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Formulation and evaluation of solid dispersions based on Eudragit RS 100 and PEG 8000 for improved delivery of trandolapril

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ABSTRACT

The objectives of this study were to formulate solid dispersions based on Eudragit RS 100 and PEG 8000 and hydrophilic carrier (urea) and further evaluate its potential as drug delivery vehicle for a poorly water-soluble angiotensin converting enzyme inhibitor (ACEI) anti-hypertensive prodrug, trandolapril. Trandolapril-loaded solid dispersions (SDs) were prepared by fusion method using varying combination ratios of Eudragit RS 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 simulated gastric fluid without pepsin (SGF, pH 1.2) and simulated intestinal fluid without pancreatin (SIF, pH 7.4).To evaluate the mechanism of release of trandolapril from the SDs, the*in vitro* release data from different batches of theSDs were fitted into differentkinetic models.Results indicate that discrete and irregularly-shaped SDs of mean particle size in the 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 RS 100 and PEG 8000. The moisture sorption studies indicated the amorphous/ microcrystalline state of trandolapril in the SDs . *In vitro* release studies revealed that there was marked increase inthe dissolution rate of trandolapril from the soliddispersions when compared to pure trandolapril. The improved dissolution, which was better in SIF than in SGF, was highest in the SDs containing Eudragit RS 100, PEG 8000 and urea. The increased dissolution rate of trandolapril may be due to the formation of microcrystals, increasedwettability and dispersibility in systems containing Eudragit RS 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 drug, trandolapril.

Key words: Trandolapril, Solid dispersion, PEG 8000, Dissolution, Eudragit RS 100, Moisture sorption, Urea

INTRODUCTION

With recent advances in molecular screening methods foridentifying potential drug candidates, an increasingnumber of poorly water-soluble drugs are being identifiedas potential therapeutic agents. In fact, it has beenestimated that 40% of new chemical entities currentlybeing discovered are poorly water-soluble [1]. Unfortunately, many of these potential drugs areabandoned in the early stages of development due to dissolution concerns [2], which is the rate-determining step in the absorption of the biopharmaceutical classification system (BCS) Class II drugs [1, 2]. An improvement in the dissolutioncharacteristics of poorly water-soluble drugsresults in higher plasma peaks and in total drug absorbed [3].It is therefore becoming increasinglymore important that methods for overcoming dissolutionlimitations be identified and applied commercially suchthat the potential therapeutic benefits of these activemolecules can be realized. This is particularly necessary since majority of these actives are intended for oral administration [4]. The oral bioavailability of a drugdepends on its solubility and dissolution rate which is therate- determining step for the onset of therapeutic activity [5-7]. To overcome the solubility and dissolution problems of poorly water soluble

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drugs, many approaches have been meticulously explored with success in some selected cases, including use of micelles, prodrugs, permeation enhancers, microemulsions, self-emulsifying systems, nanoparticles and solid dispersions, complexation with cyclodextrins, salt formation, particle size reduction (micronization or nanosizing), cogrinding,solubilization based on cosolvents, surfactants, etc.[5, 8-13].A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs. This delivery system can modify the bioavailability of encapsulated drug and can therefore be used to improve the therapeutic index of drugs by increasing their efficacy [14-16]. Solid dispersions (SD) can help overcome the delivery problems of new classes of active molecules and may also extend the therapeutic potential of established drugs [17-20].

SDs have attracted considerable interest as an efficient means of improving the dissolution rate andhence the bioavailability of a range of hydrophobic drugs. Thus, soliddispersiontechnologies are particularly promising for improving theoral absorption and bioavailability of BCS Class II drugs [1, 2]. Solid dispersion (SD) isthe dispersion of one or more active ingredients in inertcarriers at solid state prepared by fusion, solvent or solventfusion methods [21, 22]. 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 surface area), resulting in an increased dissolution rate and consequently, improved bioavailability of poorly water-soluble crystalline drugs [23-25].

