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EFFECTS OF VARIOUS POLYMERS ON DISSOLUTION IMPROVEMENT OF FABRICATED AMORPHOUS CLONAZEPAM SOLID DISPERSION-AN *IN VITRO* STUDY

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ABSTRACT

The 1,4-benzodiazepine derivative clonazepam (Biopharmaceutics Classification System [BCS] class ii) drug, which is a hypnotic and tranquiliser, is almost completely insoluble in water and lipophilic in nature. Since traditional dosage forms typically have a number of drawbacks, solid dispersion (SD) technology can be helpful in improving the way that pharmaceuticals dissolve, absorb and work therapeutically in dosage forms. Our study's objective is to create an SD formulation of the poorly water soluble medication clonazepam (CLZ) with the hydrophilic polymers PEG 4000 and PEG 6000. The main advantages of using water-soluble polymers as carriers are their low toxicity and wide applicability for the majority of medications. Using physical mixing and SD techniques, the polymers were employed with the medication CLZ in varying ratios (1:2, 1:4, 1:6). The production yield, drug content analysis and cumulative drug release of the produced formulations were evaluated. At 60 minutes, only the pure drug exhibited 51% of release. However, the solubility of the medication is significantly increased when hydrophilic polymer is added. With a better drug release by the polymer PEG 6000 and an 80.19% in vitro drug release, the formulation KSD9 showed promise. Furthermore, the other polymer exhibited 59.11% in kneading method and 57.08% in fusion method, respectively. Hence the greater carrier content and the prevention of crystallinity in the dispersion, the binary SD produced using various techniques significantly increases the drug's solubility.

Keywords: Clonazepam, Solid dispersion, Dissolution studies, Release kinetic, Amorphous solid dispersion

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INTRODUCTION

One of the biggest obstacles to pharmaceutical research and development is the low water solubility of many medications, which commonly leads to poor and variable oral absorption, decreased bioavailability and suboptimal therapeutic effects (Wu *et al.* 2018). Because it has a major impact on bioavailability, a drug's aqueous solubility is crucial for formulation, especially when creating oral dosage forms. The molecules undergo adsorption from the intestinal sites following their dispersion in gastrointestinal fluid (Budiman *et al*. 2023). As dissolution largely depends on the physicochemical properties of drugs, the formulation and process of manufacturing of the drug product is a crucial issue (Sadman *et al*. 2021).

One of the best ways to quicken the dissolution of poorly water-soluble drugs is through solid dispersion (SD) technology. The technology has been used to designate a class of dosage forms where the drug is dispersed in a physiologically inert matrix (Swarup and Agrawal 2024), which can also increase the relative bioavailability of a drug's formulation (Jyothi *et al*. 2024). Numerous carriers, including polyethylene glycol (PEG), have been shown to enhance the solubility and bioavailability of poorly water-soluble medications when it comes to SD formulation (Arun *et al.* 2016). Even though numerous chemical and formulation techniques can be used to boost solubility or expand the surface area that is accessible for dissolving. Nevertheless, improving the solubility through SD formulation techniques is the most alluring way to speed up the release rate (Heredia *et al.* 2022). Increased wettability, better drug particle dispersibility, the presence of the drug in an amorphous state (ASD) with more excellent solubility, and the lack of drug particle agglomeration contribute to fast or instantaneous drug dissolution from SD. Because surfactants and solubility-enhancing agents improve solubility, micellization, wettability and dispersibility, they increase drug dissolution in SD systems (Adhikari *et al.* 2022). PEG 4000 and PEG 6000 were employed as a dispersion carrier in the current study. The primary benefits of employing water-soluble polymers as carriers are their broad suitability for most drugs and their lack of toxicity (Malkawi *et al.* 2022). ASD can be categorised depending on how the drugs and carriers interact molecularly in solid solutions, solid suspensions or a combination of both. Drugs and carriers are entirely soluble and miscible in ASD, which leads to homogenous molecular contact between them. These systems' drug and carrier interaction energy is incredibly high, leading to authentic solution (Minhaz 2012). The crystalline form of the pharmaceutical formulation is much less soluble and dissolves more quickly than the amorphous form; nevertheless, because the amorphous state is a high-energy, physically unstable state, stability issues arise (Mendonsa *et al.* 2020). Therefore, the polymers overcome the problem, play promising role as a crystallisation inhibitor that maintains the API in a prolonged supersaturated state (Frank and Matzger 2018). Through biodistribution and residence time at the action site, polyethylene glycol-modified nanoparticles can enhance the stability, pharmacokinetics and pharmacodynamics of nanoparticles and drugs, thereby improving their in vitro intestinal permeability, lowering their toxicity, and increasing their therapeutic effect (Panel *et al.* 2024). PEG and its derivatives are considered as non-toxic, safe and inert molecules, but their toxicity depends on their concentrations, and existence form in the formulation (Ibrahim *et al.* 2022).

