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Original Article

FORMULATION AND EVALUATION OF SOLID DISPERSION TABLETS OF FUROSEMIDE USING POLYVINYLPYRROLIDONE K-30

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ABSTRACT

Objective: The objective of the present study was to improve the aqueous solubility and dissolution characteristics of the loop diuretic furosemide (FUR); a class IV drug in the Biopharmaceutical Classification System (BCS) using solid dispersion technique.

Methods: Solvent evaporation and kneading methods were used to produce solid dispersions of FUR in different ratios with the hydrophilic carrier polyvinylpyrrolidone K-30 (PVP-K30). The prepared solid dispersions were evaluated in terms of solubility study, percentage yield, drug content and Fourier transform infrared spectroscopic study (FT-IR). Tablets containing the optimized formula of solid dispersions (SD_{S3}) were formulated and their dissolution characteristics were compared with commercial furosemide tablets.

Results: The prepared solid dispersions showed an increase in aqueous solubility, especially those formulated in a 1:2 drug: carrier ratio using solvent evaporation method (SD_{S3}), it showed a four-fold increase in solubility compared to the parent drug. The absence of drug-carrier chemical interactions that could affect the dissolution was proved by FT-IR. Solid dispersion tablets exhibited a better dissolution profile in simulated gastric fluid pH 1.2 at 37°C ± 0.5 than the commercial FUR tablets in terms of mean dissolution time (8.44 min) and dissolution efficiency in 30 min (42.54%). Both FUR solid dispersions and commercial tablets followed Weibull and Krosmeyer models as the two best models of drug release kinetics proving that they were immediate release.

Conclusion: According to the results obtained in this study, solid dispersion techniques could be successfully used for the enhancement of aqueous solubility and dissolution rate of FUR.

Keywords: Furosemide, Solid dispersion, Polyvinylpyrrolidone K-30 (PVP-K30), Solvent evaporation, Kneading, Dissolution enhancement

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INTRODUCTION

Oral drug delivery, especially oral solid dosage forms such as tablets and capsules are the most desired administration route for many drugs, due to its several advantages over other formulations. It is the most commonly used route due to its greater stability, ease of administration, high patient compliance, the accuracy of doses, cost-effectiveness, and flexibility of dosage form design [1]. The bioavailability and therapeutic effectiveness of a drug administered by oral route depend on several factors, including aqueous solubility, drug permeability, dissolution rate, systemic metabolism, and susceptibility to efflux mechanisms. The most causes of low oral bioavailability are poor solubility and low permeability. Dissolution may be the rate-determining step for drug absorption, bioavailability, and thus for the onset of therapeutic activity. The dissolution rate is a function of the solubility and surface area of a drug [2, 3]. Solubility is one of the most important parameters to achieve the desired drug concentration in systemic circulation to attain the required pharmacological response. Poorly water-soluble drugs often require higher doses to reach therapeutic plasma concentrations after oral administration, also, they have slow drug absorption that leads to inadequate and variable bioavailability [2]. The improvement of drug solubility, thereby its oral bioavailability, remains one of the most challenging aspects of the drug development process, especially for an oral-drug delivery system. There are many approaches to increase the solubility of a poorly water-soluble drug and thus improve its bioavailability, such as grinding, use of surfactants, salt formation, pH adjustments, prodrugs, complexation with cyclodextrins, self-emulsifying formulations, micronization, emulsions and liposomes [4].

Solid dispersion is one of the most promising, viable, and economic techniques that can potentially enhance the aqueous solubility and the dissolution rate of hydrophobic drugs. The concept of using solid dispersions was first introduced by Sekiguchi and Obi in 1961. They demonstrated that the eutectic mixture of sulfathiazole and the physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration than sulfathiazole alone [5]. As reported by Sridhar, *et al.*, the term solid dispersion refers to a group of solid products consist of at least two components, a hydrophilic matrix and a hydrophobic drug, where the drug can be dispersed molecularly or in the amorphous state [6]. The matrix can be either crystalline or amorphous. When the solid dispersions product is exposed to an aqueous media, the carrier dissolves and the drug is released as fine colloidal particles with an enhanced surface area that produces a higher dissolution rate and improved bioavailability. The improvement of the dissolution of drugs from solid dispersions is based mainly on three different mechanisms: the reduction in particle size and increased surface area, the wettability of the drug, which is improved by direct contact with the hydrophilic matrix, and the conversion of the crystalline state to the more soluble amorphous state [7]. There are many techniques for solid dispersions preparation, such as solvent casting method, kneading, co-precipitation method, melting method, co-grinding, gel entrapment technique, spray drying, melt extrusion, lyophilization and dropping method solution [8]. Solvent evaporation is one of the most used methods as the drug is usually dispersed within the hydrophilic matrix at the molecular level. The technique involves solubilization of the drug and polymer in a solvent or a mixture of solvents such as ethanol, methanol, chloroform, or dichloromethane, which is then evaporated. The solvent must solubilize both the carrier and the drug, and it should be completely removed; the resulting film can be pulverized and milled. Evaporation occurs at low temperatures by different techniques such as vacuum drying, mixture heating, application of filtration or heating bath, supercritical fluid, rotary evaporation, and spray-drying [4, 9]. Kneading technique is one of the complex

formation-based techniques. It is based on the wetting of the carrier with water or hydro-alcoholic solution to form a paste. The drug is then added and kneaded for a specified period. The kneaded mixture is then dried and passed through a sieve if necessary. Kneading method is the most common and simple method used to prepare the inclusion complexes, it has a low cost of production in both laboratory and large scale [2].

