

Formulation and Evaluation of Solid Dispersion of an Anti-epileptic drug Carbamazepine

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Abstract: Carbamazepine (CBZ), relatively water insoluble anti epileptic candidate was selected as a model drug for the study, which is BCS class II drug (low soluble and high permeable). Solid dispersions were formulated with an aim of improving aqueous solubility, oral bioavailability and the rate of dissolution of Carbamazepine using different hydrophilic polymer like Polyethylene Glycol (PEG) 6000, Polyethylene Glycol (PEG) 4000, Polyethylene Glycol (PEG) 1500, kollidon 30, HPMC 6 cps, poloxamer 407 and povidone k 30. Binary and ternary solid dispersions were prepared by physical mixing as well as fusion method with different drug-to-polymer weight ratio. The effects of different polymers on the solubility and in-vitro dissolution behavior were investigated spectrophotometrically at 288 nm. These formulations were characterized in the solid state by Fourier Transform Infrared (FTIR) spectroscopy and Scanning Electron Microscopy (SEM). SEM study indicated CBZ was present as fine particles and entrapped in carrier matrix of PEG 6000 and poloxamer 407 solid dispersions. Fourier Transform Infrared (FTIR) spectroscopic studies showed the stability of CBZ and absence of well-defined drug-polymer interactions. It was found that only 27.06% was released within 60 minutes from active carbamazepine on the other hand the release of carbamazepine from the solid dispersion containing combined PEG 6000 and poloxamer 407 at the ratio of 1:1:1 showed the best result which was 100.12% within the same period of time. Even physical mixtures of CBZ prepared with both carriers also showed better dissolution profiles than those of pure CBZ. This can be attributed to increased wettability and dispersibility, as well as decreased crystallinity and increase in amorphous fraction of drug when they remain dispersed in polymer. In conclusions, solid dispersions could be a promising delivery of CBZ with improved oral bioavailability and immediate release profiles.

Keywords: Carbamazepine, DTA, FTIR, fusion method, PEG 6000, poloxamer 407, SEM, solid dispersion.

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I. Introduction

Carbamazepine (CBZ) is a widely prescribed antiepileptic drug having poor water solubility (~170 mg/L at 25-C) [1]. Because of having poor water solubility, its absorption is dissolution rate limited, which often results in irregular and delayed absorption [2]. The critical requirement for a poorly water-soluble drug for absorption to be possible from the gastrointestinal (GI) tract is, achieving a solution of drug in the GI fluid. Hörter and Dressman [3] defined a poorly water-soluble drug as the one whose dissolution in the GI fluid under ordinary conditions takes a longer time than its transition through the absorption sites in the GI tract. The BCS is a scientific framework for classifying a drug substance based on aqueous solubility and intestinal permeability. When combined with the *in-vitro* dissolution characteristics of the drug product the BCS takes into account 3 major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid-oral dosage form. The BCS classification scheme is subdivided into four groups with respect to aqueous solubility & intestinal permeability: (**Figure 1**) [4-5].

BCS Class IV compounds, which have low membrane permeability as well as poor aqueous solubility, are often poor candidates for development, unless the dose is expected low. The rate and extent of absorption of

class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, but care needs to be taken with formulation design to ensure to ensure consistent bioavailability. Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs [6]. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent–fusion method [7]. Since 1961, many investigators have studied SDs of poorly water-soluble drugs with the various pharmacologically inert carriers to increase the dissolution [8]. The mechanisms for the enhancement of dissolution rate of SDs have been proposed by several investigators. Molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and improvement in drug solubility and wettability due to surrounding hydrophilic carriers [9]. Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Several attempts have been reported in literature about using this technique to increase the dissolution characteristics of carbamazepine (CBZ) where Hydroxy Propyl methyl cellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol, sodium carboxymethyl cellulose, sodium starch glycolate (SSG), pregelatinized starch were used as solubilizing agents [10-12].

Present investigation explores the enhancement of solubility and dissolution of CBZ by solid dispersion technology. In our study solid dispersions were formulated with seven water soluble polymers by fusion method. Polyethylene Glycol (PEG) 6000, Polyethylene Glycol (PEG) 4000, Polyethylene Glycol (PEG) 1500, kollidon 30, HPMC 6 cps, poloxamer 407 and povidone k 30 were utilized for this purpose and determine the effect of those polymer on dissolution of CBZ.

