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Enhancement of Dissolution Profile of Torsemide by Solid Dispersion Technique

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Abstract

The objective of the present study was to improve the aqueous solubility and dissolution characteristics of the loop diuretic Torsemide (TOR); a class IV drug in the Biopharmaceutical Classification System (BCS) using solid dispersion technique. Solid TOR dispersions at various ratios were prepared using solvent evaporation and kneading techniques with the hydrophilic carrier polyvinylpyrrolidone K-90 (PVP-K30). The generated solid dispersions underwent evaluations for drug content, yield in terms of percentage, solubility, and Fourier transform infrared spectroscopy (FT-IR). The dissolution properties of torsemide commercially available tablets and tablets with the optimised solid dispersions formula were evaluated. The developed solid dispersions showed an improvement in aqueous solubility, particularly those made using the solvent evaporation method in a 1:2 drug: carrier ratio (it shown a four-fold increase in solubility compared to the parent drug). FT-IR demonstrated the lack of chemical interactions between the medication and the carrier that could have hampered the dissolution. In terms of mean dissolve time (9.01 min) and dissolution efficiency in 30 min (43.62%), solid dispersion tablets displayed a better dissolution profile in simulated gastric fluid pH 1.2 at 37°C 0.5 than the commercial TOR tablets. Weibull and Krosmeyer models were used to determine the drug release kinetics of both TOR solid dispersions and commercial tablets, demonstrating that they were instantaneous release. According to the findings of this study it can be concluded that, solid dispersion techniques can be utilized to increase the solubility and rate of TOR dissolution in water.

Keywords: K-90, Torsemide, Dissolution

Introduction

Due to its many advantages over alternative formulations, oral drug delivery, particularly oral solid dosage forms like tablets and capsules, is the preferred route of administration for many medications. Because of its greater stability, simplicity of administration, high patient compliance, precision of doses, cost-effectiveness, and flexibility of indefinite quantity type style, it is the most frequently utilized method. [1]. Drug permeability, dissolving rate, general metabolism, susceptibility to outflow mechanisms, liquid solubility, and dissolution rate are just a few of the characteristics that affect a drug's bioavailability and therapeutic effectiveness when delivered orally. The main reasons for poor solubility and low permeability in oral bioavailability. Dissolution may also play a role in determining how quickly a drug will be absorbed, how much of it will be bioavailable, and when its therapeutic effects will manifest. The area and solubility of a medicine could have an impact on the dissolving rate [2,3]. Solubility is one of the most important parameters to achieve the desired drug

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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]. One of the most difficult aspects of developing a drug is improving its solubility, which affects its oral bioavailability. This is especially true for oral drug delivery systems. Grinding, the application of surfactants, salt creation, pH modifications, and prodrugs, complexation with cyclodextrins, self-emulsifying formulations, Micronization, emulsions, and liposomes are a few methods to make a medication more soluble and boost its bioavailability. [4]

Since the dissolution rate of one component from the surface is influenced by the other component in mixtures with several components, the choice of the carrier affects the dissolving characteristics of the medicine that has been dispersed. As a result, many hydrophilic carriers have been utilised to increase the bioavailability and dissolving properties of medicines that are poorly soluble in water, including gums, sugar, mannitol, and urea.[5]

Drugs that are poorly water-soluble have been administered the solid dispersion technique [6–13] to speed up their dissolution and, as a result, their rate of absorption and overall bioavailability. Solvent evaporation, fusion, solvent evaporation, and fusion are all typical techniques for creating solid dispersion. There are a variety of methods for creating solid dispersions, including solvent casting, kneading, co-precipitation, melting, co-grinding, gel entrapment, spray drying, melt extrusion, lyophilization, and dropping method solution [14]. The medicine is often molecularly disseminated inside the hydrophilic matrix, making solvent evaporation one of the most used techniques. Using a solvent or combination of solvents such ethanol, methanol, chloroform, or dichloromethane, the drug and polymer are solubilized, and the solvent is then evaporated. The carrier and medication must both be solubilized by the solvent, which also needs to be entirely removed. The resultant film can then be ground and milled. Low temperature evaporation can be achieved using a variety of methods, including vacuum drying, mixture heating, application of filter or heating bath, supercritical fluid, rotational evaporation, and spray drying [4-15]. One of the complicated formation-based methods is the kneading technique. It is based on making a paste by soaking the carrier in water or a hydro-alcoholic solution. The medicine is then added and mixed for a predetermined amount of time. The kneaded dough is then dried and, if necessary, put through a sieve. The most popular and straightforward technique for creating inclusion complexes is kneading; both in small- and large-scale manufacturing, it is inexpensive to utilize. [2]