The selection of the carrier influences the dissolution characteristics of the dispersed drug since the dissolution rate of one component from the surface is affected by the other component in the multiple component mixtures. Therefore, various hydrophilic carriers, such as polyethylene glycols (PEGs), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), gums, sugar, mannitol, and urea have been used for the improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs [10].

Furosemide (FUR) is a potent loop diuretic used in the treatment of cardiac, renal, and hepatic failures and in the treatment of hypertension. Based on solubility, oral absorption, and permeability data, FUR is classified as class IV of the Biopharmaceutics Classification System (BCS). It has low solubility and low permeability due to the carboxyl and sulfonamide groups in the structure, with pKa of 3.8 and 9.6, respectively (fig. 1). The bioavailability problems, reported as a result of variable and erratic gastrointestinal absorption, are probably due to the low and pH-dependent solubility together with various existing polymorphic forms of FUR [11].

This study aims to improve the solubility and dissolution rate of FUR by preparing solid dispersion with PVP K-30 employing two preparation methods, solvent evaporation and kneading technique, also, it has an objective to evaluate the potential of solid dispersions for the development of FUR solid dispersion tablets.

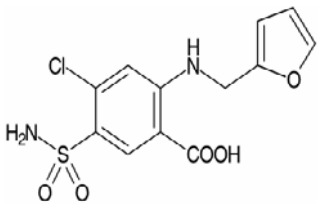

Fig. 1: Chemical structure of FUR

MATERIALS AND METHODS

Furosemide (FUR) was gifted kindly by Blue Nile Pharmaceutical Factory (Khartoum, Sudan). Polyvinyl pyrrolidone (PVP K-30) magnesium stearate, talc powder, and lactose monohydrate were obtained from Amipharma Laboratories Ltd. (Khartoum, Sudan). Microcrystalline cellulose 102 (MCC 102) and cross carmellose sodium were gifted kindly by Humavit Drugs international Co. Ltd. (Khartoum, Sudan). Absolute ethanol was obtained from Sd-Fine-Chem. Ltd. (India). Concentrated Hydrochloric acid (HCl 37%) was obtained from ATOM SCIENTIFIC® (UK). Methanol was purchased from LOBA CHEMIE Pvt. Ltd (Mumbai, India). Distilled water is used throughout the study and all other materials and chemicals were of analytical grade. Brand® A and brand® B containing furosemide 40 mg were obtained from the local drug market in Sudan.

Preparation of solid dispersions

Solvent evaporation method

FUR solid dispersions were prepared by a solvent evaporation method using PVP K-30 in different ratios (1:0.5, 1:1 and 1:2 of the drug: polymer). A minimal amount of methanol was used to dissolve the required amount of FUR and the carrier by continuous stirring with a magnetic stirrer (Stuart®, UK) for one hour at room temperature. The solvent was completely removed under reduced pressure using a rotary evaporator (SENCO Technology Co., Ltd, China) kept at 40 °C. The solid dispersions formed were further dried in an oven (Nuve®, Turkey) at 40° for 24 h. All the resulting solid dispersions were scraped, pulverized in a mortar and sieved through a 60-mesh sieve. Following that, all solid dispersions were stored in amber glass bottles and kept in the desiccator until further use [12].

Kneading method

A mixture of FUR and PVP-K30 (1:0.5, 1:1 and 1:2 by weight) was wetted using a small amount of water-ethanol solution (in 1:1 ratio) and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried for 24 h in an oven at 40 °C. Dried mass was pulverized and passed through sieve No. 60 and stored in amber glass bottles and kept in the desiccator until further use [13].

Evaluation of FUR solid dispersions

Percentage of practical yield

The percentage of practical yield is calculated to know about the efficiency of the solid dispersion preparation method, it helps in the selection of a suitable method of production. Solid dispersions of FUR were collected and weighed to determine practical yield from the following equation [14].

$$\text{Practical Yield (\%)} = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoratical mass(Drug+carrier)}} \times 100$$

Drug content

Solid dispersions containing an equivalent amount of 10 mg of FUR were weighed accurately and dissolved in 10 ml methanol. 2.5 ml of aliquots were withdrawn and diluted into 25 ml volumetric flask with distilled water. The sample was filtered through Whatman filter paper then 0.45 μm cellulose nitrate membrane filter, diluted and assayed for FUR spectrophotometrically by UV at 245 nm. Using methanol: distilled water as blank. The drug content was calculated from the calibration curve constructed at concentration range between 5 and 25μg/ml as follows:

$$\text{\% Drug content} = \frac{\text{Practical amount of solid dispersion}}{\text{Theoretical amount of solid dispersion}} \times 100$$