The Biopharmaceutics Classification System (BCS) classifies drugs according to their water solubility and intestinal permeability (Malkawi *et al.* 2022). Many drugs fall under Class II or Class IV of the BCS for solubility. Class II drugs like clonazepam (CLZ) have a low solubility in water, but once dissolved, they quickly cross biological barriers like the stomach wall. Because of this, Class II drugs have a low bioavailability when taken orally because they dissolve slowly in the aqueous environment of the gastrointestinal system. However, bioavailability can be increased by speeding up the dissolution rate (Jagdale

et al. 2011). In the current study, CLZ is an anticonvulsant that improves responses of gamma-aminobutyric acid (GABA) receptors. Due to its sluggish and variable absorption rate following oral administration, this anticonvulsant substance is virtually insoluble in water (approximately 170 mg/L at 25°C) (Moneghini *et al.* 2001). Anticonvulsants are used to treat a variety of seizure types, such as absence seizures, photosensitive epilepsy and myotonic or atonic seizures. This drug works by attaching itself to the GABA receptors' benzodiazepine site, which amplifies the electric effect of GABA binding on neurons and increases the amount of chloride ions that enter those neurons. Consequently, the central nervous system's synaptic communication is inhibited (Nandi *et al.* 2017). The powder known as CLZ is a pale yellow crystal with almost no smell. At 25°C, it is virtually insoluble in water and readily highly soluble in methanol, ethanol and acetone (<0.1 mg/mL). It is widely accepted that substances with extremely low solubility in water will exhibit absorption limited by the dissolving rate, leading to inadequate distribution, absorption and target organ transportation. Improving aqueous solubility also give rise to further advantages, like decreasing the dose, which leads to a decrease in toxicity and the emergence of negative consequences. The conventional dosage form sometimes possesses some limitations, to increase therapeutic efficacy, to reduce crystallinity in such a situation, improving water solubility by designing SD formulation is a worthwhile objective (Sikdary *et al.* 2021). Our study aimed to enhance the solubility and dissolution of fabricated CLZ-SD utilising different types of water-soluble polymers (PEG 6000 and PEG 4000) by using kneading and fusion methods. In vitro dissolution studies were conducted for different formulation to assess the % of drug release. We hypothesise that improvement of the dissolution study of CLZ-SD depends upon the type of polymers and their ratio or concentrations used in the fabricated formulation.

