Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Solid Dispersions Based on Poloxamer 188 Improve the Dissolution Rate of Trandolapril, a Poorly Water-Soluble ACE Inhibitor

KENECHUKWU FC[1*], OFOKANSI KC[1], MOMOH MA[1], OGBONNA JDN[1], NNADI CO[2] AND AKPA PA[1]

[1]Drug Delivery and Nanomedicines Research Group, Department of Pharmaceutics, University of Nigeria, Nsukka 410001, Enugu State, Nigeria

[2]Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria, Nsukka 410001, Enugu State, Nigeria

ARTICLE DETAILS

Article history:
Received on 14 February 2017
Modified on 25 September 2017
Accepted on 29 September 2017

Keywords:
Solid dispersions (SDs);
Drug dissolution;
Trandolapril;
Moisture sorption;
Poloxamer 188.

ABSTRACT

The purpose of this study was to formulate and evaluate trandolapril/poloxamer 188 solid dispersions (SDs) for improved delivery of trandolapril, a poorly water-soluble antihypertensive prodrug. Poloxamer 188 was employed as a hydrophilic carrier at various trandolapril: poloxamer 188 ratios to prepare trandolapril-loaded SDs by fusion method. Characterization based on surface morphology, particle size, entrapment efficiency and moisture sorption properties were carried out on the SDs. Compatibility study was carried out using Fourier transform infrared (FT-IR) spectroscopy while the *in vitro* dissolution of trandolapril from the SDs was performed in phosphate buffered saline (PBS, pH 7.4). The results showed that discrete and irregularly-shaped SDs of average particle size in the range 2.16 ± 0.78 to 2.94 ± 0.25 µm, which were stable over 3 months, were obtained. The moisture sorption studies indicated the amorphous/ microcrystalline state of trandolapril in the SDs, which also exhibited good entrapment efficiency (EE%) and marked increase in the dissolution rate of trandolapril from the SDs when compared to pure trandolapril (unformulated trandolapril). Spectroscopic studies indicate that there was no strong chemical interaction between the drug and poloxamer 188 which, when incorporated inside SD, had prominent effect in improvement of trandolapril dissolution. As we increased poloxamer 188 concentration in SD formulation, the dissolution rate of the drug (trandolapril) increased, which may be due to the formation of microcrystals, increased wettability and dispersibility in the formulations. The present finding has shown that trandolapril/poloxamer 188 SDs is a potential carrier system for dissolution and bioavailability enhancement of the poorly water-soluble anti-hypertensive prodrug, trandolapril.

INTRODUCTION

Recently, there is growing interest and investment in the use of polymer-based systems in drug discovery and product development to effectively overcome problems related to stability and bioavailability [1, 2]. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development [3]. Many potential drugs are abandoned in the early stages of development due to dissolution concerns [4], which is the rate-determining step in the absorption of the biopharmaceutical classification system (BCS) Class II drugs [4, 5].

Author for Correspondence:
Email: chimafrankduff@yahoo.com, frankline.kenechukwu@unn.edu.ng

An improvement in the dissolution characteristics of poorly water-soluble drugs results in higher plasma peaks and in total drug absorbed [6]. A lot of formulation techniques and strategies including use of micelles, prodrugs, permeation enhancers, microemulsions, self-emulsifying systems, nanoparticles, complexation with cyclodextrins, salt formation, particle size reduction (micronization or nanosizing), cogrinding, solubilization based on co-solvents, surfactants, etc. [7 - 12], have been employed to tackle this challenge. However, all these methods suffer from drawbacks. Solid dispersions can help overcome the delivery problems of new classes of active molecules and may also extend the therapeutic potential of established drugs [13 - 16]. SD is the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent or solvent fusion methods [17, 18]. 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 [19 – 21]. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs [22 – 24].

