RESEARCH ARTICLE

Effect of variables on Naproxen Agglomerates Engineered by Melt Sonocrystallization

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ABSTRACT

The study deals with melt sono crystallization (MSC) technique for the preparation of agglomerates of naproxen. Purpose is to improve the solubility and compressional properties of naproxen. In the present study naproxen agglomerates prepared by MSC and melt solidification technique (MST) and the effect of variables like time of sonic energy, amplitude and temperature of the deionized water on agglomerates were compared. The technique involves application of ultrasonic energy to the soft viscous or molten mass, dispersed in suitable dispersion media maintained at suitable temperature, with or without agitation. The technique developed for naproxen using 3^3 factorial designs. Obtained agglomerates were evaluated and compared on the basis of true solubility, scanning electron microscopy (SEM), Fourier transformed infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), heckle plot, particle size distribution (PSD), drug release, angle of repose, bulk and tap density. The improved compressional and solubility properties were confirmed by application of MSC. As the time of sonication and temperature was increased, the percent yield, dissolution rate and true solubility were found to be decreased. Intermediate level of time of sonication, low level of amplitude and temperature gives maximum release of drug.

Keywords: Melt Sono crystallization (MSC), Melt solidification technique (MST), 3^3 factorial design, compressibility and true solubility.

Introduction:

Particle engineering techniques are developed to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. Development of engineered drug particles has become major research due to limitations of conventional particle formation and pretreatment processes in fine-tuning the required characteristics. [1] Number of particle design techniques are reported, such as micronization [2], spray drying [3, 4], spray freezing [5], supercritical fluid processing [6], spherical crystallization [7], solution atomization and crystallization by sonication (SAXS) [8], sonocrystallization [9] and MSC [10, 11] are introduced to provide particles with novel physicochemical properties. Sonocrystallization, the application of ultrasonic energy during particle formation has been reported in the last decade. Sonocrystallization 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. [12-15] The experimental results indicate that the variation of ultrasonic energy, duration or mixture volume can be used to yield advantageous control of mean size and distribution of resulting crystals. [16, 17] Ultra sound (US) assisted compaction of various drugs with excipients such as β-cyclodextrin and Eudragit. Significant changes in the crystal properties were observed due to US treatment. [18] MSC techniques, a particle engineering technique are developed with the intension to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. This work attempts to explore further applicability of melt Sonocrystallization on naproxen.

Naproxen(S)-(+)-6-methoxy-methyl-2-naphthaleneacetic acid, (NAP) is a non-steroidal anti - inflammatory drug whose very low water solubility and its oral bioavailability is limited by the dissolution rate (BCS class II drug). [19] Naproxen has a pKa of 4.5, and its low aqueous solubility contributes to high variability in absorption after oral administration. Naproxen exists as long plate - shaped crystals that impart density and compressibility, which complicates its processing into solid dosage forms. [22-26] These

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crystals result in poor blend uniformity, have a tendency to separate out, agglomerate and form a monolithic mass upon compression in the tablet die, making it difficult to process small quantities for formulation. The aim of the present study was to investigate the effect of three independent processing variables i.e. time, amplitude of sonication and temperature of deionized water, on the properties of obtained particles. These variables were analyzed systematically through statistical factorial 3^3 design. The improved compressional and solubility properties were confirmed by application of MSC. To see the effect of MSC processing variables on agglomerates, MSC batches were compared with melt solidified batches. Melt solidified agglomerates were obtained at different processing temperature and compared on basis of percentage yield, true solubility, surface topography, Fourier-transform infra-red, differential scanning calorimetry, X-ray powder diffraction, heckle plot, particle size distribution, drug release, angle of repose, bulk density and tap density.

Materials and Methods:

1. Materials:

Naproxen was a gift sample from FDC Limited, Mumbai, India. Sodium hydroxide and potassium dihydrogen phosphate and all other excipients were of analytical grade (Merck, Mumbai, India).

2. Methods:

2.1 Preparation of MSC Naproxen agglomerates

The Naproxen (500 mg) was melted using a paraffin oil bath maintained at 160^{0}C. The molten mass obtained was poured in a vessel containing 100 mL of deionized water maintained at constant temperature using cryostatic bath (Haake Phoenix C25P, Karlsruhe, Germany), and sonicated for three different time level at three different level of amplitude using probe ultrasonicator (Sonics and materials Inc., Vibra cell, model VCX 750, Connecticut, USA). The product obtained after solidification of the dispersed droplets was separated by filtration and dried at room temperature.

2.2 Preparation of Naproxen beads by MST

Naproxen (2g) was melted on a paraffin oil bath maintained at 160^{0}C. The molten mass was poured in 100 ml aqueous phase and system was stirred continuously, using constant speed stirrer with propeller blade (Eurostar power control-visc, IKA Labortecnik, Germany). The processing temperature was maintained at 5^{0}C, 25^{0}C and 40^{0}C respectively and the speed of agitation was 600 rpm.

2.3 Effect of Variables

To study the effect of variables, batches were prepared using 3^3 factorial designs. Time of sonication, amplitude and temperature of the deionized water were selected as 3 independent variables.