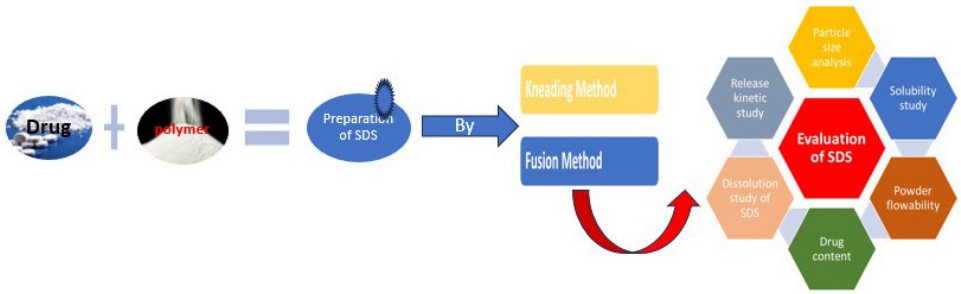

Figure 1: Schematic illustration of the formulation of CLZ-SD and their evaluation.

MATERIALS AND METHODS

Materials

Pharmaceutical-grade CLZ was obtained as a gift sample from Pharmasia Ltd., Bangladesh. The polymers PEG 4000 and PEG 6000 and the other chemicals like sodium lauryl sulfate (SLS), methanol, phosphate buffer and distilled water used during this research work were analytical grade.

Instruments

Dissolution rate test apparatus (RC100A, Intech, India), UV-VIS spectrophotometer (UV-1600, South Korea), Laboratory Drying Oven (DOF-65E, USA), Digital balance (PS. P2.610, Taiwan), Digital pH meter tester, Vacuum Desiccator (Pyrex 3081-150).

Preparation of Standard Calibration Curve of CLZ in Phosphate Buffer

To prepare a standard curve for CLZ, stock solution of 25 µg/mL was prepared in phosphate buffer. Then, serial dilutions of various concentrations were examined at 243 nm using a UV-VIS spectrophotometer (UV-1600, South Korea). A standard curve was created by plotting absorbance values versus drug concentration.

Phase Solubility Study of The Carrier

Aqueous solutions of the various polymers (PEG 6000, PEG 4000) were prepared at concentrations of 5%, 10% and 15% in order to ascertain the solubilising nature of the polymers. To create a saturated solution, too much medication was added to these solutions. Samples were then centrifuged for 10 minutes at 3000 rpm after being shaken in an orbital shaker for 24 hours at 60 rpm. The supernatant then diluted and analysed by UV-spectrophotometer at 243 nm (Mohana and Vijayalakshmi 2022). The results are shown in Table 3.

Preparation of Clonazepam Solid Dispersion (CLZ-SDS) and Physical Mixture (PM)

In a glass mortar and pestle, the necessary quantity of CLZ and polymers were completely combined for 10 minutes. The mixture was then preserved for later use by being placed in a desiccator and maintained in a screw-cap container (Ali *et al.* 2024).

FUSION METHOD

The fusion method involves the preparation of a physical mixture of a drug and carrier then heating the binary complex directly until it melts. The melted mixture then solidified in an ice bath under vigorous stirring. The final solid mass is then crushed, and sieved. This technique gives a much finer dispersion of crystallites (Mayersohn and Gibaldi 1966).

Kneading Method

SD formulations were prepared by the kneading method of the drug with selected polymers such as PEG 4000 or PEG 6000 at different ratios (1:2, 1:4, 1:6) in individual formulations. To create a homogenous mixture, a small amount of liquid, often a polymer solution, is mixed with the drug and carrier. After that, the mixture is dried to produce a SD. This technique is widely used for creating SD since it is simple to use (Ghareeb *et al.* 2009).

Table 1: Drug polymer ratio for different formulations by fusion method.

Solid Dispersion	Drug-Polymer ratio (CLZ: PEG 6000)	Solid Dispersion	Drug-Polymer ratio (CLZ: PEG 4000)
FSD1	1:2	FSD4	1:2
FSD2	1:4	FSD6	1:4
FSD3	1:6	FSD6	1:6

Table 2: Drug polymer ratio for different formulations by kneading method.