Solubility study

An excess amount of pure FUR and solid dispersions were added to 25 ml stopper conical flasks containing distilled water, completed to the mark separately and the samples were rotated for 24 h in shaking incubator (BioFree®, Japan) at 25° C. The mixtures were filtered through Whatman filter paper then 0.45μm cellulose nitrate membrane filter. The filtrates were suitably diluted with distilled water and analyzed spectrophotometrically at 245 nm using UV/VIS Spectrophotometer (model 7315 Jenway®, England) for detection of FUR. Measurement was carried out in triplicate and the average solubility was calculated [3].

Fourier transforms infrared (FT-IR) study

FT-IR spectra of moisture-free powdered samples of FUR, PVP-K30, and solid dispersions were recorded using Shimadzu IR Tracer-100 (Kyoto®, Japan). Samples of 2–3 mg were mixed with about 400 mg of dried potassium bromide (KBr) then compressed into transparent disks utilizing a hydrostatic press at 6-8 tons pressure. The scanning range was from 500 to 4000 cm^{-1} at a resolution of 4 cm^{-1} [13].

Pre-compression evaluation

Based on solubility performance, the formula with the highest solubility result was selected for the preparation of FUR solid dispersion tablets and the flow characteristics of the powder sample were evaluated to ensure the tableting ability.

The angle of repose

The angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose is designed by θ and given by the flowing equation:

$$\text{Tan } \theta = h/r \text{ or } \theta = \text{Tan}^{-1(h/r)}$$

Where h is the height of the pile (cm) and ***r*** *is the radius of the base of the pile (cm).*

The lower the angle of repose, the better is the flow properties, and generally angle of repose from 25 up to 35° results in excellent to good flow properties [15].

Compressibility index (Carr's Index)

It is one of the measurements that indicate powder flow properties. It is expressed in percentage and given as,

$$\text{Carr's index (\%)} = (Dt - Db)/Dt \times 100$$

Where Dt and Db are the tapped and bulk densities of the powder, respectively. In general, Compressibility index values from 5 up to 15% indicate excellent to good flow properties [15].

Formulation of FUR solid dispersion tablets

Tablets containing solid dispersions equivalent to 40 mg of FUR were prepared by direct compression method using different formulation excipients such as microcrystalline cellulose (MCC102) as binder, crosscarmellose sodium as a disintegrant, magnesium stearate (0.5% w/w) as a lubricant, talc (1.5% w/w) as a glidant and lactose monohydrate as a filler to adjust the weight of the tablets into 220 mg. All the ingredients required were weighed individually and screened through a 60-mesh sieve before mixing to ensure uniform particle size distribution. The blend was compressed on a single tableting press machine (Erweka®, Germany) equipped with an 8 mm round flat punch set. Tablets were stored in an airtight container for further studies.

Post compression evaluation of FUR solid dispersion tablets

Tablet thickness

The thickness of tablets was determined using Vernier caliper tester. (AEROSPACE®, China). Ten individual tablets were selected randomly and used; the average values were calculated. The thickness of a tablet should be controlled within±5% variation of a standard value depending on the size of the tablet [16].

Weight variation test

Weight variation was measured on twenty randomly selected tablets using an electronic analytical balance (KERN®, Germany), the tablets were weighed individually and then collectively, the average weight of the tablets and percentage of weight variation were calculated. The USP limit for % deviation is 7.5 % for uncoated tablets weighing 130-324 mg, and not more than two of the individual weights of tablets should deviate from the average weight [17].

Tablet hardness

The hardness of tablets was tested on ten randomly selected tablets using a hardness tester (Guoming®, China). The force required to break the tablet was measured in Kg/cm^2 and an average value was calculated [16].

Tablet friability

Friability % was determined using twenty tablets selected randomly from the batch. Tablets were weighed (W1) and placed into the plastic drum of a stabilator (Guoming®, China) rotated at 25 rpm for 4 min. The excess dust was removed from the tablets and they were reweighted (W2) for calculation of friability (%) [16]. The friability value of the tablets less than 1% is considered acceptable for most pharmaceutical tablets according to USP.

$$\text{Friability\%} = (W1\text{-}W2)/W1 \times 100$$

Drug content determination

For this test, ten tablets were selected randomly and powdered in a mortar. The amount of powder equivalent to 10 mg of FUR was dissolved in 25 ml methanol by sonication for 15 min and filtered through Whatman filter paper, then 0.45µm cellulose nitrate membrane filter. Suitable dilutions were made, and the drug content was analyzed spectrophotometrically at 245 nm using a UV-VIS spectrophotometer (model 7315 Jenway®, England). Each measurement was carried out in triplicate and the average drug content was calculated [17].