Table 1: Experimental variables and their coded levels

Variables	***Levels***		
Time of sonication (sec)	-1 (30)	0 (60)	+1 (90)
Temperature of water (^{0}C)	-1 (5)	0 (25)	+1 (40)
Amplitude (W %)	-1 (25%)	0 (50%)	+1 (75%)

Table 2: Batches of MSC and there various variables

Batch code	Drug (mg)	Time (Sec.)	Temp (^{0}C)	Amplitude (W)%
A 1	500	30	5	25
A 2	500	30	5	50
A 3	500	30	5	75
A 4	500	30	25	25
A 5	500	30	25	50
A 6	500	30	25	75
A 7	500	30	40	25
A 8	500	30	40	50
A 9	500	30	40	75
B 1	500	60	5	25
B 2	500	60	5	50
B 3	500	60	5	75
B 4	500	60	25	25
B 5	500	60	25	50
B 6	500	60	25	75
B 7	500	60	40	25
B 8	500	60	40	50
B 9	500	60	40	75
C 1	500	90	5	25
C 2	500	90	5	50
C 3	500	90	5	75
C 4	500	90	25	25
C 5	500	90	25	50
C 6	500	90	25	75
C 7	500	90	40	25
C 8	500	90	40	50
C 9	500	90	40	75

3. Characterization

3.1 Percent yield and drug loss

MSC naproxen agglomerates were weighed after drying and percent yield was calculated. Loss of drug in aqueous phase during the process of solidification was determined spectrophotometrically by measuring absorbance of supernatant at 230 nm.

3.2 True solubility determination

To evaluate increase in solubility with time of MSC agglomerates, true solubility measurement was carried out. An excess amount of MSC (-40/+60#) agglomerates was added to 100 ml of distilled water maintained 37^0C and shaken. At regular time interval up to 24 hour, 2 ml sample was withdrawn and solutions were then centrifuged at 7000 rpm for 10 min. Supernatant was suitably diluted and analyzed by UV-Spectrophotometer at 230 nm.

3.3 Particle Size Distribution (PSD)

Particle size distribution of MSC naproxen agglomerates was studied by sieve analysis technique using Ro – tap sieve shaker (Labtroics, Pune, India). Different number sieve were placed vertically. The sieves were placed according to sieve number in ascending order.

3.4 Fourier transformed infrared spectroscopy (FT-IR)

FT - IR spectra of pure crystalline drug, MSC and MST naproxen agglomerates were obtained on JASCO V5300 FT – IR. The pellets were prepared on KBr press (Spectra Lab, Pune, India). The spectra were scanned over the wave number range of 3600 - 400 cm^{-1}.

3.5 Differential scanning calorimetry (DSC)

Thermograms of pure crystalline drug and powder of different MSC agglomerates were obtained using a Mettler- Toledo DSC 821^e instrument equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder samples were hermetically sealed in aluminum pans and heated at a constant rate of 10^0C/min, over a temperature range of 20 to 200^0C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml per min.

3.6 X-ray powder diffractometry (XRPD)

The XRPD patterns of samples of pure naproxen and different batches of MSC naproxen were recorded by using a Philips PW 1729 X - ray diffractometer. Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2 to 70^0 (2θ). The voltage and current used were 30 kV and 30 mA, respectively.

3.7 Scanning electron microscopy

Scanning electron microphotographs of pure crystalline drug, MST and MSC naproxen agglomerates were obtained at different level of variables were obtained using JEOL JSM 6360 JAPAN. The samples were coated with thin gold–palladium layer by sputter coater unit. Scanning electron microscope was operated with an acceleration voltage of 10 kV.

3.8 Dissolution studies

The dissolution of MSC and MST naproxen agglomerates was studied using USP 26 Type I dissolution test apparatus (Electrolab TDT-06P, India). 300 mg of–40/+60# fraction of naproxen powder and MSC agglomerates were placed separately in the dissolution vessel containing 900 ml phosphate buffer (pH 7.4) maintained at 37±0.5^{0}C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41, concentration of naproxen was determined spectrophotometrically at 230 nm. Analysis of data was done using 'PCP Disso v3.' software, India.

3.9 Bulk Density (ρ_f) and Tap Density (ρ_t)

Pure drug, MST and MSC naproxen agglomerates were subjected to Bulk and Tap density determination using (Tap density tester USP II Electrolab TDP-1020, India). Tapping cylinder method was used for determining bulk and tap density. Initial volume (Bulk volume) and the volume after 50 tapings (Tap volume) were measured. The Bulk and Tap densities, Haussner's ratio and Carr's Index were calculated.

Haussner's Ratio = ρ_t / ρ_f

Carr's Index = $[(\rho_t - \rho_f) / \rho_t] * 100$

3.10 Determination of angle of repose

The flowability of the pure drug, MST and MSC agglomerates were assessed by determination of the angle of repose (θ) using fixed funnel method). [27]

3.11 Heckel plot study

The compressibility was studied using the Heckel equation. [28-29] Due to poor compaction behavior of naproxen, it has to granulate in most cases before tabletting; therefore this study was carried out only on MSC naproxen agglomerates. Powder (500 mg) was compressed on hydraulic press (Spectra Lab, Pune, India.) using a 13 mm flat faced punch and die set, at pressures 20, 40, 60, 80, 100 and 120kg/cm^2. The compacts were stored in vacuum chamber for 24 hour to allow elastic recovery and hardening. The weight, diameter and thickness were also determined. The data was processed using Heckel equation and mean yield pressure was determined.

