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# Design and Development of Melt Sonocrystallization Technique for Carbamazepine

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## ABSTRACT

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The aim behind the development of particle design techniques is to alter the physicochemical, micromeritics and biopharmaceutical properties of the drug. Melt sonocrystallization a novel technique of particle engineering to enhance dissolution of hydrophobic and other drugs having solubility problem and to study its effect on crystal properties of drug. Melt sonocrystallization process was developed for the drug carbamazepine in which carbamazepine melt was poured in deionized water maintained at 60°C and simultaneously subjected to ultrasonic energy. The agglomerates obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature. The agglomerates obtained were evaluated by using percent drug content, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), X-Ray Powder Diffractometry (XRPD) and *In Vitro* drug release. The agglomerates with more or less porous surface were obtained. The agglomerates comprised of crystals having different crystal habits as needles, plates, and some hollow tubes. Saturation solubility increased with the treatment of ultrasonic energy. SEM and XRPD confirmed crystal habit changes.

Carbamazepine agglomerates has yielded, comprising of irregular in shape having rough surface with pores developed by MSC technique. The MSC Carbamazepine agglomerate has shown porous surface and cracks in the crystals of the drug. Saturation solubility increased with the treatment of ultrasonic energy. The entire agglomerates look somewhat spongy in nature and have shown significantly higher specific surface area and thereby increase in saturated solubility.

**Keywords**: carbamazepine; melt sonocrystallization; saturated solubility; dissolution enhancement surface topography; stability.

## INTRODUCTION

Particle engineering techniques are developing to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. A number of particle design techniques are reported such as spherical crystallization, extrusion spheronization, spray drying, solution atomization and crystallization by sonication where simultaneous crystallization and agglomeration occur[1-6]. But pharmaceutical processing techniques, which offer freedom from organic solvents, are preferred due to stringent global environmental concerns. Hence many reports are published on techniques such as melt granulation, melt extrusion, pastillation, melt dispersion, melt solidification (MST) and melt sonocrystallization (MSC) technique etc[7].

Ultrasound (US) was introduced in the traditional process of pharmaceutical technology to increase solubility of sparingly soluble drug from few years ago. Ultrasound was used principally to influence the initial nucleation stage of crystallization, which is width of the metastable zone is reduced and nucleation starts at a lower level of supersaturation. US can modify many materials, causing plastic deformation, moulding and welding. Since many materials of pharmaceutical interest are thermoplastic, US can also affect technological processes where these materials are involved. Sonocrystallization can be used to impart a variety of desirable characteristics to high value products[8].

One of the mechanical effects cause by ultrasonification is disaggregation or deagglomeration of the particle assembling. Cavitation is an important phenomenon of ultrasonication. The energy produced due to the collapse of bubbles at very high temperature was responsible for breaking of particles. The so generated shock waves can cause the particle collide into one another with great force since these are similar charge particles problem of agglomeration is greatly reduced[2,3,9].

Several attempts were made on application of ultrasonic energy during crystallization. US energy has been used to achieve nucleation at moderate super saturation during the crystallization process or terminal treatment to achieve deagglomeration and to obtain desired crystal habit. Ultrasound has been used to direct compaction, obtaining tablets of increasing hardness and glassy appearance, but also to prepare a new generation of granulates by milling of US - compacted matrices.[10] These powders show a modified release of the active drug, different to that of granulates

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obtained under a dry traditional compaction. US asserted compaction modified the physical structures of drug or excipients and ultrasound spray congealing to improve the drug release and compaction properties of drug. Ultrasound may also act on a liquid or melt mixture, besides effect on solid, causing cavitation and extreme molecular motion which divides the drop material in to a number of microdrops of narrow size range. Ultrasonication energy has been used to achieve nucleation at moderate super saturation during the crystallization process or terminal treatment to achieve deagglomeration and to obtain desired crystal habit[11].

Several theories on the mechanism of ultrasound on nucleation, cluster forming of molecules prior to nucleation and the interfacial impact between crystals and solution, have been proposed but the contribution of ultrasound to crystallization is still not fully understood.