Disintegration time

A disintegration test was conducted *in vitro* using a Digital tablet disintegration test apparatus (SCIENTIFIC®, India). It consists of a basket-rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen. To test for disintegration time, one tablet was placed in each tube of the disintegration apparatus and the basket rack was positioned in 0.1 N HCl pH 1.2 at 37±2 °C. A standard motor-driven device was used to move the basket assembly containing the tablets up and down, the device was operated until all tablets were disintegrated, and all particles were passed through the 10-mesh screen in the time specified. 15 min is considered the disintegration time for most normal release tablets [17]

***In vitro* dissolution study**

In vitro dissolution study of FUR solid dispersion tablets and two commercially available brands of FUR in Sudan (brand A and B) was performed in a paddle-type dissolution apparatus USP II RC-6 Dissolution tester (Gouming®, China) equilibrated at 37±0.5°C and 100 rpm speed. The dissolution study was carried out in triplicate for one hour in 900 ml of Simulated Gastric Fluid (SGF, pH 1.2). Dissolution samples (10 ml) were collected at 5, 10, 15, 20, 30, 45, and 60 min and replaced with an equal volume of SGF solution to maintain the volume constant. The sample solution was filtered and analyzed by a UV/VIS spectrophotometer (model 7315 Jenway®, England) at 245 nm [18].

Dissolution profile comparison between formulated solid dispersion tablets and two marketed brands of FUR

Model-independent approach

The dissolution profiles of the optimized FUR solid dispersions, brand A® and brand B® tablets were compared using three model-independent parameters $\%DE_{30}$ (Dissolution Efficiency at 30 min), similarity factor (f_2) and mean dissolution time (MDT).

Dissolution efficiency at 30 min. ($\%DE_{30}$)

For each sample, the percentage dissolution efficiency at 30 min. was calculated as the percentage ratio of the area under the dissolution curve up to 30 min. to that of the area of the rectangle described by 100% dissolution at the same time point. Dissolution efficiency (%DE) can be calculated from the following equation [19]:

$$\%DE = \frac{\int_{t1}^{t2} y.dt}{y100(t_2 - t_1)} \times 100$$

Where y is the percentage of the dissolved product. %DE is then the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution y100 over the same time. In the current study $t_1 = 0$ and $t_2 = 30$ min.

Similarity factor (f_2)

The similarity factor (f_2) is one of the fit factors that had been developed by Moore and Flanner in 1996. It contrasts the similarity between FUR dissolved per unit time of a test with that of a reference formulation. f_2 can be defined from the following equation [20]:

$$f_2 = 50 \log \left[\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} W_t(R_t - T_t)^2\right]\right]^{-0.5} \times 10$$

Where n is the number of withdrawal points, R_t is the percentage dissolved of reference at the time point t, T_t is the percentage dissolved of the test at the time point t, and W_t is optional weight at time t. A value of 100% for the similarity factor (f_2) suggests that test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, while lower f_2 values imply an increase in dissimilarity between release profiles.

Mean dissolution time (MDT)

MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. A higher MDT value indicates a greater drug retarding ability. To understand the extent of improvement in dissolution rate of FUR from its solid dispersion

with PVP-K30, the obtained dissolution data of all samples were fitted into the following equation,

$$MDT_{invitro} = \frac{\sum_{i=1}^{n} tmid \times \Delta M}{\sum_{i=1}^{n} \Delta M}$$

Where i is the dissolution sample number, n is the number of dissolution times, t_{mid} *is a time at the midpoint between times ti and ti-1, and ΔM is the amount of furosemide in μg dissolved between times ti and ti-1* [21].

Model-dependent approach

To clarify the mechanism of release kinetics of FUR from the hydrophilic carrier PVP-K30, *in vitro* release data were fitted to various mathematical kinetic models as shown in table (1) using a software program called DDSolver which compare different dissolution profiles using model-dependent approaches [22].

Table 1: Mathematical release kinetic models

Model	Equation
Zero-order	$Q_t = Q_0 + K_0 t$
First-order	$\text{Log } Q_t = \log Q_0 - \frac{Kt}{20303}$
Higuchi	$Q = KH.\ t^{1/2}$
Hixon-Crowell	$\sqrt[3]{W0} - \sqrt[3]{Wt} = Kt$
Krosmeyer–Peppas	$M_t/M_\infty = kKPt^n$
Weibull	$F = Fmax \times \{1\text{-}Exp[-((t\text{-}T_i)\ \hat{}\ \beta)/\alpha]\}$

Where Q_0 represents the initial amount of the drug in the solution, Q_t represents the amount of the drug released at time t, (K_0, K, KH, and kKP) represent release rate constants for each model, W_0 represents the initial amount of the drug in the pharmaceutical dosage form, W_t represents the amount of the drug remains in the pharmaceutical dosage form at time t, M_t is the fraction of drug released at time t andM_∞ is the fraction of drug released at time ∞, n is the release exponent that describes the drug release operating mechanism and the diffusion pattern if n ≤ 0.45 corresponds to Fickian diffusion mechanisms. 0.45 < n < 0.89 to anomalous non-Fickian transport, n = 0.089 to case ii transport and n > 0.89 to super case ii transport. F is the fraction of the drug released at time t, α is a scale parameter which defines the time scale of the process, β is the shape parameter which characterizes the curve as either exponential (β = 1) case1, sigmoid, s-shaped with upward curvature followed by a turning point (β>1) case2, or parabolic with a higher initial slope and after that consistent with the exponential (β<1) case 3. T_i is the location parameter that represents the lag time before the onset of the dissolution or release process. F_{max} is the maximum fraction of the drug released at infinite time.

