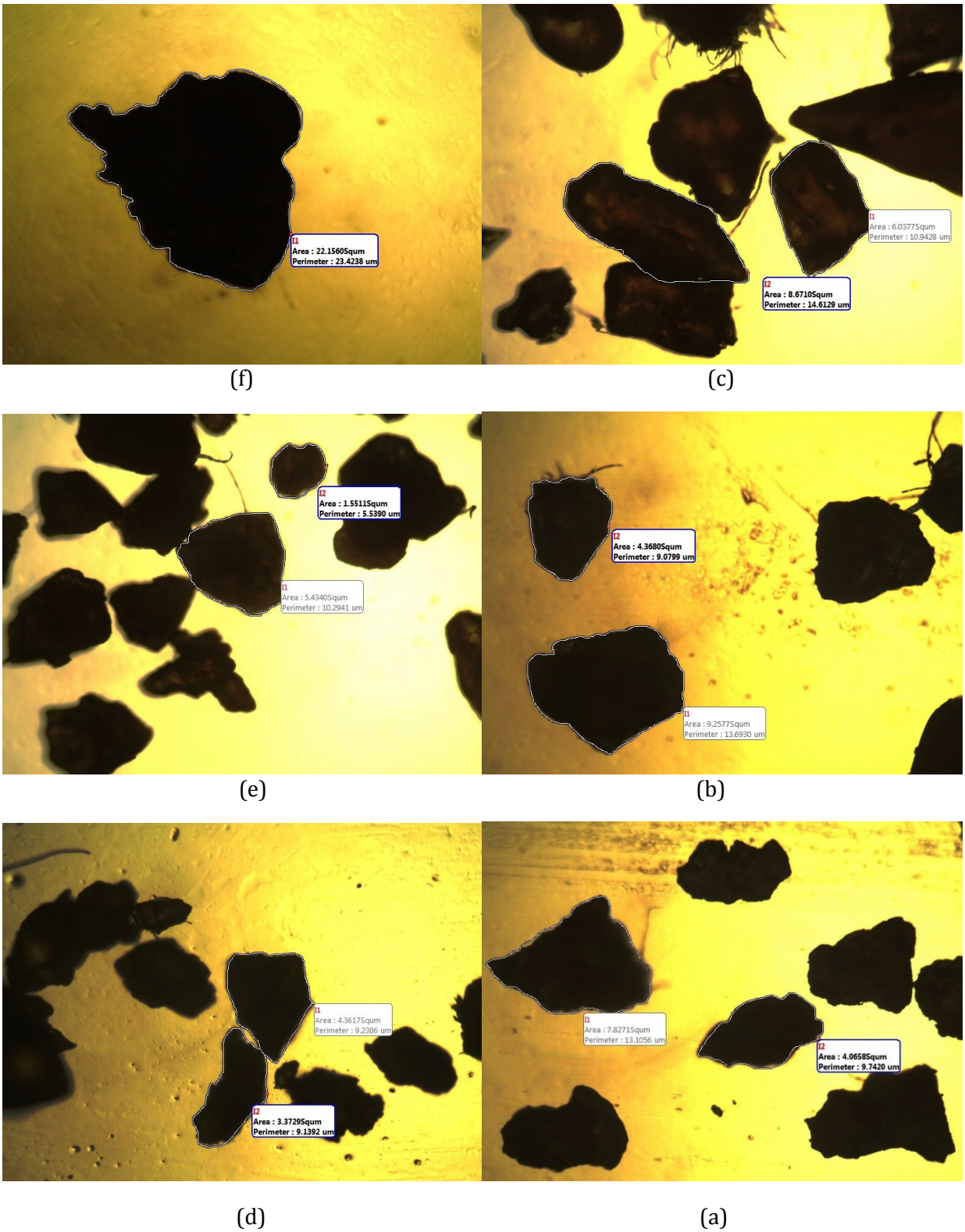

Figure 1. Photomicrographs of trandolapril solid dispersions: **(a)** F-1 **(b)** F-2 **(c)** F-3 **(d)** F-4 **(e)** F-5 **(f)** F-6

The results of the moisture sorption studies carried out at different relative humidities are shown in Fig 2. Moisture sorption is a general term used to describe adsorption and absorption as well as desorption and resorption of moisture [25]. The adsorption of moisture unto polymer materials occurs by the formation of hydrogen bonds with the hydrophilic sites on the surface of the solid [20]. Water molecules first adsorb onto the surfaces of dry materials to form a monomolecular layer (adsorption), which is subjected to both surface binding and diffusional forces. The diffusional forces eventually exceed the binding forces as more water molecules adhere to the surfaces and moisture is transferred into the material (adsorption) [26].

