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RECRYSTALLIZED AGGLOMERATES OF INDOMETHACIN BY EMULSION SOLVENT DIFFUSION (ESD) TECHNIQUE.

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ABSTRACT

The aim of present study was to prepare and characterize the recrystallized agglomerates of water insoluble non steroidal anti-inflammatory drug, indomethacin (IM) with hydrophilic polymers like polyvinyl pyrrolidone (PVP),hydroxyl ethyl cellulose (HEC) and hydroxyl propyl methyl cellulose (HPMC) by using emulsion solvent diffusion (ESD) technique for enhancing the solubility, dissolution rate,flowability,wettability and Packability of IM. The ESD technique employed three test solvents: first substance dissolution medium-good solvent (methanol); second partial dissolution medium for the substance-bridging liquid (dichloromethane) and third poor solvent for drug substance (distilled water).X-ray powder diffractometry (XRPD) and differential scanning calorimetry (DSC) were performed to examine the physical state of the IM and prepared recrystallized agglomerates. DSC thermograms showed the changes in melting peak of the IM in recrystallized agglomerates suggesting the change in crystallinity of IM. The XRD revealed a characteristic decrease in crystallinity. The solubility and dissolution studies demonstrated a marked increase in solubility and dissolution rate of recrystallized agglomerates as compared to the pure IM drug. The recrystallized agglomerates enhanced the drug solubility and dissolution about 3 and 2 folds with HPMC and HEC polymer respectively. The prepared spherical crystals with used polymers exhibited excellent physicochemical properties like flowability, packability, and wettability compared with the pure raw crystals of indomethacin.

KEY WORDS

Flowability, Packability, wettability, solubility, dissolution, Indomethacin, recrystallized agglomerates.

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INTRODUCTION

Poor aqueous solubility is actually a very challenging problem in drug formulation development, particularly BCS class II drug substances, which are having low aqueous solubility (poor dissolution characteristics), the limiting step for drug absorption from the gastrointestinal tract[1]. As an increasing number of newly developed active pharmaceutical entities present such characteristics, approaches to overcome this feature are of great importance in formulation development research. During the last decade the trend in drug discovery has been produce more and more active pharmaceutical ingredients that exhibit high lipophilicity and poor water solubility[2]. Such physicochemical characteristics lead to problematic biopharmaceutical properties, which in turn decline the chances of success in the clinical therapy[3]. Many approaches have been developed to improve solubility and dissolution rate of poorly water soluble drugs, including both modifications to the drug substance itself and the creation of specific formulations. Physical modifications often aim to increase the surface area, solubility and wettability of the powder particles and therefore typically focus on particle size reduction or generation of amorphous states[4, 5].

Among the various solubility/dissolution rate enhancement methodologies available for poorly water-soluble drug compounds (e.g. amorphous dispersions as solid dispersions/ inclusion complexes, salt formation, surfactant/lipid based excipients addition, etc.), drug particle size reduction is meeting great interest in drug formulation[6,7].One of the most common approaches used to reduce particle size is milling, a mechanical micronization process. Milling is a well-established technique which is relatively cheap, fast and easy to scale-up. However, milling has several disadvantages, the main one being the limited opportunity to control important characteristics of the final particle such as size, shape, morphology, surface properties and electrostatic charge. In addition, milling is a high energy process which causes disruptions in the drug substances crystal lattice, resulting in the presence of disordered or amorphous regions in the final product[8].

In 1986, Kawashima and their coworkers developed the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Kawashima defined spherical crystallization as “An agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process.” It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle. Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the versatile process that enables to control the type and the size of the crystals.

Emulsion solvent diffusion (ESD) is the most commonly used technique of spherical crystallization for preparation of recrystallized agglomerates. This technique employs three solvents: good solvent (solvent that dissolves drug substance), Poor solvent (solvent in which drug is insoluble) and bridging liquid (solvent that partially dissolves drug and is immiscible with poor solvent).Using this method, spherical crystallization can be carried out by using a mixed system of three partially miscible solvents, i.e. good solvent–bridging liquid–poor solvent. When bridging liquid plus good solvent of API are poured into the poor solvent under agitation, quasi-emulsion

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droplets of bridging liquid or good solvent forms the emulsion droplets in the poor solvent and induces crystallization of the drug followed by agglomeration.

