Comparative evaluation of coprecipitation, solvent evaporation, and kneading as techniques to improve solubility and dissolution profiles of a BCS class IV drug

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Received 9 January 2017
Accepted 12 June 2017

Egyptian Pharmaceutical Journal
2017, 16:121–130

Purpose
Furosemide bioavailability is limited by poor solubility and permeability. This study aimed to compare coprecipitation, kneading, and solvent evaporation as solubility and dissolution improvement techniques.
Materials and methods
Products were prepared with furosemide : polyvinylpyrrolidone : lactose at 1 : 1 : 2, 1 : 2 : 3, 1 : 3 : 4, 1 : 1 : 4, 1 : 2 : 6, 1 : 3 : 8 by coprecipitation, kneading, solvent evaporation or physical blending. They were characterized for physicochemical properties and interaction. Solubilities of furosemide from products were evaluated in water and *n*-octanol. Dissolution studies on the products were conducted in 0.1 N HCl using USP apparatus II.
Results
Solubility of pure furosemide was lowest in *n*-octanol (11.86 μg/ml) and highest in PBS (28.68 μg/ml). Infrared spectra revealed that characteristic peaks in pure furosemide were retained in its formulations, indicating chemical compatibility of furosemide and the excipients. Differential scanning calorimetry thermogram of furosemide showed a melting point at 220°C, which disappeared in its formulations – attributable to amorphization of the drug or overshadow by excipients. Furosemide significantly partitioned more ($P<0.05$) into water than into *n*-octanol. Batch 1 : 3 : 4 formulations gave the best partitioning of drug into the solvents, and was in the following order: solvent evaporation>kneading>physical mixtures>coprecipitation. Cumulative amount of furosemide dissolved from pure sample was 8%, whereas amounts from formulations were significantly higher ($P<0.05$). Coprecipitation products displayed the poorest profiles, kneading gave better profiles, but lagged behind solvent evaporation, whose products' dissolution profiles were significantly better ($P<0.05$) than other products studied.
Conclusion
All the methods improved the solubilities and dissolution profiles of furosemide to various degrees; however, solvent evaporation method was the best.

Keywords:
coprecipitation, furosemide, kneading, solubility and dissolution improvement, solvent evaporation

Egypt Pharmaceut J 16:121–130

1687-4315

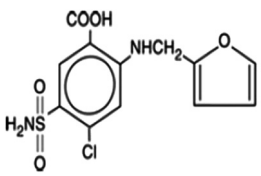
Introduction

Bioavailability of active pharmaceutical ingredients administered through the oral route depends largely on their aqueous and lipid solubilities. Technically, these solubilities have been used in classification of drugs in the biopharmaceutical classification system (BCS) into four classes: class I – high solubility and high permeability; class II – low solubility and high permeability; class III – high solubility and low permeability; and class IV – low solubility and low permeability [1]. Solubility in this classification is with respect to aqueous environment, whereas permeability, which has to do with movement across intestinal membranes into the systemic circulation, has been associated with lipophilicity (lipid solubility) of active pharmaceutical ingredients. From this classification, it is obvious that class IV drugs are the least bioavailable when administered through the oral route. Recent reports reveal that the percentage of new drug entities exhibiting poor aqueous solubilities, which translates to poor oral bioavailabilities, is increasing, whereas that of those with high aqueous solubilities and high permeability is decreasing [2]. The implication is that most new drug entities belong to

class II or class IV of BCS. This reality prompted many efforts targeted toward improvement of the solubilities/dissolution profiles of such drugs. Techniques that have been reported include particle size reduction, salt formation, cosolvency, micellar solubilization, different lipid-surfactant nanomedicine technologies, solid dispersions [kneading (KG), coprecipitation (CG), solvent evaporation (SG), hot-melt granulation, and so on], complexation, supercritical fluid, freeze drying, spray drying, and so on [3–5]. Not all these processes may easily be scaled up [4]; however, CG, KG, SG, and spray drying are established scalable processes. Solid dispersion in formulation science involves techniques by which poorly aqueous soluble drugs are dispersed in hydrophilic polymer matrices. Dispersion of such drugs may be molecularly, as amorphous particles or as crystalline particles with improved hydrophilicity [6]. In this study, the abilities of three scalable solid dispersion techniques to improve the solubility and dissolution profiles of a BCS IV drug were investigated. The BCS IV drug, furosemide, was chosen because it is commonly prescribed for some cardiovascular and renal dysfunctions. Furosemide is chemically referred to as 4-chloro-*N*-furfuryl-5-sulphamoylanthranilic acid or 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino] benzoic acid; the chemical structure is shown in Fig. 1 [7].

It is a loop diuretic used in the treatment of edematous states associated with cardiac, renal, and hepatic failure. It is also used for the treatment of hypertension. It acts by inhibiting the reabsorption of sodium and chloride in the ascending limb of Henle's loop and also in the early distal tubules [8]. The bioavailability of furosemide has been reported to be less than 50% [9], so that the amount unavailable in plasma remains in the body performing no therapeutic activity, but contributingto increased adverse effects of the drug. If therefore the solubility and permeability of furosemide could be improved, higher amount of the drug may become bioavailable, so that reduction in dose and adverse effects may be achieved. The need to actualize this desire is common, hence the many attempts by researchers to improve the solubility and permeability of furosemide [10–14]. The aim of this study was therefore to compare the impacts of three solid dispersion techniques – CG, KG, and SG – on the possible improvement of bioavailability of furosemide using in-vitro assessment parameters such as aqueous and lipid solubilities and dissolution profile.

