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Article

In-vitro evaluation of binary and ternary carbamazepine solid dispersion

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Abstract: The purpose of this research work was to improve the aqueous solubility and dissolution rate of carbamzepine by solid dispersion (SD) technique. Polyethylene Glycol 6000, Polyethylene Glycol 4000, poloxamer 407 and povidone k 30 were used as water soluble polymer for preparing solid dispersion. Solid dispersions were prepared by the solvent evaporation method. Methanol was used as solvent. Drug-carrier physical mixtures were also prepared to compare the rate of dissolution. Effects of different polymer were studied for solid dispersion formulation as well as physical mixtures. A significant increase, almost 100% in the release of carbamzepine within one hour was observed in case of the solid dispersion formulations containing PEG 6000 in combination with poloxamer 407 at the ratio of 1: 1: 5. By far, Fourier Transform Infrared (FTIR) spectroscopic studies showed the stability of carbamazepine and absence of well-defined drug-polymer interactions. The Scanning Electron Microscopy (SEM) studies indicated that the incorporation of polymers transforms crystalline carbamazepine into amorphous state, thus increasing its solubility and dissolution rate.

Keywords: carbamazepine; FTIR; PEG 6000; PEG 4000; poloxamer 407; poorly water soluble; povidone k 30; SEM; solid dispersion

1. Introduction

The rate and extent of drug absorption from gastrointestinal tract depends on the rate and extentof drug dissolution from any solid dosage form (Ahmed *et al*., 1993)**.** Extremely hydrophobic drug often shows insufficient bioavailability due to its poor water solubility and low dissolution rate, especially for Biopharmaceutics Classification System (BCS) class II substances. This series of drugs possess low solubility but high penetration and the bioavailability can be greatly improved by accelerating the dissolution process in the gastrointestinal tract (Zhao *et al*., 2014). If the aqueous solubility of a drug is less than 1mg/ml it causes serious absorption problem. Several techniques have been developed for increasing the solubility of poorly soluble drugs such as solid dispersion, inclusion complex, ultra rapid freezing process, melt son crystallization, solvent change method, melt granulation technique, supercritical solvent, supercritical and cryogenic technique, cosolvent approach. Numerous solid dispersion (SD) systems have been demonstrated in the pharmaceutical literatureto improve the dissolution properties of poorly water soluble drugs. This technique wasintroduced in the early 1970s as a multicomponent system, such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, and albendazole. Various hydrophilic carriers, such as polyethylene glycols (PEG), polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), gums, sugar, mannitol and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly water soluble

drugs (Shams *et al*., 2011). Carbamazepine (CBZ) **(**chemically**:** 5H-Dibenzb, fazepine-5-carboxamide)**,** a best-selling antiepileptic drug, is used in the treatment of epilepsy, trigeminal neuralgia & bipolar disorders. Carbamazepine is a core medicine in the World Health Organization's "Essential Drugs List", that means it is in list of minimum medical needs for a basic health care system. The conventional CBZ tablets yield peak plasma concentration varying from 4 to 32 h. This irregular & delayed absorption of CBZ is attributed to slow dissolution rate. It is poorly aqueous soluble and its oral absorption is dissolution rate limited, which leads to a potential bioequivalence problem (Sethia and Squillante, 2004). Thus, the improvement of carbamazepine dissolution for its immediate release is desirable for rapid drug absorption, which is prerequisite for quick onset of its pharmacological actions. Hence present investigation explores the enhancement of solubility and dissolution of carbamazepine. An attempt was made in this study to enhance the aqueous solubility and dissolution rate of carbamazepine by preparation of solid dispersions (SDs) formulation using hydrophilic polymers like polyethylene glycol (PEG) 6000, polyethylene glycol (PEG) 4000, povidone K 30 and poloxamer 407. The physicochemical properties of carbamazepine in solid dispersions were characterized by scanning electron microscopy and infrared spectroscopy. The effects of hydrophilic carriers on the dissolution properties of carbamazepine were investigated.