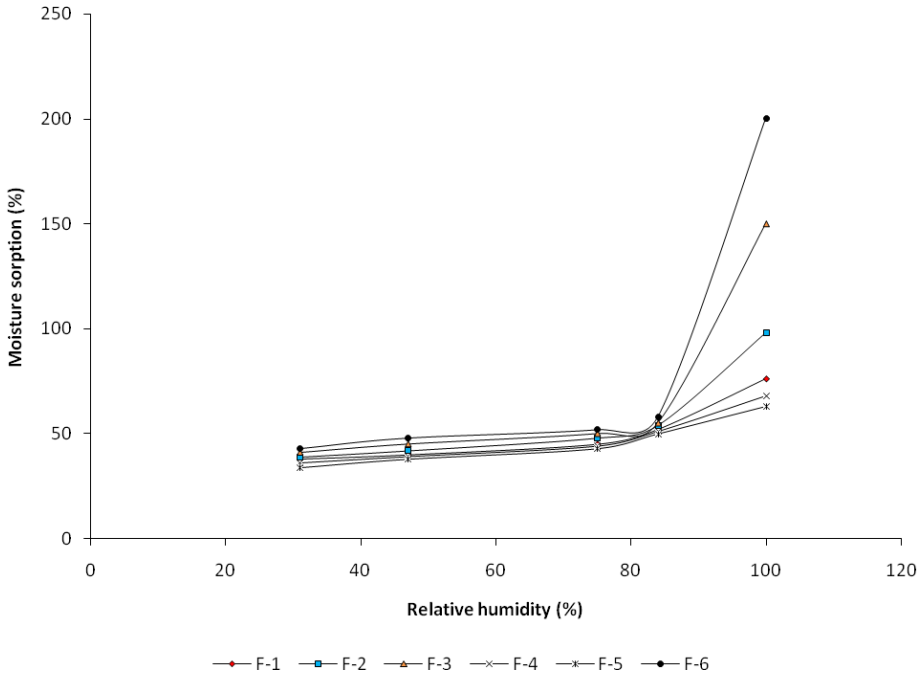

Figure 2. Moisture sorption profile for trandolapril solid dispersions

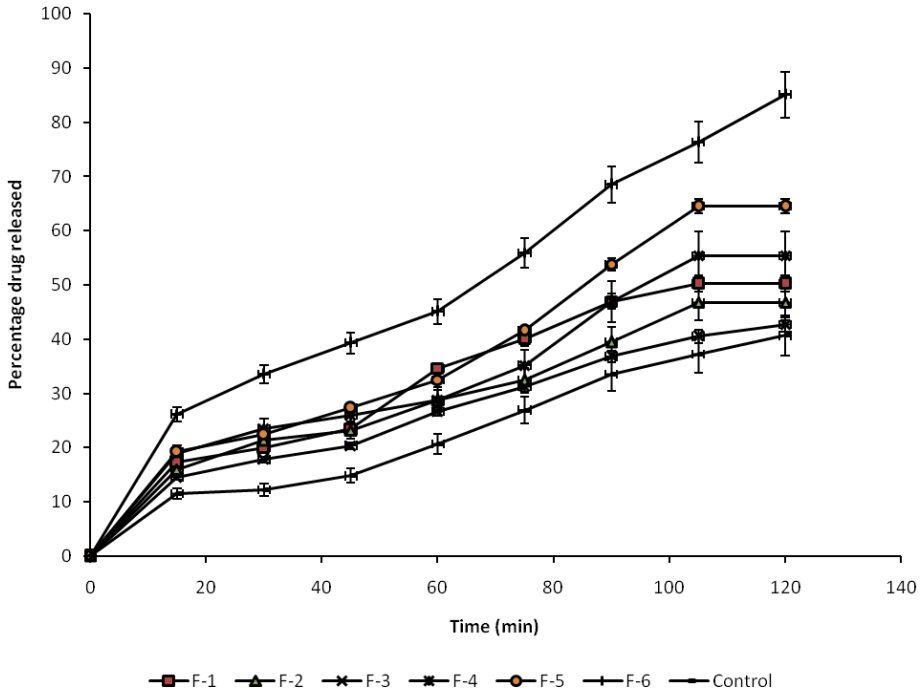

Figure 3. *In vitro* dissolution profile of trandolapril from the solid dispersions in 0.1 N HCl (pH 1.2).