It is the particle engineering technique in which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process[9, 10]. In consequence of such modifications in the crystal habit certain micrometric properties (bulk density, flow property, compactability) and physicochemical properties like solubility, dissolution rate, bioavailability and stability) can also be modified.

This technique is simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel. The spherical crystallization technique has already been successfully applied to improve the micromeritic properties of many pharmaceuticals. In the most common case, this technique is reputed to improve the wettability and dissolution rate of different drugs. Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release[11,13].Many drug substances are poorly soluble or insoluble in water (class-II class-VI drug substances) according to the biopharmaceutics classification system (BCS), which results in poor bioavailability because the solubility of a drug is an important factor in determining the rate and extent of its absorption. An enhancement in the dissolution rate of these drugs can increase the blood-levels to a clinically suitable level.

Indomethacin (IM, γ -indomethacin; 1-(pchlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) is one of the most widely used non-steroidal anti-inflammatory drug (NSAID).It is used to reduce pain/swelling involved in osteoarthritis, rheumatoid arthritis, bursitis, tendinitis, gout, ankylosing spondylitis, and headaches .The drug is described as poorly soluble and highly permeable (Class II) drug substance as per BCS classification[14]. Because water-insoluble drugs often show low absorption and weak bioavailability, improvement in dissolution rate and/or solubility is the important consideration for drug development process[15].The successful formulation of poorly-water soluble drugs is one of the major challenges in pharmaceutical manufacturing. Indomethacin may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of the gastrointestinal tract. Additionally, this undesirable physical property may increase the incidence of irritating side effects on the gastrointestinal tract because of a prolonged contact time with the GIT mucosa[16].Hence the objective of present study is to prepare recrystallized agglomerates of IM by using the emulsion solvent diffusion (ESD) technique. This study also investigated the effect of hydrophilic polymers like HPMC, HPC and PVP on the solubility, dissolution and morphology of recrystallized agglomerates. The prepared recrystallized agglomerates were also evaluated for flowability, packability, wettability and compared with the raw crystals of Indomethacin.

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MATERIALS AND METHOD

Indomethacin (IM) was generously supplied as a gift sample from Lupine Research Park, Pune (India).Polyvenylpyrrolidone (PVP), hydroxyl ethyl cellulose (HEC), hydroxy propyl methyl cellulose (HPMC) were obtained from Alembic research center (Vadodara, India). Methanol, dichloromethane, distilled water and other solvents were purchased from S. D. Fine (Mumbai, India).

***Solvents selection for recrystallized agglomeration*:**
The solubility of IM in different solvents was determined by successive addition of IM in respective organic solvents to the points at which they no longer dissolve. Measured the total quantity of IM required to achieve the saturation point. The selection of solvent is dictated by solubility characteristic of drug. A mutually immiscible three solvent system consisting of a poor solvent (suspending liquid) and a good solvent and bridging liquid are necessary. Physical form of product i.e. whether micro-agglomerate or irregular macro-agglomerates or a paste of drug substance can be controlled by selection of proper solvent proportions by using ternary phase diagram.

Emulsion Solvent Diffusion (ESD) technique for recrystallized agglomeration:

This method of spherical crystallization was carried out by using three partially miscible solvents i.e good solvent (methanol), bridging liquid (dichloromethane) and poor solvent (distilled water). Under constant agitation bridging liquid and good solvent forms emulsion droplet in to the dispersing medium and crystallization of drug followed by agglomeration due to bridging liquid. The weighed quantity of Indomethacin (IM) was dissolved in a 3:5 ratio of dichloromethane and Methanol. This solution was then added to the 100mL purified water which was agitated under 1500rpm.The precipitated recrystallized agglomerates was then filtered and dried in hot air oven at 50^0C to get final dried spherical crystals. Formulations coded as IM-PVP, IM-HPMC and IM-HPC were prepared by using 0.5% solution of Polyvinylpyrrolidone, 0.2% hydroxyl methyl cellulose and 0.2% hydroxyethyl cellulose respectively in purified water as stabilizer (table 1).

Table: 1

Product Code of recrystallized agglomerates and their formulation.