II. Materials and Methods

Materials

Carbamazepine was obtained as a gift sample from Eskayef Bangladesh Limited. PEG 6000, PEG 4000, PEG 1500, povidone k 30, HPMC 6 cps, kollidon 30 and poloxamer 407 were collected from Incepta Pharmaceuticals Ltd, Bangladesh. 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.

2.1. Preparation of solid dispersions (SDs) of carbamazepine

(a) 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 grounded powder particles were sieved through '40' mesh screen. Then the physical mixture were weighed and transferred in fresh glass vials with proper labeling. Finally, all the SDs formulations thus obtained in separate vials were stored in dessicator until further use (**Table 1**).

(b) Preparation of SDs by fusion method

Solid dispersions of carbamazepine were prepared by the fusion method. Poly ethylene glycol (PEG) was taken in a beaker and heated at 70 °C into water bath to melt it completely. Carbamazepine was added with constant stirring with a spatula and was kept at room temperature for 72 hours, cooled at room temperature until getting solid mass. The mixtures of drug and polymer were in molar ratios of 1/1, 1/3, and 1/5 for carbamazepine. The solid samples were ground with mortar and pestle, passed through a 40mm sieve. Then they were weighed and transferred in fresh glass vials with proper labeling. Finally, all the SDs formulations thus obtained in separate vials were stored in dessicator 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) were mixed with poloxamer 407, kollidon 30, HPMC 6 cps and povidone k 30 in different weight ratios.

Table-1 shows the lists of the solid dispersions prepared by this technique.

2.2 Evaluation of carbamazepine solid dispersions

(i) *In vitro* dissolution studies of carbamazepine and 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 $37 \pm 0.5^{\circ}\text{C}$ 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.

(ii) Fourier Transform Infra Red (FTIR) Spectroscopy

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 of its 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.

(iii) 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.

2.3 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 shaken 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 spectrophotometer 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.

Table-1: List of formulation of binary and ternary solid dispersions of carbamazepine

Serial No.	Polymers	Drug to polymer ratio	Methods	Dispensing (mg)	Codes used
01	PEG 6000	1:1	Physical mixtures	300:300	PA1
02	PEG 4000	1:1	Physical mixtures	300:300	PA2
03	PEG 1500	1:1	Physical mixtures	300:300	PA3
04	Kollidon 30	1:1	Physical mixtures	300:300	PA4
05	HPMC 6 cps	1:1	Physical mixtures	300:300	PA5
06	Poloxamer 407	1:1	Physical mixtures	300:300	PA6
07	Povidone k 30	1:1	Physical mixtures	300:300	PA7
08	PEG 4000	1:1	Fusion method	300:300	FA1
09	PEG 6000	1:1	Fusion method	300:300	FA2
10	PEG 1500	1:1	Fusion method	300:300	FA3
11	PEG 6000+ Poloxamer 407	1:1:1	Fusion method	200: 200:200	FE1
12	PEG 6000+ Poloxamer 407	1: 1: 0.75	Fusion method	200 : 200 : 150	FE2
13	PEG 6000+ Poloxamer 407	1: 1: 0. 50	Fusion method	200 : 200 : 100	FE3
14	PEG 6000+ Poloxamer 407	1: 1: 0. 25	Fusion method	200: 200: 50	FE4
15	PEG 6000+ Poloxamer 407	1: 1: 0. 0	Fusion method	200: 200: 000	FE5

III. Results and discussions

3.1 Physical appearance

The carbamazepine solid dispersions were prepared by fusion method. All solid dispersions were white fine powders. No discolouration was observed during preparation of SD.

3.2 Standard curve of carbamazepine

Standard curve of carbamazepine is shown in **Figure 2**.

3.3 Effect of hydrophilic polymers on the dissolution of carbamazepine solid dispersion

The graphical representations of percent release of carbamazepine (CBZ) from the optimized SD formulations are shown in **Figure 4- 6**. The dissolution rate of pure carbamazepine was low compared to that of the formulations that incorporated water soluble polymers. **Figure 3** shows that in case of pure drug, only 16.6% drug was released within 5 minutes and 27.06% was released after 60 minutes.