$\ln (1/1-D) = kP + A$

Where D is relative density, k and A are constants and P is yield pressure.

Results and discussion:

During preliminary study, it was observed that the melt was immediately forming a layer on the surface of the medium when low level sonic energy was applied. Small agglomerates were formed from the melt at the top of liquid surface, as we increase the level of sonic energy. Time of sonication gives significant effect on the percentage yield of the agglomerates. Temperature of the dispersing media gave significant effect on the solubility of the agglomerates when it was selected near to Tg of the drug. The changes in the processing variables like sonic energy, time of sonication and temperature of dispersion media were found to give different results in agglomerates. This study was designed using 3^3 factorial designs and MSC batches were compared with melt solidified batches.

1. Percent yield and drug loss

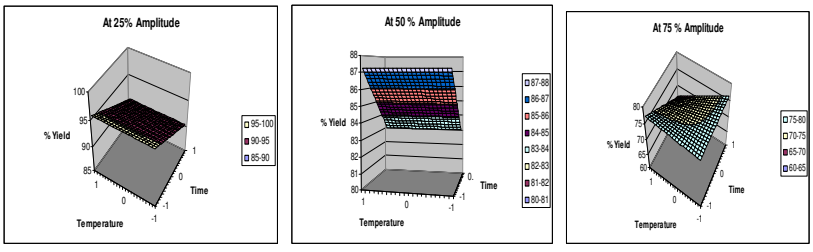
The percent yield of various batches was in the range of 67–97% (w/w). Loss of drug in aqueous phase was found to be less than 2% (w/w) for different sonication batches, although it showed increase in loss of drug with the increase in the sonication time and amplitude, it might be due to the micronization of crystals which facilitates the solubilization of the drug in aqueous phase, so that the yield of the drug gets reduced. Percent yield of all the batches were shown in **Table 3**.

Table 3: Percentage yield of all the MSC batches.

Batch code	% Yield	Batch code	% Yield	Batch code	% Yield
A 1	96.48	B 1	93.02	C 1	90.53
A 2	85.50	B 2	83.50	C 2	83.57
A 3	74.33	B 3	77.69	C 3	76.22
A 4	96.02	B 4	95.41	C 4	90.70
A 5	82.44	B 5	86.86	C 5	87.30
A 6	78.50	B 6	72.42	C 6	70.22
A 7	94.25	B 7	92.92	C 7	88.43
A 8	84.23	B 8	85.00	C 8	84.00
A 9	75.57	B 9	74.53	C 9	66.23

Effect of variables on percent yield:

Effect of temperature and time on the yield was shown in **Fig. 1**. A linear response with respect to the time and the temperature was observed. It revealed that yield decreases with increase of time. Temperature was not given effect on yield at low level of amplitude i.e. at 25%. Same result was obtained at 50 % Amplitude.

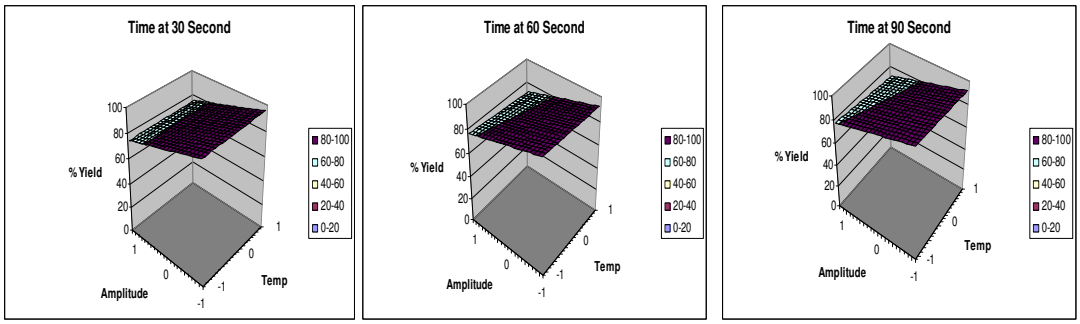


(a) (b) (c)

Figure 1: Effect of time and temperature on % yield of MSC agglomerates at (A) 25%, (B) 50%, and (C) 75% Amplitude.

At 75% amplitude yield was slightly increased with respect to time may be due to enhancement of recrystallization of naproxen. As the time and temperature was reached to its maximum level, yield of the agglomerates was minimum. By comparing all these, the yield is maximum at low level of amplitude.

