IJPSR (2011), Vol. 2, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 August, 2010; received in revised form 12 November, 2010; accepted 26 December, 2010

DISSOLUTION ENHANCEMENT OF POORLY SOLUBLE CARBAMAZEPINE BY USING POLYMERIC SOLID DISPERSIONS

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Keywords:

Poor solubility,
Solid dispersion,
Dissolution enhancement,
Poloxamer,
Povidone,
HPMC

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ABSTRACT

The purpose of this study was to improve the solubility of poorly soluble Carbamazepine by using solid dispersion technique utilizing common pharmaceutical polymers. The formulations were prepared with HPMC, PVP K30, and poloxamer 407 as polymers and methanol as solvent. The formulations were characterized by differential scanning calorimetry, Fourier transform infrared spectroscopy, in vitro dissolution study by USP type I apparatus, and recrystallization study by optical microscopy. The dissolution profiles revealed that the drug and polymer ratio and the type of polymer both play critical role in solubility enhancement. The solid dispersions formulated with drug and poloxamer ratio of 1:1 showed highest dissolution rate. The formulations containing PVP did not show any endothermic peak of the drug unlike other formulations. There were molecular interactions between drug and polymers (HPMC and PVP) which were confirmed by FTIR studies.

INTRODUCTION: Most of the recently introduced drugs suffer from poor solubility as they are developed by combinatorial chemistry and high throughput screening techniques. Solid dispersions are useful for solving the solubility and bioavailability problem of such drugs [1]. By definition solid dispersions are formulations of finely crystalline or amorphous drug dispersed in an inert matrix [2].

In the present experiment the anti epileptic Carbamazepine (CBZ) is taken as a model drug which is practically insoluble in water. It is one of the BCS class II [3] type where low solubility and high intestinal permeability drugs are included. Dissolution is the rate limiting step for the absorption and subsequent bioavailability for this type of drugs. The drug also has four polymorphs and it is well known that the different crystalline forms of a drug may have different solubility and mechanical properties.

Several attempts have been reported in literature about using solid dispersion technique to increase the dissolution characteristics of CBZ where Hydroxy Propyl methyl cellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol, sodium carboxymethyl cellulose, sodium starch glycolate, pregelatinized starch were used as solubilizing agents [4-6].

In this study solid dispersions were formulated with three water soluble polymers by solvent evaporation technique. Micronized poloxamer 407, HPMC 6 cps and PVP K30 were utilized for this purpose. Poloxamers are nonionic polyoxyethylene-poly-oxypropylene copolymers used primarily as emulsifiers, solubilizing agents, wetting agents and have been reported for enhancing the solubility and bioavailability of sparingly soluble drugs in solid dosage forms [7-9]. Solid dispersions were prepared with poloxamer by melting method for rofecoxib [10] and ibuprofen [10]. Reduced crystalline structure and improved wettability [11-12] were mentioned as the mechanism by which poloxamer can enhance dissolution from solid dispersions. On the other hand, both HPMC and PVP are known to act as crystallization inhibitors and thus they help to produce solid solutions [13-16]. They improve the dissolution characteristics due to interaction through hydrogen bonding.

The objective of the present study was to improve the solubility of Carbamazepine by using three different types of water soluble polymers. The formulations were characterized by differential scanning calorimetry, Fourier Transform Infrared (FTIR) spectroscopy, in vitro dissolution study, and optical microscopy to compare the effects of polymers on the preparation of solid dispersion and dissolution enhancement.

MATERIALS AND METHODS:

Materials: Carbamazepine sample was collected from Zydus Cadila Healthcare Ltd., Ahmedabad, India. Poloxamer 407 (Lutrol 127) was gifted by BASF, Germany. HPMC 6 cps (Shin Etsu Chemical Company Ltd., Japan), PVP K30 (BASF, Germany), and reagent grade methanol (Merck, Germany) were purchased from the market.

Preparation of solid dispersions: Solid dispersions of CBZ with HPMC and PVP K30 were prepared by solvent evaporation method which is a conventional technique used by many researchers [5, 17]. The drug was dispersed in methanol and polymer was added gradually followed by blending in mortar and pestle at room temperature.