Torsemide is used to treat congestive heart failure, liver disease, and kidney disease-related swelling and fluid retention (edema). It is a member of the class of drugs known as loop diuretics (water pills). This medication increases the flow of urine by working on the kidneys.By making solid dispersions with PVP K-90 using two different preparation techniques—solvent evaporation and kneading technique—this study aims to increase the solubility and dissolution rate of TOR. It also has the goal of assessing the potential of solid dispersions for the creation of TOR solid dispersion tablets.

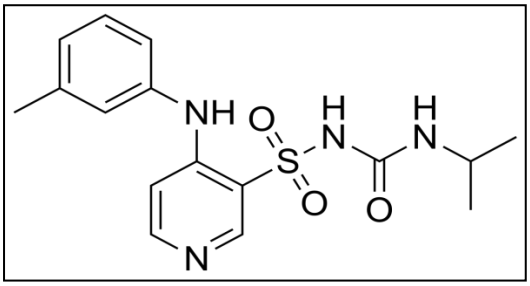

Fig. 1: Chemical Structure of TOR

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Materials and Methods

Torsemide (TOR) was gifted kindly by Maithili Life sciences. Polyvinyl pyrrolidone (PVP K-390) 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 NESCO GLOBAL, 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 torsemide 20 mg were obtained from the local drug market.

Preparation of Solid Dispersions

Solvent Evaporation Method

TOR solid dispersions were prepared by a solvent evaporation method using PVP K-90 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 TOR 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 TORther 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 dessicator until TOR their use [16].

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

Drug content

Accurate weights were used to dissolve solid dispersions in 10 ml of methanol that contained an equivalent amount of 10 mg of TOR. A 25 ml volumetric flask was filled with 2.5 ml of distilled water after being diluted with the aliquots. The material was purified using Whatmann filter paper, followed by a 0.45 m cellulose nitrate membrane filter, diluted, and spectrophotometric UV at 245 nm analysis for TOR. Using methanol, pure water is used as a reference. According to the calibration curve created at concentrations between 5 and 25 g/ml, the drug content was determined as follows:

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

Kneading Method

A mixture of TOR and PVP-K90 (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 dessicator until TORther use [17].

Evaluation of TOR Solid Dispersions

Percentage of practical yield

The percentage of practical yield is calculated to determine the effectiveness of the solid dispersion preparation method, which aids in the choice of an appropriate manufacturing technique. The practical yield from the following equation was calculated by gathering and weighing solid TOR dispersions.[18]

Solubility Study

Excess pure TOR and solid dispersions were added to 25 ml stopper conical flasks of distilled water, filled to the mark, and rotated for 24 hours in a shaking incubator (BioFree, Japan) set to 25° C. The mixtures were filtered twice: first, via Whatmann filter paper, and second, through a 0.45-m cellulose nitrate membrane filter. The filtrates were appropriately diluted with distilled water before being spectrophotometrically analyzed at 245 nm using a UV/VIS Spectrophotometer (model 7315 Jenway; England) to check for TOR. The average solubility was estimated [3] after the measurement was done in triplicate.

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Pre-compression Evaluation

Based on the solubility performance, the formulation with the highest solubility score was selected for the production of TOR solid dispersion tablets, and the flow properties of the powder samples were evaluated to confirm the compressibility.

The Angle of Repose

The angle of repose is defined as the maximum possible angle between the surface of the powder pile and the horizontal plane. The angle of repose is determined by θ and is given by the flow 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 [19].

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 [19].

Formulation of TOR solid dispersion tablets

Tablets containing solid dispersions equivalent to 20 mg of TOR were prepared by direct compression method using microcrystalline cellulose (MCC102) as a binder, croscarmellose sodium as a disintegrant, magnesium stearate (0.5% w/w) as a lubricant, talc (1.5% w/w) as a lubricant, and Lactose monohydrate as filler to adjust weight to 220 mg. All required ingredients were individually weighed and passed through a 60-mesh screen prior to mixing to ensure uniform particle size distribution. The mixture was compressed on a single tablet press (Erweka®, Germany) equipped with an 8 mm round flat punch set. The tablets were stored in an airtight container for TOR their study.