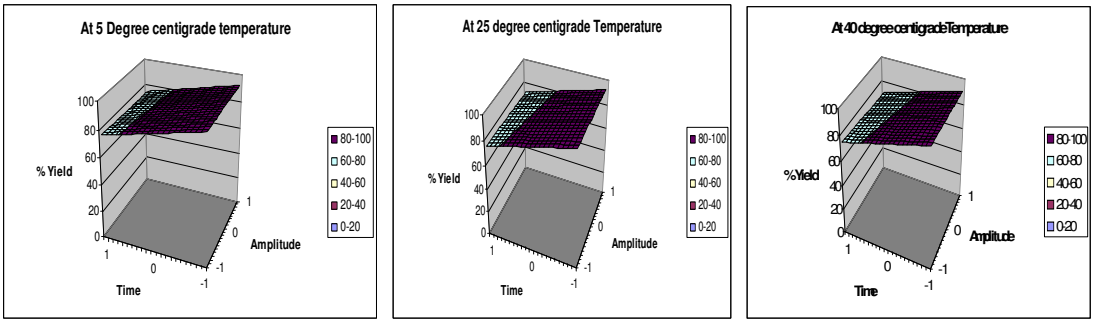
Effect of amplitude and temperature on % yield was shown in **Fig. 2**. When time was at 30 second a linear response with respect to amplitude and temperature was obtained. It revealed that yield was decreased with respect to increase in amplitude. At 60 second and 90 second temperature as well as amplitude showed there effect on yield, as the temperature and amplitude increased yield was decreased; it may be due to the increase in the solubility and micronization of the drug.



(a) (b) (c)

Figure 2: Effect of amplitude and temperature on % yield of MSC agglomerates at time A) 30 seconds B) 60 seconds C) 90 seconds.

Effect of time and amplitude on the yield is shown in **Fig. 3**. When temperature was at 5^{0}C a linear response with respect to the time and the amplitude was observed. It revealed that yield decreases with increase of time and amplitude. Same results were obtained at 25^{0}C and 40^{0}C. When time and amplitude was increased the micronization of the particle may takes place that will cause reduction in the yield. At 40^{0}C temperature the yield of agglomerates are comparatively less than the 5^{0}C temperature.



(a) (b) (c)

Figure 3: Effect of time and amplitude on % yield of MSC agglomerates at A) 40^{0}C, B) 25^{0}C, C) 40^{0}C.

2. True solubility

True solubility of MSC naproxen agglomerates was measured at room temperature. A significant increase was observed in true solubility at a certain level of sonication time and amplitude **(Table 4)**.

Table 4: Results of true solubility of MSC naproxen agglomerates

Batch code	Solubility	Batch code	Solubility	Batch code	Solubility
A1	99.05	B1	137.20	C1	76.69
A2	67.35	B2	102.55	C2	58.70
A3	62.10	B3	45.76	C3	48.50
A4	90.62	B4	48.97	C4	54.62
A5	65.36	B5	75.50	C5	58.58
A6	80.61	B6	80.53	C6	36.67
A7	37.42	B7	65.97	C7	62.88
A8	44.32	B8	97.62	C8	80.50
A9	43.91	B9	48.40	C9	70.65

Responses obtained from the batches factorial designed experiments were subjected to multiple regression analysis using unistat software. The data was fitted to the equation:-

$$Y = \beta_o + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{11}X_1X_1 + \beta_{22}X_2X_2 + \beta_{33}X_3X_3 + \beta_{123}X_1X_2X_3$$

Insignificant effects were removed by backward elimination method and adequacy of fitted model was checked by ANOVA. The results of multiple regression analysis are summarized in **Table no. 5** and the response surface plots were generated.

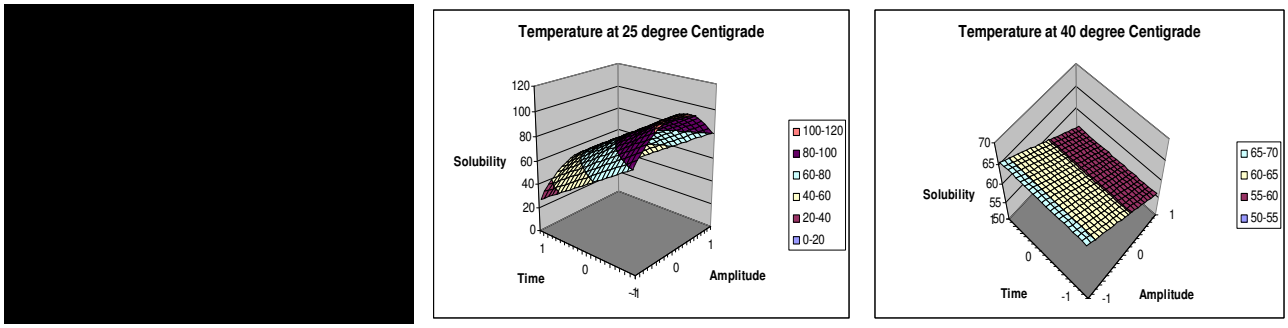
Table 5: Summary of regression results for the measured responses