RESULTS

Preparation of solid dispersions

Solid dispersions of FUR were prepared by solvent evaporation and kneading methods using PVP-K30 as a drug carrier. In the present work, six formulations were prepared and coded, their complete composition is shown in table (2). All solid dispersions prepared were found to be fine yellowish powder.

Table 2: Formulations of FUR solid dispersion

Preparation method	Batch code	Drug/carrier ratio
Solvent evaporation	SD_{S1}	1:0.5
	SD_{S2}	1:1
	SD_{S3}	1:2
Kneading method	SD_{K1}	1:0.5
	SD_{K2}	1:1
	SD_{K3}	1:2

Evaluation of FUR solid dispersion

The results of the percentage practical yield, drug content, and solubility study of all solid dispersions prepared by solvent evaporation, and kneading technique, are concluded in table (3).

Table 3: Practical yield by weight, drug content and solubility of solid dispersion formulations

Batch code	Practical yield (%)	Drug content (%)	Solubility (mg/ml)
Pure FUR	-	-	0.0699 ± 0.001
SD_{S1}	95.2	97.67 ± 0.005	0.1101 ± 0.002
SD_{S2}	77.6	99.63 ± 0.271	0.1271 ± 0.051
SD_{S3}	85.5	98.13 ± 0.007	0.2746 ± 0.002
SD_{K1}	54.9	96.63 ± 0.005	0.1041 ± 0.002
SD_{K2}	75.7	98.50 ± 0.270	0.1169 ± 0.001
SD_{K3}	79.4	98.60 ± 0.002	0.1522 ± 0.001

Percentage of practical yield by weight

The practical yield of all samples was found to be in the range of 54.9–95.2 %. The maximum yield was found 95.2 % in SD_{S1} formulation, which was prepared with a 1:0.5 drug: carrier ratio by the solvent evaporation method.

Drug content

The drug content of the prepared solid dispersions was in the range of 96.63–99.63 %, indicating the application of the present methods for the preparation of solid dispersions with high content uniformity. The maximum % drug content was found 99.63 % in SD_{S2} formulation.

Evaluation of solubility

All solid dispersions of FUR with PVP-K30 showed an enhanced aqueous drug solubility over pure FUR. The aqueous solubility of FUR at 25 °C is 0.0699 mg/ml. For comparison, the highest FUR solubility was achieved with solid dispersions prepared by the solvent evaporation method. Among all solid dispersion's formulations, SD_{S3} (1:2 ratio prepared by solvent evaporation method) showed the highest solubility results; 0.2746 mg/ml resulted in a nearly four-fold increase in the aqueous solubility compared with that of pure FUR. This formula was selected as an optimized formula for the preparation of FUR solid dispersions tablets.

Fourier transforms infrared (FT-IR) study

The FT-IR spectra of pure FUR, as well as PVP-K30 and solid dispersions, are presented in fig. (2). The spectrum of pure FUR (A) showed four absorption peaks at 3398, 3352, 3286 (due to stretching vibration) and 1670 cm^{-1} (due to bending vibration) which are related to the amino group, as well as 1561 and 1322 cm^{-1} which belong to the asymmetric stretching vibration of the carboxyl and sulphonyl groups, respectively. The spectrum of PVP (B) showed important bands at 2954 cm^{-1} due to C-H stretching and 1670 cm^{-1} due to C=O. In the spectra of SD_{S3} (C) and SD_{K3} (D), the characteristic peaks of PVP-K30 were present at the same position, whereas peaks due to FUR were absent in SD_{S3} spectra (C) indicating trapping of FUR inside PVP matrix. Lack of any new peaks in the solid dispersions and also no differences in the positions of the absorption bands indicate the absence of significant interactions between FUR and PVP-K30 during solid dispersions preparation and storage.