2. Materials and Methods

2.1. Materials

Carbamazepine was obtained as a gift sample from Eskayef Bangladesh Limited. Povidone k 30, Poloxamer 407, PEG 4000 and PEG 6000 were collected from Incepta Pharmaceuticals Ltd, Bangladesh. Methanol (Sigma-Aldrich, Germany) was procured from commercial sources. Distilled water was prepared in the laboratory (Department of pharmacy, University of Asia Pacific). All other materials used in this study were of pharmacopoeial grade.

2.2. Preparation of solid dispersion

2. 2a. Solvent evaporation method

Solid dispersions of carbamazepine in water soluble carriers PEG 6000, Povidone k 30, PEG 4000 and Poloxamer 407 in 1: 1 weight ratio were prepared by solvent evaporation method and denoted as SA1, SA4, SA5 and SA6 respectively. The first step in this method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent resulting in formation of a solid dispersion. In case of this method selection of solvent is of prime necessity and drug and carrier is dissolved in a volatile organic solvent. Accurately weighted amount of drug and carrier were taken in a screw capped test tube and dissolved in minimum volume of methanol (2-5) ml by vortexing and sonication to obtain a clear solution. This solution was kept at room temperature for 72 hours until the solvent was evaporated from the solution completely. The viscous residues thus obtained were allowed to solidify and the solidified mixture was then grounded to convert powder particles with the help of mortar and pestle. Finally they were passed through a sieve of mesh size 40 and stored in glass vial and placed into desiccator until further use.

Ternary solid dispersion using mixture of polymer was also prepared in the same way. PEG 6000 (more effective carrier in case of binary solid dispersion) was mixed with poloxamer 407 (highest effective carrier in case of binary solid dispersion) in the ratio 1:1:5, 1:1:4, 1:1:3, 1:1:2, 1:1:1 (Drug: PEG 6000: Poloxamer 407) and denoted as SC1, SC2, SC3, SC4 and SC5 respectively (Paul *et al*., 2012).

2.2b. Preparation of Physical Mixture

Accurately weighted amount of carbamazepine and polymers in 1:1 ratio were crushed and mixed together by using mortar and pestle. The mixture was sieved through '40' mesh screen. Then the physical mixture were stored in glass vials and kept in desiccator. The physical mixtures was denoted as PA3 (drug: povidone k 30), PA4 (drug: PEG 6000), PA5 (drug: PEG 4000) and PA7 (drug: poloxamer 407).

2. 3. Characterization of solid dispersion

2. 3.1. *In vitro* dissolution studies of carbamazepine solid dispersion

The release profiles of active drug and solid dispersion formulations were assessed using *in-vitro* dissolution devices and were conducted in paddle type Dissolution test apparatus Apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA) using 900 ml of dissolution medium (distilled water). The temperature of the medium was maintained at 37± 0.5^0C throughout the experiment and paddle was used at a stirring rate of 75 rpm. A fixed amount of solid dispersion containing 10 mg of carbamazepine from each batch was calculated for dissolution purpose and were placed in the dissolution medium. Dissolution was carried out for 1 hour. A 5 ml

aliquot was withdrawn at predetermined time intervals of 5, 15, 30, 45, and 60 minutes. Each and every time 5 ml dissolution sample was compensated by another fresh 5 ml distilled water (dissolution media). The samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV- mini-1240, SHIMADZU CORP., Kyoto, Japan). The absorbance of the solutions was measured at 288 nm against dissolution medium as blank. Percentage of drug release was calculated using the equation obtained from the standard curve prepared in the media.

2. 3. 2. Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectroscopy has been used frequently to characterize drug polymer interactions in solid dispersions. Using FTIR, a spectrum of solid dispersion and that ofits corresponding physical mixture is compared. Infrared spectra were recorded on a Perkin-Elmer 298 infrared spectrometer, from samples prepared in potassium bromide (KBr) discs. The scanning range was 4000 to 400 cm-1 at a scan period of 14 minute.

2. 3. 3. Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to study the morphology and surface topology of the solid power particles. A scanning electron microscope (SEM) is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity. The solid particles from the optimized batch were mounted on the SEM sample stab (aluminium stabs) which were coated with a double sided sticking tape, sealed and finally coated with gold (200Å) under reduced pressure(.001 tor) for 15 minutes using ion sputtering device. The samples were scanned using scanning electron microscope(s-3400N, Hitachi) under different magnification and photomicrographs of suitable magnification (Akter *et al*., 2015).