Firstly, physical mixtures were prepared using seven different hydrophilic polymers like Polyethylene Glycol (PEG) 6000, Polyethylene Glycol (PEG) 4000, Polyethylene Glycol (PEG) 1500, kollidon 30, HPMC 6 cps, poloxamer 407 and povidone k 30 in 1:1 weight ratio. The effect of those polymers on dissolution profile of carbamazepine is shown in **Figure 4**. All the physical mixtures show a better release profile compare to the pure drug. It was observed that physical mixtures PA4 (CBZ+ PEG 6000) and PA7 (CBZ+ Poloxamer 407) gave the better result among other physical mixtures.

Binary SD formulation of CBZ was prepared with different grades of Polyethylene glycol (PEG) e.g. PEG 6000, PEG 4000 and PEG 1500 in 1: 1 weight ratio. Drug releases from these solid dispersions is shown in **Figure 5**. Drug release was increased with time. Approximately 99.62% drug was released from SD formulation containing PEG 6000 (FA2) within an 1hr.

Again, in the ternary SD formulation, the effect of combination of PEG 6000 and a second hydrophilic polymer Poloxamer 407 on CBZ release was investigated where the amount of PEG 6000 remained constant and different percentage of Poloxamer 407 were used. Release rate of the drug from SDs was improved as the poloxamer 407 content in formulation was increased. **Figure 6** shows that the rate was the faster for the formulation that contained highest amount of polymer. About 100% release of drug was observed in case SD formulation containg PEG 6000 and Poloxamer 407 at the ratio 1: 1: 1.

The highly water soluble polymer PEG when used, PEG 6000 results better dissolution than PEG 4000 and PEG 1500. Because PEG 6000 has higher content of oxyethylene groups in its structure which in turn makes its molecular weight higher compared to the PEG 4000 and PEG 1500. PEG 6000 has molecular weight range of 7300- 9300 and PEG 4000 has molecular weight 3000-4800. This higher grades of PEG provide better solubilising effect in case of solid dispersions [13].

In addition, the dissolution improvement of CBZ from drug-poloxamer-407 solid dispersion might be due to lowering of surface tension between drug and solvent as well as decreased crystallinity of the product [14]. Also critical micellar concentration of the polymer and improvement of wetting characteristics of the drug might be played a crucial role in dissolution enhancement of the drug [15].

3.4 Fourier-Transform Infrared Spectroscopy (FTIR) Study

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 binary and ternary systems contains same characteristic peaks which were found in pure drug. The FTIR spectra of pure drug (**Figure 7**) was identical with SD formulation (**Figures 8 and 9**. From this study, it can be conclude that there was no chemical modification or interaction between the drug and carrier in SD formulation.

3.5 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 properties of the solid dispersion was in amorphous state. The surface morphology is observed and representative micrographs are shown in **Figures 9 and 10**.

Class II Low solubility High Permeability	Class I High solubility High Permeability
Class IV Low solubility High Permeability	Class III Low solubility High Permeability

Fig. 1: BCS Classification

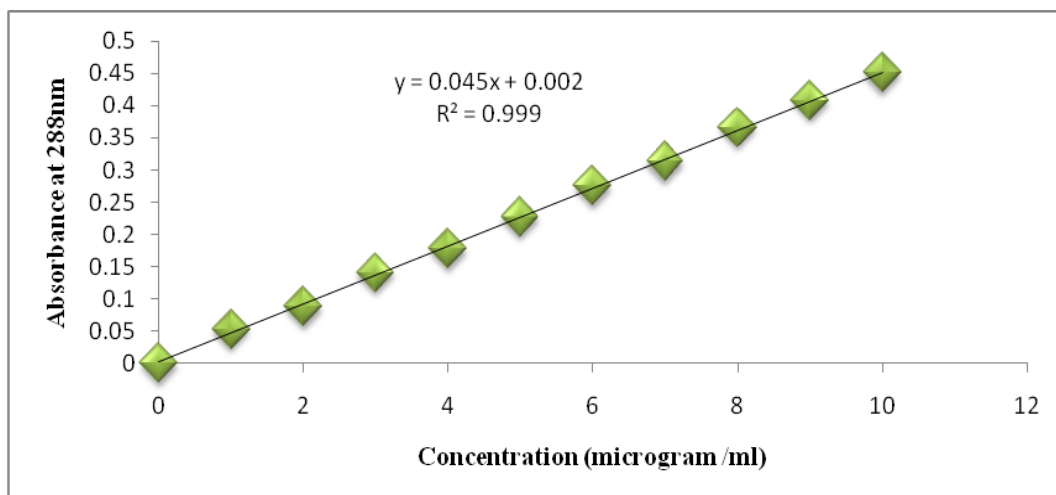


Fig. 2: Standard curve of carbamazepine (API)