Sr. No.	Parameters	Coefficients							
		B_0	B_1	B_2	B_{11}	B_{22}	B_{12}	r^2	P
1.	**% Yield**								
	At 5°C	84.53	-0.99	-8.63				0.9963	0.0000
	At 25°C	84.43	-2.45	-10.16				0.9843	0.0002
	At 45°C	82.79	-2.56	-9.87				0.9782	0.0000
	At 25%	93.08	-2.84					0.9878	0.0001
	At 50%	85.12	-2.11					0.9672	0.0007
	At 75%	73.95	-2.60	-1.96			-2.83	0.9182	0.0018
	At 30sec.	85.27		-9.72				0.9782	0.0023
	At 60sec.	84.59	-2.48	-9.45				0.9082	0.0045
	At 90sec.	84.95	-3.56	-9.45				0.9378	0.0045
2.	**True solubility**								
	At 5°C	95.17		-26.09	-26.08			0.7902	0.0302
	At 25°C	80.56		-20.47	-14.92			0.8140	0.0278
	At 45°C	60.83	-5.18					0.9163	0.0023
	At 25%	79.26	-17.24					0.9472	0.0019
	At 50%	91.89			-29.49		11.31	0.7982	0.0042
	At 75%	57.13		-7.85				0.9734	0.0006
	At 30sec.	70.74	-1.47	-13.43				0.9743	0.0004
	At 60sec.	77.02					16.96	0.8432	0.0072
	At 90sec.	49.95	-2.78	-6.39				0.8903	0.0000

Effect of variables on solubility:

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. It may be due to more time gives to drug to recrystallize.

At intermediate level of temperature the effect of amplitude was same as low level of temperature, as the amplitude increased the solubility increased 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. At higher level of temperature the solubility of the drug decreased as the amplitude increased **(Fig. 4)**.

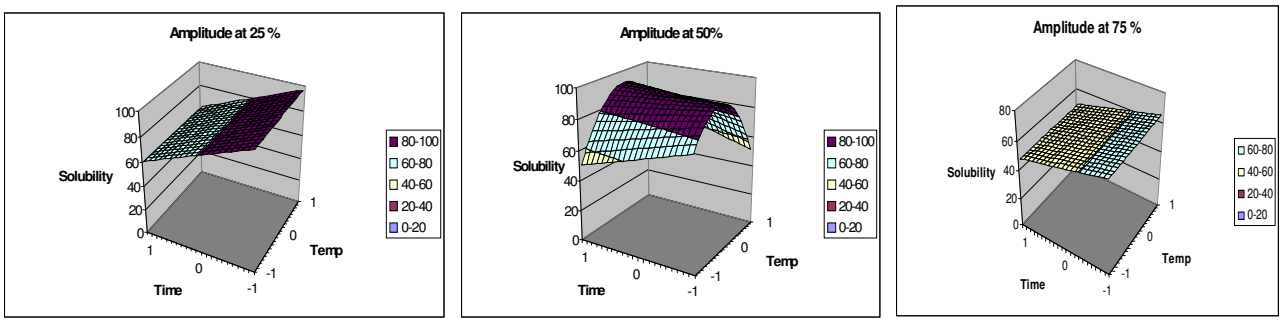


(a) (b) (c)

Figure 4: Effect of time and amplitude on solubility of MSC agglomerates at (A) 5°C, (B) 25°C and (C) 40°C.

Solubility is independent to time at higher level of temperature this might be due to that drug immediately recrystallized as we pour the melt in the dispersion media.

When amplitude was at 25 % a linear response with respect to the time and the temperature was observed. It revealed that solubility decreases with increase of time. At low level of amplitude temperature does not show effect on solubility. When amplitude was at 50%, a curvilinear response was obtained with respect to time and temperature **(Fig. 5)**.



(a) (b) (c)

Figure 5: Effect of time and temperature on solubility of MSC agglomerates at A) 25%, B) 50%, C) 75 % Amplitude

As the amplitude gets increased at a certain level after that solubility gets decreased, and with respect to time the solubility was get decreased as time increased. It may be due to regeneration of crystals. At higher level of sonication the solubility gets decrease as the sonication time increased.

Where time was at 30 second a linear response with respect to amplitude and temperature was obtained. It revealed that solubility gets decreased as the temperature of the system increased.

(a) (b) (c)

Figure 5: Effect of amplitude and temperature on solubility of MSC agglomerates at A) 30 second, B) 60 second, C) 90 seconds

At higher level of time 60 second the solubility gets decreased as temperature and amplitude is increased. At 90 second, temperature as well as amplitude showed there effect on solubility, as the temperature and amplitude increased the solubility gets decreased **(Fig. 6)**.

Percent yield and True solubility was found to decrease with increase in the amplitude. Agglomerate size decreased with the increase in the amplitude.

3. Particle size distribution

Results of particle size distribution shows **(Table 6)** that increase in the sonication amplitude while taking sonication time and temperature of dispersion media as constant there is an increase in small size agglomerates (quantity of fines increases). With respect to temperature of the dispersion medium as the temperature increases there is slightly decrease in the agglomerate size. This may be due to increase in cavitation force of ultrasonic energy results in micronization of the agglomerates. Sonication time also gives impact on particle size distribution as the

sonication time increased the amount of large agglomerates reduced when the sonication amplitude and temperature of dispersion media constant.