2. 4. Preparation of standard curve for carbamazepine

10 mg of carbamazepine was accurately weighted and taken in 100 ml volumetric flask. Then distilled water was added up to the mark and shaked properly to prepare primary stock solution. 10 ml of solution was taken in another 100 ml volumetric flask and added distilled water upto the mark. This solution, called stock solution was used as for further experiment. Serial dilution was carried out to get different drug concentrations.1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml of stock solution were gradually taken in the test tube and 9, 8, 7, 6, 5, 4, 3, 2, 1 and 0 ml of distilled water were added respectively to make 10 ml volume in each test tube. These were then analyzed by UV-Vis spectrotrophotometer at 288 nm and absorbance of each of the diluted solutions was noted. The absorbance values were plotted against drug concentrations to prepare standard curve for carbamazepine.

3. Results and Discussion

3.1. Standard curve of carbamazepine

Standard curve of carbamazepine is shown in Figure 1.

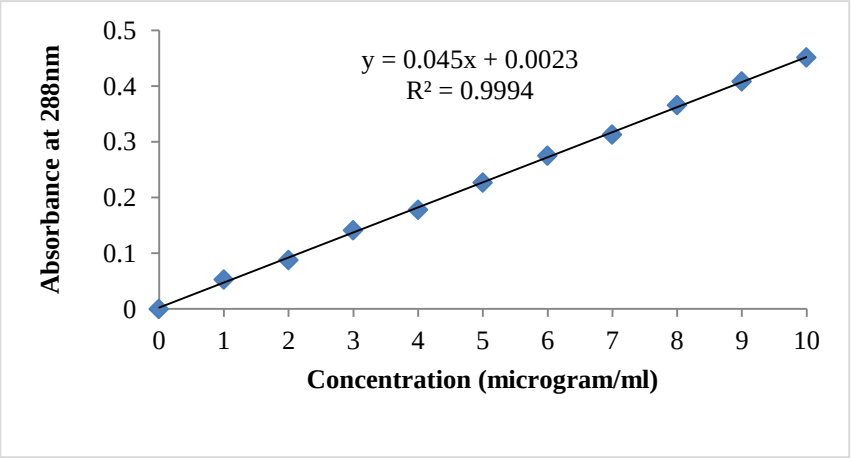

Figure 1. Standard curve of carbamazepine.

3.2. *In vitro* dissolution profile of Diclofenac sodium and SDs formulation

3.2.1. Dissolution profile of carbamazepine from binary solid dispersion

Drug release from pure drug powder was very slow compared to that of the formulations that incorporated water soluble polymers. It was found only 16.6% drug was released within 5 minutes and 27.06% was released after 60 minutes. Binary solid dispersion formulation of carbamazepine was prepared with four different polymers PEG 6000, Povidone k 30, PEG 4000 and Poloxamer 407 in 1: 1 weight ratio by solvent evaporation technique. In addition physical mixtures were also prepared using same polymers and same ratio to compare the solid dispersions against them. All the solid dispersions show a better release profile compare to the physical mixtures as well as pure drug. Drug releases from these physical mixtures and solid dispersion formulations are shown in Figures 2 and 3.

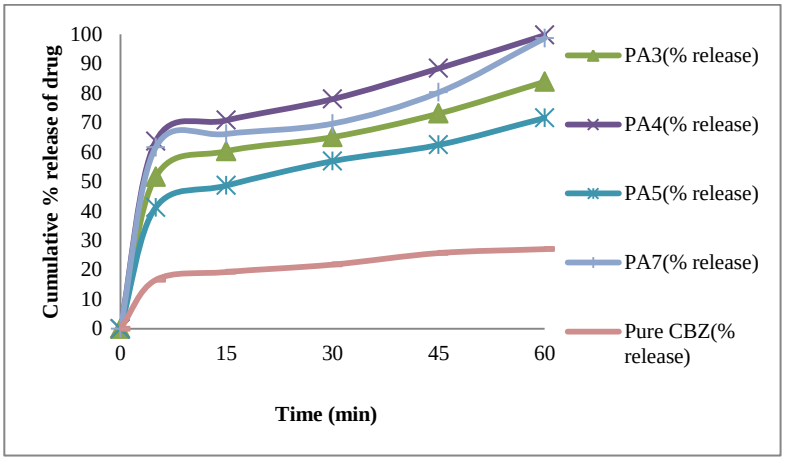

Figure 2. Average % drug release from physical mixtures of carbamazepine (CBZ) containing different polymers in 1:1 ratio.