Solid Dispersion	Drug-Polymer ratio (CLZ: PEG 6000)	Solid Dispersion	Drug-Polymer ratio (CLZ: PEG 4000)
KSD7	1:2	KSD10	1:2
KSD8	1:4	KSD11	1:4
KSD9	1:6	KSD12	1:6

EVALUATION OF SD

Solubility study of PM and SD

The PM and SD solubility analysis was carried out in distilled water and phosphate buffer pH 6.8 with SLS 0.2%. The shaking flask technique is used. 10 mL of water and 10 mL of phosphate buffer pH 6.8 with SLS 0.2% were mixed separately with the produced SD. Up until the sample settled to the bottom, an excessive amount of the samples (PM and SD) were added to these solutions. After being centrifuged for 10 minutes at 3,000 rpm, the samples were shaken in an orbital shaker for 24 hours at 60 rpm. After diluting the filtrates, the absorbance was measured at 243 nm using a UV-VIS spectrophotometer (UV-1600, South Korea) to estimate the solubility (Mohana and Vijayalakshmi 2022). The results are shown in Table 3.

Drug content

Accurately weighed prepared SD equivalent to 10 mg of CLZ was transferred to a 10 mL volumetric flask containing 10 mL of phosphate buffer, pH 6.8 with 0.2% SLS and the above content was suitably dissolved. 1 mL of this solution was diluted to 10 folds with phosphate buffer, filtered and analysed using a UV-VIS spectrophotometer (Jahan *et al.* 2017).

Characterisation of CLZ-SD flowability

The prepared SDs were evaluated by estimating their physical parameters like angle of repose, Hausner's ratio, Carr's index and particle size. The results are shown in Table 5.

Angle of repose

Angle of repose is essential to determine the flowability of the powder. It is estimated by the formula:

$\tan \theta = h/r$

$\Theta = \tan^{-1} (h/r)$

h = height, r = radius of base of pile

Carr's index (Swapna *et al.* 2018)

The relationship between % Carr's indexes with flowability can be given by:

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Hausners ratio (**Purushottam *et al.* 2021**)

It determines the granule's flow characteristics and is calculated from the formula:

Hausner's ratio = Tapped density/Bulk density

Particle size

To determine particle size, a set of sieves were taken and arranged according to the descending order of mesh size. The SD was taken on the sieves and sieving was done for about 5 minutes. The particles retained on individual sieve after sieving were collected and weighed (Mupparaju *et al.* 2021).

In vitro Dissolution Studies of SD

In vitro dissolution of SD was carried out in a USP dissolution tester (apparatus II) rotating at 75 rpm and temperature was maintained at 37°C±0.5°C. Samples were withdrawn from the dissolution medium (900 mL Phosphate buffer, pH 6.8) at 10 minute intervals and were replenished with fresh dissolution medium (Mohana and Vijayalakshmi 2022). The samples were then filtered, diluted and analysed by UV spectrophotometer at 243 nm. The results are shown in the Figure 2(a, b, c, d).

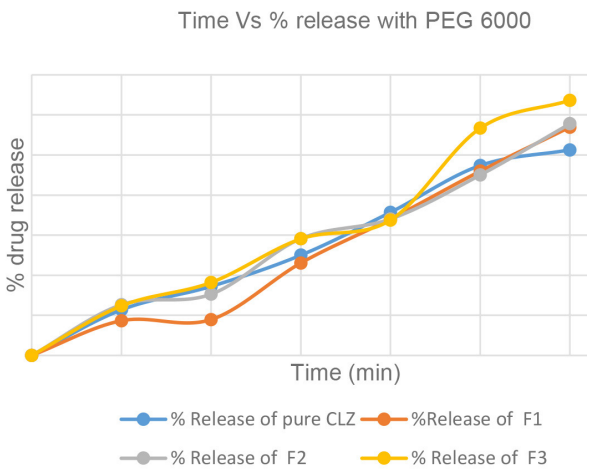

Figure 2(a): Time Vs % of drug release curve of CLZ-SD with PEG 6000 in fusion method.