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 [26]. Trandolapril, one of the newer drugs in this class, is a non-sulfhydrylprodrug 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 [27]. Trandolapril 2 to 4 mg once daily effectively controls blood pressure for at least 24 h in patients with mild to moderate hypertension [28]. 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 [29]. 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 bioavailabilityvariations probably due to its pooraqueous solubility and unsatisfactorydissolution rate [29-31]. Improvement in itssolubility and dissolution rate is the primaryreason for this study, as this improvementcould be achieved by the use of watersolublepolymers based on solid dispersiontechnology [1, 2]. Eudragit RS and polyethylene glycol 8000 have been employed in previous studies to improve the dissolution rate of a wide range of drugs via SDs [10, 32]. 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 [10, 33]. 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 RS 100, PEG 8000 and urea prepared using the fusion method for the controlled delivery of trandolapril. The SDswere 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) andEudragit RS 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.

Preparation of solid dispersions

Trandolapril-loaded solid dispersions (SDs) were prepared using varying ratios of Eudragit RS 100, PEG 8000 and urea, as shown in Table 1, by the fusion method [6]. Briefly,appropriate amount of trandolapril was dissolvedin methanol. The required amount of Eudragit RS 100 was melted in a beaker on a thermostatically controlled water bathmaintained at 70 – 80°C, followed by addition of appropriate amount of PEG 8000 to the molten Eudragit RS 100. An accurately weighed amount of trandolapril was incorporatedinto the meltedcarriers and mixed thoroughly with a glass rodfor 5 min to ensure homogeneity. The mixture was cooled rapidlyby placing the beaker in an ice bath for 5min to solidify, then powdered in a mortar,sieved through a 100-mesh screen, andstored in a screw-cap vial at roomtemperature 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.

Estimation of drug content and encapsulation efficiency

Solid dispersions equivalent to 4 mg of trandolapril were weighed accurately and dissolved in 100 ml of methanol. The solution was shaken vigorously and filtered, and the filtrate wasspectrophotometrically (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 percentage encapsulation efficiency using the formula below [23, 24]:

$$EE\ \% = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad 1$$

The above procedure was repeated to obtain the encapsulation efficiency as the mean from the replicate 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 eachof 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.

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

Table 1: Formulation compositions of the solid dispersions

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 [34]. 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

$$EMS = M_e/M_d \times 100 \quad 2$$

where M_e is the amount of moisture sorped at equilibrium and M_d is the dry weight of the material [35]. 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 soliddispersion as well as pure drug was performed using USPXXII rotatingpaddle apparatus (Erweka, Germany). Beer's plot for trandolapril at different concentrations was made at a wavelength of 241 nm in simulated gastric fluid (SGF, pH 1.2) and at a wavelength of 258 nm in simulated intestinal fluid (SIF, pH 7.4).The dissolution medium consisted of 250 ml of freshly prepared simulated gastric fluid (SGF), without pepsin (pH 1.2) maintained at 37 ± 1°C. 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 SGF 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 SGF.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 simulated intestinal fluid (SIF) without pancreatin (pH 7.4) as the release medium. Four replicate release studies were carried out in each case.

Stability study on the formulation

Stability study was carried out on the best formulation (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 SIF.

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 absolute drug contents of the solid dispersions are represented as a bar chart in Fig. 1. It is evident from the chart 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-6 containing urea in addition to PEG 8000 and Eudragit RS 100 entrapped the greatest amounts of trandolapril in comparison with the ternary systems (batches F-1 to F-5). The drug entrapment efficiency is an important variable for assessing the drug loading capacity of solid dispersions and their drug release profiles, thus suggesting the amount of the drug that would be available at the absorption site. This parameter is dependent on the preparation method, physicochemical properties of the

