DESIGNING A FORMULATION SYSTEM TO ENHANCE AQUEOUS SOLUBILITY AND DISSOLUTION OF POORLY SOLUBLE DRUG

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ABSTRACT: The main purpose of this investigation study is to enhance the solubility and dissolution rate of poorly water-soluble drug Fluconazole. Fluconazole was selected as the choice of drug as it belongs to BCS class II *i.e.,* drugs having low solubility and high permeability, which hinders *in-vivo* efficacy of drugs giving poor pharmacokinetic profile and low absorption. Solid dispersions are formed to increase the dissolution rate of a drug and solubility, thereby improving its oral bioavailability. Fluconazole solid dispersions were prepared to enhance the solubility and dissolution rate using the Kneading method and Solvent Evaporation method. Solid dispersions were formulated using different carriers like PEG, PVP, Gelucire, *etc*. The batch containing PEG 4000 as a carrier by using the Solvent Evaporation method gave maximum drug content, and solubility was selected as the optimized batch for the formulation of an oral tablet. The optimized batch was subjected for Practical yield, Drug content, Saturation solubility, Infrared (I.R.) Spectroscopy, Differential Scanning Calorimetry (DSC), X-ray powder Diffractometry, and Scanning electron microscopy. Post and pre-compression parameters were also studied. FT-IR revealed no chemical incompatibility between drug and polymer. The dissolution rate study for the tablet containing Fluconazole solid dispersion was carried out for improvement of the dissolution rate. The formulation SE-Z1 showed maximum solubility and also an increase in dissolution rate as compared to the plain drug. The tablets of fluconazole solid dispersions were successfully prepared, and the formulation was found to be stable.

Keywords:

Solid dispersion, Kneading, Solvent evaporation, Dissolution rate, Solubility, Polymers, Carriers

INTRODUCTION: In pharmaceutical formulation technology, there are various drugs, including the newly discovered drugs, which have greater therapeutic efficiency but are still recognized as poorly aqueous soluble drugs leading to incomplete absorption and giving low bioavailability [1]. In such cases, solubility is the main criteria that limits the potential of such drugs.

The drugs which are poorly soluble causes a failure of the formulation during development processes. Poor water solubility and low dissolution rate profile of the drug in aqueous G.T.T fluid leads to insufficient bioavailability.

Therefore, there is a need to enhance water solubility of such drugs as solubility is one of the major problems faced during development of oral solid dosage and in the area of newly developed formulations [2]. The drugs coming under BCS class II and Class IV [3] group are poorly water-soluble drug. During oral absorption of the drug dissolution becomes a rate limiting step for lipophilic drugs and causes incomplete absorption of drugs. So, it is important to improve dissolution profile of the drugs for better therapeutic utility. Dissolution is a process in which a solid substance goes into solution. According to Noyes-Whitney equation dissolution rate is directly proportional to the solubility of the drug[4]. Hence, solubility of the drug is important factor for dissolution profile and for good absorption and bioavailability of the drugs.

For a drug to undergo complete absorption and have good bioavailability it must be dissolved in gastric fluids. Dissolution is a process that determines the degree and the rate of absorption of the drugs [5]. Drugs having slow dissolution rates often show erratic and incomplete absorption, which causes bioavailability problems when they are administered orally. There numerous techniques available for improvement of aqueous solubility of the drugs like solid dispersion, melt granulation, direct compaction, solvent evaporation, salt formation, *etc*. [2] In these types of techniques carriers or polymers play a crucial role for improvement of solubility and dissolution rate. Sekiguchi and Obi discovered the concept of solid dispersion. Solid dispersion is a method in which hydrophobic drugs are dispersed in a fine state in hydrophilic carriers [6]. The various carriers or polymers used for preparation of solid dispersions are β-cyclodextrin [7, 8], pyrolidone (PVP) [9], urea, mannitol, polyethylene glycols (PEG) [5, 10] *etc*.

Fluconazole is a drug mainly preferred to be given through oral routes, but the drug is poorly water-soluble limits the absorption by this route; hence it is necessary to enhance the solubility and dissolution rate for the proper pharmacokinetic profile. Fluconazole active ingredients a wide spectrum triazole antifungal medicinal active. It is used in the treatment of systemic candida infections as well as vulvovaginal, esophageal, and oropharyngeal candidiasis. Fluconazole is also used in treating meningitis caused by Cryptococcus neoformans. Solid dispersions of fluconazole are formed to increase the dissolution rate of a drug and solubility, thereby improving its oral bioavailability.