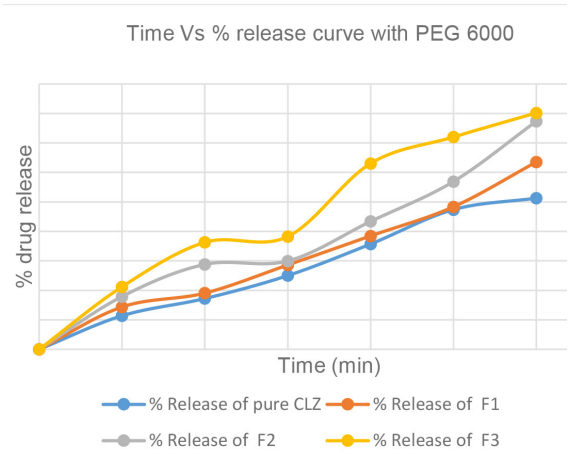

Figure 2(b): Time Vs % of drug release curve of CLZ-SD with PEG 6000 in kneading method.

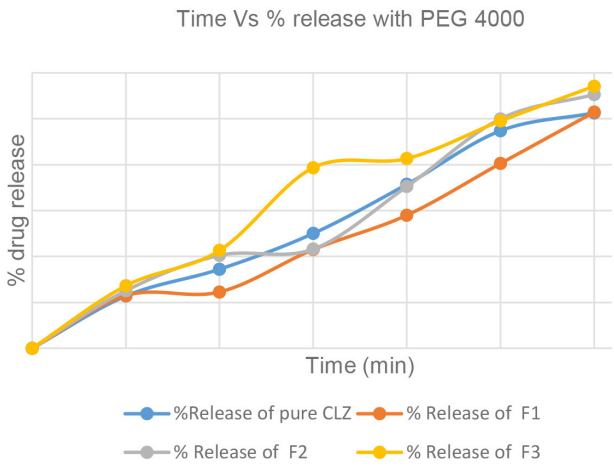

Figure 2(c): Time Vs % of drug release curve of CLZ-SD with PEG 4000 in fusion method.

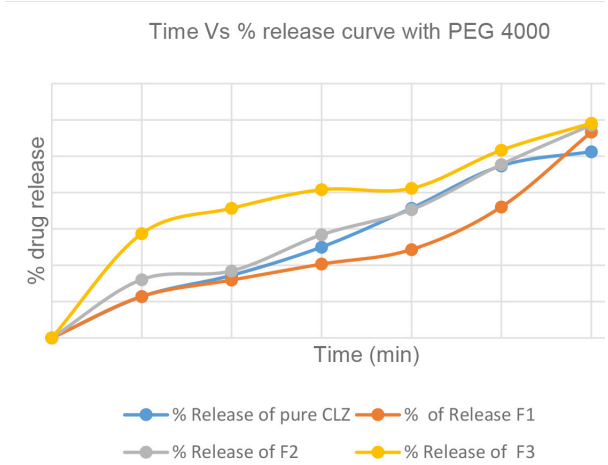

Figure 2(d): Time Vs % of drug release curve of CLZ-SD with PEG 4000 in kneading method.

The release kinetics of pure CLZ and SD formulations were estimated by different kinetics models such as zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models to find out the release pattern from pure CLZ and SD formulations. Therefore, zero order kinetics describes a release process where the polymeric chains' relaxation governs the release, regardless of the concentration of the polymer. The drug release rate is represented by the first order kinetics model, which is dependent on drug concentration. According to Higuchi model, drug release is a diffusion mechanism that is time dependent and square root based on Fick's law. The Korsmeyer-Peppas model is used when the release mechanism is unclear or when multiple release phenomena may be at play.

Depending on the values found for the release exponent, n, it is feasible to specify whether the release occurs by anomalous transport, Case-II transport, Fickian diffusion, or super Case-II transport (Sánchez *et al.* 2024).