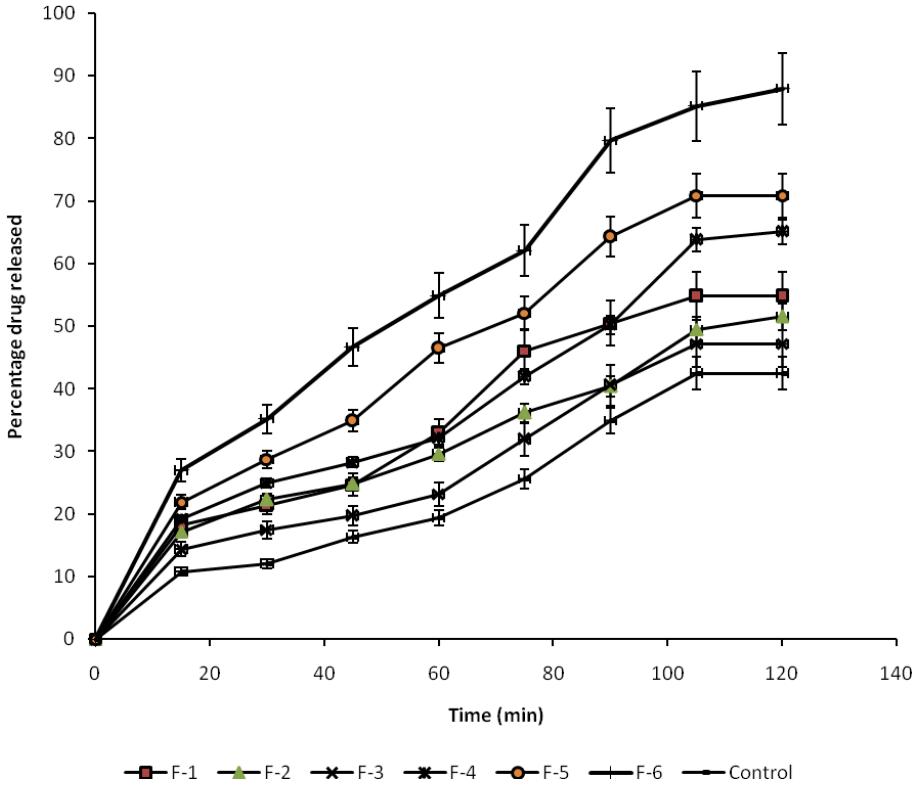

Figure 4. *In vitro* dissolution profile of trandolapril from the solid dispersions in phosphate buffer (pH 7.4).