Angiotensin converting enzyme (ACE) inhibitor therapy is a valuable treatment option for patients with hypertension, effectively lowering blood pressure without influencing cardiovascular reflexes [25]. Trandolapril [chemically described as (2S, 3aR, 7aS)-1-[(S)-N-[(S)-1-Carboxy-3phenylpropyl] alanyl] hexahydro-2-indolinecarbo-xylic acid, 1-ethyl ester], 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 [26]. Trandolapril 2 to 4 mg once daily effectively controls blood pressure for at least 24 h in patients with mild to moderate hypertension [27]. 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 [28]. Thus, trandolapril, with its favourable pharmacological profile (high lipophilicity, high enzyme affinity and long duration of action) and anti-hypertensive 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. Despite these benefits, trandolapril exhibits inter-individual bioavailability variations probably due to its poor aqueous solubility and unsatisfactory dissolution rate [28 – 30]. Our team had earlier explored combinations of Eudragit RL 100, polyethylene glycol 8000 (PEG 8000) and urea in the preparation of SDs of trandolapril by fusion method to address the solubility and bioavailablity concerns of trandolapril [31]. In the present study, SDs were formulated using poloxamer 188, a hydrophilic surfactant [32], and trandolapril. Poloxamer 188 is a block synthetic copolymer of ethylene oxide and propylene oxide. It is used as a dispersing agent, a solubilizing agent, a tablet lubricant, an emulsifying agent and as a wetting agent. When dispersed in water or ethanol at low concentrations, poloxamer 188 exists individually as monomolecular micelles. When the concentration in the system increases, this will result in the formation of multi molecular aggregates. It is readily soluble in polar and non-polar organic solvents which allow a wide range of dosage forms to be formulated with this material. Poloxamer 188 is suitable for the preparation of solid dispersions and to improve the solubility, absorption and bioavailability of low-solubility actives in solid oral dosage forms processed by melting and granulation [33].

Consequently, the purpose of this study was to prepare trandolapril/poloxamer 188 SDs by fusion method with a view to improving the solubility, dissolution and bioavailability of trandolapril. The prepared SDs were characterized in terms of particle size, morphology, entrapment efficiency, moisture sorption and drug dissolution properties.

MATERIALS AND METHODS

Materials

The materials used were trandolapril (Molecular weight = $C_{24}H_{34}N_2O_5$, Percentage purity = 99.5%) (Dr. Reddy's Laboratories Ltd., Hyderabad, India), poloxamer 188 (Synochem, Germany), potassium chloride, potassium thiocynate and calcium chloride (BDH Chemicals, UK), sodium hydroxide (Merck, Germany), monobasic potassium phosphate and methanol (Sigma Aldrich, Germany). All other reagents were of analytical grade and used without further purification. Distilled water was obtained from an all-glass still.

Methods

Preparation of Solid Dispersions

The SDs were prepared using varying ratios of trandolapril and poloxamer 188, as shown in Table 1, by the fusion method [5, 13-16]. Briefly, appropriate amount of trandolapril was dissolved in methanol. The required amount of poloxamer 188 was melted in a beaker on a thermostatically controlled water bath maintained at 60 – 80^{0}C. The drug solution was incorporated into the melted polymeric 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-4.

Table 1: Formulation compositions of the solid dispersions

Formulation code	Ratio of Drug and polymer	Trandolapril (mg)	Poloxamer 188 (mg)
F-1	1:1	1000	1000
F-2	1:2	1000	2000
F-3	1:3	1000	3000
F-4	1:4	1000	4000

Estimation of Drug Content and Entrapment Efficiency

A calibration curve for trandolpril in methanol was obtained by diluting a 2 mg % methanolic solution of trandolapril serially with the solvent to obtain several dilute concentrations ranging between 0.1 mg % and 1 mg %. The absorbance of each concentration was determined at a predetermined wavelength of 230 nm using a spectrophotometer (Phoenix-220 DPC V model). For determination of the absolute drug content, quantities of SD equivalent to 100 mg of trandolapril were weighed 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 the predetermined wavelength of 230 nm for trandolapril content [31]. The amount of drug encapsulated in the SDs was calculated with reference to a standard Beer's plot for trandolapril to obtain the percentage entrapment efficiency using the formula below [19,20]:

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

The above procedure was repeated to obtain the entrapment 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 (Leica, 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

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

$$\textbf{EMS} = M_e / M_d \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

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.

Spectroscopic Characterization (Interaction Study)

FTIR spectroscopy study was conducted using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1} with threshold of 1.303, sensivity of 50 and resolution of 2 cm^{-1} range. The procedure consisted of dispersing a 5 mg sample in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum obtained [36, 37].