Figure 1



Chemical structure of furosemide.

Materials and methods

The materials included furosemide powder (gift from Pauco Pharmaceuticals, Awka, Nigeria), polyvinylpyrrolidone (PVP) K15 (Fluka, New York, USA), lactose (Sigma-Aldrich, Schnelldorf, Germany), acetone (Sigma-Aldrich, Schnelldorf, Germany), concentrated hydrochloric acid 36.5% (Sigma-Aldrich), octanol (Sigma-Aldrich, Schnelldorf, Germany) and buffer tablets, pH 6.8 (Merck Millipore, Darmstadt, Germany); double-distilled water was used, and other reagents were of analytical grade.

Methods

Solubility study for pure drug (furosemide)

Solubility studies were conducted using the modified method by Garcia *et al.* [15]. Briefly, 20 mg of furosemide powder was added separately to 10 ml of PBS (pH 6.8), 0.1 N HCl (pH 1.3), distilled water, and *n*-octanol in screw-capped amber-coloured vials and shaken using a constant-temperature bath (SWB-110×12; Biobase, Jinan, China) at 37±0.5°C and agitation rate of 50 rpm for 12 h. The mixtures were left undisturbed overnight and again shaken for another 12 h. The mixtures were then centrifuged at 10 000*g* for 30 min (Refrigerated Centrifuge TGL-20 M; Shinova, Shanghai, China) and the supernatants were appropriately diluted and analyzed using an ultraviolet (UV)-visible spectrophotometer (model 752; Yuefeng, Shanghai, China) at λ_{max} of 273 nm.

Solid dispersion of furosemide by coprecipitation

CG was conducted using modified Maghsoodi and Kiafar method [16]. Furosemide of 2 g was dissolved in sufficient amount of acetone to give 0.133 g/ml solution, whereas a relevant amount of PVP (Table 1) was dissolved in enough distilled water to make 0.133 g/ml solution. Furosemide solution was quantitatively transferred into PVP solution in a beaker and the mixture was stirred (magnetic stirrer, Agimatic E; Selecta, London, UK) at 50 rpm and at a temperature of 50±2°C for 30 min. Thereafter, relevant amount of lactose (Table 1), serving as diluent/carrier, was added to the corresponding mixture and mixed to form a homogeneous dispersion. The dispersion was

Table 1 Furosemide solid dispersion composition

Batch[a]	Furosemide (g)	Polyvinylpyrrolidone (g)	Lactose (g)
X1 (1 : 1 : 2)	2	2	4
X2 (1 : 2 : 3)	2	4	6
X3 (1 : 3 : 4)	2	6	8
X4 (1 : 1 : 4)	2	2	8
X5 (1 : 2 : 6)	2	4	12
X6 (1 : 3 : 8)	2	6	16

[a]X-general batch code for solid dispersions formulated by different methods or physical mixtures.

allowed to air-dry for 8 h, screened through a 600 μm sieve and dried (Laboratory Oven; Ceword Medical Equipment, London, UK) at 60°C for 1 h. The resulting powder was rescreened through a 600 μm sieve, dried again at 60°C for 1 h and packed in an air-tight amber-coloured glass bottle over silica gel.

Solid dispersion of furosemide by kneading

The modified method by Ahire *et al.* [6] was used. Briefly, using a glass mortar and pestle, relevant amounts of furosemide and PVP (Table 1) were mixed in small proportions until all the powders were thoroughly mixed. The powder mix was then moistened with 4 ml of acetone and kneaded to form a homogeneous damp mass. To the damp mass, relevant amount of lactose (Table 1) was added and kneaded with the addition of 2 ml of acetone to form a wet mass. The wet mass was allowed to air-dry for 8 h, screened through a 600 μm sieve and dried (Laboratory Oven; Ceword Medical Equipment, London, UK) at 60°C for 1 h. The resulting powder was rescreened through a 600 μm sieve, dried again at 60°C for 1 h and packed in an air-tight amber-coloured glass bottle over silica gel.

Solid dispersion of furosemide by solvent evaporation

SG was carried out using a modified form of the method by Pandya *et al.* [17]. Two grams of furosemide was dissolved in acetone (30, 45, and 60 ml separately) and corresponding amounts of 2, 4, and 6 g of PVP (Table 1) were added to give a powder content of 0.133 g/ml. Each mixture was stirred (magnetic stirrer, Agimatic E; Selecta) at 50 rpm and at a temperature of 50±2°C for 30 min. Thereafter, a relevant amount of lactose (Table 1), serving as diluent/carrier, was added to each corresponding mixture and mixed to form a homogeneous dispersion. The dispersion was allowed to air-dry for 8 h, screened through a 600 μm sieve and dried (Laboratory Oven; Ceword Medical Equipment, London, UK) at 60°C for 1 h. The resulting powder was rescreened through a 600 μm sieve, dried again at 60°C for 1 h and packed in an air-tight amber-coloured glass bottle over silica gel.

Physical mixing of furosemide, polyvinylpyrrolidone and lactose

Relevant amounts of furosemide, PVP, and lactose (Table 1) were mixed for 15 min in a 250 ml stainless steel beaker using a hand-held planetary mixer (Kenwood Hand Mixer HM 330; Tokyo, Japan). The mixtures were screened through a 600 μm sieve and dried (Laboratory Oven; Ceword Medical Equipment, London, UK) at 60°C for 1 h. Each resulting powder mix was screened again through a 600 μm sieve, dried again at 60°C for 1 h and packed in an air-tight amber-coloured glass bottle over silica gel.