In acoustic cavitation caused by ultrasonic waves various sized air or vapor bubbles are formed and they vibrate along the pressure waves.[12]

Cavitation can be in general defined as the generation, subsequent growth and collapse of cavities resulting in very high energy densities. Cavitation can occur at millions of locations in a reactor simultaneously and generate conditions of very high temperatures and pressures (few thousand atmospheres pressure and few thousand Kelvin temperature) locally, with the overall environment being that of ambient conditions[13].

The effect of application of US energy on the properties of Melt Sonocrystallized Carbamazepine (MSC) was characterized by Scanning Electron Microscopy (SEM), Differential Scanning Calorimetery (DSC), X-ray Powder Diffraction (XRPD) and Saturated Solubility Study.

## MATERIALS AND METHODS

### Materials:

Commercial carbamazepine anhydrate was gift sample from Pharma R &D Cipla Ltd. Vikroli, Mumbai.). Potassium dihydrogen phosphate and sodium hydroxide of analytical grade were purchase from from Loba Chemie Pvt. Ltd. Mumbai.

### Method of preparation:

The drug (2 g) was melted in a porcelain dish on a paraffin oil bath maintained at 193°C. Molten drug mass was poured in a vessel containing 100 ml of deionized water maintained at 45 to 50°C using cryostatic bath (Haake Phoenix C25P, Germany) and sonicated for 15 minutes at an amplitude of 75 % using probe ultrasonicator (Sonics & aterials Inc. Vibra Cell model VCX 750.). Agglomerates were filtered and the obtained product was dried at room temperature overnight. Polyethylene glycol was used as a plasticizer to reduce the viscosity of molten mass. The fraction of MSC carbamazepine agglomerates were used for saturated solubility study.

## CHARACTERIZATION

### Solubility determination:

To evaluate increase in solubility of MSC carbamazepine, saturation solubility measurement was carried out. An excess amount of MSC carbamazepine was added to 10 ml of distilled water maintained at 37°C and shaken for more than 48 h. The solutions were then centrifuge at 7000 rpm for 15 min. Supernatant was suitably diluted and analyze by UV-Spectrophotometer at 285 nm.

### Surface topography:

Scanning electron microphotographs of pure crystalline drug and MSC agglomerates were obtained using optical microcopy and scanning electron microscope (Cambridge Stereoscan 120 UK) Samples were coated with gold film under vacuum using a sputter coater (SPI Sputter™ Coating Unit, SPI Supplies, Division of Structure Probe, Inc., PA, and USA) and then investigated. The photomicrographs were obtained at different magnification to study the surface topography.

### Differential Scanning Calorimetry (DSC):

Thermograms of pure crystalline drug and MSC carbamazepine agglomerates were obtained by using a differential scanning calorimeter equipped with computer analyzer (Mettler Toledo 821e, Switzerland). The powder samples of (3-7 mg) were hermetically sealed in aluminum pans Samples were heated in a nitrogen atmosphere at a heating rate of 10 ºC/min over the temperature range of 60-200 ˚C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min.

### Powder X-ray Diffractometry (PXRD):

Samples of carbamazepine and MSC carbamazepine were prepared by pulverizing in a mortar Powder X-ray diffraction (PXRD) patterns were traced employing an X-ray diffractometer (Philips PW 1729 Almelo, Netherland.) The samples were analyzed over 2θ range of 5.010-39.990˚C with scanning step size of 0.020˚ (2θ) and scan step time of 1 s. The crystalline properties of carbamazepine and MSC carbamazepine were studied by X-ray powder diffraction. The samples were irradiated with monochromatized Cu Kα radiation (1.542 A˚) and analyzed at 2θ between 2˚ and 60˚. The voltage and current used were 40 kV and 40mA, respectively. The range and the chart speed were 2 × 104 cps and 10 mm/2, respectively.