Product Code	Internal Phase		External Phase	
	Methanol	Dichloromethane	Distilled water	Stabilizer used
IM	Indomethacin (Active pharmaceutical ingredients)			
IM-Agg	5 mL	3 mL	100 mL	-----
IM-PVP	5 mL	3 mL	100 mL	0.5 gm
IM-HEC	5 mL	3 mL	100 mL	0.5 gm
IM-HPMC	5 mL	3 mL	100 mL	0.25 gm

Saturation solubility study:

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Saturation solubility profile of Indomethacin and their recrystallized agglomerates were carried out in distilled water. Each excessive quantity (50 mg) of IM and equivalent prepared recrystallized agglomerated crystals were taken in screws capped test tubes with fixed volume (10 ml) of distilled water. The resultant suspension was treated at room temperature with 100 rpm in incubator shaker. After 24 hrs samples were withdrawn and filtered through 0.2µ filters (Ultipor®N_{66}, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with distilled water and analyzed at 320 nm by UV-visible spectrophotometer (Jasco model). The study was performed in triplicate (n = 3).

Measurement of flowability and density:

The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using a density measuring apparatus (Serwell, Bangalore, India). An amount of the sample (5g) was placed in a measuring cylinder and the volume (bulk volume) was measured after applying three taps. Tapped density was measured as per USP[17]. A quantity (20g) of the material was passed through a 1 mm aperture sieve and transferred to a 100mL graduated cylinder. The surface was carefully leveled out compacting the material. The unsettled apparent volume was noted. The cylinder was tapped at a rate of 300 drops/min over a fixed drop distance of 14±2mm. After the first 500 drops, the volume of the material in the cylinder was measured. Further tapping (750 and then 1250 drops successively) was applied was applied until the difference between two volumes following successive tapping was less than 2.0%. This final volume was taken as the tapped volume. Bulk/tapped densities, Carr's index (%) and Hausner's ratio were calculated as in Eqs. 1 - 4. Angle of repose of the test materials were assessed by the fixed funnel method and computed as in Eq. 5. The results presented are the means of three determinations each.

Bulk density (ρb) = Weight / Bulk volume …… (1)
Tapped density (ρt) = Weight / Tapped volume..... (2)
Carr's Index = [(ρt – ρb) / ρt] x 100..... (3)
Hausner ratio = (ρt / (ρb) …… …….. (4)
Angle of repose (θ) = Tan-1(h/r) …… (5)

Wettability study:

Powder bed hydrophilicity test was carried out to assess the wettability of the agglomerates by placing the sample (2 g) in sintered glass tube to form a bed in the glass tube on which methylene blue crystals (≈100 mg) were placed. The tube was brought into contact with the surface of water and the time taken for water to rise by capillary movement to dissolve methylene blue crystals was noted. The shortest time corresponds to the most wettable sample. The test was performed in triplicate.

Packability study:

The packability of the recrystallized agglomerates was investigated by tapping them into a 25-mL measuring cylinder using a tapping machine. Initially, 25 g of substance was weighed and then was gently poured into a measuring cylinder. The volume of 25 g samples was recorded. The poured density (minimum density) was calculated from the powder mass (25 g) and the volume. Then the cylinder was tapped and the volume was recorded after every 100

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taps until the volume did not change significantly. The compressibility was evaluated by measuring the tapped density according to the modified Kawakita (1) and Kunos (2) equation.

$$N/C = 1/(ab) + N/a \quad (1)$$

Where as {C = (Vo-Vn)/Vo, a = (Vo-V∞) /Vo.}
N =Number of tapping, C =Difference in volume (degree of volume reduction.), a and b = constant for packability and flowability, Vo = Initial volume, Vn = Final volume after nth tapping, V∞ = Powder bed volume at equilibrium.

$$\rho f - \rho n = (\rho f - \rho o) . \exp. (-kn) \quad (2)$$

Where ρf, ρo, ρn are Apparent densities at equilibrium, nth tappeded, initial state respectively The compressibility was assessed by comparing the constants a, b, 1/b and k in equation 1 and 2 respectively. The constant a represents the proportion of consolidation at the closest packing attained and constant 1/b describes cohesive properties of powders or the apparent packing velocity obtained by tapping. The constant k in Kuno's eq. represents the rate of packing process[18,19] .

In vitro dissolution profile study:

In vitro dissolution was evaluated using a conventional dissolution test. Powder dissolution studies were carried out first on the pure drug IM and secondly on the prepared recrystallized agglomerates. Each test was carried out in 750 ml dissolution medium at 37°C (n = 6) and at a stirring speed of 100 rpm with a six-station USP type-I dissolution apparatus. The dissolution medium used was mixture of 1volume of Phosphate buffer pH 6.8 and 4 volumes of distilled water. An accurately weighed quantity of each sample equivalent to 50 mg of IM was subjected to the test. To avoid the aggregation of powder in contact with dissolution medium, samples were taken at an appropriate time interval. The volume of the dissolution medium was kept constant throughout the run by replacing the removed samples with an equivalent volume of fresh dissolution medium. Samples were filtered through a 0.44 m filter, suitably diluted and analyzed at 320 nm using a UV Vis spectrophotometer (Jasco model).