Characterization of solid dispersion and physical mixture powders

Fourier transform infrared spectroscopy

The Fourier transform infrared spectroscopy (FTIR) analysis of each powder sample was carried out using the apparatus FTIR-8400S spectrometer (Shimadzu, Nakagyo-ku, Japan). Two milligrams of each sample and 200 mg of KBr were pulverized with an agate mortar and pestle, and compressed into a pellet using the pellet press. The resulting pellet was mounted on the sample holder and the system was purged with nitrogen gas. Scanning was conducted in the range of 400–4000 cm^{-1} with a resolution of 1 cm^{-1}. Duplicate measurements were made and the spectrum with the clearer peaks was chosen.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) characterization of each powder sample was carried out using the apparatus Netzsch DSC 204 F1 Phoenix (Nietzsche, Germany). Four milligrams of each sample was carefully weighed using the analytical balance (Mettler Toledo AB54; Langacher, Switzerland) and sealed in an aluminum pan. Calibration of the calorimeter was done with indium and the purge gas was nitrogen. Heating of the sample was carried out at the rate of 10°C/min from 30 to 400°C under nitrogen flow rate of 20 ml/min, followed by cooling back to 30°C at the same rate.

Evaluation of drug content of solid dispersion and physical mixture

For each formulation, the amount of powder equivalent to 40 mg of furosemide was weighed and dispersed in 50 ml of acetone in a 100-ml screw-capped amber-coloured glass bottle. Each bottle was vortexed (Vortex Genie 2, Model C. 560 E; Scientific Industries Inc., Bohemia, New York, USA) intermittently over 6 h. The mixture was left undisturbed overnight and again vortexed intermittently for another 6 h, filtered and the filtrate was appropriately diluted with a 1 : 1

mixture of acetone and water, before being analyzed using a UV-visible spectrophotometer (model 752; Yuefeng, Shanghai, China) at λ_{max} of 273 nm with the solvent mixture as blank. Triplicate determinations were made.

Evaluation of partitioning of furosemide from solid dispersion and physical mixture into water–octanol mixture

A modification of the shake flask method reported by Patil *et al*. [12] was used to estimate the partitioning of furosemide from solid dispersion and physical mixture into water and *n*-octanol and compared with that of pure drug. A volume of 50 ml each of the two solvents was mixed in screw-capped amber-coloured glass bottles, vortexed (Vortex Genie 2, Model C. 560 E; Scientific Industries Inc.) for 1 h and allowed to equilibrate for 24 h. Thereafter, amounts of solid dispersion or physical mixture equivalent to 40 mg of furosemide were dispersed in the solvent mix and agitated. The bottles were agitated in the constant-temperature bath (REMI Rotary water bath shaker RSB-12; Mumbai, Maharashtra, India) at 37±0.5°C and agitation rate of 50 rpm for 12 h. The mixtures were left undisturbed overnight, shaken again for another 12 h and filtered using Whatman number 1 filter paper into a 150 ml separating funnel. The filtrate was allowed to stand in the stoppered funnel for 3 h before 1 ml was withdrawn from each solvent layer. The withdrawn samples were diluted with their solvents and analyzed using the UV-visible spectrophotometer at λ_{max} of 273 nm.

Dissolution test

Dissolution test was carried out on the amount of solid dispersion or physical mixture equivalent to 40 mg of furosemide using the paddle method (DBK Dissolution Rate Test Apparatus, England, UK) rotated at 50 rpm in 400 ml of 0.1 N HCl, maintained at 37±0.5°C. Samples (5 ml) were withdrawn and replaced with equal volume of fresh medium at 5 min intervals over a period of 60 min The withdrawn samples were filtered, appropriately diluted and their absorbances were determined using the UV-visible spectrophotometer at 273 nm and 0.1 N HCl as blank. The amount of furosemide released was evaluated using the calibration curve equation and triplicate determinations were performed for each batch.

Statistical analysis

Graphing was done with Excel 2007. Analysis of the results of various parameters tested was performed using one-way analysis of variance in Microsoft Excel statistical package 2007 (Microsoft, California, USA). Significant differences were defined by P less than 0.05.

Results and discussion

Furosemide was formulated as solid dispersions and physical mixtures using the polymers PVP and lactose. Six batches of formulations were made using each of the solid dispersion techniques under investigation and simple powder blending. Low viscosity grade PVPs (K5-K30) have been reported to improve drug solubility and bioavailability because of their good solubility profiles in both aqueous and some organic solvents. In addition, their surface adsorption and amorphization abilities enhance drug solubility and prevent nucleation and crystal growth [18,19]. Lactose and other sugar, because of their high hydrophilicity and ability to prevent drug crystallization, have been used as carriers in solid dispersion to improve drug solubility [20,21]. These two polymers were therefore combined in different ratios (Table 1), which are within the range reported previously [18–21], to conduct the current study.