MATERIALS AND METHODS: Fluconazole was obtained as a gift sample from Cipla Ltd., Maharashtra, India. Magnesium stearate, Talc, and Microcrystalline cellulose were obtained from S.D. Fine Chemical, Mumbai, India. Polyethylene glycol (PEG) 4000, PEG 6000, and PVP K30 were obtained from Loba Chemicals, Tarapur. Gelucire 44/13 and Gelucire 50/13 were obtained from Colorcon Asia Pvt. Ltd. Mumbai. β-cyclodextrin was obtained from Hi-Media Laboratories Pvt. Ltd. Mumbai.

Methods of Preparing Fluconazole Solid Dispersions:

Solvent Evaporation Method: [11] Formulations of fluconazole solid dispersions were prepared using different carriers like PEG 4000 and PEG 6000 [10, 9, 5] in various proportions, *i.e.*, 1:1, 1:2, 1:3 (Drug: Carrier) as shown in **Table 1**. The drug and the carriers or polymers were dissolved in ethanol in a beaker. When the drug and the carrier dissolved completely, the mixture was poured on a Petri dish. The petri dish containing the mixture was placed in an oven at 60 °C until the solvent was removed completely. The solid dispersion obtained was sieved through # 60 sieve and stored inside the desiccator for further use.

Kneading Method: [12] Formulations of Fluconazole solid dispersions were prepared using different carriers like β-cyclodextrin [7, 8], Gelucire 44/14[13], Gelucire 50/13 [14], PVP K30 [9, 11], PEG 4000 and PEG 60005 [5, 8, 10] in various proportions *i.e.,* 1:1, 1:2, 1:3, 1:4, 1:5 (Drug: Carrier) as shown in **Table 2**.

Polymers were added to the mortar and pastel, and to this small quantity of ethanol were added during trituration to obtain good slurry-like consistency. To this slurry, then the drug is added slowly continued by trituration for an hour. The slurry obtained was then subjected to air-drying at 25 °C for 24 h. Pulverized and passed through the sieve # 100 and stored in a desiccator for further use.

Evaluation and Characterization of Solid Dispersion: All the formulations were evaluated by physical appearance, practical yield, drug content, saturation solubility studies.

Physical Appearance: [5] Fluconazole solid dispersions all batches were evaluated for appearance and color.

Percent Practical Yield (PY): [5] Percentage of practical yield was measured to know the accuracy or efficiency of the method. Also, to know the exact yield obtained from the batch of solid dispersion helpful in selecting an appropriate methods for production. The practical yield (PY) was calculated using the given equation.

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] × 100

Drug Content: [5] An amount equivalent to 25 mg of the drug was taken from different batches of solid dispersions, and each batch was dissolved separately in 25 ml methanol. The solutions were sonicated, filtered, and diluted further such that their absorbances fall within the standard calibration curve range. The absorbances of the solutions were determined at 261 nm by using UV - Spectrophotometer, Shimadzu, Japan.

Saturation Solubility: [15] An amount equivalent to 50 mg of plain fluconazole, dissolved in 25 ml, and 100 mg of solid dispersions were taken from different batches of solid dispersions, dissolved in 50 ml of different solvents like 0.1N HCl, Buffer pH 6.8 and water respectively in the flasks. These solutions were then sonicated for sometimes and kept for 48 h in a horizontal shaker with continuous starring. The saturated solution obtained was then filtered, diluted further, and analyzed using UV–vis Spectrophotometer, Shimadzu, Japan.

Evaluation of Selected Solid Dispersion: The selected batch of solid dispersion was subjected to *in-vitro* dissolution studies, FTIR, DSC, SEM, and POWDER-XRD analysis.

Dissolution Studies: [16, 5] *In-vitro* dissolutions of drug fluconazole and selected Solid dispersion batch were studied using calibrated 8-station USP-II apparatus (paddle method), TDT-08L Electro lab, Mumbai, India. Samples of the drug and solid dispersions equivalent to 100 mg drug were filled in capsules and immersed in the 900 ml of different dissolution medium 0.1N HCl and phosphate buffer pH 6.8 at 75 rpm. Aliquots of 5 ml were removed at time intervals 0, 10, 20, 30, 40, 50, 60, 90, 120 min.

The samples withdrawn were then filtered using a Whatman filter paper no. 1 and analyzed at 261 nm by using UV–vis Spectrophotometer, Shimadzu, Japan. Cumulative percentages were calculated.