Microscopic observation

The shape of the IM crystals and the recrystallized agglomerated of IM with different polymers were observed under the microscope and photomicrographed at a suitable magnification.

Differential scanning calorimetric (DSC) studies

Differential scanning calorimetric (DSC) analysis of the samples was carried out with a DSC analyzer (model TA–60, Shimadzu Corporation, Kyoto, Japan). A sample (3-7 mg) was sealed in an aluminum pan with a perforated lid and heated under nitrogen atmosphere at a heating rate of 10 °C/min over the temperature range of 20 – 210 0C.The thermograms were obtained and recorded.

X-ray powder diffraction (XRPD) studies

The XRPD patterns of the samples were monitored with an x-ray diffractometer (Philips PW 1729, Analytical XRD, Holland) using Ni filtered CuK(α) radiation (intensity ratio(α1/ α2): 0.500), voltage of 40 KV, current of 30 mA and receiving slit of 0.2 inches. The samples were analyzed over 2θ range of 5.010-39.990o with scanning step size of 0.020o (2θ) and scan step time of one second. To minimize the effect of particle size on preferred orientation, all the samples were first passed through sieve no. 120 (125µm) and collected on sieve no. 240 (62.5µm).

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RESULTS AND DISCUSSION:

Spherical crystallization of Indomethacin was obtained by the Emulsion Solvent Diffusion Method (ESD).A typical spherical crystallization system involved a good solvent, a poor solvent and bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of the indomethacin in individual solvents. Since Indomethacin is highly soluble in methanol, but poorly insoluble in water, therefore in the present study methanol, dichloromethane and water were selected as good solvent bridging liquid and poor solvent respectively. In the used emulsion solvent diffusion (ESD) technique interaction between the drug and the good solvent is stronger than that of the good and poor solvents. When the good solvent with drug is dispersed in the poor solvent, producing quasiemulsion droplets. This is due to an increase in the interfacial tension between good and poor solvent. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent.

Saturation solubility:

Table: 2 show the saturation solubility study of IM and its recrystallized agglomerates. The solubility study was carried out in distilled water. The solubility of IM in distilled water was 9.5 µg/ml. There is significant improvement in ($P < 0.01$) the solubility of recrystallized agglomerates mentioned in table 2.The improvement in solubility may be due to changes in the crystal form of IM during recrystallization with used solvent and polymers. The recrystallization process changes the crystal habit, structure, and surface of IM. In some instances, solvents included into the crystal forms solvets or clathrates that change the surface properties and the reactivity of the drug particles and the internal energy of the molecules, playing an important role in increasing solubility.

Wettability study:

Table 2 indicates results of powder bed hydrophilicity study of IM and their recrystallized agglomerates prepared by ESD technique. The prepared recrystallized agglomerates showed significantly shortest rising time (** $P<0.01$) of water to its surface compared to the raw IM crystals represent better wattability of recrystallized agglomerates as compared to raw IM. The order of wettability was IM-HPMC > IM-HEC > IM-Agg > IM-PVP > IM .The reason for superior wettability of recrystallized agglomerates is due to the presence of polymers with the recrystallized IM.

Table: 2

Evaluation of Indomethacin and their recrystallized agglomerates.

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Sr.No.	Product Code	Product yield (%)	Drug content (%)	Saturation Solubility (µg/mL)	Powder bed hydrophilicity test (Water raising time-hrs)
01	IM	------	98 ±1.89	09.5 ±0.56	8.5 ±0.56
02	IM-Agg	82 ±1.25	96 ±2.48	36.5 ±0.89	6.3 ±0.57
03	IM-HEC	85 ±2.35	95 ±1.68	55.5 ±0.67	5.2 ±0.95
04	IM-PVP	87 ±1.98	97 ±2.85	45.8 ±0.88	6.4 ±0.56
05	IM-HMPC	88 ±2.69	95 ±1.68	65.5 ±0.98	4.6 ±0.44

*Each value represents mean ± S.D. (n = 3)

Density and flowability determination:

Indomethacin is a drug substance with poor flow properties having larger Angle of repose, Carr's Index (CI) and Hausner's ratio mentioned in table 3. The recrystallized agglomerates with QESDS significantly improves the flow properties of drug and addition of suitable polymer such as polyvinyl pyrolidone ,HPMC and HPC in to the dispersion medium show further improvement in flow properties. This improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction due to their more spherical shape and a lower static electric charge.