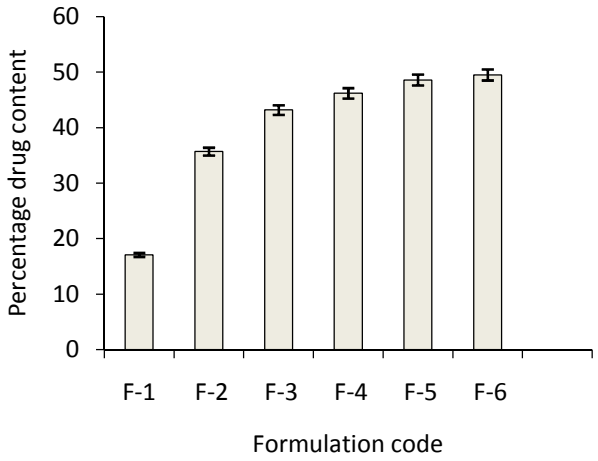

Figure 1. Percentage content of trandolapril in the solid dispersions

drug, and the formulation variables [23-25]. Relatively higher entrapment efficiency of the drug in the quarternary system (batch F-6) may be due to the enhanced solubilizing effect of urea.

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 [4, 5, 22]. 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 2. The internal matrix structure could not be seen but 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.

The results of the moisture sorption studies carried out at different relative humidities are shown in Fig 3. Moisture sorption is a general term used to describe adsorption and absorption as well as

desorption and resorption of moisture [36]. The adsorption of moisture unto polymer materials occurs by the formation of hydrogen bonds with the hydrophilic sites on the surface of the solid [34]. 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) [37]. The moisture uptake experiment was aimed at assessing thecomparative 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. 3. 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 [35]. 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 [36]. The adsorption occurs when the water molecules form hydrogen bonds with the hydrophilic sites on the surface of the polymer [34].

Table 2: Particle size distribution of the solid dispersions

Formulation code	Mean diameter* (μm ± SD)
F-1	4.78 ± 0.20
F-2	5.03 ± 0.91
F-3	3.87 ± 0.15
F-4	9.62 ± 0.68
F-5	6.18 ± 0.42
F-6	22.14 ± 1.09

*Each measurement represents the mean ± SD (n =30).
SD = standard deviation

The difference in the moisture sorption characteristics between the different batches of the SDs could be due to the differences 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 92% 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 92% 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 [37]. 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 [38]. Thus, the quaternary system (Eudragit RS 100/PEG 8000/Urea/trandolapril) is more amorphous than the ternary system (Eudragit RS 100/PEG 8000/trandolapril) (Fig. 3). 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 a physiological pH (SIF, pH 7.4) and in an acidic medium (SGF, pH 1.2) is shown in Figs 4 and 5 respectively. There was a sustained release of the drug from the SDs. However, drug release was higher in SIF than in SGF. 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 30 % of the loaded drug was released. 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 [17-20, 23]. 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.