Solubility of pure drug in various media

The solubility of furosemide in the solvents was lowest in octanol (11.86 μg/ml) and highest in PBS (28.68 μg/ml) (Table 2). Drug solubility in a solvent is affected by some factors, which include nature of drug (organic/inorganic, crystalline/amorphous), nature of solvent (aqueous/nonaqueous, pH), pKa/pKb of drug, operating temperature and pressure, rate of agitation of mixture and so on. In the present study, solvent properties are the key factors influencing furosemide solubility. The highest solubility in PBS may be explained by the interaction between PBS components and the –COOH moiety of furosemide to form salt, which then dissolved in accordance with the Henderson–Hasselbalch theory [22]. Furosemide being a weak acid with a pKa value of 3.8 [6] dissociated more at a pH of 6.8 and went into solution than it did in water of neutral pH. This may be attributed to the weaker potential of $-H^+$ in water in comparison with the Na^+ and K^+ from PBS to interact with –COOH of furosemide, leading to faster dissociation and consequently increased solubility.

Table 2 Solubility of furosemide in various media

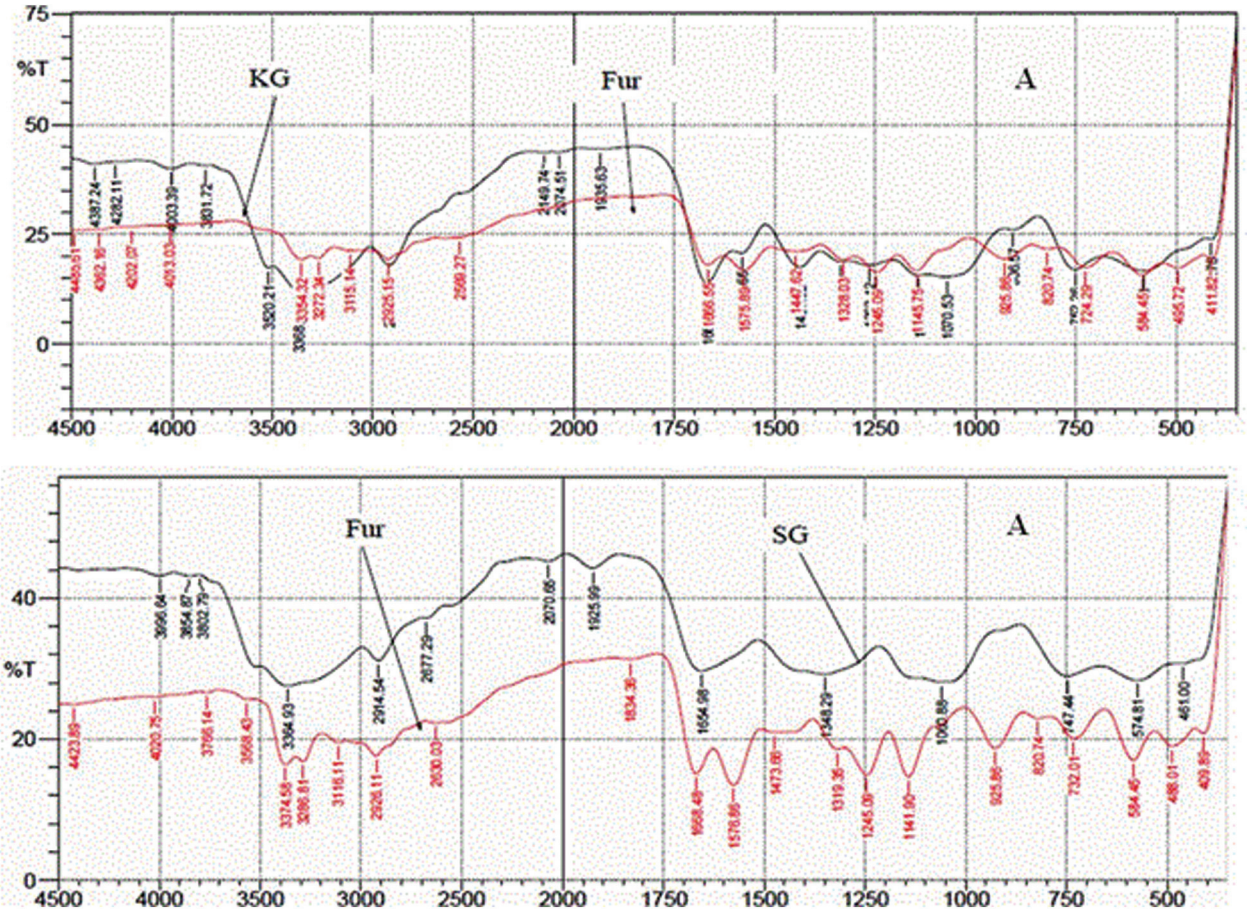
Medium (solvent)	Solubility (μg/ml)
Water	21.096±0.877
PBS (pH 6.8)	28.679±3.194
0.1 N HCl (pH 1.3)	15.665±2.467
n-Octanol	11.857±3.186

Furosemide dissociated very little in 0.1 N HCl, hence its significantly lower ($P<0.05$) solubility, in comparison with values in water or PBS. Furthermore, in *n*-octanol, solubility of furosemide was lowest – an observation that may be attributed to the relatively nonionic nature of the solvent, which in essence caused much less dissociation of the weak acidic drug.