Post Compression Evaluation of TOR Solid Dispersion Tablets

Tablet Thickness

A vernier caliper was used to measure the thickness of the tablets. (AEROSPACE, China). Ten individual tablets were randomly selected and used. Mean values were calculated. Depending on the size of the tablet, the thickness of the tablet should be kept within ±5% of the standard value [20].

Weight Variation Test

The weight variation of 20 randomly selected tablets was determined using an electronic analytical balance (KERN, Germany), the tablets were weighed individually, and then the average tablet weight and percentage weight variation were calculated. The USP percentage deviation limit for uncoated tablets weighing 130-324 mg is 7.5%, and no more than two individual tablet weights should differ from the average weight [21].

Tablet Hardness

A hardness tester (Guoming, China) was used to gauge the hardness of ten tablets that were chosen at random. An average value was determined [22] by measuring the force needed to break the tablet in kg.

Tablet Friability

Twenty tablets chosen at random from the batch were used to calculate the friability %. Tablets were weighed (W1) and put into a stabilator in Guoming, China, where they revolved for 4 minutes at a speed of 25 rpm. To calculate the friability (%), the tablets were reweighted (W2) after the extra dust was removed from them[20]. According to USP, most pharmaceutical tablets with a friability rating of less than 1% are acceptable.

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

Drug Content Determination

Ten tablets were randomly selected and crushed up in a mortar for this test. After being dissolved in 25 ml of methanol using a sonicator for 15 minutes, the powdered substance corresponding to 10 mg of TOR was filtered using Whatman filter paper and a 0.45 m cellulose nitrate membrane filter. A UV-VIS

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spectrophotometer (model 7315 Jenway, England) was used to make the appropriate dilutions and conduct the spectrophotometric analysis of the drug content at 245 nm. The average drug content was computed after each measurement was made in triplicate[21].

Disintegration Time

A digital tablet disintegration test device (SCIENTIFIC, India) was used to conduct an in vitro disintegration test. It comprises of a basket-rack assembly holding six open-ended clear tubes with USP-specified dimensions vertically on a 10-mesh stainless steel wire screen. One tablet was put in each tube of the disintegration equipment to test the disintegration time, and the basket rack was set up in 0.1 N HCl pH 1.2 at 372 °C. The basket assembly housing the tablets was moved up and down by a conventional motor-driven device. The device was run until all tablets had broken down and all particles had passed through the 10-mesh screen within the allotted period. Most regular release pills are thought to disintegrate within 15 minutes. [21]

***In Vitro* Dissolution Study**

A paddle-type dissolution apparatus USP II RC-6 Dissolution tester (Gouming®, China) was used to conduct an in vitro dissolution study on two brands of TOR that are commercially available in Sudan (brand A and B) and TOR solid dispersion tablets. In 900 cc of Simulated Gastric Fluid, the dissolution study was carried out in triplicate for one hour (SGF, pH 1.2). To keep the volume constant, dissolution samples (10 ml) were obtained at 5, 10, 15, 20, 30, 45, and 60 min and replaced with an equivalent volume of SGF solution. Model 7315 Jenway, made in England, UV/VIS spectrophotometer was used to filter the sample solution before analysis.[22]

Dissolution Profile Comparison Between Formulated Solid Dispersion Tablets and Two Marketed Brands of TOR

Model-Independent Approach

Three model-independent parameters $\%D^{E10}$ (Dissolving Efficiency at 30 min), similarity factor (^{f2}), and mean dissolution time were used to compare the dissolution patterns of the optimised TOR solid dispersions, brand A, and brand B tablets (MDT).

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

The percentage dissolution efficiency at 30 minutes for each sample was determined by dividing the area under the dissolution curve up to that time by the area of the rectangle that would represent 100% dissolution at the same time. The following equation [23] can be used to compute dissolution efficiency (%DE):

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

Where y represents the product's percentage of dissolution. The area under the dissolution curve between time points, or %DE, is then calculated as a percentage of the curve at maximum dissolution, or y100, during the same time period. In the current investigation, 0 and 30 minutes are equal.