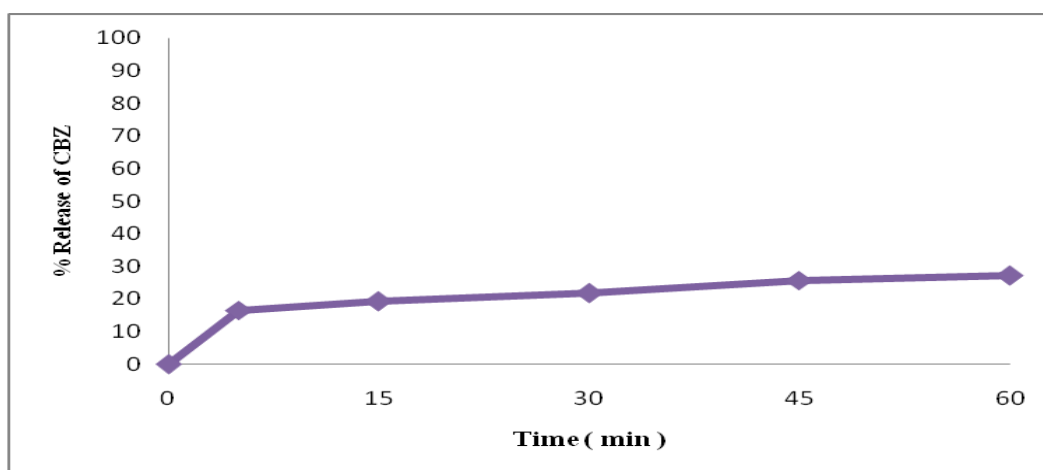


Fig. 3: Percent release of active carbamazepine

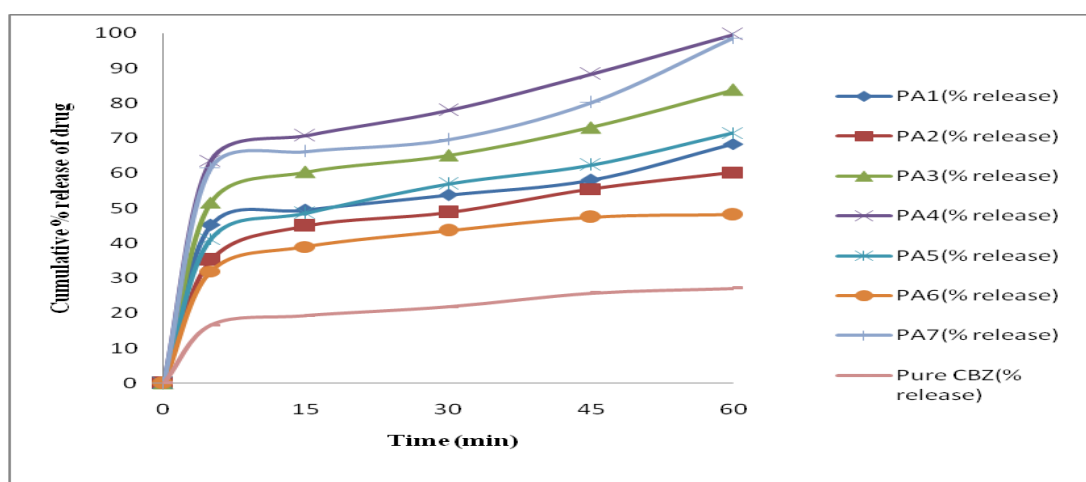


Fig. 4: Average % release of drug from binary SD containing different polymers (physical Mixtures)