In Vitro Drug Release Studies

Drug dissolution 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 258 nm in phosphate buffered saline (PBS, pH 7.4). The dissolution medium consisted of 250 ml of freshly prepared PBS (pH 7.4) maintained at 37 ± 1ºC. The polycarbonate dialysis membrane (Spectrum Laboratories, Rancho Dominguez, Canada) (MWCO = 6000-

8000; pore size 0.22 mm) used was pre-treated 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 (10 min), 5 ml portions of the dissolution medium were withdrawn, filtered and analyzed spectrophotometrically (Unico 2102 PC UV/Vis Spectrophotometer, USA) at 258 nm [31]. For each sample withdrawn, an equivalent volume (5 ml) of PBS 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 PBS. A positive control was set up for each batch by similarly weighing amounts of pure trandolapril equivalent to that in the SDs. Three replicate release studies were carried out in each case.

Stability Study on the Formulation

Stability study was carried out on the best formulation (F-4) at 40ºC 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 PBS.

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

In drug design and formulation technology, surfactants are employed in oral dosage forms to increase solubility of the drugs having slow dissolution rate. Increase in solubility by surfactant is attributed to either wetting phenomena or prevention of recrystallization [32]. In this study, trandolapril (BCS Class II drug) was employed to evaluate the effect of surfactant (poloxamer 188) on dissolution of trandolapril when incorporated in solid dispersion. The various amounts of trandolapril entrapped in each batch of the solid dispersions are presented in Figure 1. It is evident from Figure 1 that the drug contents were dependent on the amount of poloxamer in the solid dispersions. The higher the poloxamer content of the solid dispersion the higher the drug entrapment efficiency in the solid dispersions. Thus formulation F1 with the least amount of poloxamer had the least entrapment efficiency while formulation F4 with the highest poloxamer content had the highest entrapment. The higher values of the entrapment efficiency observed may be due to increase in molecular solubilization of the drug in the poloxamer. 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 [19 - 21]. Overall, batch F-4 containing highest amount of poloxamer 188 entrapped the greatest amounts of trandolapril. This may be due to the enhanced solubilizing effect of poloxamer 188.

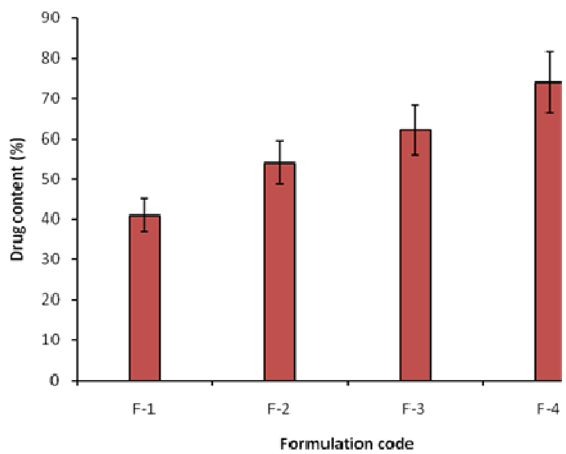

Figure 1: Percentage content of trandolapril in the solid dispersions

Table 2: Particle size distribution of trandolapril solid dispersions

Formulation code	Mean diameter* (µm±SD)
F-1	2.48 ± 0.30
F-2	2.57 ± 0.81
F-3	2.94 ± 0.25
F-4	2.16 ± 0.78