Similarity Factor (f_2)

In 1996, Moore and Flanner created the similarity factor (f_2), one of the fit factors. It compares how closely dissolved TOR in a test formulation and a reference formulation are similar over time. It can be determined by the equation found below:

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

Where n is the total number of withdrawal points, is the percentage of reference that has been dissolved at time t, is the percentage of test that has been dissolved at time t, and is optional weight at time t. The similarity factor (f_2) has a value of 100% if the test and reference profiles are identical. Lower values show an increase in the dissimilarity across release profiles, while values between 50 and 100 indicate similarity between the dissolution profiles.

Mean Dissolution Time (MDT)

The MDT, which measures the time it takes for a drug to dissolve, is the initial statistical point in the cumulative dissolution process to accurately measure the drug release rate. An increased MDT value denotes a stronger drug-retarding capacity. The obtained dissolution data of all samples were fitted into the following equation to determine the extent of improvement in the rate of TOR's dissolution from its solid dispersion with PVP-K90.

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$$MDT = \frac{\sum_{i=1}^{n} t_{mid} \times \Delta M}{\sum_{i=1}^{n} \Delta M}$$

Where I is the number of the dissolution sample, n is the number of dissolution times, is the time between times ti and ti-1, and M is the quantity of TORosemide in g dissolved between times ti and ti-1.[24]

Model-Dependent Approach

The in vitro release data were fitted to various mathematical kinetic models, as shown in table 1, to clarify the mechanism of TOR's release kinetics from the hydrophilic carrier PVP-K90. DDSolver is a piece of software that compares various dissolution profiles using model-dependent approaches [25].

Table No.1: Mathematical Release Kinetic Models

Model	Equation
Zero-order	$Q_t = Q_0 + K_0 t$
First-order	$\text{Log } Q_t = \log Q_0 - \frac{Kt}{2.303}$
Higuchi	$Q = KH. t^{1/2}$
Hixon-Crowell	$\sqrt[3]{W_0} - \sqrt[3]{W_t} = Kt$
Krosmeyer–Peppas	$M_t/M_\infty = k KPt^n$
Weibull	$F = F_{max} \times \{1-Exp[-((t-T_i)^{\beta})/\alpha]\}$

Results and Discussion Preparation of Solid Dispersions

PVP-K90 was used as a drug carrier to create solid TOR dispersions utilizing solvent evaporation and kneading techniques. Six formulations were created and coded in the current study, and their whole composition is displayed in the table 2. It was discovered that all of the created solid dispersions were fine, yellowish powders.

Table No.2: Formulations of TOR 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 TOR Solid Dispersion

The results of the study on the solubility of all solid dispersions prepared using the solvent evaporation and kneading techniques, as well as the % practical yield, drug content, and solubility results, are presented in table 3.

Table No.3: Practical Yield By Weight, Drug Content and Solubility of Solid Dispersion Formulations

Batch code	Practical yield (%)	Drug content (%)	Solubility (mg/ml)
Pure TOR	-	-	0.0701 ± 0.001
SD_{S1}	96.3	98.54 ± 0.006	0.1203 ± 0.002
SD_{S2}	78.7	99.54 ± 0.362	0.1372 ± 0.051
SD_{S3}	86.6	97.12 ± 0.008	0.2645 ± 0.002
SD_{K1}	55	95.73 ± 0.006	0.1140 ± 0.002
SD_{K2}	76.8	97.50 ± 0.380	0.1264 ± 0.001
SD_{K3}	80.5	98.34 ± 0.003	0.1624 ± 0.001

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Percentage of Practical Yield by Weight

The practical yield of all samples was found to be in the range of 55–96.3 %. The maximum yield was found 96.3 % 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 ranged from 95.73 to 99.54%, demonstrating the effectiveness of the current procedures for producing solid dispersions with excellent uniformity of content. The SD_{S2} formulation contained 99.54% of the maximum allowed drug level.

Evaluation of Solubility

All solid TOR dispersions with PVP-K90 showed enhanced aqueous drug solubility compared to pure TOR. TO R dissolved in water 0.0701 mg/ml at 25 °C. For comparison, solid dispersions prepared using the solvent evaporation method had the highest TOR solubility. The formulation with the highest aqueous solubility among all solid dispersion types (1:2 ratio created by solvent evaporation method), with a solubility of 0.2645 mg/ml that was nearly four times greater than that of pure TOR. For the development of TOR solid dispersions tablets, this formula was chosen as the best one.