**Fourier Transform Infra Red Spectroscopy (FTIR)**

FT-IR spectra of Carbamazepine and Optimazed batch (MSC Batch 2) were recorded on Shimadzu FTIR – 8400 spectrophotometer (Shimadzu Corporation, Tokyo, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. The pellets were prepared in KBr press using mixture of sample and KBr in 1:10 ratio. Each spectrum was derived from single average scans collected in the region 400 – 4000 $cm^{-1}$ at spectral resolution of 2 $cm^{-1}$ and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

## RESULTS AND DISCUSSION

Melt sonocrystallization is a novel particle design technique which involves application of ultrasonic energy to the soft viscous or molten mass, dispersed in suitable dispersion media maintained at constant or suitable temperature, with or without agitation. Carbamazepine has problem of solubility. Ability of this technique to cause significant changes in crystal properties has stimulated us to exploit the potential further.

**Preparation of Carbamazepine Agglomerates by Melt Sonocrystallization Technique:**

**Preliminary Studies:**

Melt Sonocrystallization (MSC) process was designed for Carbamazepine. It was observed that the melt was immediately forming a layer on the surface of the medium when low level of sonic energy was applied. As we increase the level of sonic energy, small agglomerates were formed from the melt at the top of the liquid surface. Time of sonication gives significant effect on the percentage yield of the agglomerates. Processing was carried at room temperature, which is well above the Tg of Carbamazepine (280 °C), so that US energy can apply to the melt for longer time.

**Percentage yield and drug loss in aqueous phase:**

The process yield of various batches was in the range of 83 – 96 % w/w. Loss of drug in aqueous phase was found to be less than 1 % w/w for different sonicated batches. Also it showed increase in loss of drug with the increase in the sonication time and amplitude. It might be due to the micronization of crystals which facilitates the solubilization of the drug in aqueous phase. As the sonication time and amplitude increase number of micronized particle also increases so that the yield of the drug gets reduced. Percentage yield of all the batches were shown in Table No 1. The changes in the processing variables like sonic energy and time of sonication were found to give different results in agglomerates. This study was designed using $3^2$ factorial design, using variables as shown in Table No. 1. Maheshwari et al. reported novel melt sonocrystallization technique that is a single step and solvent free technique to obtained particle with improve micromeritics and dissolution properties. But Carbamazepine shows shear dependent crystallization is difficult to process. Polyethyleneglycol (PEG) was incorporated in Carbamazepine melt to reduce the viscosity of melt, which not only facilitated pouring of Carbamazepine but also increase wettability and high exposure of ultrasonic energy to Carbamazepine and increased percentage yield.

**Table 1: Experimental variables and their coded Levels.**

| Variables | Level |
|---|---|
| Time of sonication | -1 (30 sec), 0 (2 min), +1 (4 min) |
| Amplitude | -1 (30 sec), 0 (2 min), +1 (4 min) |

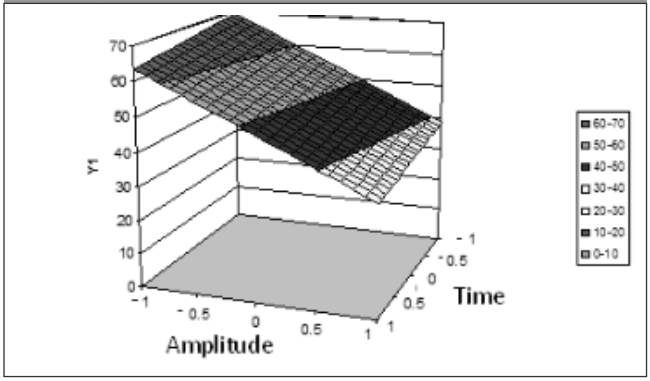
**Effect of variables on Percentage Yield:**

Effect of variables on the percentage yield is shown in fig. 1 and coefficient values for percentage yield are in Table No. 1. It revealed that yield decreases with increase of time and amplitude. When time and amplitude was increased the micronization of the particle may takes place that will cause reduction in the yield. At intermediate level of time and amplitude it shows maximum percentage yield.