Fourier transform infrared spectroscopy

The FTIR spectra of pure furosemide and its formulated products are shown in Fig. 2a and b. Figure 2a shows the spectrum of pure drug, solid dispersion products from KG and SG, whereas Fig. 2 shows those of CG and physical mixture (PM). The formulations chosen for this analysis were those of combination ratio 1 : 1 : 2 (drug : PVP : lactose), as chemical interaction between them can best be manifested when they are almost at equal ratios unlike what may occur when one grossly outweighs others. The spectrum of pure furosemide showed peaks between 495 and 1447 cm^{-1}, a region that is normally referred to as the fingerprint section of the infrared spectrum. This region is very useful in authenticating samples of a compound whose spectrum is already established. The peaks between 724 and 925 cm^{-1} suggest the presence of aryl-chloro stretching vibration and those at 1145–1245 cm^{-1} may be ascribed to amine C–N stretch. The peak at 1447 cm^{-1} may likely be due to methyl C–H asymmetric bend and that at 1575 cm^{-1} may be ascribed to asymmetric stretching vibration of the carboxyl group, 1666 cm^{-1} to bending vibration of the amino group or carbonyl C=O vibration and the weak peaks at 1822 to 1937 cm^{-1} may be ascribed to a five-membered ring furanyl group. The weak peaks between 2589 and 2925 cm^{-1} may be ascribed to C–H and HO–C=O stretching vibrations of carboxylic acid. The peak at 3272 cm^{-1} is likely due to the stretching vibration of sulfonylamino group (SO_2NH_2), whereas that at 3354 cm^{-1} may be ascribed to NH_2 stretching vibration of Ar-$NHCH_2$ [9]. After the shoulder spectrum, the peaks between 3748 and 4012 cm^{-1} are characteristic of -OH stretching vibration from water or alcohol groups, which may be present as residual solvents [23,24]. The solid dispersions and

Figure 2



FTIR spectra of pure furosemide (FUR) and solid dispersion products: (a) kneading (KG) and solvent evaporation (SG); (b) coprecipitation (CG) and physical mixture (PM).

physical mixtures of furosemide, PVP and lactose (1 : 1 : 2, respectively) displayed spectra that are almost super-imposable on the spectrum of pure furosemide. Except for the spectrum of solid dispersion formulated by SG, other formulation spectra retained the functional groups (identified by corresponding wave numbers) present in pure furosemide (Fig. 2a and b). The peaks that disappeared or shifted in SG were not the major characteristic ones, and the disappearance or shifting may be accounted for by the possible interaction between the –OH groups in lactose and the $-H^+$ from –COOH of furosemide, which possibly resulted in a complex that retained all the principal functional groups in furosemide. This finding is similar to previous reports, in which cogrinding of aceclofenac and neusilin [25] and solid dispersion of indomethacin and soluplus [26] both resulted in the disappearance of peaks and were attributed to amorphization of aceclofenac and indomethacin through –COOH and –H interaction. In essence there was no deleterious chemical interaction between the drug and the excipients used in the formulation process.

Differential scanning calorimetry

The DSC thermograms of furosemide and its formulated products are shown in Fig. 3a and b, respectively. The thermogram of furosemide showed the occurrence of desolvation, a relatively broad endothermic peak at about 56°C. Thereafter, melting (another endothermic event) occurred at about 220°C (see arrow), followed immediately by an exothermic event: decomposition at about 225°C. This observation is very similar to previous report by Babu *et al.* [27]. The thermograms of furosemide solid dispersions formulated at a ratio of 1 : 1 : 2 (drug : PVP : lactose) (Fig. 3b) displayed prominent peaks that are characteristic of lactose [28,29]. The absence of furosemide peaks may be attributed to either complete amorphization of the drug in the presence of the excipients or the higher content of lactose overwhelming the manifestation of furosemide thermal characteristics in the DSC thermogram.

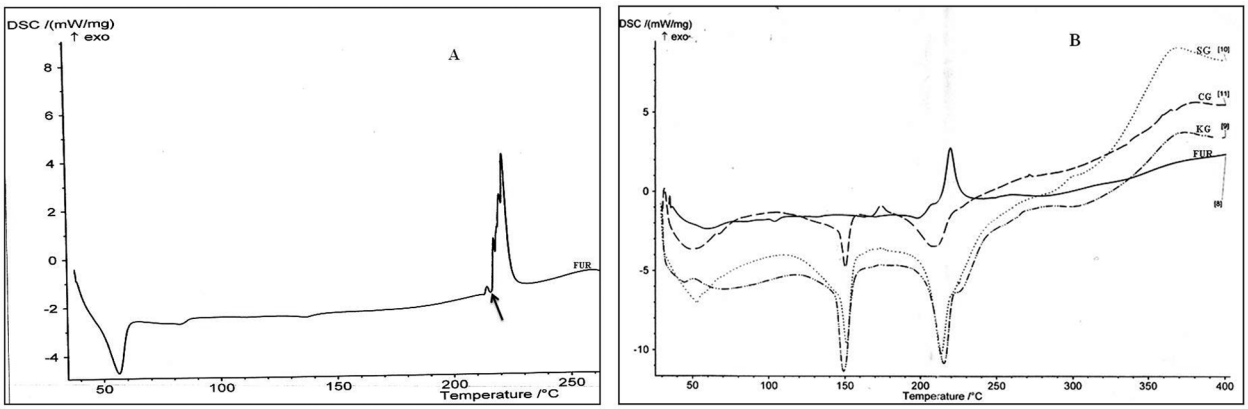
Drug content of solid dispersions and physical mixtures

Percentage content of furosemide in solid dispersions and physical mixtures was in the range of 90.13 ±1.70–102.38±0.71% (Fig. 4). The lower range was predominant among the physical mixtures even though none of them was below 90%, which is the tolerance for furosemide content in tablets [30]. In addition, the relative SDs of all the formulations were less than 6%, which is the specification for solid dosage forms [31].