Pre-compression Evaluation

The sample's angle of repose was 31.23° and its compressibility index (Carr's Index) was 16.5%. This sample is excellent for tableting because these values show good flow and compressibility characteristics.

Post compression Evaluation of TOR Solid Dispersion Tablets Physical Characterization

Torsemide solid dispersions prepared from the optimised formulation had round, yellowish-colored tablets with flat, smooth surfaces and normal size, smooth texture, thickness, and diameter. These tablets had good visual overall look. With a relatively small percentage variance (0.580%), the average weight was 214.5 mg ± 1.47. The mean value of the tablet hardness was 5.282 kg/c, which is within the usual range of 4.32 to 5.84 kg/c. TOR Furthermore, the friability was 0.842%, which is less than 1%. The disintegration time was less than 10 mins, and the amount of drug recovered was 100.47% 4.16, showing that the values obtained were within the range approved by the USP Pharmacopeial.

***In Vitro* Dissolution Studies**

According to USP guidelines for dissolution, dissolution studies were carried out on two commercially available brands of TOR (brand A and B). It is advised that no less than 70% of the API should be released in 30 minutes from immediate-release tablets using SGF pH 1.2. Figure 1 depicts the TOR dissolution profiles of tablets from brands A, B, and over the period of an hour in SGF pH 1.2. (3). The amount of TOR that dissolved on average from () tablets in 30 minutes was 79.13%, while the amounts that dissolved from brand A and brand B were 41.25% and 34.6%, respectively. This indicates that the amount of TOR that dissolved on average from () tablets was accepted, and the high percentage release highlights the importance of solid dispersions as a method for enhancing the dissolution characteristics of the poorly soluble drug TOR. Because 45.75% and 39.37% of the drug from Brand A and Brand B, respectively, were dissolved within an hour, it can be seen that the dissolving rate of pure TOR was low in both brands. Pills had a twice-increased dissolving rate compared to commercial formulations; 85.44% of the tablets were dissolved in an hour.

Dissolution Profile Comparison between Formulated Solid Dispersion Tablets And Two Marketed Brands of TOR

The average TOR % Dissolution rate in 30 min (%DE30 min), similarity factor (f2), and mean dissolution time were utilized as model-independent comparison tools to compare the dissolution profiles of TOR from the optimised formula SDS3 and brands (A and B) (MT). These parameters' estimated values are shown in table (4). It is clear from the data that SDS3 tablets outperformed the other two brands in terms of their ability to dissolve their contents. In SDS3 tablets (43.62%), the values of%DE30 min for brands A and B (39.49% and 39.76%, respectively)

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rose. MDT for TOR in SDS3 pills was shorter (9.04 min) than for brands A and B. (14.77 min and 15.95 min, respectively).

The FDA Centre for Drug Evaluation and Research (CDER) (Food and Drug Administration, 1997) has approved the fit factor, or similarity factor (f2), as a rating criterion of similarity and difference between two in vitro dissolution profiles. The FDA states that f2 values over 50 should guarantee parity between the dissolution curves [26].

Fit factor, or similarity factor (f^2), has been approved by the 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. The FDA states that values greater than 50 should guarantee equality between the dissolution curves [26]. This rule states that since values for the comparison were less than 50, the release profile curves of TOR corresponding to the optimised formula and brands were different (23.13 and 21.56 for brand A and brand B, respectively). In terms of %DE and MDT, the dissolving characteristics of tablets were superior to those of the reference brands of TOR. Additionally, fit factor data demonstrated differences between the dissolving profiles with tablets being superior.