During mixing the methanol was evaporated and the resulting solid mass was dried in an oven at 60^{o}C for 2 hours. The dried samples were milled and screened through 30 mesh screen to obtain fine particles which were stored in a desiccator until use. A slightly different approach was warranted for solid dispersions containing poloxamer as it is low

melting substance (m.pt. 52-57^{o}C) and melting method was most suitable for this polymer [10, 11]. The drug was dispersed with methanol in a glass flask and heated in a water bath at 50^{o}C. Poloxamer was added to the dispersion and it was melted at that temperature. The solvent was evaporated during constant mixing and the resulting solid mass was dried at 40^{o}C in hot air oven. The dried samples were crushed in mortar and pestle followed by sieving through 30 mesh screen. The ratio between drug and polymer was kept at 1:1, 1:2 and 1:9.

Assay: The formulations were assayed by UV Visible Spectrophotometer (UV-1201 PC, Shimadzu, Japan) at 285 nm. The stock solution was prepared by dissolving drug in methanol and appropriately diluted with distilled water.

***In vitro* dissolution studies:** Powders of pure drug, solid dispersions, and physical mixtures equivalent to 100 mg Carbamazepine was tested with USP dissolution testing apparatus type-I rotated at 100 rpm. The samples were withdrawn from 900 ml distilled water at 5,10,15,20,30 and 40 minutes and suitably diluted and analyzed with UV Visible Spectrophotometer (UV 1201 PC, Shimadzu, Japan) at 285 nm.

Differential Scanning Calorimetry: The pure drug, polymers, and solid dispersions were examined by DSC Q100 (TA instruments, New Castle, USA) where 5-6 mg samples were placed in Aluminium pan at a heating rate of 10^{o}C/min with purging of dry nitrogen at a constant rate of 50 ml/min. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale.

FTIR studies: FTIR spectroscopy (Perkin Elmer, USA) was used for pure drug, polymers and solid dispersions. The samples were prepared by KBr disk method and the semitransparent disks were analyzed over the wavelength range 3500-400 cm^{-1} with FTIR spectrophotometer.

Optical microscopy: The growth of CBZ crystals in water from the various solid dispersions was observed using a light microscope (Nikon Inc., Melville, NY) and the photos were captured by digital camera (Sony Electronics Inc., Japan).

RESULTS AND DISCUSSION: The effects of three water soluble polymers (HPMC, PVP and poloxamer) on the formulations of CBZ solid dispersions were compared. The potencies of CBZ in prepared solid dispersions were analyzed by UV spectrophotometer and the results were within 99-100% in all cases which indicates uniform mixing of the dispersions.

Differential Scanning Calorimetry: Different polymorphic forms of CBZ were reported in the literature [18]. The thermogram of CBZ revealed one small endothermic peak at 174.13 which corresponds to polymorphic form III and another sharp melting endotherm 194.58 for form I. The polymorphic form III is more stable below the transition temperature since it has lower free energy and at elevated temperature it melts and immediately recrystallizes to form I [19]. CBZ has enantiotropic polymorphs which can undergo reversible solid transformation at a transition temperature below the melting point of either of the polymorphs [20].

After processing CBZ with polymers at different ratios, the endothermic peaks corresponding to pure drug disappeared in some solid dispersions. It happens when the polymers like PVP and HPMC act as crystallization inhibitors and keep the drug in amorphous state [21, 22]. The solid dispersions with drug and HPMC at 1:1 and 1:2 ratios showed the presence of form III crystals in DSC. When the HPMC content was further raised (1:9 ratio), endothermic peaks abolished which indicates that drug was probably in amorphous state at 1:9 ratio (**Fig. 1**).