Fourier Transform Infrared Spectroscopy: [15] FTIR spectra of pure fluconazole, PEG 4000, and the selected sample of solid dispersion were recorded on IR, Bruker, India, and ATR pellet method. 10 mg of the solid dispersion was taken with 40-50 mg of ATR powder and filled within the pellets for scanning at range 4000 to 400 cm^{1}.

Differential Scanning Calorimetry: [17] DSC analysis of plain Fluconazole, PEG 4000, and the selected sample of solid dispersion were performed using EX STAR DSC 6620 (Measurement and standard analysis software). Samples weighing 4 to 5 mg were heated in aluminum pans, which were hermetically sealed over a temperature range of 30-300 °C at a constant rate of 10°C/min under nitrogen stream.

X-Ray Powder Diffractometry: [17, 18] Thermogram were recorded during X-ray powder diffractometry process of plain fluconazole and the selected sample of solid dispersion using a Philips pan analytical XPERT-PRO diffractometer 1780 with CuK radiation. The scanning rate employed was 2°/min over the 4°–60° 2θ range. The patterns were collected with tube voltage 45 kV and the tube current 40mV in the step scan mode (step size: 0.0170; counting time: 29.8450 seconds per step).

Scanning Electron Microscopy: [17, 18] The plain fluconazole, PEG 4000, and a selected sample of solid dispersion were studied for shape and surface morphology by using scanning electron microscopy (SEM), JEOL, JSM 7600F, Tokyo, Japan. The samples were placed on double-sided adhesive tape secured on copper stubs and then were analyzed using the accelerating voltage of 5kV.

Compression of Solid Dispersion Tablets: [12] Tablet of fluconazole solid dispersions were prepared to weigh 400 mg each. The tablet was prepared using a selected sample of solid dispersion 1:1 ratio containing 100 mg of drug fluconazole and 100 mg polymer PEG 4000. Microcrystalline cellulose, crospovidone, aerosol, and magnesium stearate were used as the directly compressible diluent, super disintegrate, lubricant and glidant, respectively. All the ingredients were mixed together passed through a sieve and were compressed by the direct compression method using 12 mm punches employing rotary tablet press Cad Mach, Ahmedabad, India. The tablet hardness was kept between 5 to 6 kg/cm^2. The prepared tablets were evaluated for drug release studies.

Evaluation of Fluconazole Powder Blends:

Pre-compression Parameters for Fluconazole Solid Dispersions: [12]

Bulk Density (Db): Bulk density is the total weight of the bulk powder measured by transferring the powder in a measuring cylinder and the initial volume of the powder is noted which is calculated using formula Db = M / Vb where Vb is the bulk volume of powder, M is the mass of powder. It is denoted in terms of g/ml.

Tapped Density (Dt): Tapped density is total mass of the powder obtained after tapping the powder 100 times. The tapped volume noted if less than 2% in the difference between the two volumes and if it is more than 2% tapping is done again for 200 times. It is calculated by using formula Dt = M / Vt Where, Vt is the tapped volume of the powder and M is the mass of powder. It is denoted by g/ml.

Carr's Index or % Compressibility: Carr's index is studied for determination of flow properties of the powder and given in terms of percentage. It is calculated using formula I = (Dt – Db) / Dt × 100, where, Db is the bulk density of the powder and Dt is the tapped density of the powder.

Hausner's Ratio: Hausner's ratio is used to study the flow of powder *i.e.,* the ease of powder flow. It is calculated using the formula H = Dt / Db Where, Db is the bulk density, and Dt is tapped density. If Hausner's ratio is < 1.25 better flow of powder.

The Angle of Repose (Ɵ): The angle of repose (Ɵ) is used to measure the frictional force of the powder. It is calculated using the formula Ɵ = $\tan^{-1}$ (h / r) Where, "r" is the radius in cm and "h" is height in cm.

Compression Parameters for Fluconazole Solid Dispersions:

Hardness: Hardness in compression means the force required to break a tablet. The tablets hardness was determined using the Monsanto tablet hardness tester and expressed in terms of kg/cm^2.

Thickness: The tablets were selected on a random basis from batches and a Vernier caliper was used to measure their thickness.

Friability: About 10-15 tablets were selected for Friability testing using Roche fibrillatory machine. The tablets were allowed to revolve for 50 times at 25 rpm subjected to both abrasion and shock in the chamber. After revolutions the tablets were removed, dusted using a muslin cloth and then weighed. This is calculated using the formula F = Initial weight – Final weight.