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

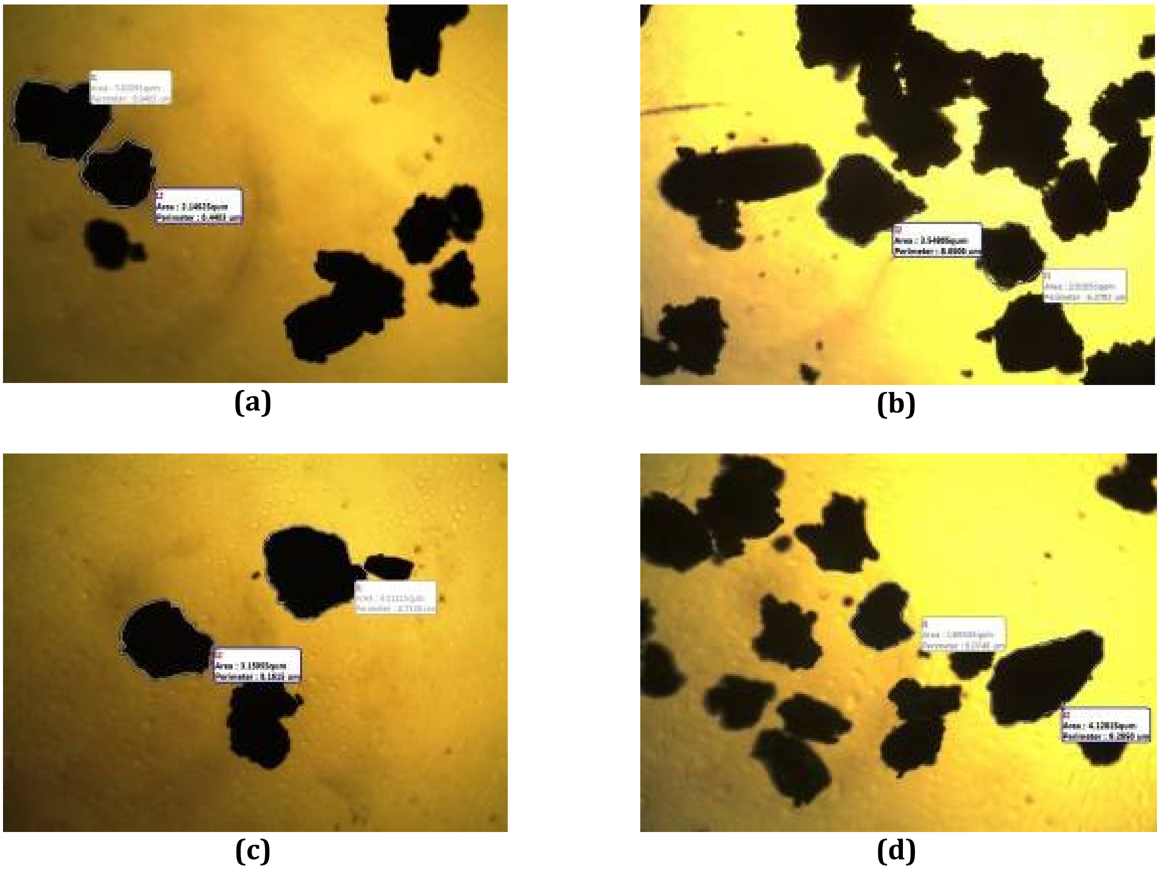

Figure 2: Photomicrographs of trandolapril solid dispersions: (a) F-1 (b) F-2 (c) F-3 (d) F-4.

Table 2 shows that the mean particle diameters of the solid dispersions ranged from 2.16 ± 0.78 to 2.94 ± 0.25 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 [5, 7, 18]. 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 depicted in Figure 2 showed that discreet, irregular-shaped, brownish-amber coloured SDs were obtained. In addition, the SDs showed different surface characteristics that varied with the compositions of the SDs.

The results of the moisture sorption studies carried out at different relative humidities are shown in Figure 3. 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]. 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 carrier and the drug in SDs produced from colloidal mixture of the carrier and the drug by fusion method. The isothermic moisture sorption profiles of the SDs are shown in Figure 3. All batches of the SDs were observed to be moderately hygroscopic. 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.

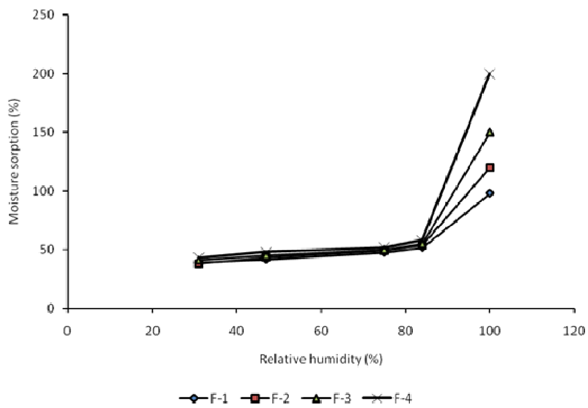

Figure 3: Moisture sorption profile for trandolapril solid dispersions.

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.