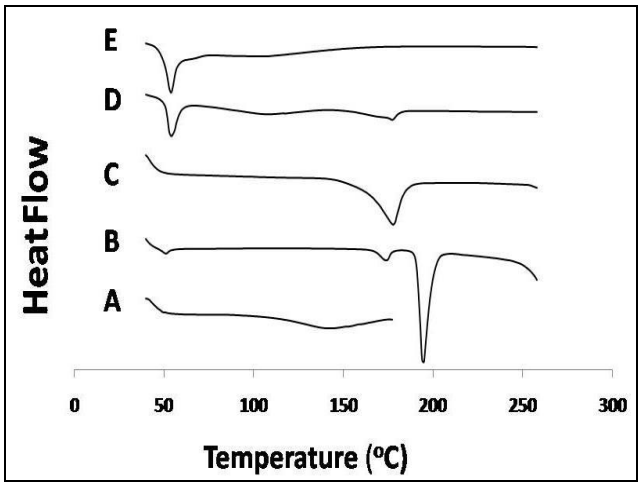

FIG. 1: DSC THERMOGRAM OF (A) HPMC 6CPS, (B) PURE CBZ, (C) CBZ/HPMC 1:1, (D) CBZ/HPMC 1:2, (E) CBZ/HPMC 1:9

On the other hand, PVP K30 showed broad endotherm at 119.29°C which corresponds to loss of water due to extremely hygroscopic nature of PVP polymers [19]. The formulations containing PVP K30 did not showed any endotherm around the melting point of both forms of CBZ (**Fig. 2**). It suggested the lack of crystalline structure in those formulations.

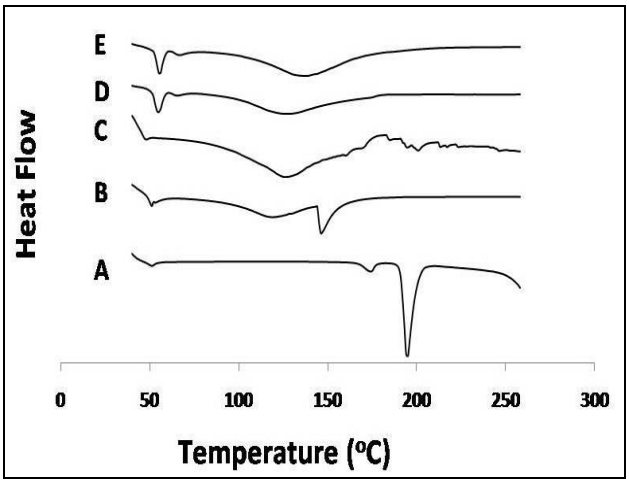

FIG. 2: DSC THERMOGRAM OF (A) PURE CBZ, (B) PVP K30, (C) CBZ/PVP K30 1:1, (D) CBZ/PVP K30 1:2, (E) CBZ/PVP K30 1:9

In case of Poloxamer 407, it showed a characteristic melting endotherm at 60.19°C alone and in combination with CBZ at different ratios. Two polymorphic forms were observed when the drug and polymer ratio was 1:1, but when the polymer content was further increased, the melting endotherm for crystalline CBZ was not observed (i.e. at 1:2 and 1:9 ratio) (**Fig. 3**). Some of the formulations did not show the characteristic endothermic peak of CBZ which is due to the formation of amorphous drug in the presence of water soluble polymers. For example, the drug was in amorphous state in the formulations containing PVP and high amount of HPMC (1:9 ratio). This amorphousness may be due to the hydrogen bonding between drug and polymer and/or drug entrapment in polymer matrix during solvent evaporation. As the solvent is removed the drug molecules lose their mobility and entrapped in polymer without any crystal structure.

