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Formulation and evaluation of Solid dispersion of clobazam for improved dissolution rate

Deepu Kumar Gupta, Reena Shende, Ajay Kumar*, Sailesh Kumar Ghatuary

Bhabha Pharmacy Research Institute, Bhopal, Madhya Pradesh, India

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ABSTRACT

Oral administration is highly dependent on solubility of the drug whereas the newer high throughput techniques of drug discovery usually consider a lower solubility. Clobazam indicated for epilepsy and seizures exhibits low solubility in aqueous solution and has a poor bioavailability. In the present work, we aim to to improve the dissolution rate of clobazam by formulating as solid dispersion using various polymers. PEG 8000, PVP K 30 and SLS were used to prepare solid dispersion using physical mixture, kneading and solvent evaporation methods. Solubility of clobazam in solid dispersion was measured using UV spectrophotometer. The solid dispersion were evaluated for drug content, crystalline state by differential scanning calorimetry, dissolution and drug release. Formulation CSDF8 with 1:8 ratio of clobazam and SLS was found to be the optimum formulation.

*Corresponding Author

Ajay Kumar

Email: aj.bpri@gmail.com

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Introduction

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. Solid dispersion systems have shown promising results in increasing bioavailability of poorly water-soluble drugs in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles (Chiou and Riegelman, 1971; Leuner and Dressman, 2000; Serajuddin, 1999).

Clobazam is a 1,5-benzodiazepine drug indicated for treatment and management of epilepsy and seizures associated with Lennox-Gastaut syndrome (drugbank, 2021). It is considered as a partial agonist of the GABA-A receptor. The drug exhibits low solubility in aqueous solution and has a poor bioavailability.

Several approaches have been reported for improving the solubility and bioavailability of clobazam over the past few years (Patil, 2016; Bala et al., 2014). The objective of the current work was to improve the dissolution rate of clobazam by formulating as solid dispersion using various polymers.

Material and Methods

Clobazam was procured from Yarrow Pharmaceuticals, Mumbai. All other chemicals and reagents were procured from CDH, Loba, Rankem and Oxford and were used without any purification or drying.

Preformulation Study

The pure drug, Clobazam was subjected to preformulation characterization for physicochemical properties, loss on drying, identification by FT-IR spectroscopic analysis, and moisture content determination using previously reported methods.

Calibration curve

The λ_{max} of Clobazam was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer. Carefully prepared dilutions of 5-25 µg/mL of Clobazam were prepared by appropriately diluting the stock solution (1000 µg/mL) using ethanol as the solvent. The absorbance of these solutions was observed as the obtained λ_{max} and the calibration curve of concentration against absorbance was plotted.

Preparation of solid dispersions

PEG 8000, PVP K 30 and SLS solid dispersion were used to prepare at weight ratios of 1:1, 1:2, 1:4 and 1:8, using three different preparation methods, physical trituration, kneading and solvent evaporation (Goswami et al., 2017; Ghobashy et al., 2020).

Physical mixture

Drug and PEG 8000, PVP K 30 and SLS were weighed, sieved and mixed evenly by slowly adding drug into PEG 8000, PVP K 30 and SLS separately in a mortar with light trituration. The mixture was continuously mixed for an hour until a homogeneous mixture was obtained. The mixtures were passed through a #65 mesh sieve and kept in a closed container.

Kneading method

PEG 8000, PVP K 30 and SLS in a mortar were wetted with sufficient amount of water (10% w/w) to obtain a paste and drug was slowly added into the paste. Kneading was performed manually for an hour and suitable amount of water was added from time to time to maintain the consistency of the paste. The mixture was dried overnight at 50°C in a hot air oven. The dried complex was ground using mortar and pestle. After sieving through a #65 mesh sieve, the complex was kept in a closed container.

Solvent evaporation method

Drug was dissolved in 25 mL of ethanol, while PEG 8000, PVP K 30 and SLS were dissolved in 50 mL of distilled water. The two solutions were mixed together and stirred for

1 h. Ethanol was evaporated off by heating at 40°C under constant stirring. Water was then removed under reduced pressure using rotary evaporator. The mixture was placed overnight for 24 h in hot air oven at 40°C to remove the residual solvent. The inclusion complex was ground using mortar and pestle. After sieving through a #65 mesh sieve, the solid dispersion was kept in a closed container.

Solubility Study

Solubility study was performed by adding an excess amount of solid dispersions in 50 mL of distilled water. The flasks were vortex-mixed for 3 min and agitated at 120 rounds per minute in a water bath maintained at 30°C for 72 hours. Samples of 3 mL were withdrawn and filtered through a 0.45 µm nylon membrane filter. Filtrate (0.1ml) was diluted appropriately and measured spectrophotometrically at 238nm.