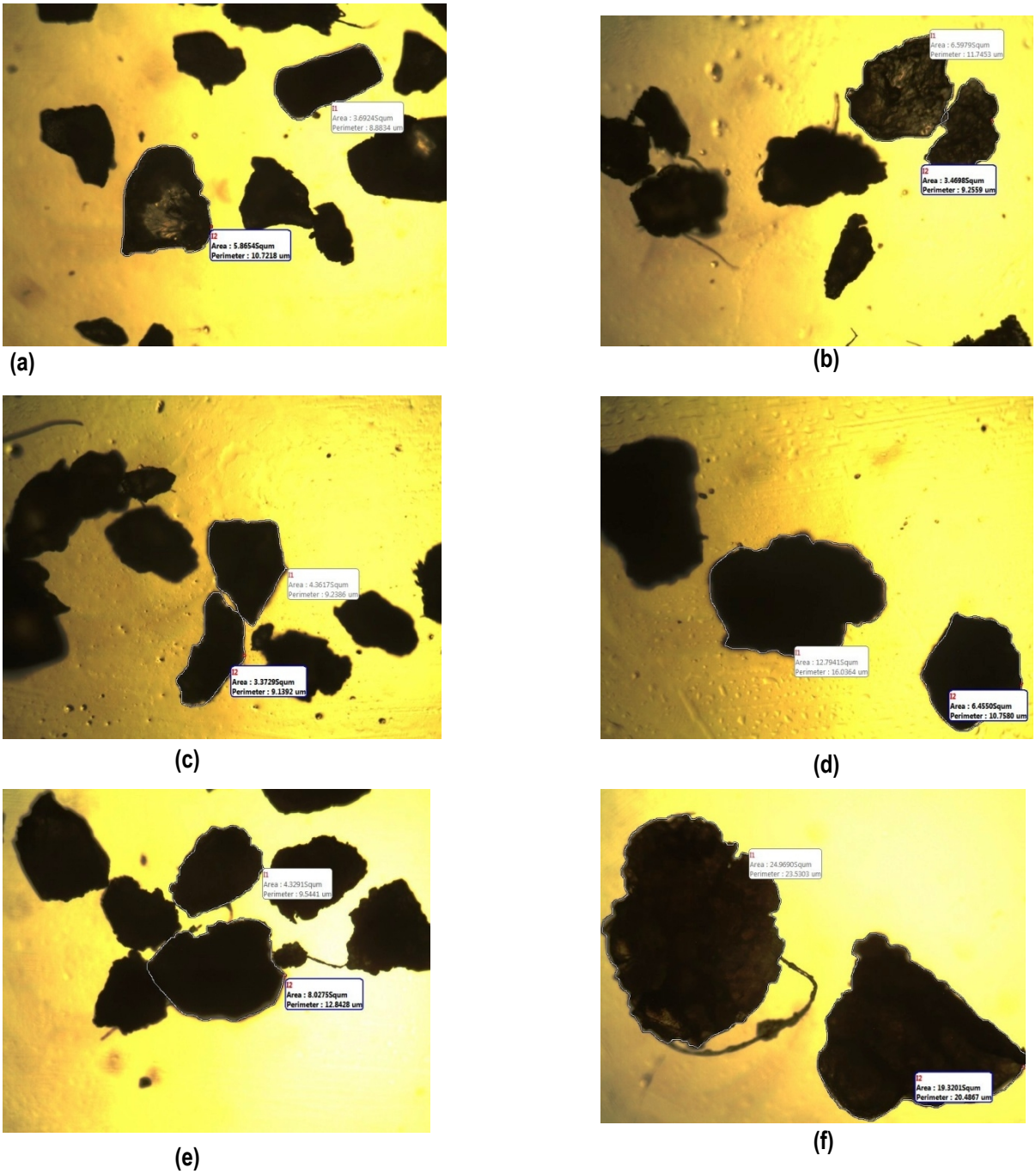

Figure 2. Photomicrographs of trandolapril solid dispersions: **(a)** F-1 **(b)** F-2 **(c)** F-3 **(d)** F-4 **(e)** F-5 **(f)** F-6

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 all the SD formulations. All the batches of the formulation also had the tendency to sustain the release of trandolapril.

The release profile of an entrapped drug in solid dispersions predicts how adelivery system might function and gives valuable insightinto its *in vivo* behaviour [21, 22].*In vitro* release studies revealed that there was marked increase inthe dissolution rate of

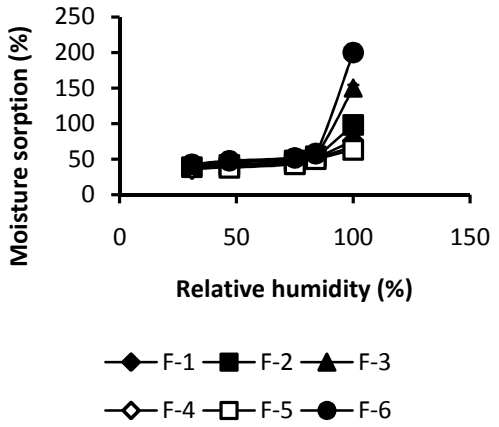

Figure 3. Moisture sorption profile for trandolapril solid dispersions

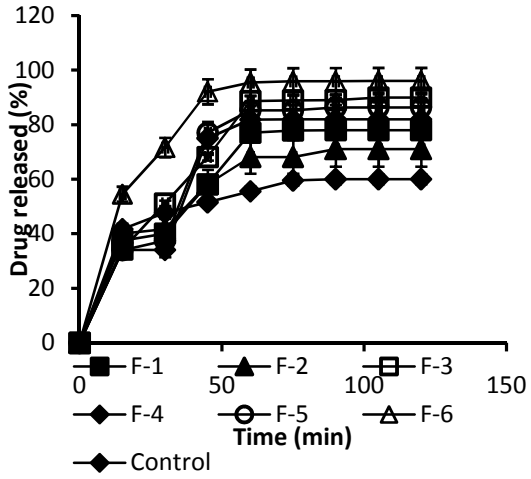

Figure 4. *In vitro* dissolution profile of trandolapril from the solid dispersions in SIF