Table 6: Particle size distribution of all MSC batches

Batch code	% (+44#)	% (-44/+60#)	% (-60/+85#)	% (-85/+100#)	Fines
A 1	77.66	8.66	14.00	-	-
A 2	84.00	4.57	8.57	-	-
A 3	44.15	16.00	6.46	29.38	-
A 4	90.75	6.00	-	-	-
A 5	85.29	9.41	-	-	-
A 6	83.48	5.40	4.20	7.20	-
A 7	85.71	12.33	-	-	-
A 8	67.93	8.78	5.46	7.83	4.51
A 9	57.50	21.66	9.33	4.23	-
B 1	91.63	4.23	-	-	-
B 2	88.20	9.23	-	-	-
B 3	43.89	18.48	11.88	13.20	7.59
B 4	86.60	3.21	-	-	-
B 5	81.19	8.26	3.13	6.00	-
B 6	46.73	16.33	7.18	14.70	10.78
B 7	82.53	11.64	-	-	-
B 8	70.58	13.60	14.70	-	-
B 9	25.8	19.35	13.62	27.59	12.90
C 1	80.44	4.95	4.95	6.43	-
C 2	88.60	9.55	-	-	-
C 3	48.98	15.87	10.13	11.82	10.81
C 4	90.03	5.86	-	-	-
C 5	68.33	11.94	2.77	7.77	4.72
C 6	27.33	21.22	13.30	22.66	12.58
C 7	73.12	8.52	8.52	-	-
C 8	58.73	13.09	6.74	11.90	-
C 9	27.16	17.05	17.05	19.36	22.25

4. FTIR spectra analysis

The FTIR spectrum of pure naproxen, MST and MSC agglomerates exhibits a infrared band at 1727 cm^{-1} attributed to the free or non hydrogen bonded carboxylic group (monomer) and a band centered at 1684 cm^{-1} corresponding to the hydrogen bonded carboxylic group **(Fig. 7)**. There was no difference in infrared spectra of pure drug, MST agglomerates and MSC agglomerates. By that it might be expected that there was no degradation after MST and MSC.

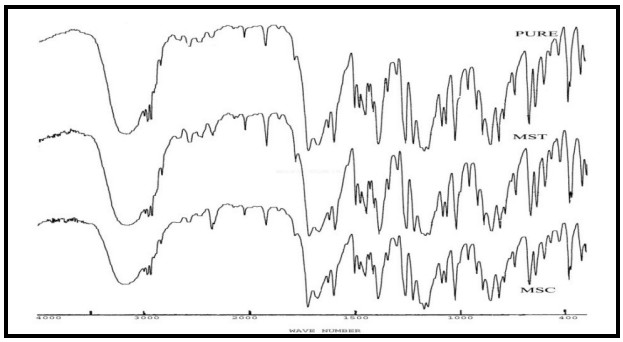
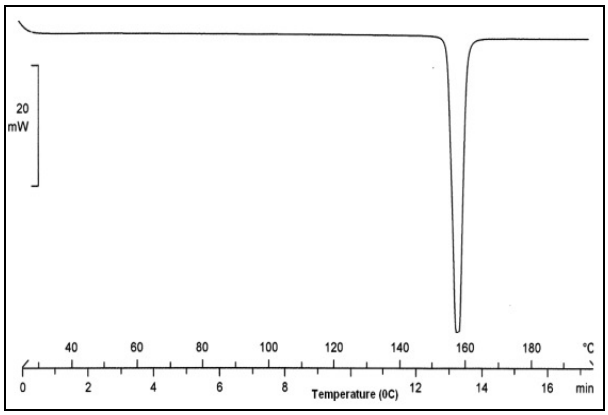


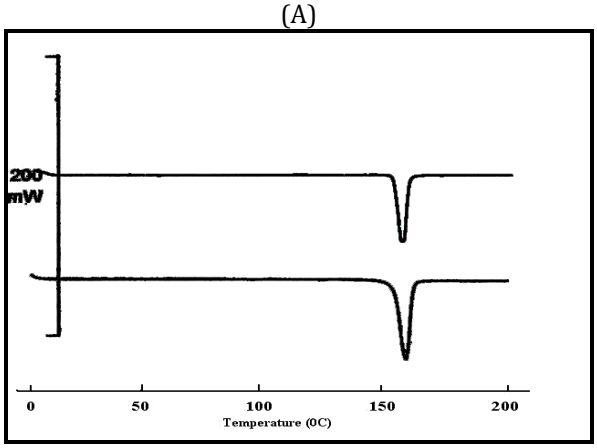
Figure 7: FT - IR spectra of pure naproxen, MST and MSC naproxen agglomerates.

5. Differential scanning calorimetry

DSC thermogram of pure drug and MSC naproxen agglomerates was shown in **Fig. 8**. DSC curve of pure drug shown endotherm at 161.34^{0}C with normalized energy 147.17(J/g) is ascribed to drug melting. The thermogram of MSC naproxen agglomerates shows decrease in normalized energy as compare to pure crystalline drug. As increase in the amplitude and the time of sonication the normalized energy got increased. There is no significant difference in the melting point temperature.



(A)



(B)

Figure 8: DSC Thermogram of A) Pure Drug, B) MSC agglomerates Batch B1 and Batch A9.