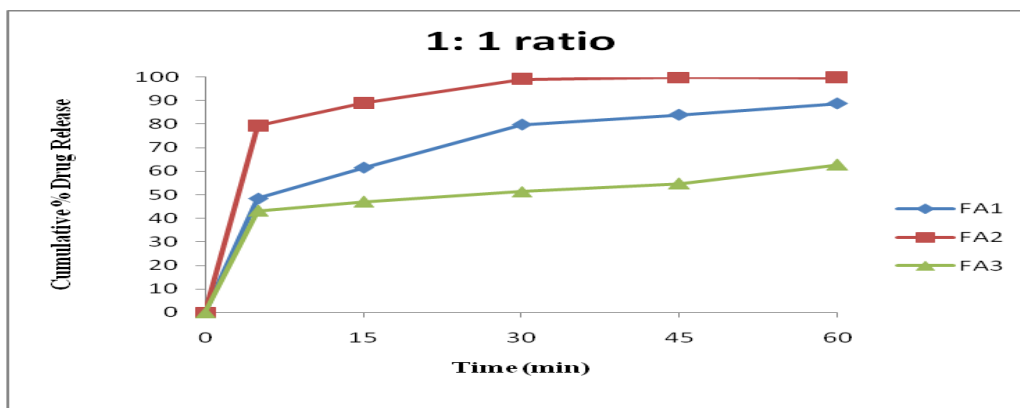


Fig. 5: Average % release of drug from binary SD containing PEG 6000, PEG 4000 and PEG 1500 (fusion method)

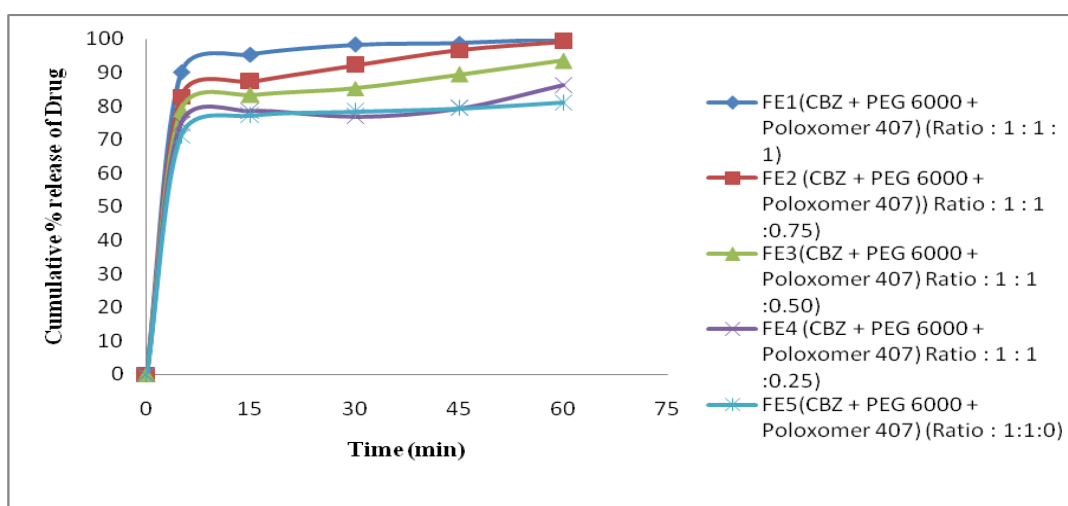


Fig. 6: Average % release of drug from ternary SD containing PEG 6000 and Poloxamer 407 (fusion method)