Dissolution study:

In the dissolution study, IM-HPMC showed 96 % cumulative drug releases in 20 min (figure 1) followed by IM-HPC (94%), IM-PVP (90%), and IMAGG (87%) from recrystallized agglomerates as compared with IM (56 %).The order of improving the dissolution rate is IM-HPMC> IM-HPC> IM-PVP> IM-Agg> IM.The reason for this faster dissolution was linked to the change in crystal habit and polymorphism of the raw crystal of IM. Incorporating the water soluble polymers as stabilizers in the dispersed system which was adsorbed on the recrystallized agglomerates and stabilize it. The slightly improvement in the %CDR of recrystallized agglomerates with different stabilizers compared to without stabilizers may be due to deposition of polymer onto the recrystallized drug surface and increase the wettability of the recrystallized agglomerates followed by its solubility and dissolution rate.

Table: 3

Densities and flowability determination of Indomethacin and their recrystallized agglomerates.

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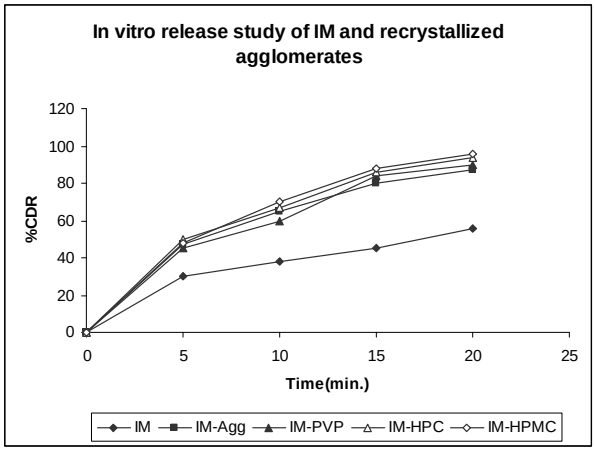
Sr. No.	Product Code	Bulk Density (gm/mL)	Tap Density (gm/mL)	Angle of repose (Degree)	Carr's Index(CI)	Hausner's ratio
01	**IM**	0.386	0.545	42.76	29.17	1.412
02	**IMAGG**	0.266	0.325	24.56	18.15	1.222
03	**IM-PVP**	0.254	0.295	22.36	13.90	1.161
04	**IM-HPC**	0.237	0.378	23.86	14.75	1.173

Figure: 1
In vitro release studies of IM and their prepared recrystallized agglomerates.

Packability study



Packing process of the recrystallized agglomerates in a measuring cylinder by tapping was described by Kawakitas and Kunos equation. The packing ability was assessed by comparing the constants a, b and k in Kawakitas and Kunos equation (table

4).The constant a for the recrystallized agglomerates was smaller than the raw crystals of IM. This indicated that the recrystallized agglomerates were easily packed, even without tapping. The larger b values of the recrystallized agglomerates proved that the packing velocity of the recrystallized agglomerates by tapping was slower than that of the crystals which are not agglomerated. Kunos equation showed that agglomerates have a significantly larger value ($P < 0.01$) of parameter k.From the values of all these parameters; it is proved that the agglomerated crystals showed a higher packability than that of raw IM crystals. The increasing packability of the agglomerated crystals may be due to the lower surface and the wider particle size distribution of the spherical crystals. During the tapping process, smaller particles might have infiltrated into the voids between the larger particles and resulted in improved packability.

Microscopical observation:

Microscopic observation (Figure 2) of raw CBZ crystals and the prepared agglomerated crystals showed that the raw crystals were irregular and stone shaped as compared with the agglomerated crystals, which were spherical in shape and were composed of minute needle-like crystals. We can conclude that polymorphism or solvation would have occurred during the agglomeration process. The prepared recrystallized agglomerates showed a lower melting point (figure: 3) as compared with the raw crystals of IM. The lower melting point observed in the recrystallized samples as compared with the raw crystals may be

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attributed to the variation in crystallinity due to the alteration in the packing arrangement of the molecules in the crystals and the altered hydrogen bonding.