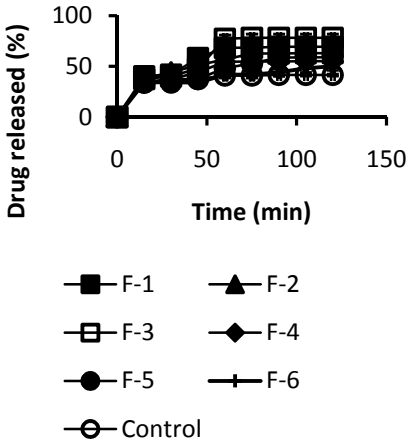

Figure 5. *In vitro* dissolution profile of trandolapril from the solid dispersions in SGF

trandolapril from the soliddispersions when compared to pure trandolapril.

The improved dissolution was better in SIF than in SGF.The carriers (Eudragit RS 100, PEG 8000 and urea), which are more soluble at high pH (SIF) than low pH (SGF),sterically stabilized the surface of thehydrophobic drug (trandolapril). The drug is then adsorbed on thesurface of carriers in an extremely fine state ofsubdivision. The resulting decrease in particle size and theconcomitant increase in the surface area served toincrease the thermodynamic activity of the drug, which inturn greatly enhanced the dissolution of the drugcompared to the pure drug alone. Various mechanisms (reduction of particle size ofincorporated drug, partial transformation of the crystalline drug to the amorphous state, formation of solidsolution and complexes, reduction of aggregation and agglomeration, improved wetting of drug andsolubilisation of the drug by the carrier of the diffusion layer) have been reported [4, 5, 10, 14-16] to be responsible for improving aqueous solubility/dissolution properties of solid dispersions.The increase in the dissolution kinetics of trandolapril from the SDs mightbe due to the reduction in crystal size,absence of aggregation of drug crystals andconversion of the drug from crystalline toamorphous/microcrystalline state. Improvementin the wettability of the trandolapril mighthave resulted from the formation of a film of hydrophilic carriers around it, thus reducingthehydrophobicity of their surfaces.Fromthe *in vitro* drug release profile, it can be seen thatformulation F-6 containing urea showed higher dissolution rate compared to otherformulations in SIF. This may be attributed to the increase in drugwettability, conversion to amorphous form and solubilisationof the drug due to the hydrophilic carrier. The observedeffect can be attributed to the additive solubilising effect of the surfactant in the microenvironment surroundingthe dissolving drug particles, together with its favourable influence on improving drug wettability andspreadability by decreasing the interfacial tension between drug particles and dissolution medium [17-20, 23].Relatively higher dissolution enhancement in suchcases could be credited to more intimate drug carrierinteraction during formulation of solid dispersions, ostensibly accountingfor enhancement in dissolution rate of batch F-6 vis-à-vis pure drug and the ternary systems in SIF.

In order to understand the mechanism and kinetics of drugrelease, the results of the *in vitro* drug release study werefitted into various kinetic equations like zero order(Cumulativepercent drug released vs. Time), first order (Logcumulative

percent drug retained vs. Time), Higuchi(cumulative percent released vs. √T), Peppas (Log ofcumulative 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 datawas evaluated by comparing the regression coefficient (r)values obtained in various models. In the Peppas (Fickian diffusion) model, mechanisms of drug release are characterized using the release exponent ('n' value). 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 [39].