***In-vitro* Dissolution Time:** [16, 5] *In-vitro* dissolution of tablets of fluconazole solid dispersions were studied using a calibrated 8- station USP-II apparatus (paddle method), TDT-08L Electro lab, Mumbai, India. Sample of the tablets were immersed in the 900 ml of different dissolution medium 0.1N HCl and Phosphate buffer pH 6.8 at 75 rpm. Aliquots of 5 ml were removed at time intervals 0, 10, 20, 30, 40, 50, 60, 90, 120 min. The samples withdrawn were then filtered using a Whatman filter paper no. 1 and analyzed at 261 nm by using UV–vis Spectrophotometer, Shimadzu, Japan. Cumulative percentages were calculated.

Stability Studies: [15] The stability testing studies were performed for optimized batch of formulation as per the ICH (International Conference on Harmonization) guidelines. The guidelines were followed for stability testing. The optimized batch of tablets were stored in aluminum foil, and the stability testing was carried for

3 months. According to ICH guidelines the temperature was kept 40 ºC ± 2 ºC and relative humidity of 75% RH ± 5%. The samples were tested after every one month and analyzed for changes like in its appearance and drug content. The changes observed were noted.

RESULTS AND DISCUSSION:

Physical Appearance: All the batches observed were white, free flowing powders.

Percent Practical Yield and Drug Content Uniformity: Practical yield of all batches of fluconazole Solid dispersions were found to be between 83% and 98%. The drug content of all the batches of fluconazole solid dispersions were found to be between 68.92% and 99.01% with low standard deviations. Solid dispersions were prepared by different methods as shown in **Table 3** and **Table 4**. It indicated that the drug is uniformly dispersed. The batch SE-Z1 batch prepared by Solvent evaporation method using polymer PEG 4000 gave the highest practical yield 98% and drug content 99.01%. Therefore, the method used appears to be reproducible for preparation of solid dispersion and the ratio of drug: hydrophilic carrier was decided to be 1:1.

Saturation Solubility: Saturation solubility studies were carried out for plain fluconazole and all the batches of Fluconazole Solid dispersions in 0.1N HCl, Buffer pH 6.8 and water. **Table 5** and **Table 6** shows the saturation solubility for different batches of solid dispersions. From this table, it can be concluded that the use of hydrophilic carriers improved the apparent solubility of fluconazole. All solid dispersions showed more solubility in comparison to pure drug. The solvent evaporation method showed more solubility in comparison kneading method.

Dissolution Studies: Dissolution study showed that the release rates of batch SE-Z1 were faster as compared to pure drug fluconazole in both the medium 0.1N HCl and buffer pH 6.8. In 0.1N HCl the release rate of plain drug fluconazole was 44.72% in 90 min whereas in case of solid dispersion batch SE-Z1 was found to be 102.38% in 90 min.

CONTAINING POLYMER PEG 4000 IN BUFFER pH 6.8

The dissolution rates in 0.1N HCl is given in **Table 7,** and the dissolution profile graph is shown in **Fig. 1**. In buffer pH 6.8, the release rates of pure drug fluconazole were found to be 43.29%, whereas in solid dispersion batch, SE-Z1 was found to be 99.62%. The dissolution rates in buffer pH 6.8 are given in **Table 8,** and the dissolution profile graph is shown in **Fig. 2.** Hence, the preparation of solid dispersions improved the dissolution rates.

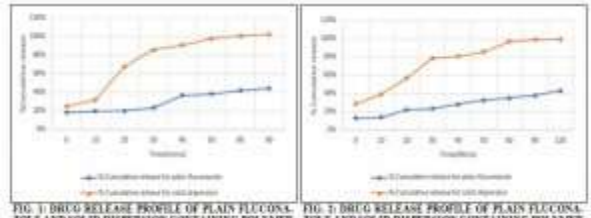

FIG. 1: DRUG RELEASE PROFILE OF PLAIN FLUCONAZOLE AND SOLID DISPERSION CONTAINING POLYMER PEG 4000 IN 0.1N HCl

FIG. 2: DRUG RELEASE PROFILE OF PLAIN FLUCONAZOLE AND SOLID DISPERSION CONTAINING POLYMER PEG 4000 IN BUFFER pH 6.8

Fourier Transform Infrared Spectroscopy: The FTIR spectra of pure fluconazole, PEG 4000, and their solid dispersion are shown in **Fig. 3**. The FTIR studies indicated that there is no chemical interaction taking place between drug fluconazole and polymer PEG 4000 during the preparation of fluconazole solid dispersions.