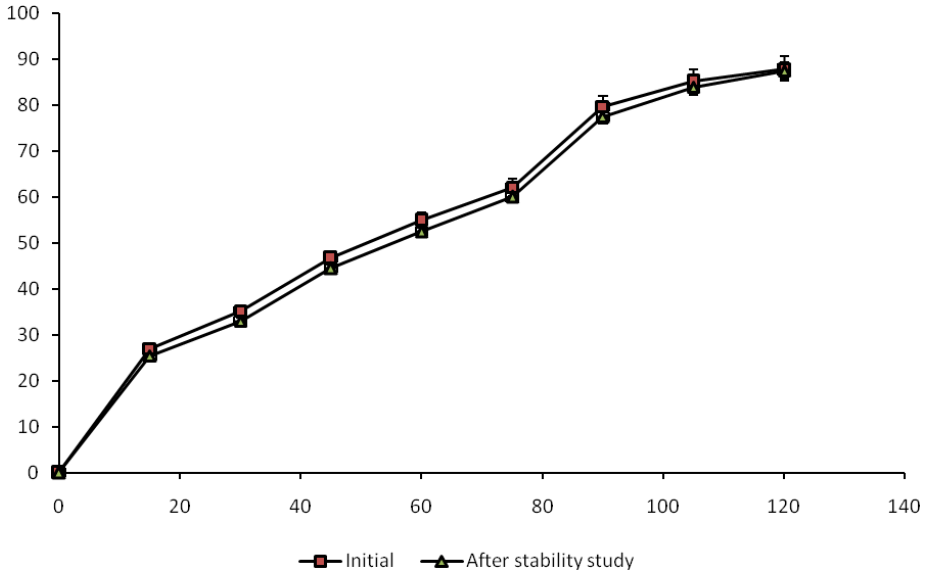

Figure 5. Drug release profile of trandolapril in phosphate buffer before and after stability study for formulation F-6.

Table 3: Kinetics of release of trandolapril from the solid dispersions

Media	Formulation Code	Zero-order (r^2)	First-order (r^2)	Higuchi (r^2)	Hixson-Crowell (r^2)	Ritger-Peppas parameters		
						r^2	K	n
0.1 N HCl	F-1	0.9461	0.9427	0.9635	0.9606	0.9329	0.4789	0.59
	F-2	0.9506	0.9715	0.9678	0.9704	0.9516	0.5306	0.54
	F-3	0.9586	0.9869	0.9752	0.9879	0.9535	0.4573	0.56
	F-4	0.9456	0.9238	0.9314	0.9323	0.8912	0.5691	0.55
	F-5	0.9670	0.9317	0.9208	0.9434	0.9101	0.4447	0.64
	F-6	0.9689	0.9229	0.9580	0.9533	0.9465	0.6858	0.58
Phosphate buffer	F-1	0.9480	0.9378	0.9513	0.9499	0.9210	0.4710	0.61
	F-2	0.9576	0.9689	0.9647	0.9752	0.9496	0.5480	0.54
	F-3	0.9614	0.9418	0.9180	0.9467	0.8980	0.3389	0.63
	F-4	0.9637	0.9250	0.9245	0.9395	0.9178	0.5089	0.61
	F-5	0.9616	0.9698	0.9693	0.9755	0.9729	0.5752	0.62
	F-6	0.9614	0.9485	0.9717	0.9706	0.9786	0.6047	0.69

n=Release exponent; k= Release kinetic constant; r^2= Coefficient of determination.

The moisture uptake experiment was aimed at assessing the comparative amorphicity or crystallinity of the SDs, to provide evidence of cross-linking between the polymer carriers and the drug in SDs produced from colloidal mixture of the carriers and the drug by fusion method. The isothermic moisture sorption profiles of the SDs are shown in Fig. 2. Batches F-1, F-4 and F-5 were observed to be slightly hygroscopic, while batches F-2, F-3 and F-6 were observed to be moderately hygroscopic. Moisture sorption characterization has been reported to be the most sensitive technique for assessing variation in the amorphous content of polymers as well as predicting some physicochemical and functional properties of polymers [21, 27]. The amount of water adsorbed is dependent on the affinity between the surface and water molecules, temperature and relative humidity as well as on the amount of surface area exposed [25]. The adsorption occurs when the water molecules form hydrogen bonds with the hydrophilic sites on the surface of the polymer [20]. The difference in the moisture sorption characteristics between the different batches of the SDs could be due to the difference in the polar groups available for intermolecular interaction with water molecules. There was a gradual increase in the moisture sorption by the SDs batches between 31 % and 84 % RH, after which there was a sharp increase. This may be due to the gradual saturation of the monomolecular layer of the SD powder beds between 31 and 92 RH. The sharp increase in moisture uptake between 84 % and 100% RH corresponds to the total saturation of monomolecular layer and subsequent diffusion of excess moisture into the bulk powder bed or the formation of a multimolecular layer [26]. The amount of moisture taken up by a hydrophilic polymer depends on its amorphous or crystalline composition. For similar polymeric materials, the moisture uptake profile for the amorphous form exhibits a higher shift when compared to that of the more ordered crystalline form [27, 28]. Thus, the quaternary system (Eudragit RL 100/PEG 8000/Urea/trandolapril) is more amorphous than the ternary system (Eudragit RL 100/PEG 8000/trandolapril) (Fig. 2). The higher amorphous domain in the quaternary system relative to that of the ternary system is evidence of additional cross-linking between urea and the ternary system.

