International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1312-1317, Oct-Dec 2009

Improvement in Physicochemical Properties of Indomethacin by Melt Granulation Technique

Deshpande O.A[1] and Yadav V.B.[1]*

[1]Shree Santkrupa College of Pharmacy, Ghogaon, Karad-Satara (MS) India

Corres. Author :venkat_yadav3@rediffmail.com

ABSTRACT: Indomethacin (IM), most widely used non-steroidal anti-inflammatory drug widely used in developing countries, is classified in Class II in the Biopharmaceutics Classification
Systems; this means that IM has very low water solubility and high permeability, thus the dissolution is the absorption rate-limiting factor. The aim of this work was to evaluate the suitability of melt granulation technique for enhancing the solubility, dissolution rate and other physicochemical properties of IM.Granules prepared by melt granulation using polyethylene glycol 4000 and poloxamer 188 as meltable binders and microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) as filler and superdisintegrants respectively. The results showed that all the prepared melt granules shows higher solubility and improvement in dissolution rate comparative to pure IM and their physical mixture. The melt granules with MCC and SSG had a significant (** $P<0.01$) higher solubility dissolution rate in 15 minutes comparative to other granules and pure IM. The melt granule also shows improvement in flowability and wettability. In conclusion, melt granulation could be proposed as solvent free, rapid and low expensive manufacturing methods to increase the solubility and in vitro dissolution rate of IM.
KEY WORDS: Indomethacin, Melt granulation, superdisintegrants, solubility, flowability, dissolution, wettability.

INTRODUCTION

Bioavailability of poorly water-soluble drugs that undergo dissolution rate-limited gastrointestinal absorption can generally be improved by formulation techniques, such as preparation of solid dispersions. There are number of research articles solid dispersions comprising variety of carriers, drug/carrier ratios and methods of preparation have been published. Solid dispersed systems can be obtained by hot melt or solvent method. Because of toxicity and ecological problems associated with the use of organic solvents, hot melt approach represents the advantageous means of solid dispersion preparation, where only thermostable components are relevant(1).
Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a binder which can be a molten liquid, a solid or a solid that melts during the process (2).This process can be used for the preparation of sustained released dosage forms by using lipophilic binders, such as glycerol monostearate (3), a combination of a hydrophobic material such as a starch derivative and stearic acid (4) or a combination of hydroxypropyl methyl cellulose and hydrophobic polymers (5). It also can be used to prepare fast release formulations by utilizing water-soluble binders, such as PEG and poloxamer (6). PEG has been widely used in melt granulation because of its favorable solution properties, low-melting point, rapid solidification rate, low toxicity, and low cost.
In recent years, the interest in melt granulation has increased due to the advantage of this technique over traditional wet granulation, that is, elimination of water or organic solvents from the melt granulation process. This negates any risk originating from residual solvents; moreover, in melt granulation the drying step is not necessary, thus the process is less consuming in terms of time and energy as compared to wet granulation.
In current years, melt granulation technique has been successfully employed to improve the dissolution rate of poorly soluble compounds. Passerini and their coworkers have proved that melt granulation can be used to enhance the in vitro dissolution rate of ibuprofen, employing poloxamer 188 as a melting binder (7).
Indomethacin (γ -indomethacin; 1-(pchlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid), being sparingly

soluble in aqueous media, is one of the most widely used non-steroidal anti-inflammatory drugs. This drug was selected due to their low solubility and high permeability (Class II, Biopharmaceutical Classification System, BSC and thus the increase on their solubility will improve their bioavailability (8-9).

In the present work, the feasibility of melt granulation has been considered. Indomethacin was chosen as a water-insoluble model drug and PEG, poloxamer as a hydrophilic polymer and surfactant. Polyethylene glycol (PEG) and poloxamer were employed as a melting binder, in consideration of its favorable solution properties, low melting point, rapid solidification rate, low toxicity and low cost. Along with these binders effect study the effect of diluents like MCC and superdisintegrants like SSG. Saturation solubility, In-vitro release and flowability of the melted granules were investigated and compared to that of the pure drug and drug excipient physical mixtures.

MATERIALS & METHODS

Materials:

Indomethacin (IM) was supplied as a gift sample from Lupin Research Park (Pune, India). Polyethylene glycol-6000(PEG-6000), Poloxamer was procured from Alembic Research Center (Vadodara, India).Microcrystalline cellulose, Sodium starch glycolate was obtained as gift sample from Torrent Research Center (Ahmadabad, India).