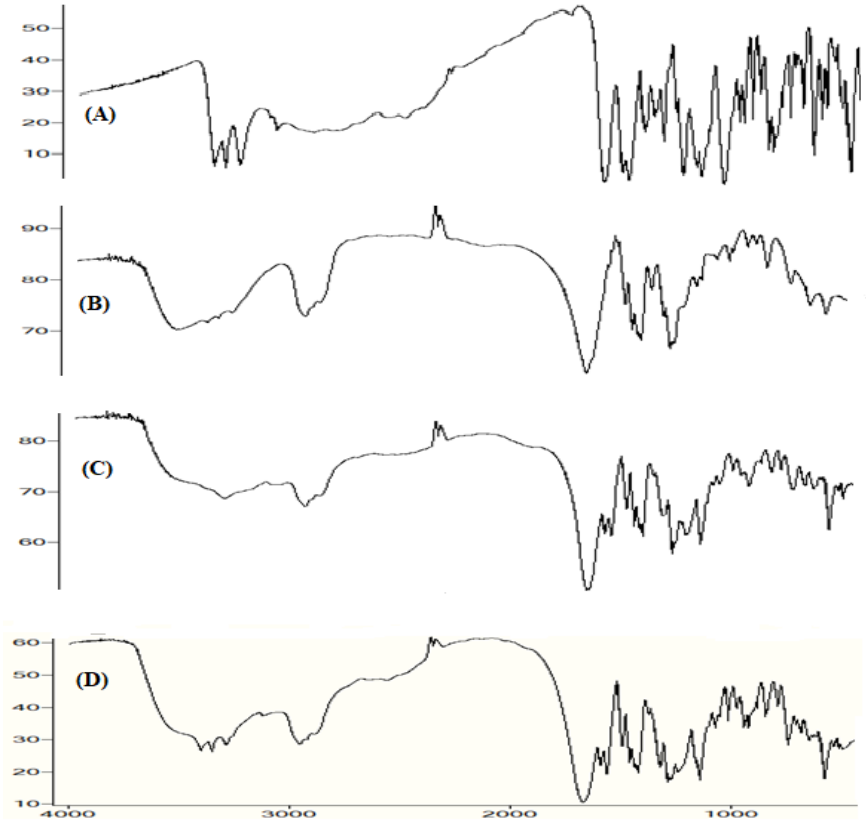

Fig. 2: FT-IR Spectra of (A) = Pure FUR, (B) = PVP-K30, (C) = SD_{S3} and (D) = SD_{K3}

Pre-compression evaluation

Compressibility index (Carr's Index) and the angle of repose of the SD_{S3} sample were 16.3% and 32.27°, respectively. These values indicate good compressibility and flow properties making this sample suitable for tableting.

Post compression evaluation of FUR solid dispersion tablets

Physical characterization

Tablets prepared from the optimized formula of furosemide solid dispersions (SD_{S3}) experienced good visual general appearance with normal size, smooth texture, and normal thickness and diameter; they were round yellowish colored tablets with flat and smooth surfaces. The average weight was 216.2 mg ± 1.67 with a very low percentage deviation (0.571%). The hardness of the tablets was in the normal range (4.36-5.87 kg/cm^2) with a mean value of 5.171 kg/cm^2 ± 0.3848. Besides, the friability was 0.842% (less than 1%). The disintegration time was less than 15 min and, the drug content was 100.44% ± 4.14 indicating that the values obtained complied with the USP Pharmacopeial limits.

***In vitro* dissolution studies**

Dissolution studies were carried out for (SD_{S3}) tablets and two commercially available brands of FUR in Sudan (brand A and B) according to USP specifications for dissolution. It's recommended that the percentage of API released in 30 min from immediate-release tablets using SGF pH 1.2 must be not less than 70%. Dissolution profiles of FUR from SD_{S3}, brand A and brand B tablets over one hour in SGF pH 1.2 are shown in fig. (3). Mean percentage amount of FUR dissolved from (SD_{S3}) tablets was 78.03% within 30 min, while the amount dissolved from brand A and brand B were 40.45% and 33.4%, respectively, that means the percent of dissolution of FUR solid dispersions tablets was accepted and its high percentage release highlights the significance of solid dispersions as a technique for improving the dissolution characteristics of poorly soluble drug FUR. It can be observed that the dissolution rate of pure FUR was low in both brands because 46.65% and 40.34% of the drug was being dissolved within one hour from Brand A and Brand B, respectively. Double increase in the dissolution rate was found with SD_{S3}tablets, concerning the commercial formulations as 82.24% was being dissolved over one hour.

Dissolution profile comparison between formulated solid dispersion tablets and two marketed brands of FUR

Model-independent approach

A comparison between the dissolution profiles of FUR from the optimized formula SDS3 and brands (A and B) was made by model-independent approaches; dissolution efficiency in 30 min (%DE30 min), similarity factor (f2) and mean dissolution time (MT). The calculated values of these parameters are presented in table (4). From this table, it is evident that SDS3 tablets showed good dissolution efficiency when compared with the two brands. The values of %DE30 min for brand A (38.59%) and brand B (38.46%) were increased in SDS3 tablets (42.54%). MDT of FUR in SDS3 tablets was lower (8.44 min) than those of brand A and brand B (13.87 min and 14.93 min, respectively).