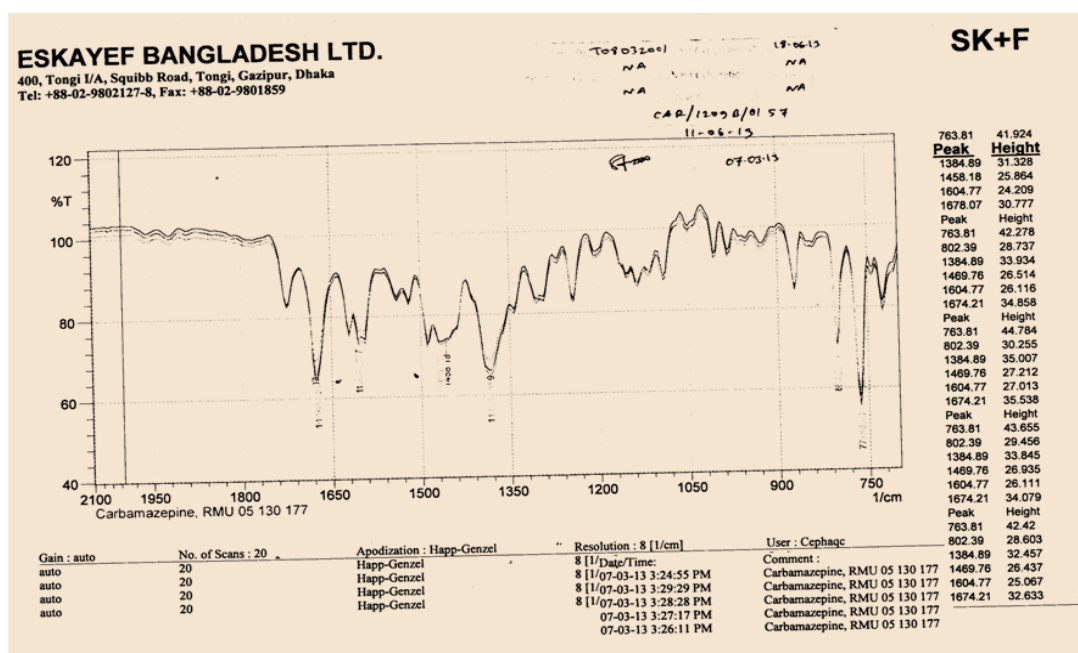


Fig. 7: FTIR spectra of Carbamazepine

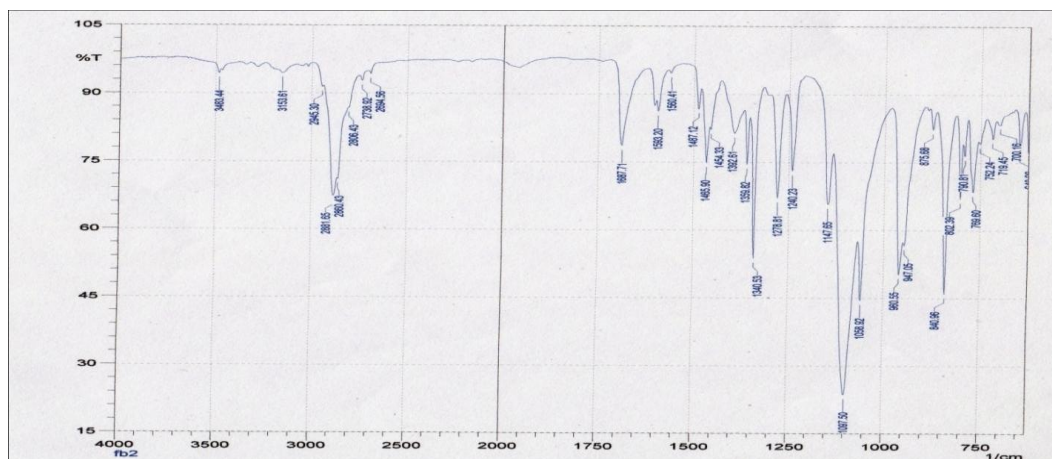


Fig. 8: FTIR spectra of solid dispersion containing carbamazepine and PEG 6000 (Formulation code: FB2)