Method:

Melt granules were prepared in a porcelain dish. Initially, the mixture of Indomethacin and polymer (Polyethylene glycol) or surfactant (poloxamer-F68) with different excipients (mentioned in Table:1) was dry blended for 10 min .Then this mixture was placed in hot porcelain dish and supply the heat around 60^0C on temperature controlled water bath so as to melt the polymers or surfactant in which the drug was dispersed . The formed molted mass is then cooled to room temperature and at the end of the granulation process the granules were allowed to solidify at room temperature by spreading them out in thin layers on glass trays. Pass the melted granules through sieve no # 20 so as to form uniform granules. The cooled granules were stored in sealed bags for their evaluation.

Prepared the physical mixtures of the same formulation and compared the solubility and dissolution rate with the melt granules.

Yield and Drug Content:

The prepared melt granules were weighed after cooling, and process yield was calculated. Melted granules (200mg) were powdered, from which powder equivalent to 50 mg Indomethacin (IM) was weighed and extracted using three portions of 100 ml phosphate buffer pH 7.2. Each portion was filtered through a G-4 sintered glass filter and volume was adjusted to 100 ml. After sufficient dilution with phosphate buffer pH 7.2, samples were analyzed spectrophotometrically at 320 nm. Indomethacin content was calculated by comparison with standard solution.

Saturation solubility studies:

Saturation solubility studies were carried out using distilled water as a solvent. Each excessive quantity (200 mg) of Indomethacin and equivalent prepared melt granules were taken in seven 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 hr samples were withdrawn and filtered through 0.2m filters (Millipore, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with distilled water and analyzed at 320 nm by UV visible spectrophotometer (Jasco model).

Flow properties:

Flow properties of the drug and prepared melt granules were studied by determining the bulk density (σ_b), tap density (σ_t), Carr's Index and Hausner ratio. A weighed quantity of the samples was taken to determine the bulk and tap density. The properties were determined using following equations.

Bulk density (σ_b) = Mass / Poured volume (1)

Tap density (σ_t) = Mass / Tapped volume (2)

Carr's Index = $[(\sigma_t - \sigma_b) / \sigma_t] \times 100$ (3)

Hausner ratio = $(\sigma_t / (\sigma_b)$ (4)

Angle of Repose:

"The **angle of repose** is an engineering property of granular materials. The angle of repose is the maximum angle of a stable slope with the horizontal determined by friction, cohesion and the shapes of the particles." When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area, and coefficient of friction of the material. Material with a low angle of repose forms flatter piles than material with a high angle of repose. In other words, the angle of repose is the angle a pile forms with the ground.

Angle of repose = 1/tan [h/r]

Where, h = height of heap
r = mean radius of circle

Wettability/ Powder Bed Hydrophilicity Study:

The untreated drug and prepared melt granules were placed on a sintered glass disk forming the bottom of glass tube on which methylene blue crystals were placed. The whole device was brought into contact with water. Measure the time taken for the capillary rising of water to

the surface so as to dissolve methylene blue crystals was noted. Minimum is the time required to reach the water to surface maximum is its wettability.

In-Vitro Dissolution Studies:
The in vitro dissolution study was carried out by using dissolution apparatus type I (Basket) at rotation speed of 100 rpm. Dissolution was carried out for 50mg IM and an equivalent melt granule containing 50 mg of the IM. As per USP one volume of phosphate buffer pH 7.2 and four volumes of distilled water was used as dissolution media. The volume and temperature of the dissolution media were 450 ml and 37^0C ±0.2 ^{0}C respectively. After fixed time intervals, 10 ml of samples were withdrawn and replace the same quantity of fresh dissolution medium so as to maintain the sink condition. These samples were assayed through ultraviolet absorbance measurement at 320 nm using UV-Visible Spectrophotometer (Jasco model) by an analytically validated method (r2 = 0.9995). To increase the reliability of the observations, the dissolution studies were performed in triplicate.

RESULTS AND DISCUSSION
From the above observation it was concluded that all melted granules shows production yield and drug content above 92%.The loss in production yield may be due to sticking of product to porcelain dish and sifting loss.

Saturation solubility:
The saturation solubility of all prepared granules was shows significantly higher solubility as compared to the pure drug and its physical mixtures. The saturation solubility of pure Indomethacin was very low (9.5 ± 0.85 µg/mL**)**.The order of increasing solubility include IMPOLS> IMPOLM> IMPEGS > IMPEGM > IMPOL > IMPEG >IM.
The melt granules with meltable polymer poloxamer shows higher solubility due to their surfactant activity compared to polyethylene glycol. In the case of granules containing super disintegrants, a large enhancement in saturation solubility was observed relative to both, melt granules with diluents and with IM alone.