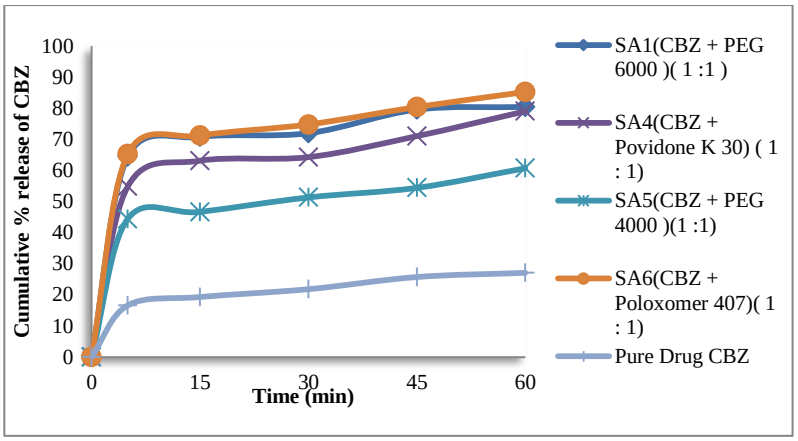

Figure 3. Average % drug release from solid dispersion of carbamazepine (CBZ) containing different polymers in 1:1 ratio.

Figure 2 and Figure 3 indicate that drug release from SDs was faster from their pure drug. It was found the drug release depend on the nature of carrier. The improvement in the in vitro drug release profile may be due to the reduction of particle size of drug and hence improving drug wettability and significantly better dissolution. With 5 minutes 40-60% drug was released from solid dispersion containing PEG 6000, Povidone k 30, PEG 4000 and Poloxamer 407. About 8 fold increase of drug release was found in this solid dispersion formulation.

3.2.2. Dissolution profile of carbamazepine from ternary solid dispersion

Ternary solid dispersion of carbamazepine was prepared with mixture of PEG 6000 and Poloxamer 407 in different weight ratios. They were found more effective to increase the dissolution rate than binary solid dispersion. The amount of PEG 6000 was kept constant and the percentage of poloxamer changed gradually.

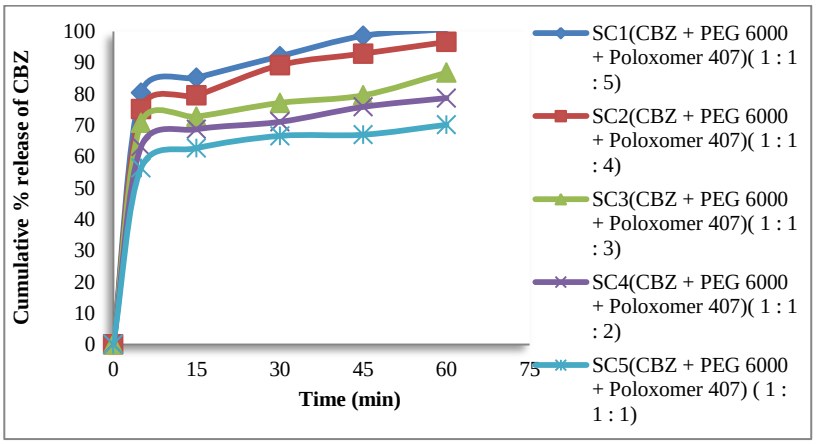

Figure 4. Average % drug release from solid dispersion of carbamazepine (CBZ) containing PEG 6000 and poloxamer 407.

However, Figure 4 shows among all solid dispersions of carbamazepine, the formulation containing highest amount of poloxamer 407 SC1 (1:1:5) showed maximum drug release rate (80.4% after 5 minutes and 100. 76% after 60 minutes). Finally it was observed that the release rate has been increased when the amount of polymer is increased in the formulation. It might be caused by the structural composition and higher molecular weight of poloxamer 407.

Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers; the polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. Greater hydrophilic and hydrophobic content of Poloxamer 407 might be responsible for the better emulsifying property which in turn demonstrates higher solubility followed by better dissolution (Collett, 2009).

This highly water soluble polymer when used in combination with PEG 6000. Because PEG 6000 has higher content of oxyethylene groups in its structure which in turn makes its molecular weight higher. PEG 6000 has molecular weight range of 7300-9300. Thus higher grades of PEG provide better solubilising effect in case of solid dispersions (Wallick, 2009).

This observation indicated that the increased dissolution rate of carbamazepine from carbamazepine solid dispersions may be due to the presence of drug in amorphous state as compared to the physical mixtures where drug is present in crystalline state (Ghosh *et al*., 1998).

3.3. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of pure carbamazepine showed sharp characteristic peaks at wave numbers 1386.86, 1488.86, 1605.79 1680 cm^{-1}. The infrared spectrum of the ternary systems contains same characteristic peaks which were found in pure drug (Figures 5 and 6). From this study, it can be conclude that there was no chemical modification or interaction between the drug and carrier in SD formulation.

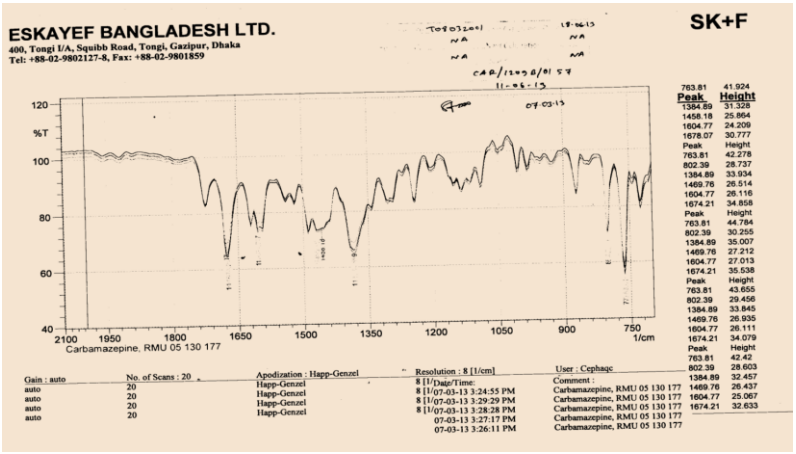

Figure 5. Infrared spectra of pure carbamazepine.

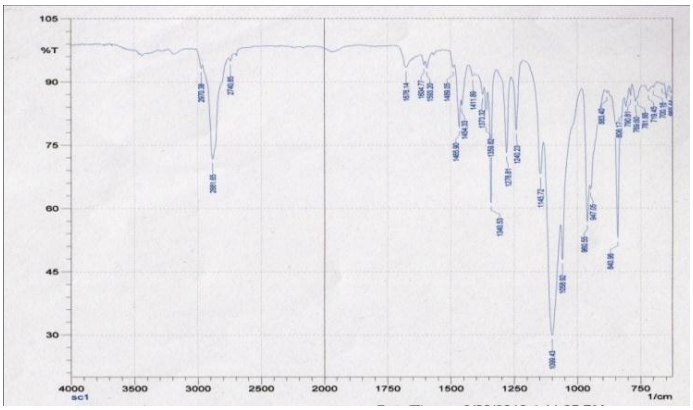

Figure 6. Infrared spectra of solid dispersion containing carbamazepine, PEG 6000 and poloxamer 40.

3.4. Scanning Electron Microscopy (SEM)

Solid dispersion of carbamazepine (SC1) containing PEG 6000 and Poloxamer 407 observed by SEM to see the morphological change that occurred due to formulation variation. SEM studies showed the surface morphological property of the solid dispersion was in amorphous state. The surface morphology is observed and representative micrographs are shown in Figures 7 and 8.