**Effect of variables on Solubility:**

Effect of variables on the solubility was shown in fig.2. A curvilinear response was obtained with respect to the time and the amplitude was observed. It revealed that solubility was increased with increase of amplitude at a certain level after that solubility gets decreased because the enhancement of the recrystallization of the drug and with respect to time solubility gets decreased. More time to drug to recrystallize may be due to increase in time of sonication. As the amplitude increases the solubility increases to a certain level after that it decreased may be due to enhancement of recrystallization. As the time increased the solubility gets decreased may be due to more time of sonication gives more time to recrystallize.

**Fig. 1: Response surface plot showing effect of variables on Percentage Yield Y = 50.96-15.40X1-2.96X2.**



**Surface topography:**

SEM photography and typical surface morphology of pure crystalline drug and MSC agglomerates were shown in fig. 3 and fig. 4.

SEM photograph of pure carbamazepine (fig. 3) shows plate like structure with white in appearance while SEM photograph of MSC carbamazepine agglomerates (fig. 4) shows somewhat more or less smooth outer surface and found to be physicaly stable.

**Powder X-ray Diffractometry (PXRD):**

Powder X-ray diffraction pattern of pure crystalline drug was shown in fig. 5. In this figure characteristic intensity peak was found at specified values. PXRD patterns of the MSC carbamazepine agglomerates have shown slight difference as compared to the pure crystalline drug which was showing same characteristic intensity peak but the value of intensity gets somewhat decreased as compared to pure drug. This decrease in intensity of peaks leads conversion to amorphous form of the drug. The decreased intensity of peak shows change in crystal habit.

**Differential Scanning Calorimetry:**

DSC thermogram of pure Carbamazepine and MSC Carbamazepine agglomerates obtained were shown in fig. 6. DSC curve of pure drug showed endotherm at 170.51˚C with normalized energy 67.43 (J/g) is ascribed to drug melting. The thermogram of MSC (B2) batch Carbamazepine agglomerates shows decrease in normalized energy as compare to pure crystalline drug. The onset and end set temperature and enthalpy of melting for each sample has given in Table No.4.

Transitions in DSC thermograms of Carbamzepine and MSC (B2) batch, there is no significant difference in the melting point temperature. The melting endotherm is sharp but asymmetric; it may be due to presence of different crystal structure. These observation were in confirmation with change thermal properties of Carbamzepine after sonication, where asymmetry, enthalpy change was ascribed different crystal size and crystal habit of Carbamazepine.

**Drug Release Study:**

The release rate of carbamazepine and MSC carbamazepine were studied by using USP Type II dissolution test apparatus Electrolab TDT-06P (Mumbai, India), containing 900ml of 1% SLS in distilled water and maintained at 37ºC ± 0.5ºC and stirred at 50rpm. Samples were collected periodically and replaced with a fresh dissolution medium. Analysis of data was done using PCP Disso v2.08 software, (Poona College of Pharmacy, Pune, India). Release pattern of pure drug and MSC agglomerates were as follow.

Fig. 2: Response surface plot showing effect of factorial variables on solubility. Solubility = 111.60 + 29.74X1 + 9.5X2 -18.17$X_1^2$

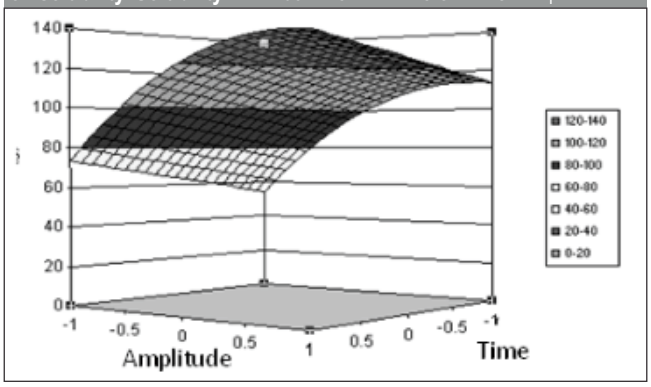



Table 2: Various batches of MSC and there various Variables

| Batch Code | Drug (mg) | Time (sec) | Amplitude (W)% |
|---|---|---|---|
| A1 | 200 | 30 | 30 |
| A2 | 200 | 30 | 75 |
| A3 | 200 | 120 | 30 |
| A4 | 200 | 120 | 75 |
| A5 | 200 | 240 | 30 |