Flowability:
Indomethacin is a drug substance with poor flow properties having larger Angle of repose, Carr's Index (CI) and Hausner's ratio mentioned in above table 3.According to the literature, powders with a Compressibility Index (CI) between 5 to 15%, Hausner ratio below 1.25 and angle of repose below 30 shows good flowability. The prepared melt granules (Table 3) possess a CI between 7 and 17%, Hausner ratio was below 1.16 and angle of repose were below 30.The prepared melt granule for indomethacin significantly improves the flow properties of drug. This improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction, due to their size enlargement and a lower static electric charge.

Wettability/Powder bed hydrophilicity study:
Table 4 indicates results of powder bed hydrophilicity study of IM and their granules prepared by melt granulation. The melt granules showed significantly shortest rising time (** $P<0.01$) of water to its surface compared to the raw IM crystals represent better wattability of prepared granules as compared to raw IM. The order of wettability was IMPOLS > IMPOLM, IMPEGS > IMPOL> IMPEGM > IMPEG > IM.The reason for superior wettability of melt granules and liquisolid systems is due to the presence of polymers with the IM.

Dissolution study:
The in vitro dissolution profiles of the granules prepared by melt granulation were compared with that of pure drug. The dissolution rate of pure Indomethacin was very low, with the amount of drug dissolved in 20 min being 56%. The in vitro dissolution rate of all prepared granules was higher as compared to the pure drug. In the case of granules containing super disintegrants, a significant enhancement of was dissolution rate was observed in the relative to both, the drug with meltable polymer and the drug alone.
The increase in dissolution rate could be attributed to the higher hydrophilic character of the system due to the presence of water-soluble carriers and that part of the drug dissolves in the binder. These results show that melt granulation can be a useful technique to improve the dissolution rate of Indomethacin.

CONCLUSIONS
In conclusion, melt granulation technique has been proved to be a important process to increase the solubility, wettability , dissolution and of IM using PEG and Poloxamer as a melt binder, without using any solvents. The granules displayed a significant improvement in solubility and in vitro drug dissolution behavior. The dissolution profiles of granules containing PEG and Poloxomer were found to be superimposable to IM and physical mixture. However, the intragranular addition of microcrystalline cellulose and sodium starch glycolate were found significant improvement in solubility and dissolution comparative to melt granules without microcrystalline cellulose and SSG.

Table: 1 Formulation of melt granules and physical mixtures with different polymers and excipients.

Granule code	Indomethacin	Poloxamer	PEG-6000	Microcrystalline Cellulose (MCC)	Sodium starch glycolate (SSG)
IM	API	-----	-----	-----	-----
IMPOL	1 gm	1gm	-----	-----	-----
IMPOLM	1 gm	1gm	-----	0.5 gm	-----
IMPOLS	1 gm	1gm	-----	-----	0.25 gm
IMPEG	1 gm	-----	1gm	-----	-----
IMPEGM	1 gm	-----	1gm	0.5 gm	-----
IMPEGS	1 gm	-----	1gm	-----	0.25 gm
IMPOL(pm)	1 gm	1gm	-----	-----	-----
IMPOLM(pm)	1 gm	1gm	-----	0.5 gm	-----
IMPOLS(pm)	1 gm	1gm	-----	-----	0.25 gm
IMPEG(pm)	1 gm	-----	1gm	-----	-----
IMPEGM(pm)	1 gm	-----	1gm	0.5 gm	-----
IMPEGS(pm)	1 gm	-----	1gm	-----	0.25 gm

Table: 2 Product yield and drug content of prepared melt granules with different excipients.

Product Code	Product Yield (%)	Drug Content (%)	Solubility (µg/mL)
IM	-------	98 ±2.00	9.5 ± 0.85
IMPOL	92 ±2.50	94 ±2.00	90 ±1.88
IMPOLM	94 ±2.50	95 ±3.00	120 ±2.35
IMPOLS	93 ±3.00	94 ±2.50	140 ±2.68
IMPEG	95 ±1.50	96 ±1.50	75 ±1.27
IMPEGM	94 ±2.00	95 ±2.00	95 ±1.62
IMPEGS	94 ±3.00	96 ±1.00	115 ±2.15
IMPOL(pm)	95 ±2.00	96 ±1.50	24 ±0.78
IMPOLM(pm)	96 ±1.50	98 ±2.00	28 ±0.98
IMPOLS(pm)	98 ±2.00	97 ±2.50	30 ±0.66
IMPEG(pm)	96 ±2.50	98 ±1.00	15 ±0.73
IMPEGM(pm)	95 ±3.00	98 ±1.50	17 ±0.47
IMPEGS(pm)	98 ±2.50	96 ±3.00	22 ±0.34

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

Table: 3 Flowability parameters of IM and their melted granules.