The dissolution profile of pure trandolapril and of the ternary and quarternary systems in 0.1 N HCl (pH 1.2) and in PBS (pH 7.4) is shown in Figs. 3 and 4 respectively. There was a sustained release of the drug from the SDs. However, drug release was higher in PBS than in 0.1 N HCl. In both release media, a somewhat biphasic pattern of drug release was observed. This was characterized by an initial drug release which occurred rapidly in less than 20 min into the release experiment in which more than 20 % of the loaded drug was released from the various batches (except batch F-3) of the SDs. This initial "burst release" was followed by a more gradual and extended release over the next 2h. The amounts of trandolapril released as a result of burst effect may likely represent the amounts that adhered weakly to the surface of the formulated SDs. The remaining amounts which were released in a more gradual pattern most

likely represented the amounts that were entrapped into the core (matrix) of the SDs. Burst release resulting in biphasic release pattern may be utilized in therapeutic design of dosage forms. This has severally been reported for SDs [5, 29]. It may be an advantage because it would lead to high initial blood concentration of the drug and a gradual release of the remaining drug. In the management of hypertensive emergencies, the objective is always to instantly reduce the blood pressure. This is possible if a bolus dose of an antihypertensive drug is administered. The bolus dose, when required, will be provided by the initial burst as seen in the SD formulations.

The release profile of an entrapped drug in solid dispersions predicts how a delivery system might function and gives valuable insight into its *in vivo* behaviour[30]. *In vitro* release studies revealed that there was marked increase in the dissolution rate of trandolapril from the solid dispersions when compared to pure trandolapril. The improved dissolution was better in PBS than in 0.1 N HCl.The carriers (Eudragit RL 100, PEG 8000 and urea), which are more soluble at high pH (PBS, pH 7.4) than low pH (0.1 N HCL, pH 1.2), sterically stabilized the surface of the hydrophobic drug (trandolapril). The drug is then adsorbed on the surface of carriers in an extremely fine state of subdivision. The resulting decrease in particle size and the concomitant increase in the surface area served to increase the thermodynamic activity of the drug, which in turn greatly enhanced the dissolution of the drug compared to the pure drug alone. Various mechanisms (reduction of particle size of incorporated drug, partial transformation of the crystalline drug to the amorphous state, formation of solid solution and complexes, reduction of aggregation and agglomeration, improved wetting of drug and solubilisation of the drug by the carrier of the diffusion layer) have been reported [15, 16, 22, 23] to be responsible for improving aqueous solubility/dissolution properties of solid dispersions. The increase in the dissolution kinetics of trandolapril from the SDs might be due to the reduction in crystal size, absence of aggregation of drug crystals and conversion of the drug from crystalline to amorphous/microcrystalline state. Improvement in the wettability of the trandolapril might have resulted from the formation of a film of hydrophilic carriers around it, thus reducing the hydrophobicity of their surfaces. From the *in vitro* drug release profile, it can be seen that formulation F-6 containing urea showed higher dissolution rate compared to other formulations in both 0.1 N HCl and PBS. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilisation of the drug due to the hydrophilic carrier. The observed effect can be attributed to the additive solubilising effect of the surfactant in the microenvironment surrounding the dissolving drug particles, together with its favourable influence on improving drug wettability and spreadability by decreasing the interfacial tension between drug particles and dissolution medium [5, 29]. Relatively higher dissolution enhancement in such cases could be credited to more intimate drug carrier interaction during formulation of solid dispersions, ostensibly accounting for enhancement in dissolution rate of batch F-6 vis-à-vis pure drug and the ternary systems in both 0.1 N HCl and PBS.

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted into various kinetic equations like zero order (cumulative percent drug released vs. time), first order (Log cumulative percent drug retained vs. time), Higuchi (cumulative percent released vs. $\sqrt{T}$), Peppas (Log of cumulative percent drug released vs. log Time) and Hixson-Crowell's cube root model ((Percentage retained)$^{1/3}$ vs Time) as depicted in Table 3. The kinetic model that best fits the dissolution data was evaluated by comparing the coefficient of determination (r^2) values obtained in various models. In the Peppas (Fickian diffusion) model, mechanisms of drug release are characterized using the release exponent ('n' value), indicative of the mechanism of release, and the kinetic constant ('K' value, with units of per min) that incorporates the structural characteristics of the release device. An 'n' value of 1 corresponds to zero-order release kinetics (case-II transport); $0.5 < n < 1$ means an anomalous (non-Fickian) diffusion release model; n=0.5 indicates Fickian diffusion and $n > 1$ indicates a super case-II transport relaxational release; high K values indicate higher order of release[31].