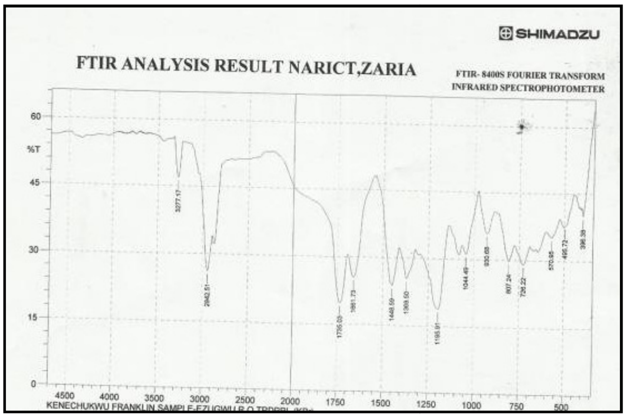

Figure 4: FT- IR of trandolapril pure sample

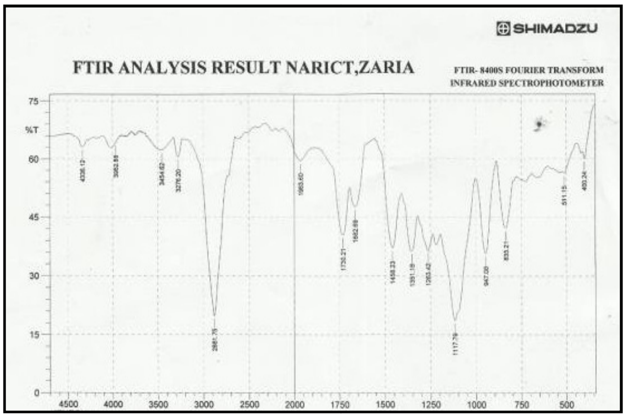

Figure 5: FT-IR spectrum of batch F-1

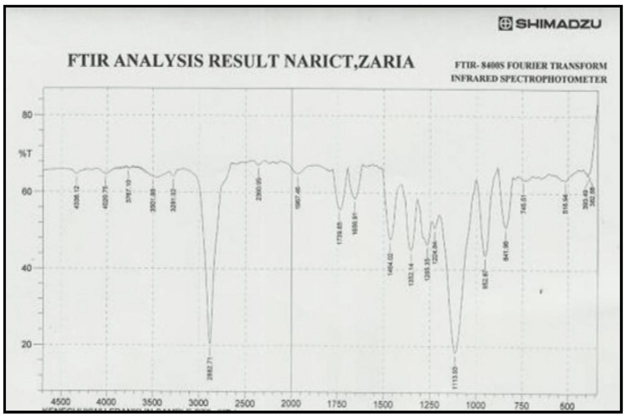

Figure 6: FT-IR spectrum of batch F-2

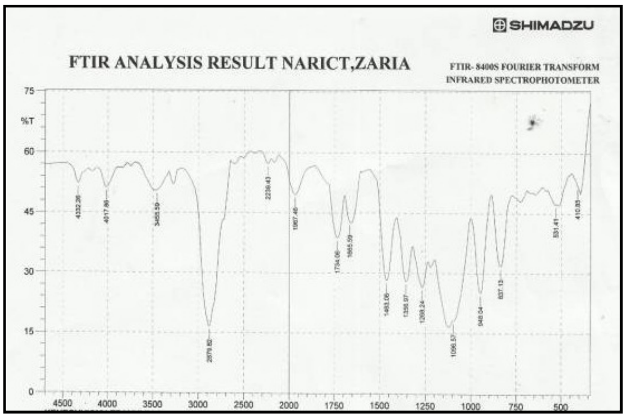

Figure 7: FT-IR spectrum of batch F-3

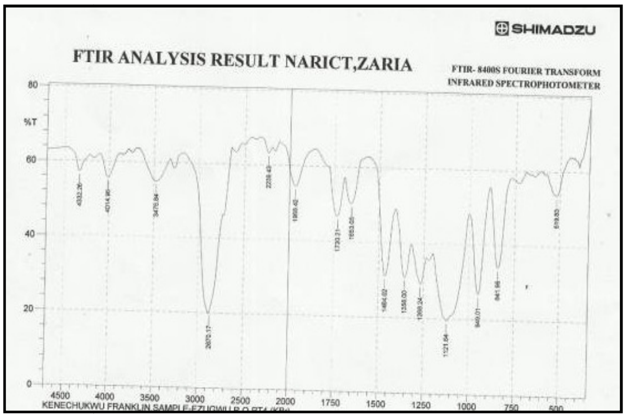

Figure 8. FT-IR spectrum of batch F-4

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 [35, 38].

The FT-IR spectrum of a given compound is always unique and characteristic. Thus, IR spectroscopy is a quick and relatively cheap technique for identifying compounds [36 - 37, 39 – 40].