***XRD study*:**

Investigation of the X-ray diffractograms (Figure 4) revealed a number of changes in the location of the peaks (appearance and disappearance) of the different crystal forms of agglomerates with respect to IM. There is difference in d-spacing between the XRD spectra of IM and the agglomerated samples, referring to the habit modification and change in the intensity of the peaks, which indicate a different arrangement of the molecules hence confirming the development of a different polymorphic form. A few diffuse peaks or decrease in crystallinity were observed in the agglomerated crystals with used polymers, which may indicate a slight physical interaction of the drug with the polymers.

Table: 4

Packability studies of Indomethacin and their recrystallized agglomerates by Kawakitas and Kunos parameters.

Parameters	IM	IM-Agg	IM-PVP	IM-HPC	IM-HPMC
a	0.566	0.194	0.214	0.227	0.235
b	0.0013	0.0119	0.0049	0.0070	0.0105
k	0.0056	0.0136	0.0143	0.0130	0.0138

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Figure: 2

Microscopical photographs of IM and prepared recrystallized agglomerates.
DSC study

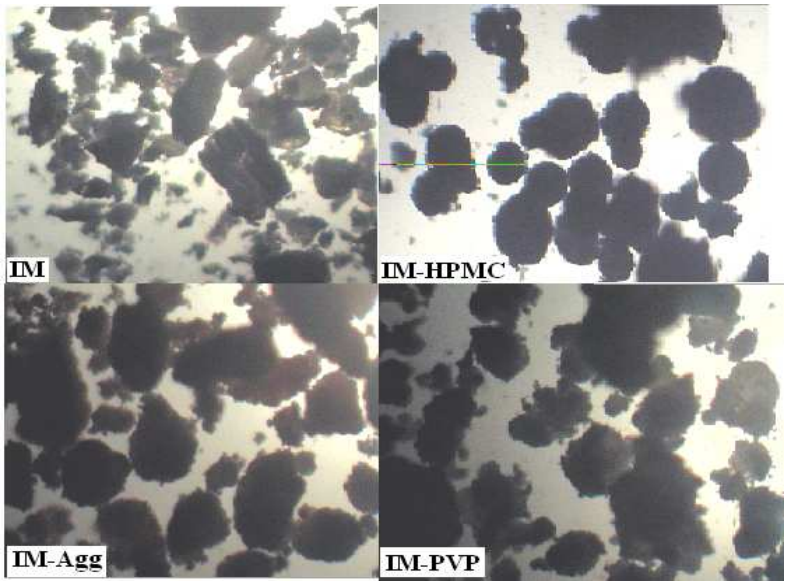


Figure: 3
DSC of IM and prepared recrystallized agglomerates.

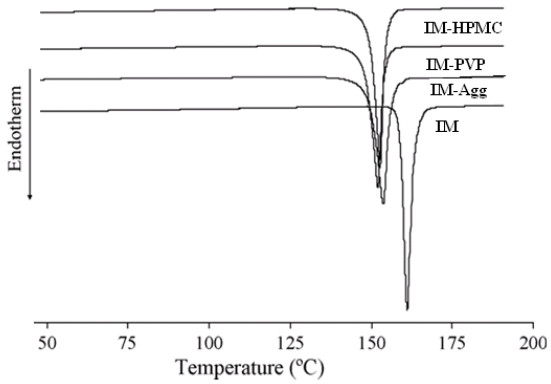
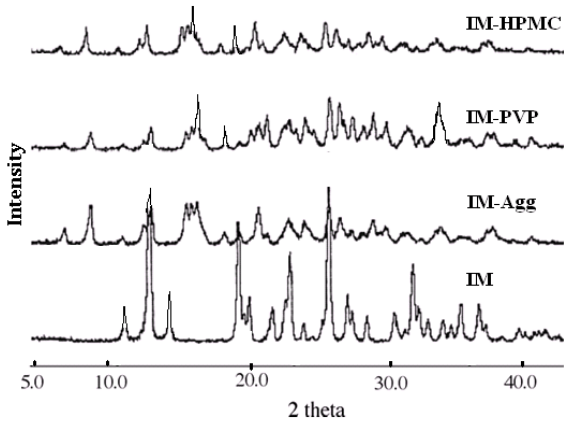


Figure: 4

RECRYSTALLIZED AGGLOMERATES OF INDOMETHACIN BY EMULSION SOLVENT DIFFUSION (ESD) TECHNIQUE.