Statistical Analysis

Experimental values of dissolution studies were evaluated. The results obtained were in triplicates, the mean along with standard deviation (± SD) were calculated**.** Dissolution studies were analysed by comparison between different SD formulations and pure drug to find out the variance and best formulation.

RESULTS

Solubility Study of SD and PM

The solubility study of SD and PM has been described in Table 3. The amorphous state of drug provides a lower thermodynamic barrier to solubility where the drug molecule is dispersed in the polymer, which could account for the fact that the PM has significantly lower solubility enhancement compared to the corresponding prepared SD systems for all formulations (Ali *et al.* 2024). The pure drug has a solubility of 0.0082 mg/mL in the distilled water and 0.2154 mg/mL in phosphate buffer having pH 6.8 with SLS 0.2%.

The formulation KSD9 showing better solubility compared to the other SD formulation. The increased solubility may be attributed to the presence of high polymer concentration, increasing surface area and inhibition of crystallinity (Mohana and Vijayalakshmi 2022). In the ASD there is a limited intermolecular interaction and no lattice energy needed to overcome. However, when the materials are in a crystalline state, the lattice energy needed to disrupt.

Table 3: Solubility study of SD and PM.

Formulations	Phosphate Buffer (pH 6.8) mcg/mL	Inference	Distilled Water mcg/mL	Inference
Pure drug	0.2154	Very slightly soluble	0.0082	Practically insoluble
KSD7	0.5164	Very slightly soluble	0.2163	Very slightly soluble
KSD8	0.7924	Very slightly soluble	0.4392	Very slightly soluble
KSD9	1.0062	Slightly soluble	0.6381	Very slightly soluble
PM1	0.2391	Very slightly soluble	0.1499	Very slightly soluble
PM2	0.4381	Very slightly soluble	0.2100	Very slightly soluble
PM3	0.6985	Very slightly soluble	0.5154	Very slightly soluble

Note: SD = Solid dispersion; PM = Physical mixture

Phase solubility study of polymers

The phase solubility study of polymers such as PEG 4000 and PEG 6000 is described in Table 4. Based on the result SD was prepared in the ration of 1:2, 1:4 and 1:6 with PEG 6000.

Table 4: Phase solubility study of drug with aqueous solution of polymers.

Polymers	5% mg/mL	Inference	10% mg/mL	Inference	15% mg/mL	Inference
PEG 6000	0.0861	Practically insoluble	0.1232	Very slightly soluble	0.1691	Very slightly soluble
PEG 4000	0.0458	Practically insoluble	0.0762	Practically insoluble	0.10	Very slightly soluble

Drug content

The selected drug was subjected to the determination of drug content. The drug content was found to be in the range of (94 ± 0.577)%. A negligible loss of drug may occur probably during preparation to the very small area of mortar.

Powder flowability study

The preformulation study was done with drug and different polymers. The observed range indicated good to excellent flowability. When all the estimated parameters were compared to the free pure drug, a sharp improvement in micromeritic properties was observed. Results are shown in Table 5.

Table 5: Pharmaceutical characteristics of PM of CLZ pure drug and different polymers used in the SD formulations.

Formulation Code	Drug content (%±SD)	Bulk Density (%±SD)	Tapped Density (%±SD)	Carr's Index (%±SD)	Hausner Ratio (%±SD)	Angle of repose (%±SD)
D: Poly 1	94 ± 0.577	0.72 ± 0.01	0.81 ± 0.04	9.19 ± 0.02	1.17 ± 0.05	26.16 ± 0.06
D: Poly 2	94 ± 0.577	0.64 ± 0.01	0.83 ± 0.0051	12.27 ± 0.05	1.14 ± 0.02	24.35 ± 0.08

Note: D: Poly 1 = CLZ : PEG 4000 and D: Poly 2 = CLZ : PEG 6000; PM = Physical mixture; CLZ = Clonazepam