Partitioning of furosemide from solid dispersions and physical mixtures into water–octanol mixture

The relative partitioning of furosemide into water and octanol is shown in Fig. 5. The drug significantly partitioned more ($P<0.05$) into water than into *n*-octanol. Untreated furosemide partitioned significantly lower ($P<0.05$) into both solvents than furosemide from solid dispersion products: KG (Fig. 5a), SG (Fig. 5b) and CG (Fig. 5c), and blends of drug and excipients: PM (Fig. 5d). Among the various formulations, batch X3 (containing 1 : 3 : 4 of drug, PVP, and lactose, respectively) gave the best partitioning of drug into the two phases, as shown by KG3, SG3, and PM3. The explanation for CG3's apparent deviation could not be emphatically deduced directly, but the plausible reason may be formation of less soluble

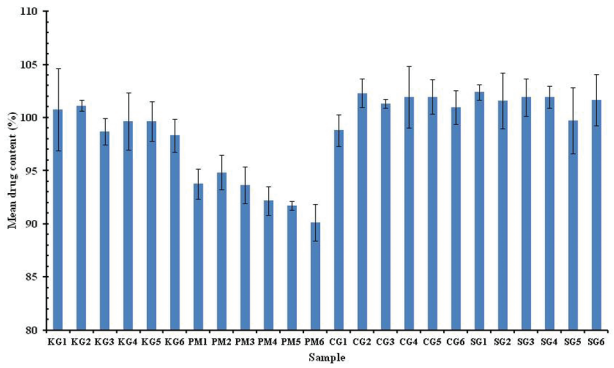
Figure 3



Differential scanning calorimetry (DSC) thermograms of (a) pure furosemide (FUR) and (b) superimposed thermograms of pure FUR and solid dispersion products (KG, kneading; SG, solvent evaporation; CG – coprecipitation).

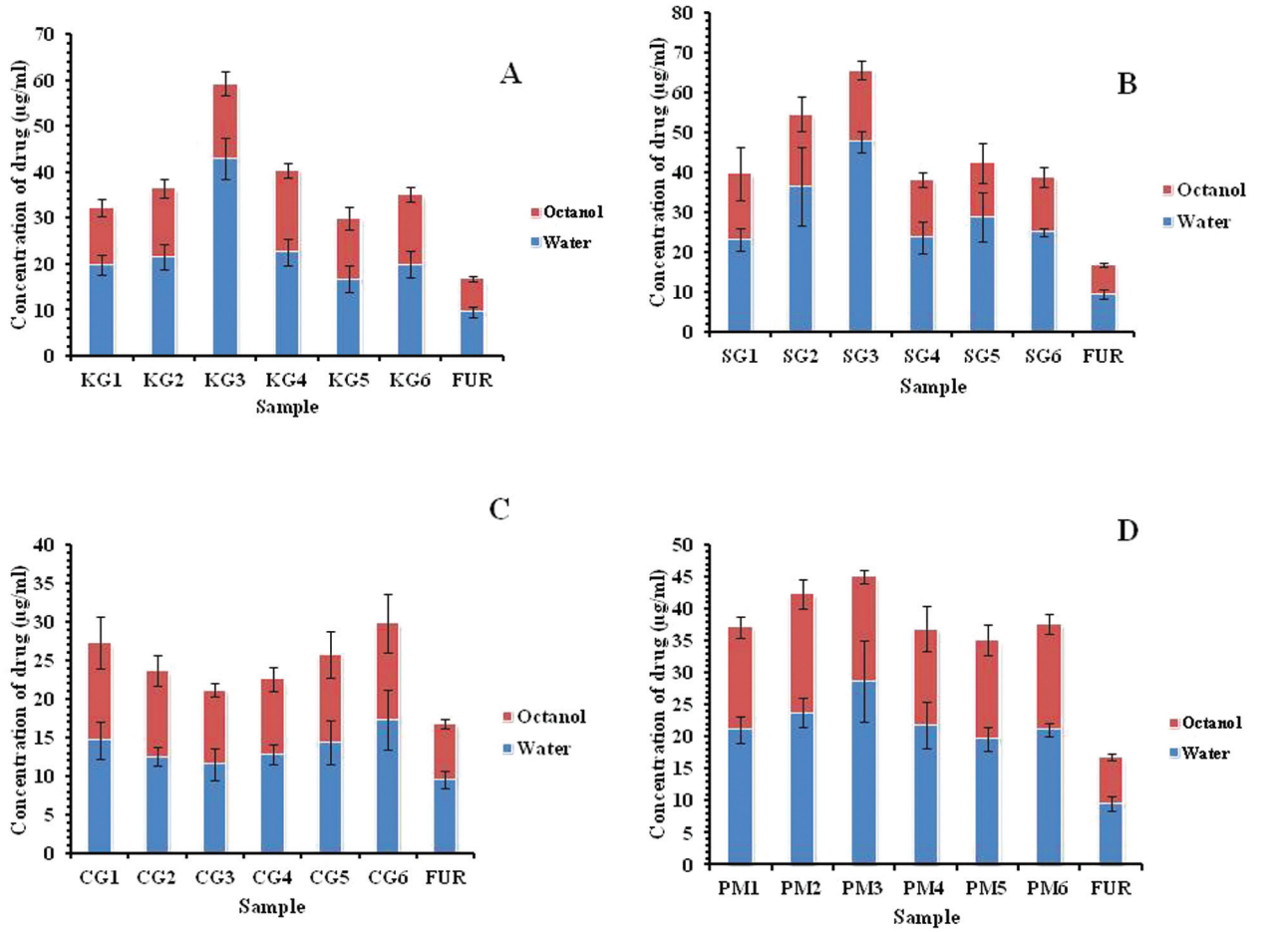
complex between the excipients and the drug. Comparatively, partitioning of drug from formulated products into the solvent mix was in the following order: products formulated by SG>products formulated by KG>products formulated by CG>physical mixtures (PM). Statistical analysis of drug partitioning from SG and KG revealed insignificant difference in the ability of the two processes to enhance differential solubility in both solvents. Hydrophilicity and lipophilicity of drugs influence their absorption rates at various points along the gastrointestinal tract. Furosemide was reported to be better absorbed in the gastric region at pH of 3.0–3.5 [32], which implied that it possessed better hydrophilic and lipophilic profiles in this region, because extreme of either would negate permeability, hence bioavailability [33]. In SG3 and KG3, differential solubility of furosemide in water was increased five times while in *n*-octanol it was two and a half times, a finding that may be attributed to the abilities of the two techniques and the functionality of excipients in improving both hydrophilicity and lipophilicity. It is noteworthy that even though PVP and lactose are known hydrophilic polymers they substantially improved