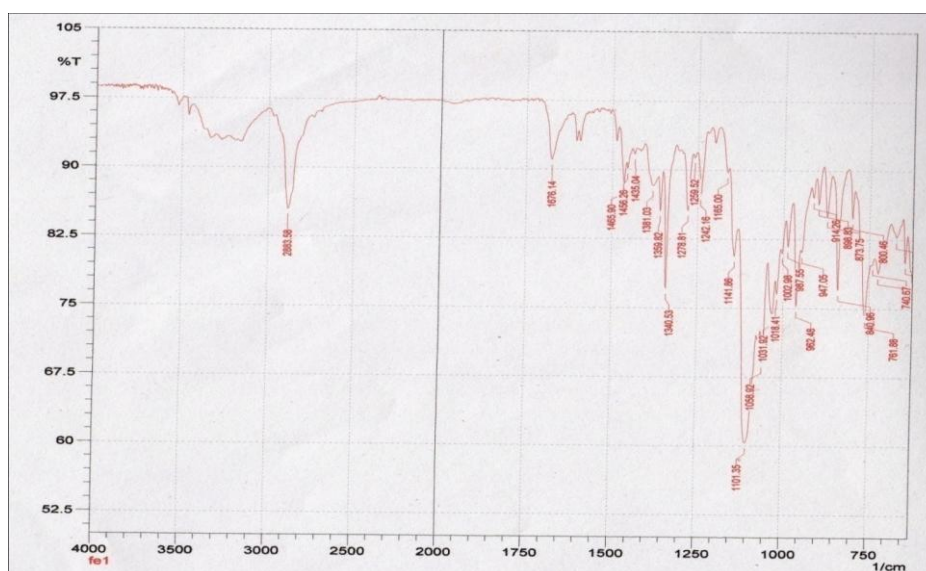


Fig. 9: FTIR spectra of solid dispersion containing carbamazepine, PEG 6000 and Poloxamer 407 (Formulation coding: FE1)

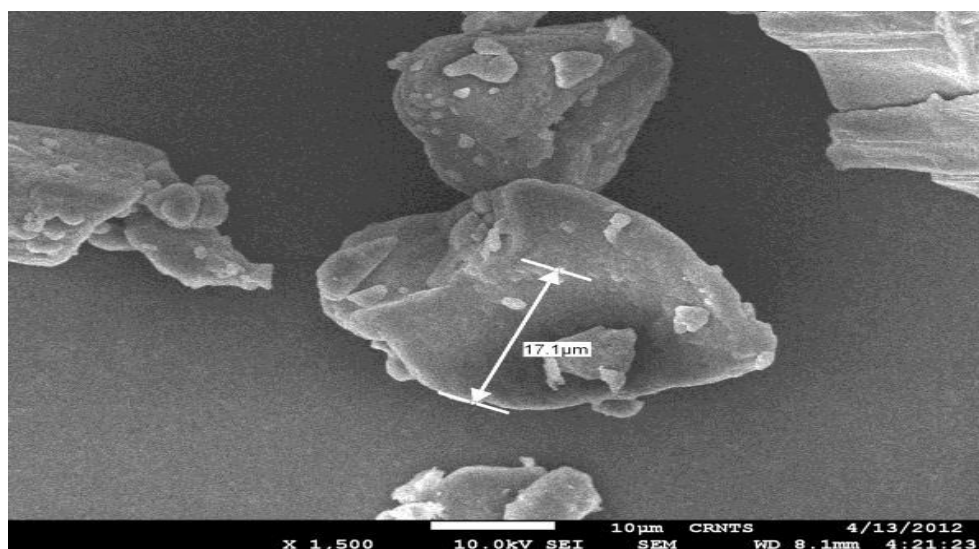


Fig. 10(a)