The result of the kinetic study indicated that in SIF, with the exception of batch F-4, the release data of the formulations were successfully fitted into Higuchi, First order and Hixson-Crowell models, whereas batches F-1, F-3, F-4 and F-5 obeyed Zero order kinetic model. In SGF, however, the predominant mechanism of drug release was diffusion. Therefore, the kinetic analysis of the release data indicated that the SDs obeyed the Higuchi membrane diffusion-controlled model better than other models in both SIF and SGF and thus exhibited diffusion-controlled release characteristics. With respect to the Fickian diffusion model, the values of the release exponent, n, indicate that the release of trandolapril from the SDs in SIF predomIn 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 was not significantly changed on storage. The *in-vitro*release profile of trandolapril before and after storage is shown in Fig.6. The result indicates that the formulation was stable after storage for more than three months.

inantly occurs by diffusion following non-Fickian transport mechanism.

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
SIF	F-1	0.9029	0.9200	0.9541	0.9218	0.8292	8.5251	0.5106
	F-2	0.6701	0.9999	0.9599	0.9888	0.9597	18.8018	0.2854
	F-3	0.9643	0.9999	0.9697	0.9201	0.9906	5.3370	0.6765
	F-4	0.9197	0.8602	0.8854	0.8526	0.7612	4.4771	0.6985
	F-5	0.9376	0.9094	0.9008	0.9046	0.8296	4.2697	0.7235
	F-6	0.7874	0.9561	0.9887	0.9347	0.9776	17.1830	0.4267
SGF	F-1	0.8080	0.9143	0.9718	0.9839	0.8268	12.8913	0.3913
	F-2	0.3917	0.9000	0.8468	0.9000	0.9007	24.5301	0.1203
	F-3	0.8572	0.9200	0.9095	0.9218	0.7069	9.8537	0.4550
	F-4	0.7306	0.9999	0.9645	0.9783	0.8672	13.8420	0.3166
	F-5	0.7478	0.7860	0.9047	0.7627	0.5611	13.1039	0.3181
	F-6	0.5524	0.8000	0.9091	0.6743	0.8084	17.1199	0.2022

n=Release exponent; k= Release kinetic constant; r^2 = Square of correlation coefficient.

CONCLUSIONS

This study has shown that the dissolution rate of trandolapril could be enhanced by the use of hydrophilic-based SDs. The solubilizationeffect of hydrophilic carriers resulted in the reduction ofparticle aggregation of the drug, eliminationof crystallinity, increased wettability anddispersibility, and alteration of the surfaceproperties of the drug particles, and this isprobably responsible for the enhancedsolubility and dissolution rate of trandolapril inthe SDs. Trandolapril SDs could provide apromising approach to enhance the solubilityand dissolution rate of trandolapril. Ternary solid dispersion of trandolapril in Eudragit RS 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, as the quarternary system allowed achievement of 95% dissolved drug in SIF after 45 min (in comparison with 50 % for drug alone and 55 – 76 % for ternary systems).Therefore, the Trandolapril-PEG 800-

Eudragit RS 100-urea system appears to be a promising system for developing fast releaseformulations of the drug, which could be particularly useful in the treatment of clinical condition requiringquick blood pressure reduction.

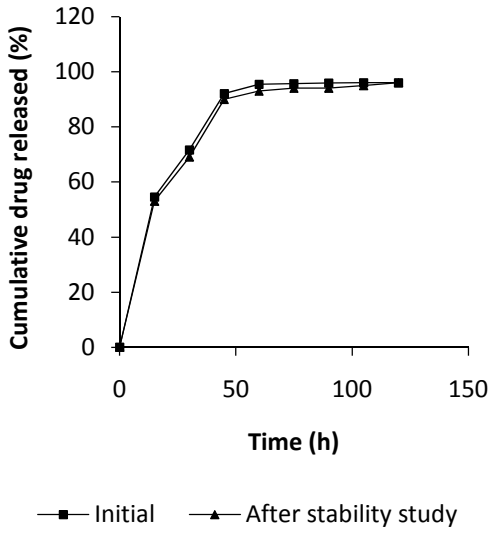

Figure 6. Drug release profile of trandolapril in SIF before and after stability study for formulation F-6.

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