Table 3: Percentage yield of formulations

| Batch code | % Yield |
|---|---|
| A1 | 81.50 |
| A2 | 95.50 |
| A3 | 86.33 |
| A4 | 92.02 |
| A5 | 95.48 |
| A6 | Pure Drug |

Table 4: Transitions in DSC thermograms of Carbamzepine and MSC (B2) batch

| Sample | Normalized energy(J/g) | Onset temperature ($^0$C) | Endset temperature ($^0$C) | Peak temperature ($^0$C) |
|---|---|---|---|---|
| Carbamazepine | 67.43 | 170.27 | 173.84 | 173.51 |
| MSC batch (B2) | 60.15 | 169.64 | 172.44 | 175.47 |

Table 5: Percent drug release from Carbamazepine agglomerates

| Time | | Sample | | | | | |
|---|---|---|---|---|---|---|---|
| h | min | A1 | A2 | A3 | A4 | A5 | A6 (Pure drug) |
| - | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| - | 15 | 10.32 | 20.2 | 19.43 | 14.1 | 17.3 | 95.94 |
| - | 30 | 20.87 | 32.02 | 22.51 | 28.36 | 22.20 | 28.02 |
| 1 | 60 | 38.32 | 65.31 | 26.92 | 46.19 | 43.43 | 50.0 |
| 2 | 120 | 63.24 | 84.28 | 34.75 | 65.76 | 57.24 | 64.03 |
| 3 | 180 | 74.97 | 99.06 | 37.95 | 78.05 | 71.49 | 87.37 |

**Fig. 3: SEM photograph of pure carbamazepine at A) 3,000 X, B) 10,000 and C) 20,000 X**

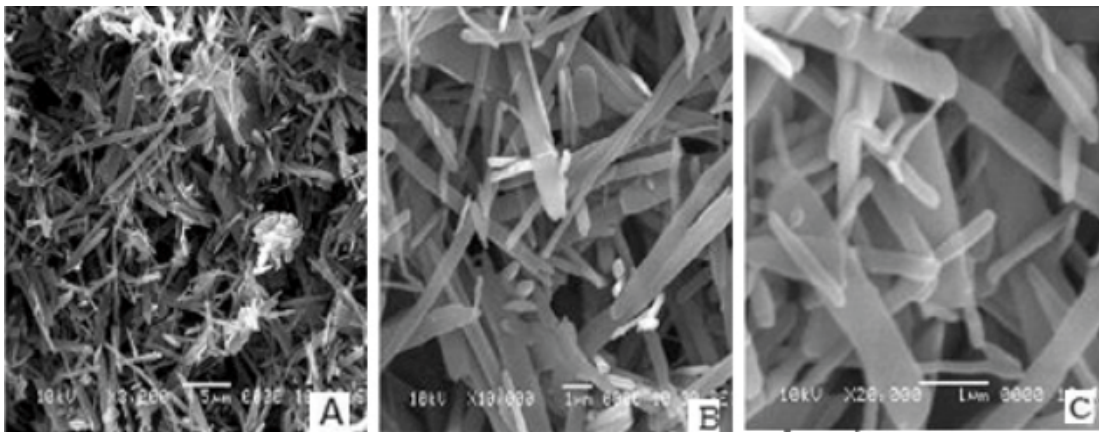
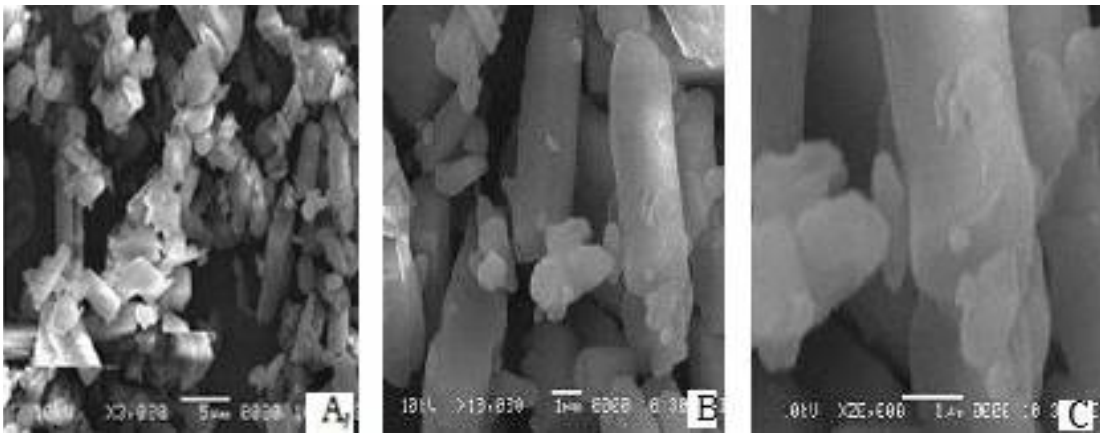