Evaluation of the optimized solid dispersion

The best solid dispersion obtained was subjected to evaluation of drug content, Differential Scanning Calorimetry (DSC), flow properties, dissolution and drug release study.

Drug content

Dispersion granules equivalent to 10 mg of drug, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernatant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed.

Differential scanning calorimetry (DSC)

Sample was weighed into a non-hermetically sealed aluminum pan. The samples were heated from 25 to 400 °C at a heating rate of 5°C/min for drug and solid dispersion.

Angle of Repose

The fixed funnel method was used to determine the angle of repose of the optimized solid dispersion formulation (Pandey et al., 2017). Angle of repose was calculated using the formula:

$$\tan\theta = {}^{h}/_{r}$$

Where h is the height of the heap of powder (measured as the fixed distance of funnel tip from ground)

r is the radius of the base of the heap

Bulk and Tapped density

Accurately weighed quantity of solid dispersion was taken in a 50 ml capacity measuring cylinder and the volume was measured (Pandey et al., 2017). The measuring cylinder was tapped for 250 times on a plane hard wooden surface and the volume was again measured. The bulk and tapped density were calculated by the formula density = mass/ volume.

Hausner's Ratio

It was calculated from the bulk and tapped density using the formula

$$Hausner's\ Ratio = {}^{Tapped\ density}/_{Bulk\ density}$$

Dissolution rate study

The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. A solid dispersion equivalent to 10mg placed in dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml with ethanol. The samples withdrawn were assayed spectrophotometrically at 238nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of Clobazam.

The data was statistically evaluated using various mathematical models to determine the drug release profile from the solid dispersion.

Results and Discussion

Preformulation Characters

The preformulation parameters play vital role in formulation. They ascertain the iden-

tity as well as suitability of the drug and the excipients for formulation. The results of pre-formulation study of Clobazam are reported in table 1.

FTIR Spectrum of Clobazam

The FTIR spectrum of clobazam revealed the peaks for stretching of C-C, C=O, C-N and C-Cl at the corresponding wavenumbers, confirming the identity of the drug (figure 1).

Calibration curve of Clobazam

The absorption maximum of the drug in ethanol was found to be 238 nm (figure 2A). The calibration curve of clobazam was prepared in ethanol at 238 nm (figure 2B). The equation for linear regression was found to be Abs = 0.030 (conc.) + 0.002, with a regressin coefficient of 0.999. This equation was used to calculate the concentration of clobazam in the samples of release and in solid dispersion.

Solubility Analysis of solid dispersion

Solid dispersions were prepared with an objective to improve the solubility and release profile of clobazam on oral administration. The solubility of the solid dispersion prepared using different methods and ratio of the polymers was determined quantitatively using UV Visible spectrophotometer after 72 h. The results of solubility analysis are presented in table 2.

Formulation CSDF8 exhibited the most optimum solubility in all the methods and was used for evaluation of the other parameters of the solid dispersion.

Drug content

The amount of clobazam in CSDF8 was determined spectrophotometrically by extracting the drug with methanol. 99.20 ± 0.03% drug content was found in the 10 mg solid dispersion used for analysis.

DSC Study

The DSC thermogram revealed no endothermic peak corresponding to the melting point of clobazam suggesting that the drug was uniformly distributed in the amorphous polymeric matrix (figure 3A & 3B).

Flow properties

The bulk density, tapped density, angle of repose and Hausner's ratio of CSDF8 were found to be 0.465 g/cm^3, 0.574 g/cm^3, 26.21° and 1.239 respectively. All these parameters suggest that the solid dispersion possessed good flowability and might be suitable for formulating as tablets and other oral dosage forms.

Dissolution and release study

The formulation CSDF8 was subjected to dissolution study to assess the release profile for a period of 6h. The results of dissolution and release are presented in table 3 .

The release data was subjected to statistical analysis using zero and first order mathematical models. The regression coefficient indicated that the release of clobazam from CSDF8 followed first order kinetics (figure 4) .

Conclusion

Aqueous solubility is one of the key determinants in development technologies. The objective of the present investigation was to improve the solubility of clobazam eventually increasing its oral release. Solid dispersion with PVP K30 in ratio 1:8 was able to achieve a good improvement in solubility of clobazam.