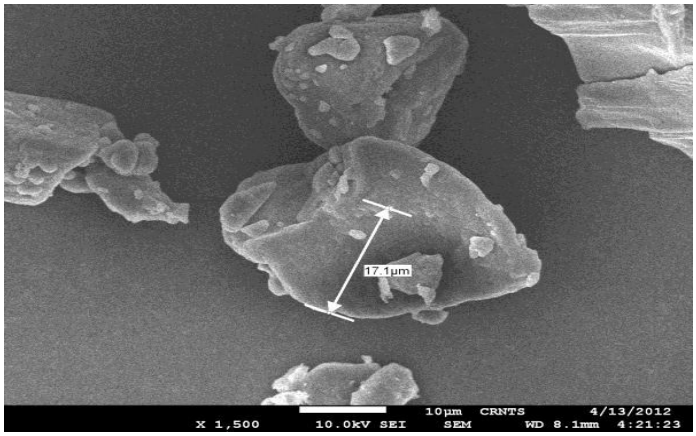

Figure 7(a)

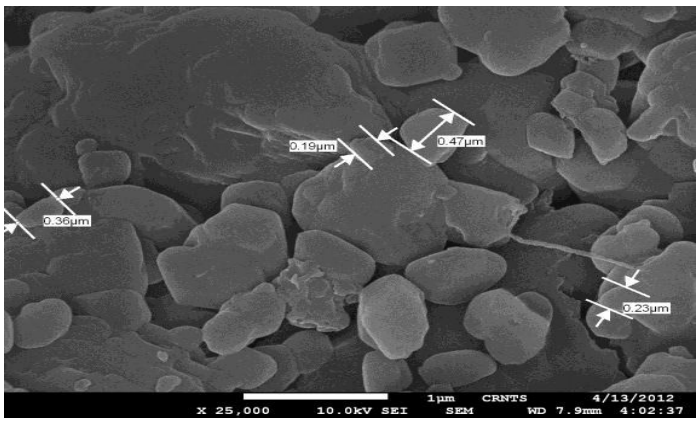

Figure 7(b)

Figure 7(a+b). Scaning Electronic Microscopic image of carbamazepine.

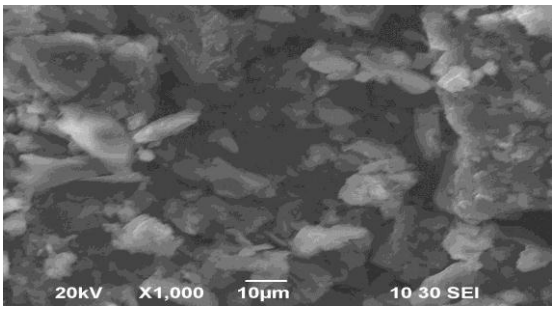

Figure 8(a)

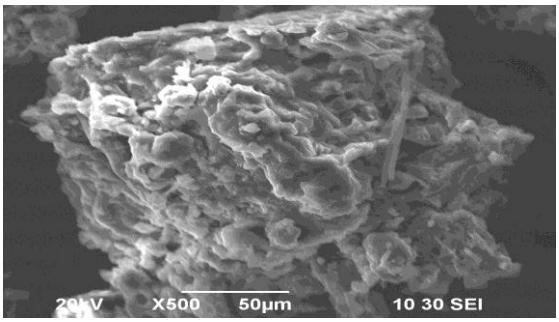

Figure 8(b)

Figure 8(a+b). Scaning Electronic Microscopic image of solid dispersion containing carbamazepine and poloxamer 407 (a) Magnification at X1000SE (b) Magnification at X500SE.

4. Conclusions

In this study the solid dispersion of carbamazepine with different carriers in different ratios were prepared to improve dissolution characteristics. Solvent evaporation method was employed to prepare solid dispersions. A significant increase in the release of the drug was observed in each batch with different polymers. The solubility of carbamazepine increased significantly in the solid dispersions with different carriers. The infrared spectroscopy study showed that there were no significant interactions between drug and the carriers in solid dispersion. The scanning electron microscopy study of carbamazepine revealed that the carriers added in the solid dispersions with carbamazepine transforms crystalline structure of carbamazepine into amorphous structure. Solid dispersion preparation by the method demonstrated in this study thus may be an ideal means of drug delivery system for poorly aqueous soluble drug.

Conflict of interest

None to declare.

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