Product Code	Bulk density (gm/mL)	Tap density (gm/mL)	Carr's Index	Hausner ratio	Angle of repose(^{0})
IMC	0.386	0.545	29.17	1.412	42.76
IMPOL	0.266	0.322	17.39	1.211	24.56
IMPOLM	0.254	0.301	15.61	1.185	23.36
IMPOLS	0.244	0.280	12.86	1.148	25.58
IMPEG	0.237	0.275	13.82	1.160	22.56
IMPEGM	0.265	0.287	7.67	1.083	21.85
IMPEGS	0.238	0.268	11.19	1.126	25.68

Table: 4 Wettability (Powder Bed Hydrophilicity) studies of IM and their melted granules.

Product Code	water raising time (hrs)*
IMC	8.5 ± 0.365
IMPOL	4.0 ± 0.558
IMPOLM	3.5 ± 0.785
IMPOLS	3.0 ± 0.979
IMPEG	5.0 ± 0.778
IMPEGM	4.5 ± 0.996
IMPEGS	3.5 ± 0.667

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

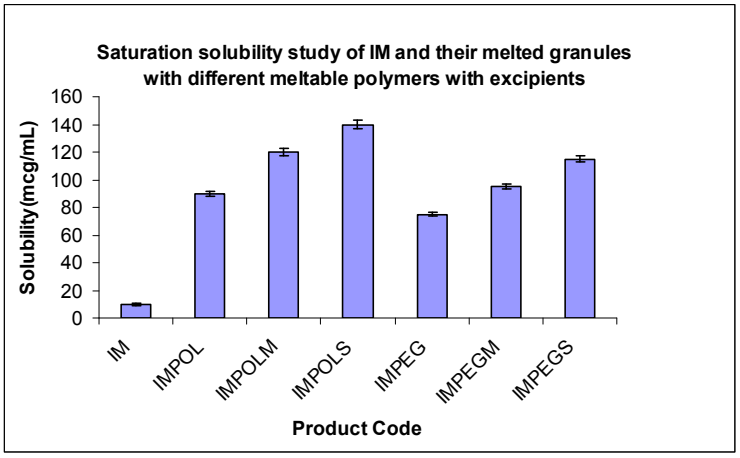

Figure: 1 Saturation solubility of IM and their melted granules in distilled water.

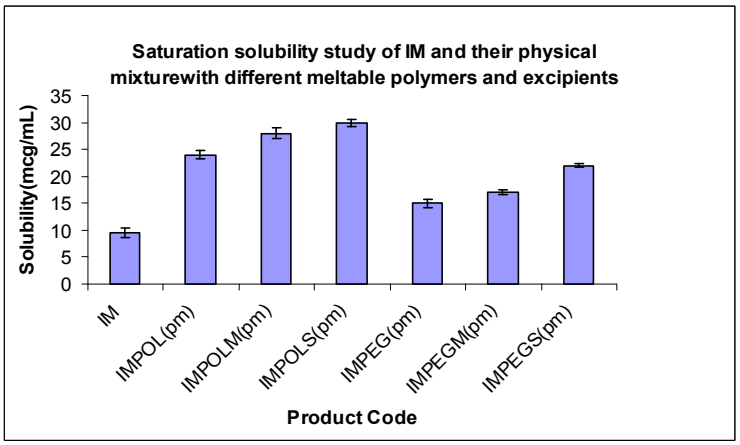

Figure: 2 Saturation solubility of IM and their physical mixtures with different excipients in distilled water.