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Table 1. Preformulation parameters

Color	Odor	Solubility	Melting Point	Moisture Content	LOD
White powder	Odorless	Soluble in Ethanol, methanol, Slightly soluble in chloroform, water and 0.1N HCl	181-183°C	0.109%	0.466 %

Table 2. Solubility of solid dispersions of clobazam

Formulation Code	Drug – Polymer Ratio	Solubility (mg/mL)		
		Physical Mixture	Kneading Method	Solvent Evaporation Method
	Pure Drug	0.188		
CSDF1	PEG 8000 (1:1)	0.190	0.225	0.332
CSDF2	PEG 8000 (1:2)	0.196	0.325	0.365
CSDF3	PEG 8000 (1:4)	0.223	0.365	0.421
CSDF4	PEG 8000 (1:8)	0.245	0.378	0.565
CSDF5	PVP K30 (1:1)	0.223	0.332	0.356
CSDF6	PVP K30 (1:2)	0.256	0.356	0.458
CSDF7	PVP K30 (1:4)	0.325	0.385	0.556
CSDF8	**PVP K30 (1:8)**	**0.456**	**0.398**	**0.658**
CSDF9	SLS (1:1)	0.321	0.325	0.221
CSDF10	SLS (1:2)	0.456	0.395	0.265
CSDF11	SLS (1:4)	0.569	0.421	0.369
CSDF12	SLS (1:8)	0.625	0.485	0.421

Table 3. In vitro drug release data from CSDF8

Time (min)	15	30	60	120	240
Cumulative Drug Release (%)	11.23	22.23	36.65	43.32	49.98