In addition, FT-IR is a very powerful technique for detecting the presence of interaction in drug-carrier solid dispersions. The appearance or disappearance of peaks and/or the shift of their positions are often an indication of interactions such as hydrogen bonding [37]. Figures 4 – 8 show FT-IR spectra of trandolapril and the solid dispersions. Their FT-IR was carried out as finger prints to identify solid dispersion of the drug relative to the pure drug sample. FTIR of trandolapril (Figure 4) showed that principal peaks were observed at wave numbers of 726.22-807.24, 930.68, 1195.91, 1369.5, 1448.59, 1661.73, 1735.03, 2942.51, 3277.17 cm^{-1} corresponding to aromatic C – H deformation (2 adjacent free H's), aromatic C – H bending (1 adjacent free H's), C – O stretching (strong), C – H deformation (CH3), C = H deformation (CH3CH2), C = C stretching of α-β unsaturated ring, C – H stretching and O – H stretching respectively. As principal peaks of FT-IR spectrum of pure drug appeared in the trandolapril solid dispersions (Figures 5 – 8), it can be concluded that there was no strong chemical interaction between the drug and poloxamer 188 [36 – 37, 39 – 40].

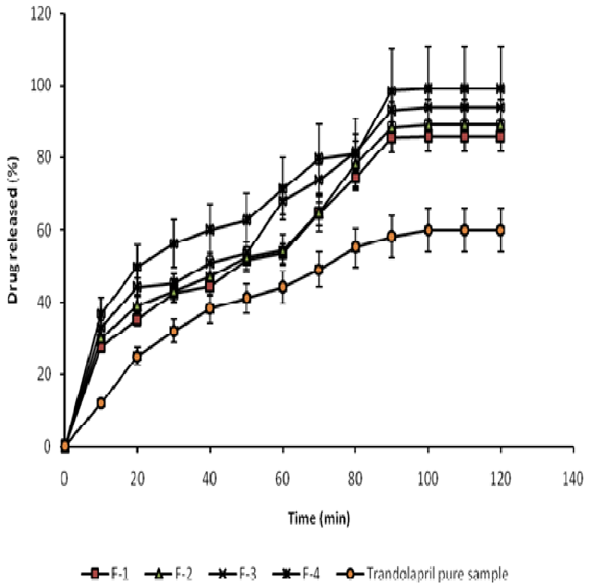

Figure 9: *In vitro* dissolution profile of trandolapril from the solid dispersions in PBS (pH 7.4)

Figure 9 shows the *in vitro* dissolution profile of trandolapril from the solid dispersions in PBS (pH 7.4) The release profile of an entrapped drug in SDs predicts how a delivery system might function and gives valuable insight into its *in vivo* behaviour [17,18]. The results revealed that there was marked increase in the dissolution rate of trandolapril. The surfactant, poloxamer 188 sterically stabilized the surface of the hydrophobic drug (trandolapril), which is then adsorbed on the surface of carrier 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 to be responsible for improving aqueous solubility or dissolution properties of SDs [4 – 5, 12, 14]. The enhanced 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. It could be deduced from Figure 9 that formulation F-4 containing the highest amount of poloxamer 188 showed highest dissolution rate among the formulations. 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 [19 – 21, 33].

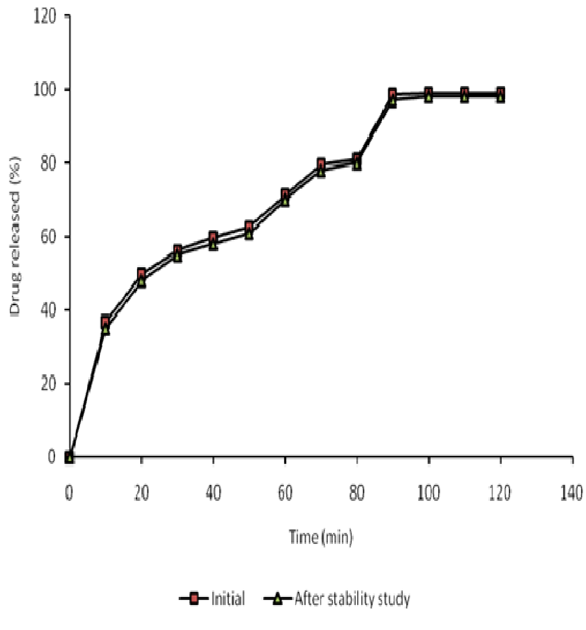

Figure 10: Drug release profile of trandolapril in PBS (pH 7.4) before and after stability study for formulation F-4.