When temperature and amplitude of sonication was maximum the normalized energy was 140.02 (J/g) the melting endotherm is sharp but asymmetric, it may be due to presence of different crystal structure. These observations were in confirmation with change thermal properties of naproxen after sonication, where asymmetry, enthalpy change was ascribed different crystal size and crystal habit of naproxen. At higher level of sonication the increase in normalized energy is might be due to the recrystallization of the drug; this was also observed in XRPD results.

6. X-ray Powder Diffraction

Comparative study of X - Ray powder diffraction of the drug and MSC agglomerates at different ultrasonic time and amplitude was studied. The characteristic intensity peak was found at specified value of 2θ. MSC batch no. A9 and B2 shows same characteristic intensity peak at same 2θ but the value of intensity get increased comparatively to pure drug. Batch no. B1 showing same 2θ as pure drug and the intensity peak is also same as pure crystalline drug **(Fig. 9)**. There was no change in the d-spacing value. The increase in the intensity peak was due to recrystallization of drug at higher level amplitude and time.

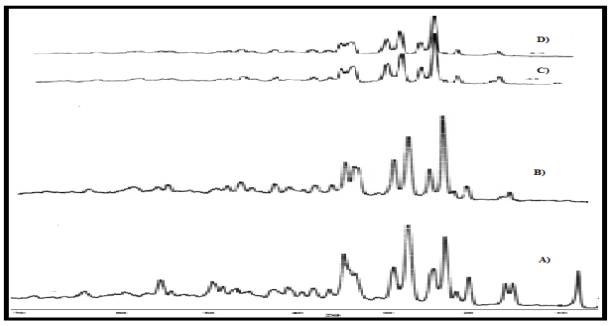


Figure 9: XRPD pattern of A) Pure crystalline drug B) Batch B1 C) BatchA9 D) Batch B2.

7. Surface Topography By Scanning Electron Microscopy (SEM)

Crystal morphology influences various pharmaceutical engineering and biopharmaceutical parameters such as flowability, packing, compaction, compressibility, solubility and dissolution characteristic of drug powder. The SEM of pure drug, MST and MSC naproxen agglomerates was shown in **Fig. 10**.

It was in the form of irregular shaped crystals, having rough surface. Application of ultrasonic energy to pure drug showed some changes such as development of cracks on the surface of agglomerates, reduction in the particle size and surface roughness. SEM photograph of MST shows melt solidified bonds on the surface; at higher magnification cracks was observed on the surface of the MST agglomerates. SEM photograph of MSC (B1) batch, observed irregular shaped agglomerates, lots of cracks on the surface of the agglomerates, slightly aggregation of the small particle on the surface of the larger agglomerates. Dark black pores were observed on the surface of the agglomerates, may be due to these pores there is an increase in the surface area of the agglomerates which may be the cause of the enhancement of the solubility. The SEM photograph of the batch (A9) observed that regular needle shaped crystals. Dark black holes are present but they are very few in number. As increase in the sonication time and the amplitude the crystalline property of the drug will also enhanced.

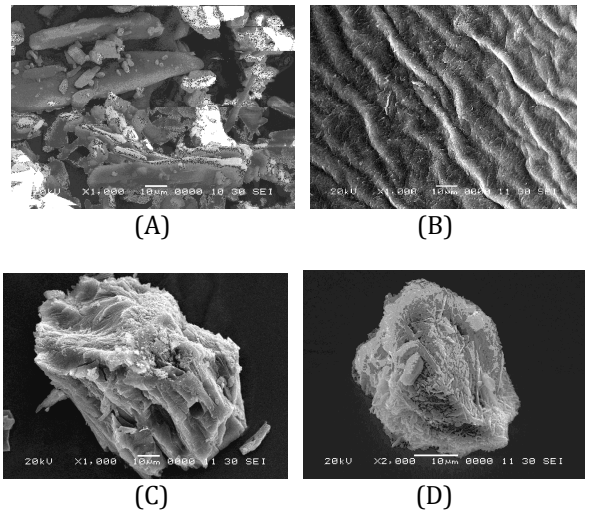
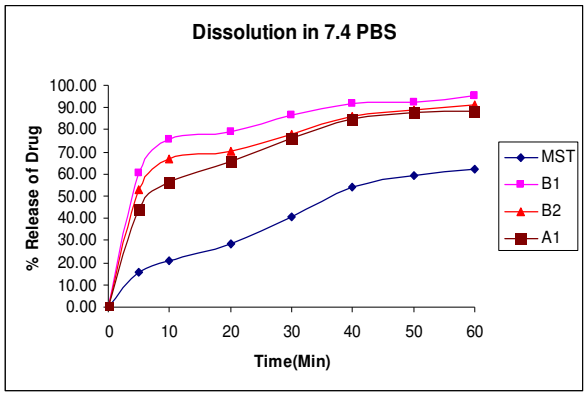


Figure 10: SEM photograph o f A) pure drug B) MST agglomerate C) MSC Batch A9 D) MSC Batch B1.