The result of the kinetic study (Table 3) indicated that in both PBS and 0.1 N HCl, the release data of the formulations were successfully fitted into Higuchi, First order, Zero order and Hixson-Crowell models; however, the predominant mechanism of drug release was diffusion. Therefore, the kinetic analysis of the release data indicates that the SDs obeyed the Higuchi

membrane diffusion-controlled model better than other models in both 0.1 N HCl and PBS and thus exhibited diffusion-controlled release characteristics. It is evident from Table 3 that the values of the release rate constant, K, ranged between 0.4447 and 0.6858 in 0.1 N HCl, and between 0.3389 and 0.6047 in PBS. With respect to the Fickian diffusion model, the values of the release exponent, n, indicate that the release of trandolapril from the SDs in both 0.1 N HCl and PBS predominantly occurs by Fickian diffusion.

In order to determine the change in physicochemical parameter and *in-vitro* release profile on storage, stability study was carried out. The physicochemical parameter of the best formulation (i.e. batch F-6) was not significantly changed on storage. The *in-vitro* drug release profile before and after storage is shown in Fig.5. The result indicates that the formulation was stable after storage for more than three months.

CONCLUSIONS

This study has shown that the dissolution rate of trandolapril can be enhanced by the use of hydrophilic-based SDs. The solubilisation effect of hydrophilic carriers results in the reduction of particle aggregation of the drug, elimination of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles, and this is probably responsible for the enhanced solubility and dissolution rate of trandolapril in the SDs. Trandolapril SDs could provide a promising approach to enhance the solubility and dissolution rate of trandolapril. Ternary solid dispersion of trandolapril in Eudragit RL 100 and PEG 8000 was effective in improving the drug dissolution properties. However, the addition of urea when preparing the ternary solid dispersions improved trandolapril dissolution properties in comparison with the simple ternary product. Therefore, the Trandolapril-PEG 800-Eudragit RL 100-urea system appears to be a promising system for developing fast release formulations of the drug, which could be particularly useful in the treatment of clinical condition requiring quick blood pressure reduction.

REFERENCES

[1] Lipinski CA, Lombardo F, Dominyl BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev, 1997;23:3–25.

[2] Lipinski CA. Avoiding investment in doomed drugs, is poor solubility an industry wide problem? Curr Drug Dis, 2001; 4: 17-19.

[3] Lipinski C. Poor aqueous solubility- an industry wide problem in drug discovery. Am Pharm Rev,2002; 5: 82-85.

[4] Dannenfelser R, He H, Joshi Y, Bateman S, Serajuddin ATM. Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol polysorbate 80 solid dispersion carrier system. J Pharm Sci, 2004;93:1165–75.

[5] Newa M, Bhandari KH, Kim JO, Im JS, Kim JA. Enhancement of solubility, dissolution and bioavailability of ibuprofen in solid dispersion systems. Chem Pharm Bull, 2008; 56(4): 569-574.

[6] Hernandez-Trejo N, Hinrichs WLJ, Visser, MR, Muller RH, Kayser O, Frijlink E. Enhancement of the in vitro dissolution rate of the lipophilic drug buparvavone by incorporation into solid dispersions. In: PharmSci, fair. Nice, France, 2005.

[7] Weuts I, Kempen D, Verreck G, Decorte A, Heymans K, Peeters J, Brewster M and Van den Mooter G. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying. Eur J Pharm Biopharm, 2005; 59: 119-126.

[8] Guay DRP. Trandolapril: A newer angiotensin-converting enzyme inhibitor. Clinical Therapeutics, 2003; 25: 713-775.