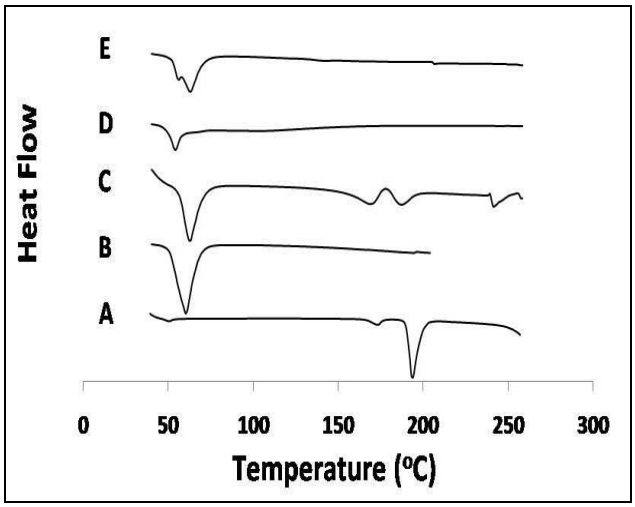

FIG. 3: DSC THERMOGRAM OF (A) PURE CBZ, (B) POLOXAMER 407, (C) CBZ/POLOXAMER 1:1, (D) CBZ/ POLOXAMER 1:2, (E) CBZ/ POLOXAMER 1:9

FTIR spectroscopy: Generally, the interaction between drug and polymer is demonstrated through the band shifts exerted by the functional groups as well as through broadening in IR spectra compared to their individual spectra. To confirm the presence of any interactions between drug and polymer, the FTIR spectra of solid dispersions were compared with pure drug and individual polymers (**Fig. 4**).

If the drug and polymer interact then the functional groups will demonstrate band shifts and broadening in IR spectra compared to their individual spectra. The FT IR spectra of

CBZ matched as polymorphic form III reported earlier [23-25] where characteristic bands appeared at 3469 cm^{-1} and 3160 cm^{-1} (-NH stretching vibration), 1680 cm^{-1} (-CO-R vibration), 1605 and 1596 cm^{-1} (-C=C-,-C=O vibration and –NH deformation), 1370 cm^{-1} (C-NH_2 stretching vibration) (**Fig. 4A**).

HPMC 6 cps showed characteristic bands at 1120 cm^{-1} (-C-O-C- stretching vibration), 3480 cm^{-1} (-OH stretching vibration) and 2939 cm^{-1} (C-H stretching vibration) (**Fig. 4B**). The solid dispersions containing 90% HPMC were unlike any other as all characteristic bands disappeared due to molecular interaction of drug and polymer (**Fig. 4E**). The N-H and C=O bond of CBZ can form hydrogen bond with –OH of HPMC.

The presence of intermolecular bonding is probably responsible for amorphous state of CBZ in formulations containing high amount of HPMC. The spectrum of PVP K30 showed a broad band at 3400 cm^{-1} due to presence of water [26], characteristic bands at 2950 cm^{-1} (C-H stretching) and 1680 cm^{-1} (C=O vibration) (**Fig. 4C**). It also showed a broader band in place of N-H vibration bands (3469, 3160 cm^{-1}) of CBZ which indicates -NH_2 group may form hydrogen bond with PVP K30 (**Fig. 4**F).

Both the =N- and C=O group of povidone can be involved in hydrogen bonding but the steric hindrance of the former atom makes carbonyl group more suitable for the interaction [27]. Poloxamer 407 showed IR pick around 3000 and 1030 cm^{-1} (**Fig. 4D**).The spectrum of poloxamer solid dispersion did not indicate any interaction or hydrogen bonding between CBZ and polymer as none of the characteristic bands of drug and polymer were shifted (**Fig. 4G**). In other words it suggests that CBZ is immiscible in poloxamer matrix.