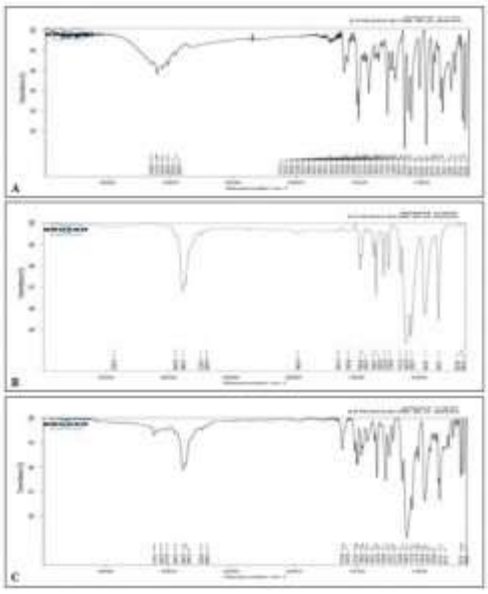

FIG. 3: FT-IR FOR PLAIN DRUG (A), PEG 4000 (B) AND SOLID DISPERSION CONTAINING POLYMER PEG 4000 (C)

Differential Scanning Calorimetry: DSC studies were carried out for plain fluconazole and solid dispersion containing polymer PEG 4000 given in **Fig. 4** indicated that fluconazole was homo-geneously distributed within the carrier in an amorphous state and no drug crystallized out of the dispersion suggesting that drug and polymer exist in the form of a mixture rather than the reaction product.

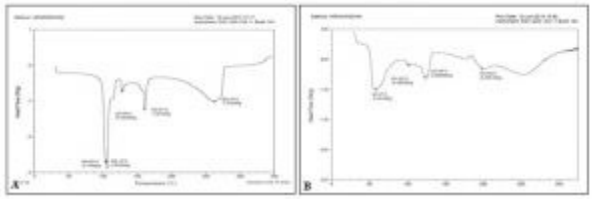

FIG. 4: DSC FOR PLAIN DRUG (A) AND SOLID DISPERSION CONTAINING POLYMER PEG 4000 (B)

X-ray Powder Diffractometry: The XRD diffraction spectra of plain fluconazole showed distinct peaks giving the presence of a high crystalline state. The peak observed in plain fluconazole showed characteristic peaks with higher intensity while the batch of solid dispersion of fluconazole showed characteristic diffraction peaks with low intensity. The diffraction pattern of the drug fluconazole and solid dispersion of fluconazole is shown in **Fig. 5**.

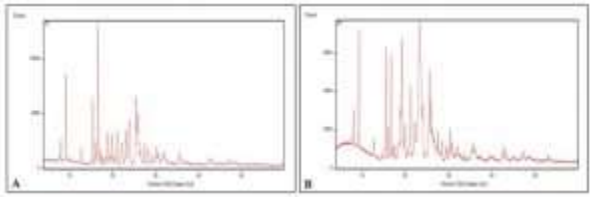

FIG. 5: XRD-POW FOR SOLID DISPERSION CONTAINING POLYMER PEG (A) AND PLAIN DRUG (B)

The study revealed that the crystallinity and the sharpness of the peaks were reduced in solid dispersion form as compared to pure fluconazole. The polymer PEG 4000 used for preparing solid dispersion of fluconazole inhibited the crystallinity of the drug resulting in amorphous state of the drug in solid dispersion. In the XRD diffraction pattern of the solid dispersion of fluconazole the characteristic peaks of the drug eventually disappeared, giving diffractions of lower ratios.

Scanning Electron Microscopy: The SEM study was performed for plain fluconazole, polymer PEG 4000, and solid dispersion of selected batch SE-Z1 for size and surface morphology, as shown in **Fig. 6**. The study revealed that pure fluconazole existed in form crystals, which were flat broken needles of different sizes.

The polymer PEG 4000 existed in the form of irregularly shaped crystals, while solid dispersion of fluconazole existed in form compacted spherical forms. The original morphology of component disappeared, stating that fluconazole in solid dispersion was homogeneously dispersed into PEG 4000 at a molecular level.