In vitro Dissolution Study

The SD prepared by kneading method using PEG 6000 alone as a polymer showed better improvement in solubility (80.19% at 60 minutes) than the corresponding SD formulation that were prepared by the fusion method (38.63% with the same polymer). Among the polymer used PEG 6000 showed better solubility compared to the other polymer, PEG 4000. The solubility increased as drug polymer ratio enhanced. The enhancement was observed in the basic media (pH 6.8) and the enhanced ratio of the polymer (PEG 6000 with kneading method) which suggests that the SD for a weakly acidic drug could offer an advantage in

targeting the distal part of the gastrointestinal tract (GIT). The dissolution study of CLZ-SD was carried out by using a paddle-type dissolution apparatus. Dissolution was performed to simulate the lower part of the small intestine. The order of improvement of the dissolution profile was KSD7 < KSD8 < KSD9. The explanation for the insufficient dissolution with the other method may be the insufficient distribution of drug within the polymer that could lead to incomplete interaction between drug and polymer. Again increased viscosity of dissolution media may obstruct the release of the drug from the powder materials. Consequently, the SD prepared by fusion method causes reduced drug-polymer intermixing then increased viscosity of the polymer that may increase the thickness of diffusion layer causes less solubility of the drug. However, the improvement of dissolution is the reason of conversion of the drug into the amorphous state. The results of time Vs % of drug release are showing in Figure 2(a, b, c, d).

DRUG RELEASE KINETIC STUDY

Drug release kinetic study was achieved by different kinetic models like, zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model. The formulation KSD9 was fitted for zero order kinetics having R^2 value 0.976. The formulation FSD3 was better fitted for first order kinetics having R^2 value 0.968 (see Table 6). According to Korsmeyer-Peppas model pure CLZ and most of the formulations followed super Case II transport as the value of n was greater than 0.89 (see Table 6). However, the formulation FSD1, FSD2, FSD4 and KSD10 showed anomalous non-Fickian diffusion. When more than one type of drug release phenomenon is involved the model Korsmeyer-Peppas is helpful.

Table 6: Interpretation of release rate constants and correlation coefficient (R^2) values for different release kinetics.

Formulation	Zero Order		First Order		Korsmeyer-Peppas		Hixson- Crowell Model		Higuchi model	
	R^2	K_o	R^2	K_1	R^2	n	R^2	K_{HC}	R^2	K_H
Pure CLZ	0.990	0.872	0.979	–0.005	0.995	0.957	0.780	0.052	0.910	0.679
FSD1	0.884	0.466	0.893	–0.002	0.969	0.824	0.693	0.041	0.905	3.84
FSD2	0.931	0.470	0.948	–0.003	0.965	0.820	O.638	0.040	0.973	3.91
FSD3	0.955	0.643	0.968	–0.004	0.983	0.895	0.695	0.046	0.960	5.24
FSD4	0.945	0.505	0.957	–0.002	0.975	0.830	0.681	0.042	0.954	4.12
FSD5	0.958	0.666	0.967	–0.004	0.982	0.899	0.697	0.046	0.953	5.40
FSD6	0.961	0.839	0.956	–0.005	0.985	0.949	0.725	0.050	0.928	6.70
KSD7	0.928	0.635	0.909	–0.003	0.974	0.902	0.752	0.062	0.874	5.89
KSD8	0.917	1.120	0.814	–0.009	0.968	0.996	0.742	0.055	0.823	8.65
KSD9	0.976	1.350	0.948	–0.012	0.977	1.060	0.734	0.059	0.933	10.73
KSD10	0.916	0.470	0.914	–0.002	0.965	0.804	0.747	0.042	0.857	3.69
KSD11	0.919	0.600	0.921	–0.003	0.950	0.857	0.667	0.044	0.899	4.83
KSD12	0.965	0.924	0.966	–0.006	0.972	0.973	0.701	0.051	0.941	7.42

Note: n is the release exponent, and K_0, K_1 and K_{HC} are the kinetic constants.