Figure 4



Percentage drug content of products from solid dispersions by kneading (KG), coprecipitation (CG) and solvent evaporation (SG); PM powders from physical mixture all formulated at 1 : 1 : 2 (1), 1 : 2 : 3 (2), 1 : 3 : 4 (3), 1 : 1 : 4 (4), 1 : 2 : 6 (5) and 1 : 3 : 8 (6) ratios of drug : PVP : lactose, respectively (n=3).

Figure 5



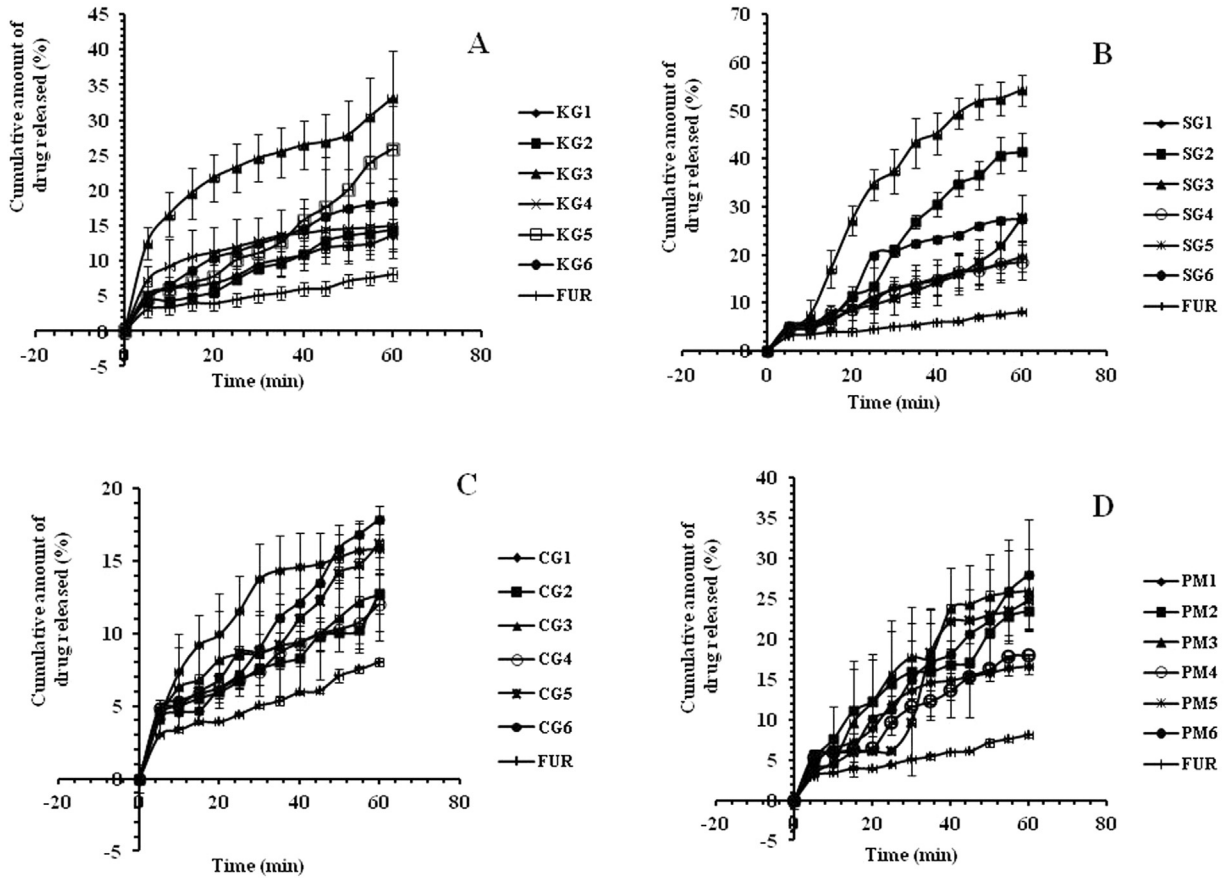
Concentration of furosemide (FUR) partitioned into water or *n*-octanol from FUR (pure drug), solid dispersions (KG, kneading; CG, coprecipitation; SG, solvent evaporation) and physical mixture (PM) all formulated at 1 : 1 : 2 (1), 1 : 2 : 3 (2), 1 : 3 : 4 (3), 1 : 1 : 4 (4), 1 : 2 : 6 (5) and 1 : 3 : 8 (6) ratios of drug : PVP : lactose, respectively (n=3).

the lipophilicity of furosemide, invariably impacting positively on its permeability.