Fit factor, namely; similarity factor (f2) has been accepted by FDA Centre for Drug Evaluation and Research (CDER) (Food and Drug Administration, 1997) as a rating criterion of similarity and difference between two in vitro dissolution profiles. According to the FDA, $f2$ values greater than 50 should ensure equivalence between the dissolution curves [23].

Fit factor, namely; similarity factor (f_2) has been accepted by FDA Centre for Drug Evaluation and Research (CDER) (Food and Drug Administration, 1997) as a rating criterion of similarity and difference between two in vitro dissolution profiles. According to the FDA, f_2 values greater than 50 should ensure equivalence between the dissolution curves [23]. According to this guideline, the release profile curves of FUR corresponding to the optimized formula and

brands were dissimilar since f_2 values for the comparison were less than 50 (22.11 and 20.55 for brand A and brand B, respectively). The dissolution profile of SD_{S3} tablets were better in terms of %DE and MDT than the dissolution profiles of the reference brands of FUR. Also, fit factor results showed dissimilarity between the dissolution profiles with superiority to SD_{S3} tablets.

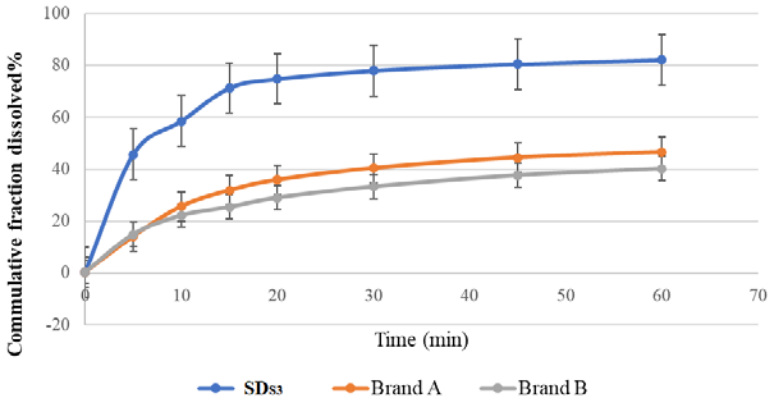

Fig. 3: Dissolution profiles of (SD_{S3}), brand A and brand B tablets in SGF pH 1.2

Table 4: Parameters of the dissolution profiles comparison using model-independent approaches

Code	$\%DE_{30min}$	MDT (min)	f_2
SD_{S3}	42.54	8.44	-
Brand A®	38.59	13.87	22.11
Brand B®	38.46	14.93	20.55

Model-dependent approach

The dissolution profiles corresponding to SD_{S3} tablets and the two reference brands were evaluated by fitting the experimental data to zero-order, first -order, Hixson-Crowell, Higuchi, Krosmeyer-Peppas, and Weibull models. The values of the kinetic parameters; adjusted correlation coefficient (R^2 adj), Akaike information criteria (AIC), and model selection criteria (MSC) obtained are shown in table (5). The result showed that the Weibull model had the best fit; as it had the highest R^2 adj values, highest (MSC) and lowest (AIC) in all samples of FUR tablets followed by Krosmeyer-Peppas model.

Table 5: Values of the kinetic parameters obtained from the models applied to FUR dissolution profiles curve

Code	Statistics	Zero-order	First-order	Higuchi	Hixon crowell	Krosmeyer peppas	Weibull
SD_{S3}	R^2 adj	0.4118	0.8252	0.6830	0.7270	0.9726	0.995
	AIC	73.4	56.7	61.4	60.3	42.6	28.2
	MSC	0.5940	1.4960	0.9016	1.0494	3.253	5.0567
Brand A®	R^2 adj	0.3445	0.6420	0.9210	0.5546	0.9612	0.9997
	AIC	58.3	53.4	40.9	55.2	36.5	-1.87
	MSC	0.1989	0.8173	2.3740	0.5935	2.9311	7.7245
Brand B®	R^2 adj	0.3411	0.5853	0.9424	0.5112	0.9907	0.9984
	AIC	55.3	51.5	34.9	52.8	21.7	6.77
	MSC	0.1845	0.6545	2.7313	0.4874	4.3750	6.2466

Table 6 presents the values of the best-fit parameters of the Krosmeyer-Peppas and Weibull model. The values of release exponent (n) extracted from the equations proposed by the Krosmeyer-Peppas model was <0.45 for all samples, it suggested that FUR release is governed by Fickian diffusion; also the values found for release rate constant kKP demonstrate that FUR was released more rapidly from PVP matrix (kKP was 37.8 in solid dispersions tablets). Values of shape parameter β extracted from the equation proposed by the Weibull model were less than 1 in all samples, which indicates that the shape of the curves was parabolic, displaying a high initial slope and a consistent exponential character.