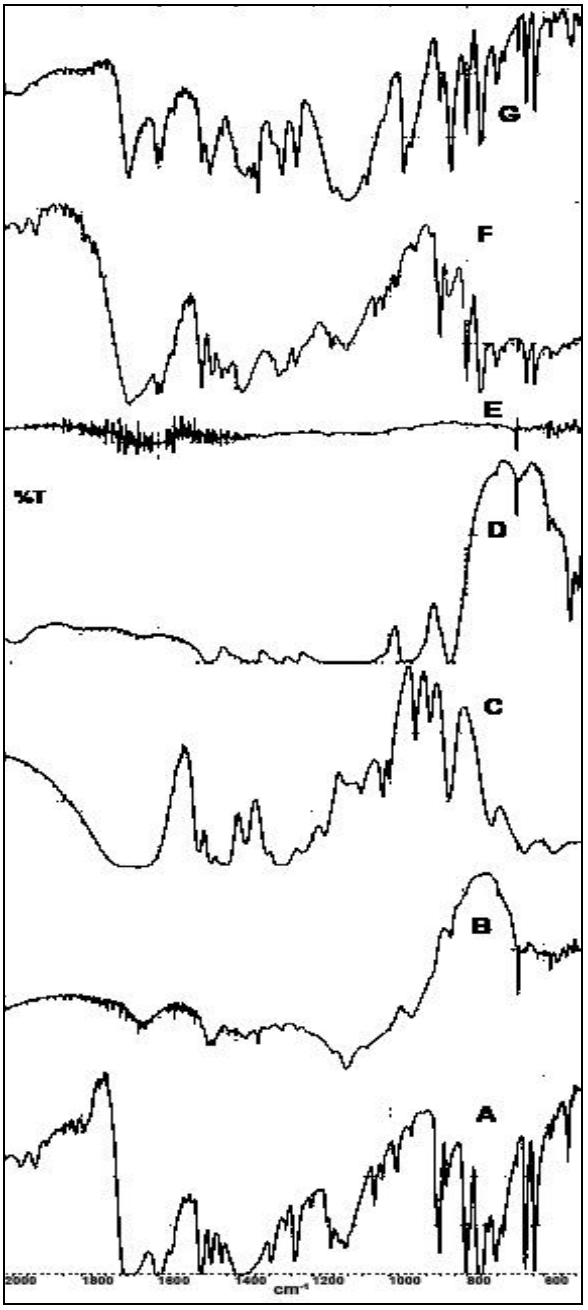

FIG. 4: FT IR SPECTRA OF CBZ AND SOLID DISPERSIONS. CBZ (A), HPMC (B), PVP K30 (C), POLOXAMER (D), CBZ AND HPMC SOLID DISPERSION AT 1:9 RATIO (E), CBZ AND PVP K30 SOLID DISPERSION AT 1:1 RATIO (F), CBZ AND POLOXAMER SOLID DISPERSION AT 1:2 RATIO (G).

Dissolution studies: The in vitro dissolution testing was performed for 40 minutes to ascertain the effect of formulations on immediate drug release enhancement. The enhancement of polymers on drug release from physical mixtures was evaluated by comparing

the solubility of drug present in the mixtures as well as of pure drug. Theoretically the solid dispersions improve drug dissolution by decreasing particle size, formation of amorphous forms and improved wettability [1]. The drug release was reduced by higher amount of HPMC. The polymer, when used at high concentration, forms a gelatinous layer around drug particles upon contact with aqueous media and which acts as a barrier to drug release. The drug is released slowly from such matrix by diffusion process. Usually the higher molecular weight HPMC (such as HPMC K15, K100) are used for sustained release effect in tablet formulations but in case of solid dispersions even the low molecular weights are capable of achieving the same objective.

Though the formulation containing 1:9 drug-polymer ratios showed amorphous nature of drug, the drug release was lowest due to gel barrier (**Fig. 5**). At low concentration HPMC provides wetting of drug and improves dissolution [6]. It is supported by the fact that 1.5 fold increased drug release was observed with formulations containing drug/polymer 1:1 ratio (Fig. 5). This formulation contained small amount of crystal lattice (confirmed by DSC) compared to pure drug alone which indicates reduction of drug particle size may be responsible for improved dissolution.

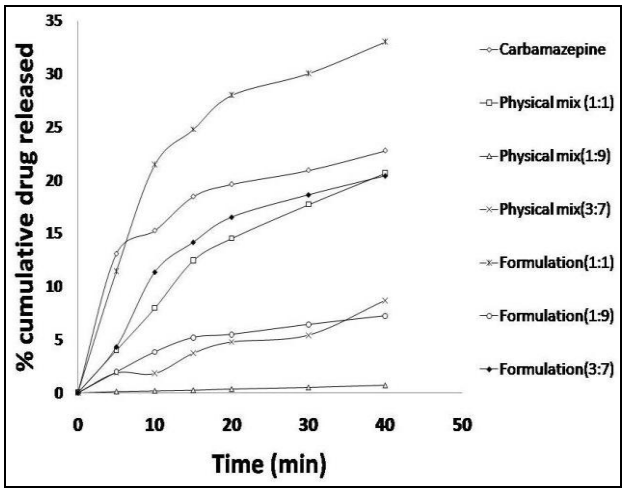

FIG. 5: DRUG RELEASE FROM HPMC FORMULATIONS (N=3, ERROR BARS NOT SHOWN TO ENSURE CLARITY)