DISCUSSION

This research examines how various SD techniques improve the solubility of CLZ. The study found that the solubility of CLZ was significantly boosted when various polymers, such as PEG 6000 and PEG 4000 were used in SD formulation. A drug's solubility is determined by its particle size, porosity and wettability. The polymers that are employed up close to one another typically fill all of the vacant space; the medication does this by filling in the gaps in the polymeric chain, which makes the polymer chain fairly flexible. Additionally, the powder's flow characteristics demonstrated superior flow behavior and outstanding compressibility. Additionally, the study indicates that the drug's and SD's solubility was pH dependent, with the drug's solubility being higher in phosphate buffer (pH 6.8).

The drug content was found to be in the range (not more than 110% and not less than 90%). Pre-formulation study was conducted using several polymers and CLZ. The ranges of the bulk density and tapped density are (0.64 ± 0.01) to (0.72 ± 0.01) and (0.81 ± 0.04) to (0.83 ± 0.0051), respectively. The observed ranges for Carr's index and Hausner ratio were (9.19 ± 0.02) to (12.27 ± 0.05) and (1.14 ± 0.02) to (1.17 ± 0.05), respectively. The range that was observed showed good to exceptional flowability. A notable improvement in micromeritic characteristics was seen when all calculated parameters were contrasted with the free pure drug. Nonetheless, it was shown that the manufactured product's medicinal qualities were significantly influenced by the correlation between the degree of compactness and polymer concentration.

For various polymers, the improved properties of dissolution were noteworthy. The formulation with the highest carrier content demonstrated a higher rate of dissolution. This is due to the fact that using various carriers typically transforms an insoluble medication into an amorphous state that speeds up the rate of solubility. The decrease in the physical-chemical characteristics and crystal size of the polymers utilised in SD formulations is the second mechanism that increases drug dissolution rate. The carrier PEG 6000 in the kneading method demonstrated maximum drug release at 60 minutes, for the formulation KSD9 which is 80.19%. Additionally, the drug release from the SD formulation using the fusion method with PEG 6000 was 63.63%, whereas the drug release from the pure drug in both cases was 51.27%. The order of the dissolution rate increases is PEG 6000 > PEG 4000. So, the dissolution rate with PEG 6000 significantly enhances drug dissolution compared to the other polymer used in our current research. PEG 6000, on the other hand, was out to be the most effective polymer for raising CLZ solubility. The results showed that the kneading method performed as the best method in terms of drug release, achieving 80.19% in 60 minutes as compare to the fusion method 63.63%. Every graph demonstrated that increasing the polymer ratio led to significantly more medication release. When it comes to pure drugs, all things considered, this work highlights the possibility of using SD techniques to make poorly soluble medications like CLZ more soluble, as well as the necessity of choosing the right polymer and procedure to get the intended results.

CONCLUSION

In this study, SD based on hydrophilic polymer appeared to improve the solubility, dissolution rate and bioavailability of CLZ. Particle size, physical shape, solubility and solubility are affected by the type and proportion of hydrophilic polymer used in the formulation. The choice of the appropriate drug-to-polymer ratio changed the structure from crystalline to amorphous, which increased the solubility of poorly water-soluble drugs

and ultimately increase the bioavailability. Therefore, SD can be considered as a useful approach in the pharmaceutical industry to improve the therapeutic effect of poorly water soluble drugs.

CONFLICT OF INTERESTS

The authors declare no conflict of interest of the authors.

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AUTHOR CONTRIBUTIONS

Khurshid Jahan: Conceptualisation, supervision, designing the layout of the research, collection of all materials, data analysis and manuscript writing. Mousumi Akter: Draft writing of the manuscript, data interpretation, review and conducted research in the lab. Tonmoy Bhowmick, Md. Harun or Rashid, Sadia Tasnim and Rubaya Rahman Rimi: conducted research in the Lab. All the authors read and approved the final manuscript.

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