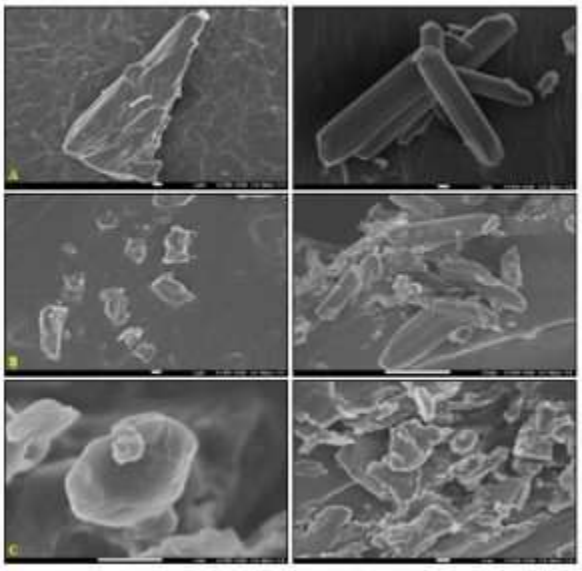

FIG. 6: SEM FOR PLAIN DRUG (A), PEG 4000 (B) AND SOLID DISPERSION CONTAINING POLYMER PEG 4000 (C)

Evaluation of Pre-compression Parameters: The powder mixture of fluconazole solid dispersion was evaluated for flow properties, and the results are mentioned in **Table 8**. The observed parameters stated that solid dispersion of fluconazole was free-flowing powder with good flow properties.

FLUCONAZOLE SOLID DISPERSION BY SOLVENT EVAPORATION

Evaluation of Post-compression Parameters: The developed formulation SE-Z1 batch of solid dispersion of fluconazole by solvent evaporation method was subjected to post-compression analysis, and the results are given in **Table 9.**

FLUCONAZOLE SOLID DISPERSION BY SOLVENT EVAPORATION

***In-vitro* Dissolution Studies:** The dissolution medium used: 0.1N HCl and phosphate buffer pH 6.8, the volume of dissolution medium: 900 ml, dissolution apparatus type: type II (Paddle type), paddle stirring speed: 75 rpm, temperature: 37 ºC ± 1 ºC, sampling intervals: 5, 10, 20, 30, 40, 50, 60 and 90 min, sample volume withdrawn: 5 ml. The *in-vitro* dissolution studies of formulations were conducted, and the results were represented in **Table 10** and **Fig. 7**. The amount of drug release from formulation using 0.1N HCl was found to be 98.37%, and from phosphate buffer pH 6.8 was found to be 96.21% at the end of 90 min.

6.8 AND 0.1N HCl

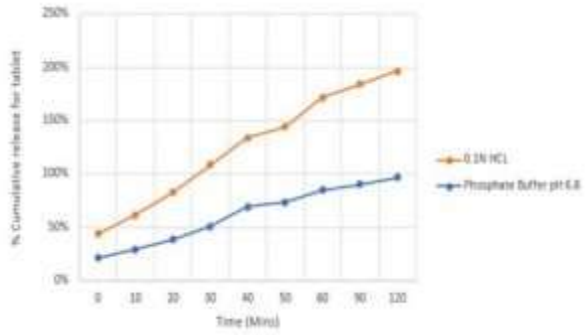

FIG. 7: DRUG RELEASE PROFILE OF SOLID DISPERSION TABLET IN PHOSPHATE BUFFER pH 6.8 AND 0.1N HCl

Stability Studies: The optimized batch of fluconazole solid dispersion were observed for stability parameters for three months. The formulation SE-Z1 subjected to stability testing every month stated that there were no such changes observed in the formulation's physical appearance and drug contents. The test results are shown in **Table 11**. Hence, it proved that formulation of fluconazole solid dispersion had good stability for 3 months.

CONCLUSION: The data obtained from all the studies stated that the solubility and dissolution rate of poorly water-soluble drug fluconazole improved by preparing solid dispersions. The solid dispersions were prepared by using different polymers, but PEG 4000 was found to be the best carrier to give maximum solubility. The solvent evaporation method gave the highest practical yield and drug content as compared to the kneading method. The formulation SE-Z1 showed maximum solubility and also an increase in dissolution rate as compared to the plain drug. Thus, tablets of fluconazole solid dispersions were successfully prepared. Stability studies proved that the formulation was found to be stable.

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CONFLICTS OF INTEREST: Nil

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