On the other hand, the formulations containing PVP K30 and drug successfully inhibited crystal formation in all ratios. The drug release was increased at low PVP combination (1:1 ratio) compared to pure drug (**Fig. 6**) which eventually indicates that amorphous nature of the drug facilitated drug release from those formulations. The formulation having 1:9 ratios showed very slow drug release due to high quantity of the PVP. It may be explained by the binding property of povidone which is utilized as binder in granulation process. High amount of binder produced very hard agglomerates after solvent evaporation which was partially responsible for retarded drug release.

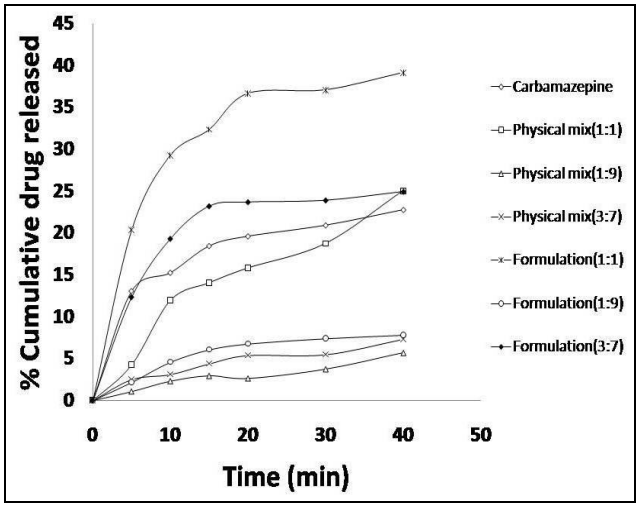

FIG. 6: DRUG RELEASE FROM PVP K30 FORMULATIONS (N=3, ERROR BARS NOT SHOWN TO ENSURE CLARITY)

Poloxamer 407 can act as gelling agent at high concentration and it can affect drug dissolution from solid dispersions. Drug release was very rapid (3 folds compared to drug in 5 min) compared to other two polymers at 1:1 ratio. But similar to PVP, higher amount of poloxamer did not facilitated drug release. When the poloxamer concentration was increased the drug remained dissolved in molten carrier but due to the gel barrier drug release was poor from the matrix **(Fig. 7**). Although the metastable form of the drug dissolves faster than the crystalline state, the dissolution rate depends on the drug–polymer ratio [28-30] in all cases. It is found that the drug and polymer

ratio is critical factor for dissolution enhancement. As dissolution is the rate limiting factor for the bioavailability of BCS class II drugs, little enhancement in solubility can greatly improve bioavailability due to the presence of different surface active agents in the alimentary tract.

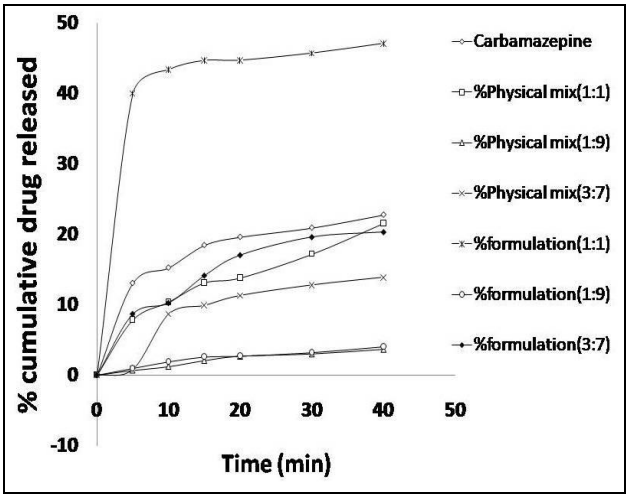

FIG. 7: DRUG RELEASE FROM POLOXAMER 407 FORMULATIONS (N=3, ERROR BARS NOT SHOWN TO ENSURE CLARITY)

Optical microscopy: Although dissolution rate for poorly water-soluble drug can be enhanced by converting the drug into its amorphous form [31] but it can be thermodynamically unstable, and under certain levels of heat and humidity, could recrystallize into a more stable, poorly water-soluble form [32]. Among the formulations tested, CBZ crystallized out of the formulations from poloxamer containing solid dispersions (**Fig. 8A, 8B**) after contact with aqueous media.