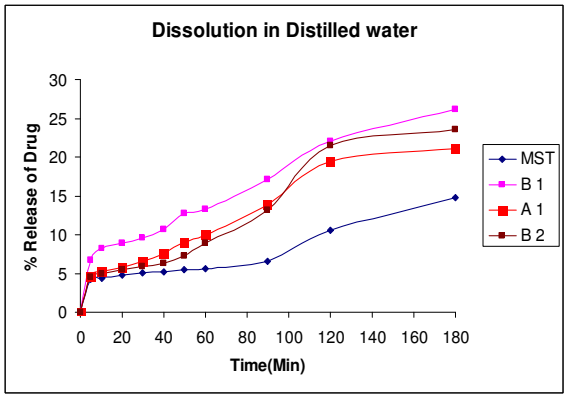
8. Dissolution study

Dissolution profile of MST agglomerates and various batches of MSC naproxen agglomerates were measured in distilled water and pH 7.4 phosphate buffer. It was observed that at low level of

temperature, amplitude and intermediate level of ultrasonication time gave maximum drug release in distilled water. As the amplitude increased to intermediate level, release of drug decreased. At low level of sonication temperature and time, least release was observed may be due to not proper sonication to the melted drug. Higher dissolution rate of MSC batches in both pH 7.4 phosphate buffer and distilled water was observed as compared to MST batch **(Fig. 11)**. It may be due to ultrasonic treatment which cause increase in the surface area due to decrease in size of the individual crystal and thus, the porous nature of agglomerate of crystal obtained.



(A)



(B)

Figure 11: Dissolution profile of MST agglomerate and different MSC batches in A) pH 7.4 Phosphate Buffer, B) distilled water.

9. Bulk density, Tapped density and Angle of repose

There is significant difference in bulk density and tap density of pure drug, MST and MSC agglomerates. MSC shows better compressibility and flow properties than pure drug **(Table no. 7)**.

Angle of repose was maximum at intermediate level sonication and time and low level of temperature. At lowest level of time, amplitude and temperature the batch obtained by MSC was showing low level of angle of repose. MST was showing lowest level of angle of repose in comparison of all the batches. Pure drug shows highest level of angle of repose that means lowest flow property.

Table 7: Comparison of bulk density, tap density and angle of repose of pure naproxen, MST and MSC naproxen agglomerates

Sample	Bulk Density (gm/ml)	Tap Density (gm/ml)	Carr's Index (%)	Haussner Ratio	Angle of repose (θ)
Pure drug	0.225 ± 0.0	0.3731 ± 0.02	39.69 ± 0.01	1.65± 0.1	42.80 ± 3.45
MST	0.550 ± 0.01	0.5823 ± 0.02	5.54 ± 0.01	1.06 ± 0.1	28.43 ± 4.21
MSC (A_1)	0.5826 ± 0.01	0.6283 ± 0.02	7.27 ± 0.01	1.08 ± 0.1	30.95 ± 2.72
MSC (B_1)	0.5683 ± 0.03	0.6045 ± 0.01	5.99 ± 0.01	1.06 ± 0.1	32.45 ± 5.31
MSC (B_2)	0.5542 ± 0.02	0.6125 ± 0.02	9.51 ± 0.01	1.10 ± 0.1	32.54 ± 3.92

10. Heckel plot

Naproxen crystal shows disadvantage concerning the properties affecting the manufacturing properties. Due to bad compaction behavior naproxen has to granulate in most cases before tabletting. Another problem in manufacturing is the high tendency for sticking and capping to the punches. Compressibility describes the reduction of volume in the die applied punch pressure. Therefore, heckei plot study **(Table no. 8)** was carried out only on the melt sonocrystallized naproxen agglomerates.

Table 8: Hardness and tensile strength of MSC naproxen agglomerates.

Sr. No.	Pressure (kg /cm²)	Tablet Wt. (gm)	Tablet Thickness (mm)	Tablet Diameter (mm)	Hardness (pa)	Tensile Strength (kg/cm²)
1.	20	0.493	4.02	13.30	1.60	5.37
2.	40	0.520	3.82	13.30	1.80	5.74
3.	60	0.489	3.74	13.28	2.00	6.23
4.	80	0.476	3.45	13.27	3.20	9.20
5.	100	0.478	2.64	13.25	3.50	7.68
6.	120	0.463	2.45	13.22	3.90	7.93

It was observed that mean yield pressure (P) required for naproxen agglomerates was 48.26 Kg/cm^2. At which stable compact could be obtained and sticking was not observed for melt sonocrystallized naproxen agglomerates during compression of agglomerates, it might be due to melt solidified bond form during Ultrasonication.

From the above results it was observed that the product obtained after MSC shows higher rate of dissolution and better compression behavior as compared to pure crystalline drug.

Thus, this study has focused on many important aspects in the area of melt sonocrystallization for naproxen and the effect of various variables on particle design by melt sonocrystallization.

Conclusion:

Melt Sonocrystallization technique is the melt solidification technique along with the application of ultrasonic energy. Naproxen has problem due to its poor solubility and compressibility. An attempt has been made to overcome these problems by the application on melt sonocrystallization technique. The present study shows the effect of variables like time of sonic energy, amplitude of energy and temperature of the dispersing media on particle design during MSC. The product obtained after MSC shows higher rate of dissolution and better compressed behavior compared to pure crystalline drug and MST product. Percent yield and True solubility was found to decrease with increase in the amplitude.

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