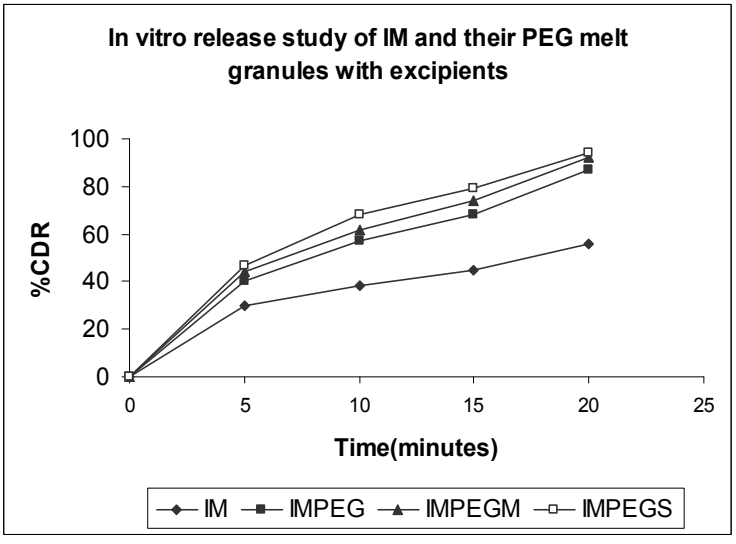

Figure: 3 In viro dissolution of IM and their melted PEG granules with different excipients.

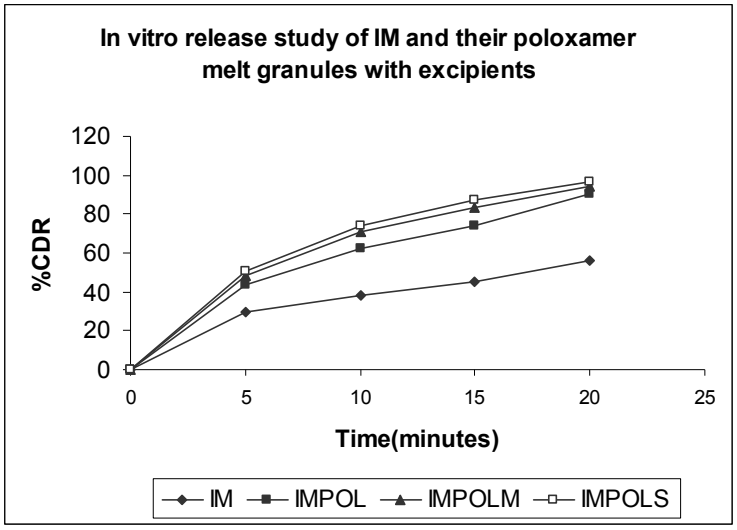

Figure: 4 In viro dissolution of IM and their melted poloxamer granules with different excipients.

ACKNOWLEDGEMENT

The authors are thankful to Lupin Research Park, Pune (MS) India for providing Indomethacin as gift sample for this research work. The authors are also grateful to the Principal of the Shree Santkrupa College of Pharmacy, Ghogaon, Karad (MS) India for
Providing laboratory facilities and constant encouragement.

REFERENCES

1. Leuner C., Dressman J., Improving drug solubility for oral delivery using solid dispersions, Eur. J. Pharm. Biopharm., 2000, 50, 47–60.
2. Schaefer T., Melt agglomeration with polyethylene glycols in high shear mixer. Ph.D. thesis, 1997, The Royal Danish School of Pharmacy, Denmark.
3. Thies R., Kleinebudde P., Melt pelletisation of a hygroscopic drug in a high shear mixer. Part 1. Influence of process variables, Int. J. Pharm., 1999, 188,131–143.
4. Zhou F., Vervaet C., Remon J.P., Matrix pellets on the combination of waxes, starches and maltodextrins, Int. J. Pharm., 1996,133, 155–160.
5. Ochoa L., Igartua, M., Hernandez R.M., Gascon A.R., Pedraz J.L.,Preparation of sustained release hydrophilic matrices by melt granulation in a high-shear mixer, J. Pharmacy Pharm. Sci., 20058 (2), 132–140.
6. Rodriguez L., Cavallari C., Passerini N., Albertini B., Gonzalez-Rodrigues M.L., Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques, Int. J. Pharm., 2002, 242 (1–2), 285–289.
7. Passerini N., Albertini B., Gonzalez-Rodriguez M.L., Cavallari C., Rodriguez L., Preparation and characterization of ibuprofen-poloxamer 188 granules obtained by melt granulation, Eur. J. Pharm., 2002, Sci. 15, 71–78.
8. Wu C.Y., Benet L.Z., Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system, Pharm. Res., 2005, 22, 11–23.
9. Watanabe T., Wakiyama N., Usui F., Ikeda M., Isobe T., Senna M., Stability of amorphous indomethacin compounded with silica, International Journal of Pharmaceutics, 2001,226, 81–91.

*****