Poloxamers rapidly dissolved away from the solid dispersions and amorphous CBZ reverted back to its crystalline state. The FTIR spectra of poloxamer solid dispersions revealed that the drug has no molecular interaction with this polymer and it explains the emergence of immiscible crystals in the water. This rapid reversion from amorphous to crystal was not observed in case of HPMC and PVP K30 containing formulations.

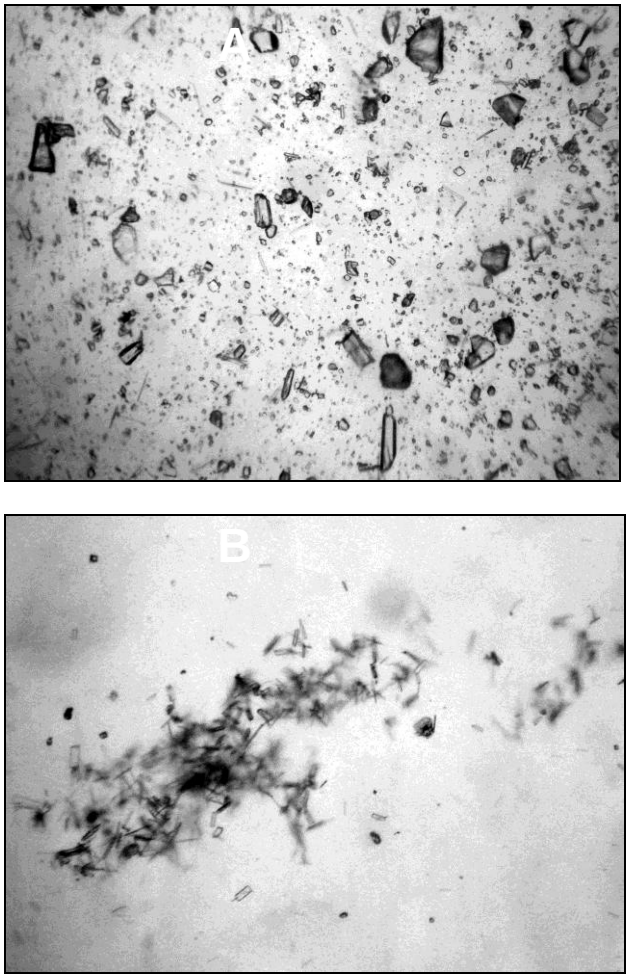

FIG. 8: RECRYSTALLIZATION OF CBZ AFTER ADDING WATER IN (A) DRUG-POLOXAMER (1:2) top one; (B) DRUG-POLOXAMER (1:9) bottom one; MIXTURE AS SEEN UNDER LIGHT MICROSCOPE

CONCLUSION: Solid dispersion is proven to be a useful technique to improve the solubility of poorly soluble drugs like CBZ. Thermal analysis indicated that among the polymers only PVP K30 form amorphous mixture with the carrier at different ratios. Among the three polymers, the solid dispersions with poloxamer 407 showed better solubility enhancement at 1:1 ratio compared to HPMC and PVP K30. At this particular ratio the drug retained its crystal lattice and molecular interaction was absent with Poloxamer. The later polymers showed tendency for molecular interaction with the drug and converted drug in to stable amorphous states which did not recrystallize upon contact with dissolution media.

Depending on experimental data it is concluded that the type of polymer and drug-polymer ratio are the critical factors for the development of solid dispersions.

ACKNOWLEDGEMENT: The authors are grateful to Renata Ltd. for providing DSC and FTIR facilities for the experiments.

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