[9] Sakonjo H, Nakanishi J-i, Fukuda Y. Pharmacological action of a novel angiotensin converting enzyme (ACE) inhibitor, RU 44570, namely (-) –(2S,3aR, 7aS)-1-[(S)-N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]alanyl]hexahydro-2indolinecarboxylic acid: *in vivo* ACE inhibiting effect and antihypertensive effect in various hypertensive models of rats [in Japanese]. Pharmacometrics, 1993; 45: 15-25.

[10] Arakawa K, Limura O, Abe K. Clinical evaluation of RU 44570 (trandolapril), a novel angiotensin converting enzyme inhibitor, in the long-term treatment of patients with essential hypertension [in Japanese]. Rinsho Iyaku, 1992; 8(7): 141-69.

[11] Lynda RW and Donna MT. Trandolapril: A Review of its Pharmaco-dynamic and Pharmacokinetic Properties, and

Therapeutic Use in Essential Hypertension. Pharmacometrics, 1994; 42: 18-25.

[12] Zsolt M, Janos B, Istvan E, Klara P. Evaluation of the effects of lactose on the surface properties of alginate coated trandolapril particles prepared by a spray-drying method. Carbohyd Polym, 2008; 74: 712-716.

[13] Parfitt, K. Martindale, the complete drug reference, 32nd ed., London: Pharmaceutical Press, 1999.

[14] Leuner C, and Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 2000; 50: 47-60.

[15] Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. Pak J PharmSci, 2009; 22: 234-246.

[16] Aftab M and Pralhad T. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS PharmSciTech, 2006; 7(3):68.

[17] Sadeghi F, Afrasiabi GH, Ghodsi A. Evaluation of solid dispersion systems of acetaminophen and ethyl cellulose, eudragit RSor RL and the effect of solvent used in preparation of these systems on characteristic of matrices. J Pharm Sci, 2006; 1: 47-54.

[18] Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer-surfactant combinations using solubility parameters and testing the processability. Int J Pharm, 2007; 328: 119-29.

[19] Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. J Pharm Sci, 1993; 82: 979-986.

[20] Beristain C, Perez-Alonso CI, Lobato-Calleros C, Rodriguez-Huezo ME, Vernon-Carter EJ. Thermodynamic analysis of the sorption isotherms of pure and blended carbohydrate polymers. J Food Eng, 2006; 77: 753-760.

[21] Lin YC, Chen X. Moisture sorption-desorption-resorption characteristics and its effects on the mechanical behaviour of the epoxy system. Polymers, 2005; 46: 11994-12003.

[22] Leuner, C and Dressman, J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 2000; 50: 47-60.

[23] Wong SM, Kellaway IW, and Murdan S. Enhancement of the dissolution rate and oral absorption of a poorly soluble drug by formation of surfactant-containing microparticles. Int J Pharm, 2006; 317: 61-68.

[24] Habib MJ, Venkataram S, Hussain MD. Fundamentals of solid dispersions, In: Pharmaceutical solid dispersion technology, Lancaster: Technomic, 2001; pp. 16-26.

[25] Airaksinen S. Role of excipients in moisture sorption and physical stability of solid pharmaceutical formulations, Academic dissertation, University of Helsinky, Finland, 2005.

[26] York P. Analysis of moisture sorption hysteresis in hard gelatin capsule maize starch and maize starch: drug powder mixture. J Pharm Pharmacol, 1981; 33: 269-273.

[27] Mackin L, Zanon R, Park MJ, Foster HO, Demonte M. Quantification of low levels (<10 %) of amorphous content in micronised active batches using dynamic vapours sorption and isothermal microcalorimetry. Int J Pharm, 2002; 231: 227-236.

[28] Burnett DJ, Theilman F, Sokoloski T, Brum J. Investigation of the moisture-induced crystallization kinetics of spray-dried lactose. Int J Pharm, 2006; 313: 23-28.

[29] Dehghan MHG, Jafar M. Improving dissolution of Meloxicam using solid dispersions. Iranian J Pharm Res, 2006; 4: 231-8.

[30] Habib MJ. Historical background of solid dispersions. In: Habib MJ, (ed.).Pharmaceutical solid dispersion technology, Lancaster: Technomic, 2001, pp 1-6.

[31] Ofokansi KC, Adikwu MU and Okore VC. Preparation and evaluation of mucin-gelatin mucoadhesive microspheres for rectal delivery of ceftriaxone sodium. Drug Dev Ind Pharm, 2007; 33:691-700.