**Fig. 4: SEM photograph of MSC carbamazepine at A) 3,000 X, B) 10,000 and C) 20,000 X**



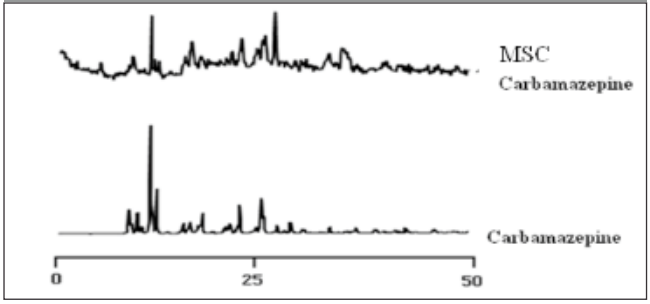
The drug release pattern for different batches of MSC Carbamazepine was carried out in 1% SLS in distilled water. The release pattern was shown in Table No. 5. The optimized batch A2 was found to be more uniform and provided better-controlled release profile. The percent drug content of batch A2 was found to be maximum and was depends upon the time and amplitude. At intermediate level of time and amplitude it shows maximum percentage yield.

Carbamazepine is constant over all the above batches. The optimized batch (A2) was found to give maximum drug release (99.06%) at 180 min. as compared to other batches and pure drug.

**Stability study of MSC (A2) batch:**

To study stability of formed MSC (A2) batch carbamazepine agglomerates was determined on storage at room temperature**.** In the present study, accelerated stability studies were performed at 40°C/ 75 %RH as per the ICH guidelines.

**Fig. 5: X-ray Diffraction Pattern of Carbamazepine and MSC Carbamazepine**



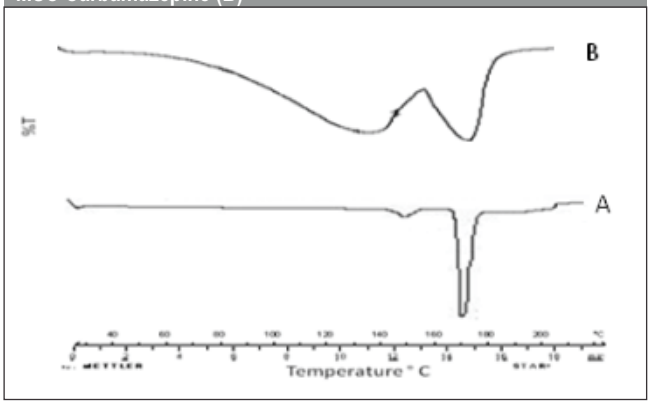

Based on the result (Table No. 6) of initial characterization the MSC (A2) batch was thought to be the superior**.** In case of the dissolution rate of MSC (B2) batch by using dissolution medium 1% SLS in water, at 50rpm, there was no significant changes over the period of 1 month and 2 months. Thus carbamazepine agglomerates prepared by MSC can be stable up to 2 month.