Relatively higher dissolution enhancement in such cases could be credited to more intimate drug carrier interaction during formulation of SDs, ostensibly accounting for enhancement in dissolution rate of the formulations vis-à-vis pure drug (trandolapril).

Furthermore, there was an increase in the dissolution rate of the drug from the SDs. All the batches of the formulation also had the tendency to improve the release of trandolapril. A somewhat biphasic pattern of drug release was observed. This was characterized by an initial drug release which occurred rapidly in less than 30 min into the release experiment in which more than 25 % of the loaded drug was released. This initial "burst release" was followed by a more gradual and extended release over the next 90 min. The quantities 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 [22, 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.

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 anti-hypertensive drug is administered. The bolus dose, when required, will be provided by the initial burst as seen in the SD formulations. Thus, these formulations would be particularly useful in the treatment of clinical condition requiring quick blood pressure reduction.

Stability study was carried out in order to determine the change in physicochemical parameter and *in-vitro* release profile on storage. Stability could be viewed from the degradation of the active ingredient or the excipients [2]. The physicochemical parameter of the best formulation (F-4) was not significantly changed on storage. The *in-vitro* release profile of trandolapril before and after storage is shown in Figure 10. The result indicates that the formulation was stable after storage within three months of study.

CONCLUSIONS

This study investigates the effect of surfactant (poloxamer 188) on dissolution rate of trandolapril, a poorly soluble anti-hypertensive drug when incorporated in solid dispersion. The solubilization effect of hydrophilic carrier 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. Therefore, the trandolapril-poloxamer 188 could be exploited for developing fast release formulations of the drug, which could be particularly useful in the treatment of clinical condition requiring quick blood pressure reduction, thus encouraging further development of these formulations. This study has shown that trandolapril-poloxamer 188 solid dispersion is a potential carrier system for dissolution enhancement of trandolapril. Further studies would seek to investigate other solid state charcterizations (e.g. DSC, PXRD) as well as pharmacokinetics and anti-hypertensive effects of the solid dispersions.

ACKNOWLEDGEMENTS

We wish to thank the National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna State, Nigeria, for assistance in FT-IR analyses, as well as Synochemm Germany and Dr. Reddy's Laboratories Limited, Hyderabdad, India for provision of poloxamer 188 and trandolapril respectively used in the study.

REFERENCES

[1] Ofokansi KC, Kenechukwu FC, Isah AB, Okigbo EL. Formulation and evaluation of glutaraldehyde-crosslinked chitosan microparticles for the delivery of ibuprofen. Trop J Pharm Res. 2013; 12(1):19-25.

[2] Ofokansi KC, Adikwu MU. Formulation and evaluation of microspheres based on gelatin-mucin admixtures for rectal delivery of cefuroxime sodium. Trop J Pharm Res. 2007; 6(4):825-832.

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

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

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

[6] Sugimoto M, Okagaki T, Narisawa S, Koida Y, Na-kajima K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water soluble-polymer. Int J Pharm. 1998; 160: 11–19.

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

[8] Vogt M, Kunath K, Dressman JB. Dissolution improvement of four poorly water soluble drugs by cogrinding with commonly used excipients. Eur J Pharm Biopharm. 2008; 68: 330-337.

[9] Ozeki T, Beppu S, Mizoe T, Takashima Y, Yuasa H, Okada H. Preparation of two-drug composite microparticles to improve the dissolution of insoluble drug in water for use with a 4-fluid nozzle spray drier. J Control Rel. 2005; 107:387-394.

[10] Palmwe AM. New horizons in drug metabolism, pharmacokinetics and drug discovery. Drug News Perspect. 2003; 16:57-62.

[11] Bo T, Gang C, Jian-Chun G, Cai-Hong X. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Disc Today. 2008; 13(4): 606-612.

[12] Allahham A, Stewart PJ. Enhancement of the dissolution of indomethacin in interactive mixtures using added fine lactose. Eur J Pharm Biopharm. 2007; 67: 732-742.

[13] Jain R, Jani K, Setty CM, Patel D. Preparation and evaluation of solid dispersions of aceclofenac. Int J Pharm Sci Drug Res. 2009; 1(1): 32-35.

[14] Biswal S, Sahoo J, Murthy PN, Giradkar PR, Avari JG. Enhancement of dissolution rate of gliclazide using solid dispersions with polyethylene glycol 6000. AAPS Pharm Sci Tech. 2008; 9(2): 563-570.