FTIR spectra of IM and prepared recrystallized agglomerates.



CONCLUSION

In the used emulsion solvent diffusion method, different polymers were successfully employed as protective stabilizers of the prepared dispersions. This stabilizing effect is possibly attributed to the formation of polymer network by intermolecular interaction of polymer molecules that could prevent aggregation and crystal growth of the dispersed particles. The prepared IM recrystallized agglomerates exhibited excellent physicochemical and micromeritic properties like solubility, dissolution rate, flowability, wettability and packability compared with pure raw crystals of IM drug. The prepared IM recrystallized agglomerates showed a uniform particle size distribution with an average particle size in the range of 300–500µm. The prepared recrystallized agglomerates with HPMC and HPC polymers exhibited excellent physicochemical properties like solubility, dissolution flowability, Packability and wettability as compared to the pure raw crystals of indomethacin. Therefore if this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed spherical agglomerates with improving the physicochemical and micromeritic properties.

REFERENCES:

1. Lobenberg R, Amidon GL, Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur. J. Pharm. Biopharm, 50: 3–12, (2000).
2. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev, 23: 3–25, (1997).
3. Testa B, Caldwell J, Prodrugs revisited: The ‘‘ad hoc’’ approach as a complement to ligand design. Med. Res. Rev, 16: 233–241, (1996).
4. Hancock BC, Zografi G, Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci, 86: 1–12, (1997).

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5. Grau MJ, Kayser O, Muller RH, Nanosuspensions of poorly soluble drugs – reproducibility of small scale production. Int. J. Pharm, 196: 155–157, (2000).
6. Rasenack N, Hartenhauer H, Muller BW, Microcrystals for dissolution rate enhancement of poorly water-soluble drugs. Int. J. Pharm, 254: 137–145, (2003).
7. Mosharraf M, Nystrom C, The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. Int. J. Pharm, 122: 35–47, (1995).
8. Saleki-Gerhardt A, Ahlneck C, Zografi G, Assessment of disorder in crystalline solids. Int. J. Pharm, 101: 144, (1994).
9. Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya K, Development of agglomerated crystals of Ascorbic acid by the spherical crystallization techniques. KONA, 20(3):251-61, (2002).
10. Goczo H, Szabo RP, HasznosNezdei M, Farkas B, Development of spherical crystals of Acetyl salicylic acid for direct tablet making.Chem.Pharm.Bull, 48(12):1877-81, (2000).
11. Kawashima Y, Okumura M, Takenaka H, Spherical crystallization: direct spherical agglomeration of Salicylic acid crystals during crystallization. Science, 216(4): 1127-28, (1982).
12. Goczo H, Szabo RP, Hasznos NM, Farkas B, Development of spherical crystals of Acetyl salicylic acid for direct tablet making. Chem.Pharm.Bull, 48(12): 1877-81, (2000).
13. Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya K, Development of agglomerated crystals of Ascorbic acid by the spherical crystallization techniques. KONA, 20(3):251-61, (2002).
14. Lobenberg R, Amidon GL, Modern bioavailability, bioequivalence and biopharmaceutics classification system; new scientific approaches to international regulatory standards. Eur. J. Pharm. Biopharm, 50: 3 –12, (2000).
15. Hirasawa N, Ishise S, Miyata H, Danjo K, Physicochemical characterization and drug release studies of nilvadipine solid dispersions using water-insoluble polymer as a carrier. Drug Dev. Ind. Pharm, 29: 339-44, (2003).
16. Alsaidan SM, Alsughayer AA, Eshra AG. Improved dissolution rate of indomethacin by adsorbents. Drug Dev.Ind. Pharm, 24: 389-94, (1998).
17. United States Pharmacopoeia (USP) 30/NF 24.United States Pharmacopoeial Convention Inc.Rockville, USA,, 2007, p. 242.
18. Ueda M, Nakamura Y, Makita H, Imasato Y, Kawashima Y. Particle design of Enoxacin by spherical crystallization technique II, Characteristics of agglomerated crystals. Chem Pharm Bull, 39: 1277-81, (1991).
19. Di Martino P, Barthélémy C, Piva F, Joiris E, Palmieri GF, Martelli S.Improved dissolution behavior of Fenbufen by spherical crystallization.Drug Dev Ind Pharm, 25:1073-81,(1999).