**Table 6: Stability Analysis Repot of MSC Carbamazepine agglomerates**

Product Name: MSC Carbamazepine agglomerates — Mfg. Date: 16.06.2011
Strength: 178.5 — Date In: 21.06.2011
Batch No.: A2 — Pack: HDPE (RW)
Batch Size: 500 mg

| Sr. No. | Test | Initial | 40 °C/75%RH | |
|---|---|---|---|---|
| | | | 1 Month | 2 Month |
| 1. | Appearance | White to off white | No Change | No Change |
| 2. | Dissolution Test (Media- 1% SLS in water, 50 rpm, 900 mL) | | | |
| | 15 min. | 20.21±1.9 | 20.01±1.2 | 21.06±1.7 |
| | 30 min. | 32.02 ±1.5 | 31.62±1.5 | 32.61±1.3 |
| | 60 min. | 65.31 ±2.3 | 63.57±1.9 | 64.46±1.6 |
| | 120 min. | 84.28 ±2.5 | 82.93±1.7 | 84.09±1.8 |
| | 180min. | 99.06 ±1.9 | 98.86±0.5 | 98.27±1.2 |
| 3. | Drug Content | | | |
| | | 96.39±0.5 | 95.22±0.3 | 95.88±0.2 |

**Fig. 6: DSC thermograms of Carbamazepine (A) and MSC Carbamazepine (B)**




### Fourier Transform Infra Red Spectroscopy (FTIR)

State of drug molecules with excipients was determined using FT-IR. fig. 7 showed IR spectra of carbamazepine (pure drug) and optimized batch (MSC batch 2) respectively. There is no shift of peaks after interaction with excipients of the drug substances; indicating no change in chemical structure of drug.

## CONCLUSION

Carbamazepine agglomerates has yielded, comprising of irregular in shape having rough surface with pores developed by MSC technique. The MSC Carbamazepine agglomerate has shown porous surface and cracks in the crystals of the drug. The entire agglomerates look somewhat spongy in nature and have shown significantly higher specific surface area and thereby increase in saturated solubility.

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**Fig. 7: FTIR Spectra of Carbamazepine (A) and MSC Batch (B2)**

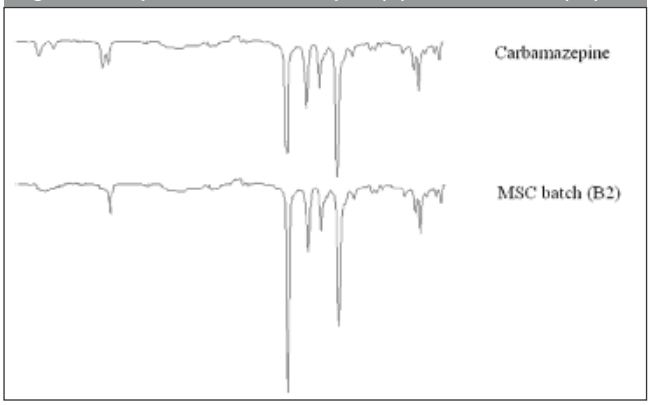
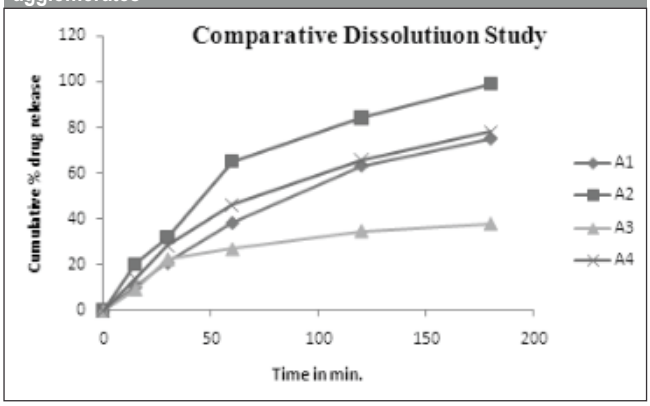



**Fig. 8: Comparative dissolution profile of different Carbamazepine agglomerates**

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