Dissolution profiles of formulations

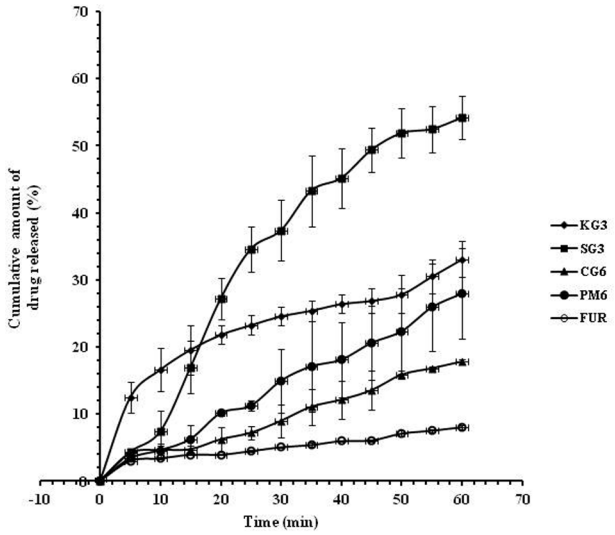
Figure 6 shows the dissolution profiles of the formulations in comparison with that of pure drug. The cumulative amount of drug dissolved from pure drug (furosemide) in 60 min was about 8%. On the other hand, products from solid dispersion techniques manifested diverse release profiles, with cumulative amounts of drug released significantly higher ($P<0.05$) than 8%. Solid dispersion products formulated by CG displayed the poorest profiles even in comparison with the profiles of the physical mixtures (PM). This observation concurs with the finding in differential solubility in water and octanol, and one plausible explanation may be the formation of a poorly dissolving physical complex between drug and polymers during CG and mixing. It may also be possible that the CG affected just the ease of dispersion of PVP in aqueous medium, hence its ability to reduce surface tension, which is one of its mechanisms of enhancing solubility/dissolution. Uzun *et al.* [34] using supercritical fluid technique in coprecipitating cefuroxime and PVP made a similar observation in that the process produced extended-release cefuroxime. The physical mixtures in contrast seemingly performed better because PVP properties might not have been modified by the simple blending process, and thus it was better able to reduce surface tension and cause better improved dissolution than CG. The profiles of products formulated by KG were better than those of PM, but lagged behind those of SG. Among KG and SG products, the best profiles were from KG3 and SG3 (formulated with drug : PVP : lactose at 1 : 3 : 4 ratio) (Fig. 6a and b). Conversely, for CG and PM products, it was CG6 and PM6 (formulated with drug : PVP : lactose at 1 : 3 : 8 ratio) (Fig. 6c and d). This finding suggests that possible combination of PVP and furosemide to improve the drugs solubility/dissolution is at a ratio of 1 : 3 (furosemide : PVP). Lactose performing primarily as diluents may be used at four or eight times the amount of drug, depending on the process of production. A plot of the best release profiles from the formulations (KG3, SG3, CG6, and PM6) (Fig. 7)

Figure 6



Dissolution profiles of products: furosemide (FUR) (pure drug), solid dispersions [KG-kneading (A); SG-solvent evaporation (B); CG-coprecipitation (C) and PM-physical mixture (D)] all formulated at 1 : 1 : 2 (1), 1 : 2 : 3 (2), 1 : 3 : 4 (3), 1 : 1 : 4 (4), 1 : 2 : 6 (5) and 1 : 3 : 8 (6) ratios of drug:PVP : lactose, respectively (n=3).

Figure 7



Comparison of dissolution profiles of best products from kneading (KG) and solvent evaporation (SG) formulated at 1 : 3 : 4; coprecipitation (CG) and physical mixture (PM) formulated at 1 : 3 : 8 ratios of drug : PVP : lactose, respectively, and pure drug (furosemide – FUR) (n=3).

and analysis of variance revealed SG product to be significantly better ($P<0.05$) than any other process product studied. Disparity in the amount of drug released can be related to the solubility of drug in the aqueous compartment, as seen in the partitioning experiment. Enhanced solubility of furosemide from solid dispersion products and physical mixtures might have resulted from the presence of the carriers PVP and lactose, findings that were reported previously [35–38]. In general, the performance of products from the various processes is of the following order: SG>KG>PM>CG>furosemide. In-vitro dissolution performance of immediate-release solid oral dosage forms is a tool recommended by Food and Drug Administration for assessment of suitability of a product for further development [39]. From the above observations, SG and KG stood out as relevant processes for further development for use in the enhancement of hydrophilicity and lipophilicity of BCS class IV drugs.

Conclusion

The study used PVP and lactose as excipients to compare the abilities of CG, SG, and KG as techniques useable to improve solubility and dissolution of furosemide, a BCS class IV drug. The three methods proved to impart no chemical interaction between furosemide and the excipients. All the methods improved the aqueous/lipid solubilities and dissolution profiles of furosemide to various degrees. Comparatively, SG method was the best, although there was no significant difference between its ability and that of KG method to improve differential solubility in water and octanol.

Acknowledgements

The authors are grateful to Pauco Pharmaceuticals Nigeria Ltd for the provision of furosemide powder used in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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