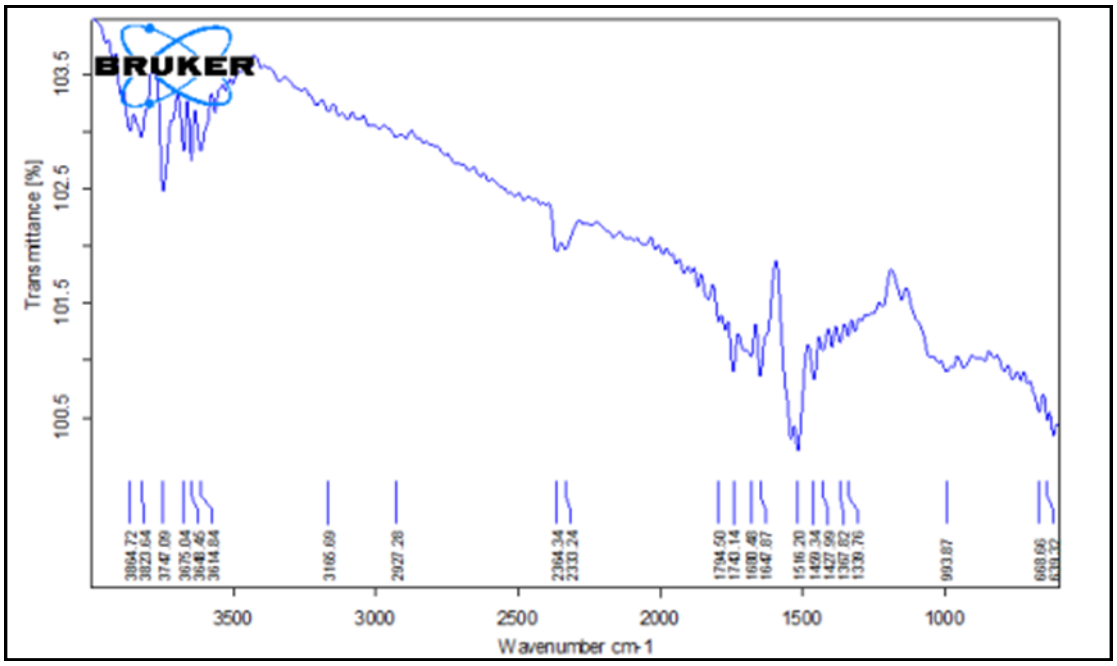

Figure 1. FTIR spectrum of Clobazam

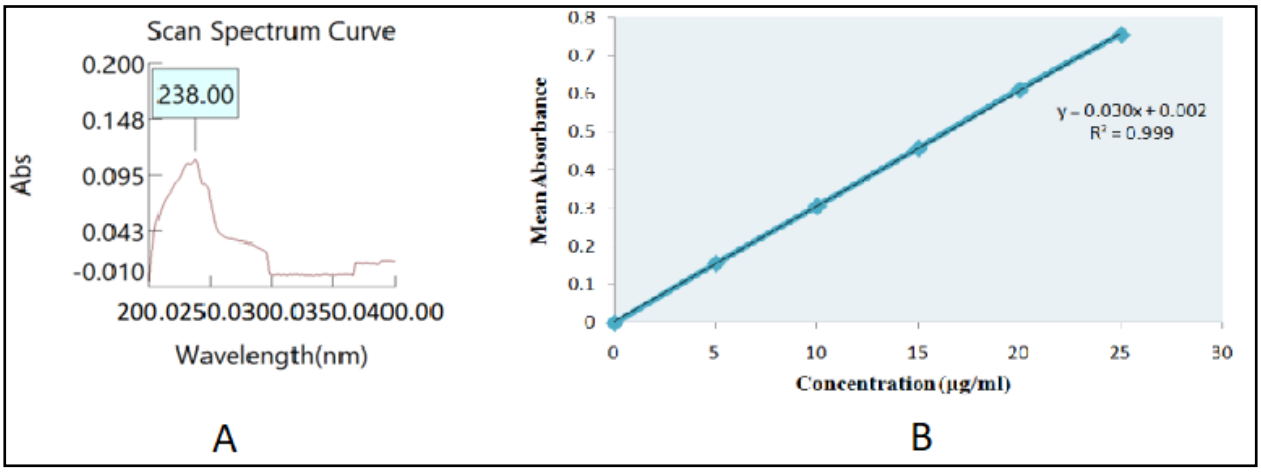

Figure 2. Absorption maximum and calibration curve of clobazam in ethanol

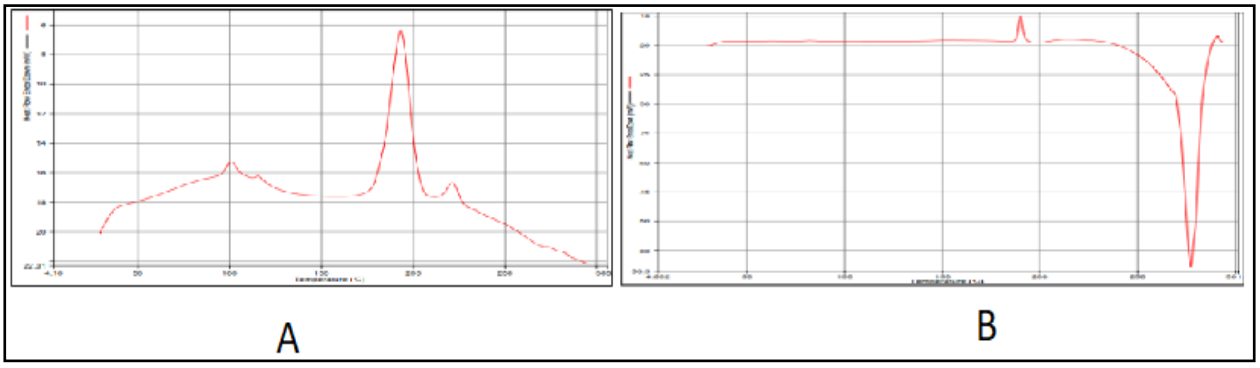

Figure 3. DSC thermogram. A) Clobazam, B) CSDF8

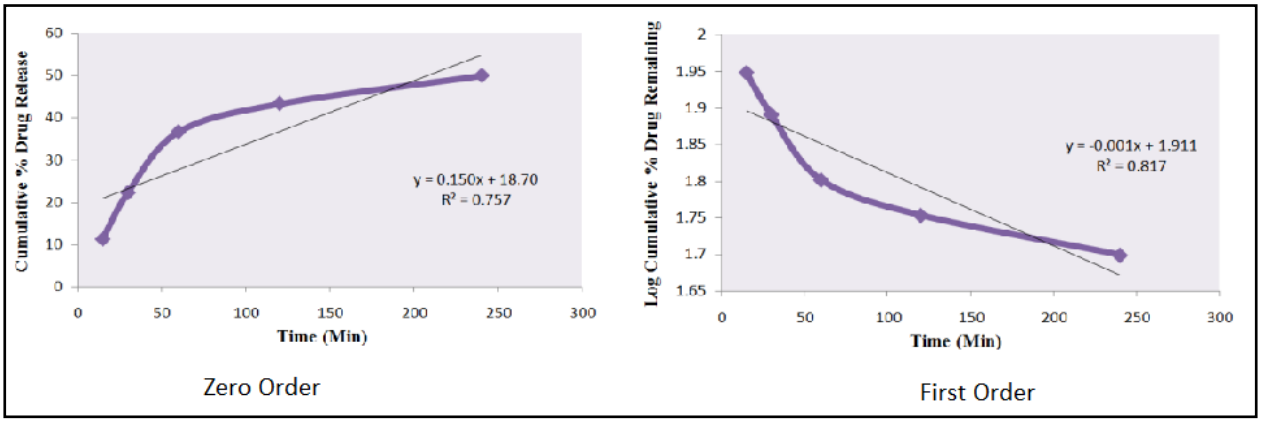

Figure 4. Release profile of clobazam from CSDF8.

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