Table 6: Best fit values for the parameters of krosmeyer-peppas and weibull models

Model	Parameter	SD_{S3}	Brand A®	Brand B®
Krosmeyer-Peppas	n	0.203	0.373	0.338
	kKP	37.8	10.9	10.3
Weibull	β	0.744	0.609	0.469

DISCUSSION

The rationale of this work was to improve the solubility and dissolution rate of FUR by preparing solid dispersion using the hydrophilic polymer PVP-K30 as a drug carrier employing two preparation methods, solvent evaporation and kneading technique. Solubility enhancement was observed in all solid dispersion formulae compared to pure FUR. Mechanisms for solubility enhancement by solid dispersion include particle size reduction, an increase of surface area, increase in wettability and porosity of the drug due to direct contact with hydrophilic carrier [24]. The most soluble FUR was achieved with solid dispersions prepared by the solvent evaporation method. This may be because the solvent evaporation method results in more uniform molecular dispersions of the drug in the hydrophilic carrier matrix as compared with the kneading technique [3].

It can be noticed that; with increasing the drug: carrier ratio the solubility increased to a great extent due to the enhanced wettability of particles dispersed in the hydrophilic carrier. Our findings in this study are in agreement with the study results of Meenakshi and Khan; they found that solid dispersions of FUR with PVP-K30 prepared by solvent evaporation method in 1:4 drug: carrier ratio enhanced the solubility to a greater extent compared with pure FUR [25]. Soni *et al.* evaluated the aqueous solubility of FUR solid dispersions prepared by the solvent evaporation method with PEG and PVP-K30, solid dispersions with PVP-K30 in 1:2 ratio showed a 4.5-fold increase in aqueous solubility of FUR compared with pure FUR [12]. Solubility study of FUR solid dispersions with PEG and PVP-K30 prepared by fusion and solvent evaporation method indicated that increasing the concentration of the carrier will enhance the aqueous solubility of the poorly soluble drug; this finding is reported by Patel *et al.*, they found that the solubility of FUR-PVP K30 solid dispersions in a ratio of 1:10 was enhanced by 23-fold compared with poorly soluble FUR [21].

According to solubility performance, solid dispersion prepared by the solvent evaporation method in a ratio of 1:2 FUR: PVP was selected for tablets preparation and evaluation. Dissolution studies for the formulated tablets were carried out according to USP specifications using SGF pH 1.2 and compared with a marketed brand of FUR. Release of FUR from tablets containing $SD_{S3}$was faster and greater compared with conventional tablets containing FUR. This confirmed the advantages of improved aqueous solubility of FUR in its solid dispersions form, which can be formulated as tablets with better dissolution characteristics. This finding is in accordance with the study carried out by Chaulang *et al.*, who found that tablets prepared from solid dispersions of FUR-Cross PVP exhibited better dissolution profile than commercial tablets [26]. Also, immediate-release tablets of FUR–PVP solid dispersions have been formulated and evaluated by Akbuga *et al.*, solid dispersions system was prepared by the co-precipitation method and the ratio of FUR: PVP was 1:6. The results were compared with similar tablets prepared by physical mixture, showed significant enhancement in dissolution profile of solid dispersions tablets and the drug release from these tablets was 17 times greater than that from tablets prepared from physical mixture [27].

Enhancement of the dissolution rate in tablets containing solid dispersions system with PVP-K30 can be explained by many factors, including; particle size reduction during solid dispersions process, the lower surface tension effect of the carrier PVP [13, 28], the improved drug wetting in the dissolution medium [21] local solubilization in the diffusion layer and consequently larger surface area resulting in increased dissolution rate [18, 29].

Regarding the kinetics of drug release, the Weibull model provided the best adjustment curve for both the formulated solid dispersion tablets and the reference brands, with the higher adjusted correlation coefficients (R^2 adj) and smallest AIC values. Better dissolution efficiency and less mean dissolution time for the formulated solid dispersion tablets, when compared to the marketed brand of FUR, highlighted the significance of solid dispersion technique in the enhancement of the dissolution behavior of FUR.

CONCLUSION

This study showed that solid dispersions of FUR with PVP-K30 in different ratios successfully enhanced the aqueous solubility and dissolution rate of FUR. Solid dispersions prepared by the solvent evaporation method showed more improvement in the solubility than those prepared by the kneading technique, and out of the six prepared formulations SD_{S3} (1:2 drug: carrier ratio prepared by solvent evaporation method) showed a four-fold increase in the aqueous solubility when compared with pure FUR. Characterization studies by FT-IR showed that no chemical interaction was encountered between FUR and the carrier. Tablets with satisfactory properties were formulated from the optimized formula of FUR-PVP solid dispersions and all formulated tablets complied with all quality control tests. Comparison of the *in vitro* dissolution profiles of FUR solid dispersions tablets with two commercially available brands of FUR in the local markets showed that the dissolution rate of FUR can be enhanced to a great extent by solid dispersions technique; twice increase in the dissolution rate was found with SD_{S3} tablets. Hence FUR-PVP K30 binary mixture could be considered for the formulation of immediate-release tablets of FUR to enhance the dissolution characteristics of the poorly soluble drug upon optimizing drug: carrier ratio that will give the maximum dissolution enhancement without affecting the drug release. *In vivo* pharmacokinetics study should also be considered.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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