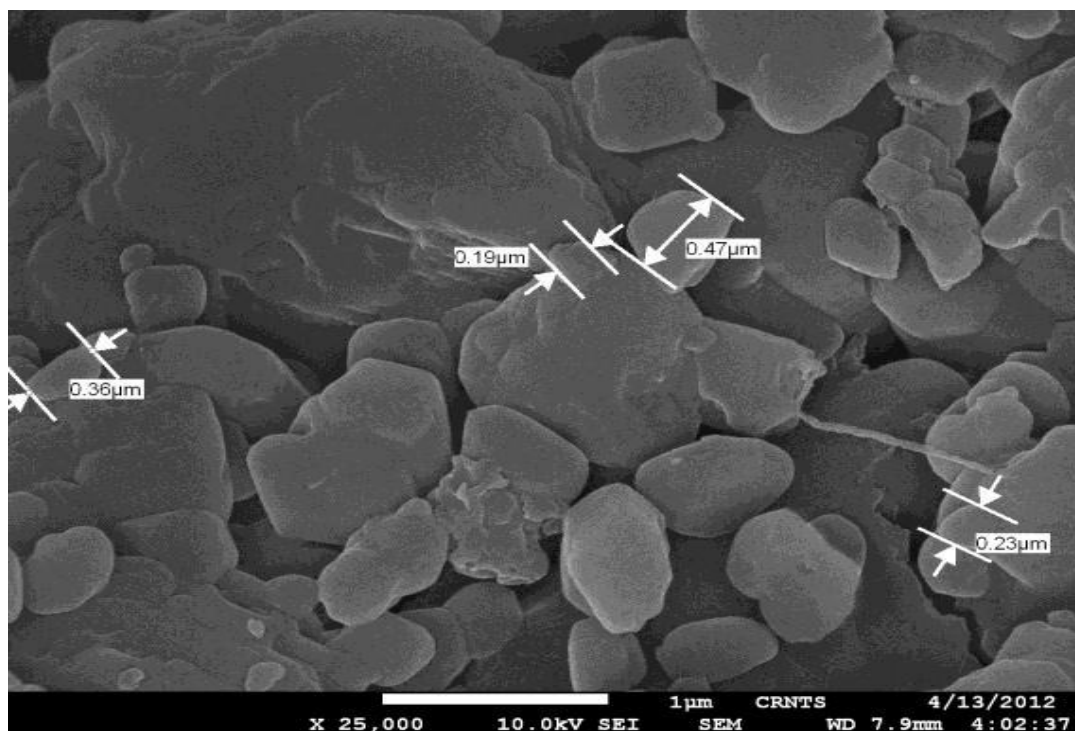


Figure 10(b)

Fig. 10(a+b): Scanning Electronic Microscopic image of carbamazepine.

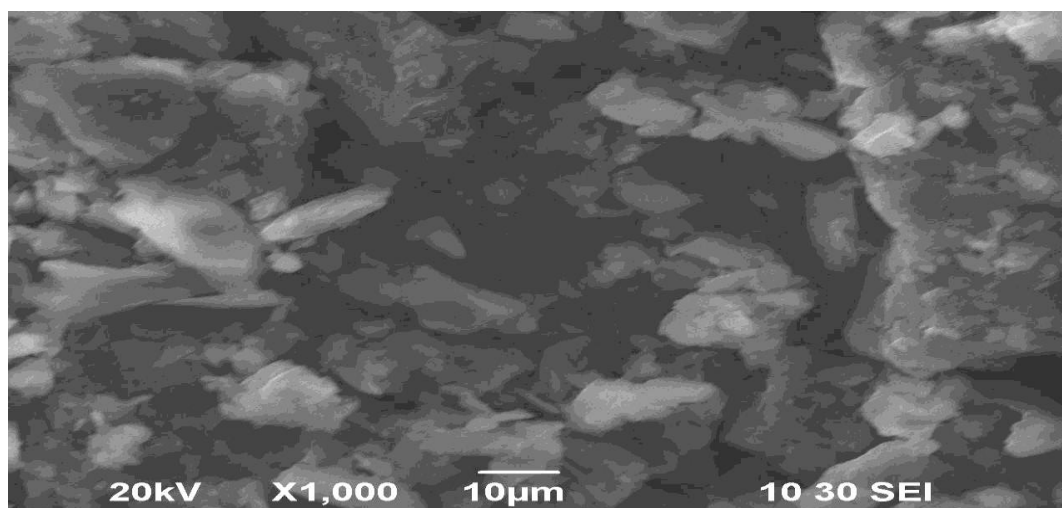


Fig. 11: Scanning Electronic Microscopic image of solid dispersion containing carbamazepine and poloxamer 407

IV. Conclusion

This study is an opportunity of preparing solid dispersions with improved aqueous solubility and dissolution rate, which will solve the difficulties in the development of pharmaceutical dosage forms of carbamazepine. Solid dispersions were prepared by fusion method where the active drug were fused at hydrophilic polymer: Poly ethylene glycol (PEG), poloxamer 407. 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 carbamazepine and the carriers in solid dispersion. The scanning electron microscopic study of carbamazepine revealed that the carriers added in the solid dispersions with carbamazepine transforms crystalline structure of carbamazepine into amorphous structure. In a nutshell, solid dispersion preparation by the method demonstrated in this study thus may be an ideal means of drug delivery system for poorly water soluble drugs.

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Statement of Conflict of interest

The authors declare that they do not have any conflict of interest.

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