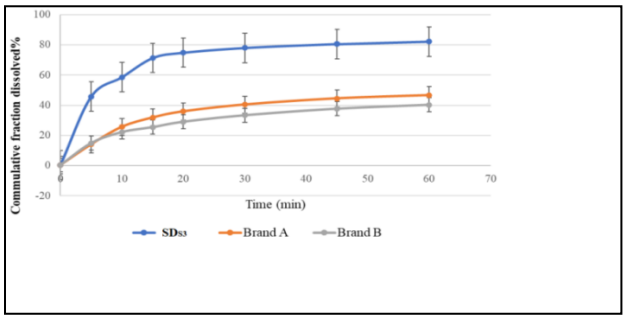

Figure No. 3: Dissolution Profiles of (SD_{S3}), brand A and brand B Tablets in SGF pH 1.2

Table No.4: Parameters of the Dissolution Profiles Comparison Using Model-Independent Approaches

Code	% DE_{30min}	MDT (min)	f_2
SD_{S3}	43.62	9.04	-
Brand A^{Φ}	39.49	14.77	23.13
Brand B^{Φ}	39.76	15.95	21.56

Model-dependent Approach

By fitting the experimental data to models such as zero-order, first-order, Hixson-Crowell, Higuchi, Korsmeyer-Peppas, and Weibull, the dissolving profiles corresponding to the tablets and the two reference brands were evaluated. The values of the kinetic parameters, adjusted correlation coefficient (adj), Akaike information criteria (AIC), and model selection criteria (MSC) computed are displayed in table 5. The results demonstrated that the Weibull model had the best fit, having the highest adj values,highest (MSC), and lowest (AIC) in all samples of TOR pills, followed by the Krosmeyer-Peppas model.

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 Korsmeyer-Peppas model was <0.45 for all samples, it suggested that TOR release is governed by Fickian diffusion; also the values found for release rate constant kKP demonstrate that TOR was released more rapidly from PVP matrix (kKP was 38.6 in solid dispersions tablets). Values of shape parameter β extracted from

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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 No.5: Values of the Kinetic Parameters Obtained From the Models Applied to TOR Dissolution Profiles Curve

Code	Statistics	Zero-order	First-order	Higuchi	Hixon crowell	Krosmeyer peppas	Weibull
	R^2adj	0.3118	0.8272	0.6450	0.7540	0.9746	0.985
SD_{33}	AIC	74.4	57.9	61.7	60.3	42.6	28.3
	MSC	0.6740	1.4570	0.9646	1.0544	3.3543	5.0767
	R^2adj	0.4447	0.6540	0.9670	0.6746	0.9642	0.9977
Brand A*	AIC	54.5	53.8	41.1	55.8	36.5	-1.90
	MSC	0.1999	0.8543	2.3560	0.5545	2.9541	7.7365
	R^2adj	0.3417	0.5543	0.9434	0.5672	0.9757	0.9874
Brand B*	AIC	52.6	51.6	34.9	52.2	21.8	6.78
	MSC	0.1945	0.6555	2.7543	0.4564	4.3560	6.2326

Table No.6: Best Fit Values for the Parameters of Korsmeyer-peppas and Weibull Models

Model	Parameter	SD	Brand A*	Brand B*
Korsmeyer-Peppas	n	0.203	0.374	0.335
	kKP	38.6	10.4	10.2
Weibull	β	0.744	0.607	0.468

The Weibull model, which had the highest adjusted correlation coefficients (adj) and minimum AIC values, provided the best adjustment curves for the kinetics of drug release for both the reference brands and the created solid dispersion tablets. When compared to the marketed brand with TOR,

Conclusion

This study demonstrated that adding PVP-K90 to solid TOR dispersions in various ratios successfully increased TOR's water solubility and rate of dissolution. Out of the six prepared formulations (1:2 drug: carrier ratio prepared by solvent evaporation method), four showed a four-fold increase in the aqueous solubility when compared with pure TOR. Solid dispersions prepared by the solvent evaporation method also showed more improvement in the solubility than those prepared by the kneading technique. FT-IR characterization studies revealed the solid dispersion technique's importance in improving TOR's dissolving behavior was underlined by the formulated solid dispersion tablets' improved dissolution efficiency and shorter mean dissolution time.

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that there was no chemical interaction between the carrier and the TOR. The optimised formula of TOR-PVP solid dispersions was used to produce tablets with satisfactory qualities, and all formulated tablets passed all quality control tests. The in vitro dissolution profiles of TOR solid dispersions tablets compared to two commercially available brands of TOR in the local markets revealed that the solid dispersions technique can significantly increase the rate of TOR dissolution; a twofold increase in dissolution rate was observed with tablets. As a result, the TOR-PVP K90 binary mixture could be taken into consideration while developing TOR immediate-release tablets in order to improve the poorly soluble drug's dissolving properties.

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