[15] Emara LH, Badr RM, Abed EA. Improving the dissolution and bioavailability of nifidepine using solid dispersion and solubilizers. Drug Dev Ind Pharm. 2002; 28: 795-807.

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

[17] Habib MJ. Historical background of solid dispersions. In: Habib MJ, (ed.). Pharmaceutical solid dispersion technology, Technomic, Lancaster: 2001.

[18] Habib MJ, Venkataram S, Hussain MD. Fundamentals of solid dispersions, In: Pharmaceutical solid dispersion technology, Technomic, Lancaster: 2001.

[19] 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.

[20] Hernandez-Trejo N, Hinrichs WLJ, Visser, MR, Muller RH, Kayser O, Frijlink E. (2005). Enhancement of the *in vitro* dissolution rate of the lipophilic drug buparvavone by incorporation into solid dispersions. Int J Pharm Sci Tech. 2005; 5: 34-39.

[21] Weuts I, Kempen D, Verreck G, Decorte A, Heymans K, Peeters J, Brewster M, Van den Mooter G. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG 6000 prepared by spray drying. Eur J Pharm Biopharm. 2005; 59: 119-126.

[22] Trapani G, Franco M, Latrofa A, Tullio C, Provenzano MR, Serra M, Muggironi M, Biggio G, Liso G. Dissolution properties and anticonvulsant activity of phenytoin polyethylene glycol 6000 and polyvinylpyrrolidone K-30 solid dispersions. Int J Pharm. 2001; 225: 63–73.

[23] Tashtoush BM, Al-Qashi ZS, Najib NM. *In vitro* and *in vivo* evaluation of glibenclamide in solid dispersion systems. Drug Dev Ind Pharm. 2004; 30: 601-607.

[24] Barzegar-Jalali M, Maleki N, Garjani A, Khandar AA, Haji-Hosseinloo M, Jabbari R, Dastmalchi S. Enhancement of dissolution rate and anti-infammatory effects of piroxicam using solvent deposition technique. Drug Dev Ind Pharm. 2002; 28(6): 681-686.

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

[26] 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-2indoline-carboxylic acid: *in vivo* ACE inhibiting effect

and antihypertensive effect in various hypertensive models of rats [in Japanese]. Pharmacometrics. 1993; 45: 15-25.

[27] 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.

[28] Lynda RW, Donna MT. Trandolapril: A review of its pharmaco-dynamic and pharmacokinetic properties, and therapeutic use in essential hypertension. Pharmacometrics. 1994; 42: 18-25.

[29] 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.

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

[31] Ofokansi KC, Kenechukwu FC, Isah AB, Ogbonna JDN. Solid dispersion as an approach for dissolution enhancement and delivery of trandolapril, a poorly water-soluble ACE inhibitor. Indian J Novel Drug Deliv. 2012; 4(4):284-294.

[32] Shah S, Joshi S, Lin S, Madan PL. Preparation and characterization of spironolactone solid dispersions using hydrophilic carriers. Asian J Pharm Sci. 2012; 7(1):40-49.

[33] Kenechukwu FC, Momoh MA, Nnamani PO, Ogbonna JDN, Umeyor CE, Attama AA. (2014). Improved bioactivity of gentamicin from novel solid lipid microparticles based on beeswax. Nig J Pharm Res. 10(1): 35-45.

[34] 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.

[35] 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.

[36] Sahoo S, Chakraborti CK, Behera PK. FTIR and Raman spectroscopic investigations of ofloxacin / carbopol 940 mucoadhesive suspension. Int J PharmTech Res. 2012a; 4(1):382-391.

[37] Builders PF, Kunle OO, Adikwu MU. Preparation and characterization of mucinated agarose: a mucin-agarose physical crosslink. Int J Pharm. 2008; 356: 174–180.

[38] 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.

[39] Sahoo S, Chakraborti CK, Mishra SC, Naik S. Analytical characterization of a gelling biodegradable polymer. Drug Invention Today. 2011; 3(6): 78- 82.

[40] Sahoo S, Chakraborti CK, Behera PK. FTIR and Raman spectroscopic investigations of a controlled release ciprofloxacin / carbopol 940 mucoadhesive suspension. Asian J Pharm Clin Res. 2012b; 5(1): 125-130.