International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1072-1078, Oct-Dec 2009

Enhancement of solubility and dissolution rate of indomethacin with different polymers by compaction process

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ABSTRACT: The purpose of this study was to develop a compaction technique to enhance the solubility, dissolution rate and other physicochemical properties of poorly water-soluble drug indomethacin (IM) with different polymers. The IM was compacted with the different polymers like hydroxy propyl methylcellulose (HPMC), Kollicoat IR, Chitosan, Polyvinyl Pyrrolidone without using any binder and solvent. Polymer and drug were dry-blended, compressed into slugs on a tablet press, and then milled into a granular powder. Dissolution testing of the milled compacted granules were performed in 750 ml dissolution medium at 37°C (n = 6) and at a stirring speed of 100 rpm using six-station USP type-I dissolution apparatus. The compaction processes enhanced drug dissolution rate relative to drug alone and physical mixtures of IM and polymers. The compaction method produced granules with comparable solubility, dissolution and flowability enhancement compared to raw IM. The mechanism for dissolution enhancement is believed to be a microenvironment polymer surfactant effect facilitated by keeping the polymers and drug particles in close proximity during drug dissolution. The compaction method may provide a lower cost, quicker, readily scalable alternative for formulating poorly water-soluble drug substances.
KEYWORDS: Hydroxypropyl methylcellulose; Kollicoat IR; Chitosan; Polyvinyl Pyrrolidone; Indomethacin; Drug dissolution; compaction.

INTRODUCTION

Poorly water-soluble drugs present a problem in pharmaceutical formulations. Improving dissolution properties is a major obstacle that must be overcome because many new drugs discovered by combinatorial chemistry and high-throughput screening are poorly water-soluble, making them poor candidates as new drugs. It is important to improve the solubility and/or dissolution rate for poorly water-soluble drugs because these drugs possess low absorption and bioavailability. Various methods to improve the dissolution of poorly water-soluble drugs have been reported. A common approach to improve the dissolution rate of poorly water-soluble drugs and improve oral bioavailability is by formation of a solid dispersion with a water-soluble rate-enhancing polymer, such as polyethylene glycol. Typical methods for fabricating solid dispersions include solution methods and melt methods, but these techniques are not readily scalable and have the disadvantages of solvent use and potential drug degradation at elevated temperatures.

Compatibility is the process of volume reduction and bond formation in a powder bed during compression, which produces compacts of a certain mechanical strength. When pressure is applied to a powder bed, particle rearrangement occurs first, followed by particle fragmentation and deformation (plastic and elastic deformation), and bond formation on the contact surfaces. Plastic deformation is an irreversible process of particle shape changing that contributes to stronger tablets, while elastic deformation is reversible and leads to elastic recovery of compacts in the decompression phase and the breakage of some previously formed bonds, which results in lower tablet strength and capping problems. In the case of plastically flowing material, the particle shape changes during compression, but the surface area remains nearly unchanged. On the other hand, primary particles of materials that fragment break into smaller parts during compression, leading to an increased surface area and increased number of contact points suitable for bond formation. In both cases plastic deformation occurs at later stages of compression and adequate tablet strength can be obtained. Typical

examples of materials with mainly plastic flow include microcrystalline cellulose (MCC), pregelatinized starch, sodium chloride, etc.; typical materials that mainly fragment include dicalcium phosphate dihydrate (Emcompress), crystal lactose, paracetamol, ascorbic acid, etc.[1]

The main bonding mechanisms involved in compact formation are:

1. Solid bridges, which represent the strongest bonds between particles,
2. Intermolecular or long distance forces (van der Waals forces, electrostatic forces, hydrogen bonding),representing weaker attraction forces, and
3. Mechanical interlocking, denoting hooking and twisting of irregularly shaped particles.[2]

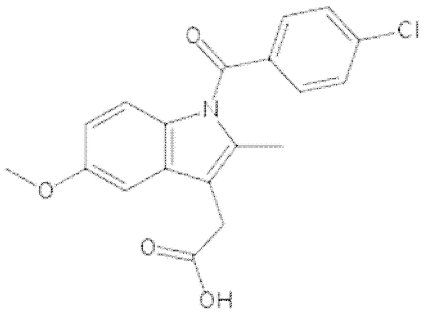
The most common dominant bonding mechanisms for pharmaceutical materials are long distance forces, especially van der Waals forces and hydrogen bonds in some cases. The tensile strength of tablets is generally higher if the particle size is smaller.[3] If the material undergoes fragmentation during volume reduction, the particle size and shape will have a minor effect on tablet strength. Poor compactibility of powders, weak bonds between particles, or extensive elastic relaxation of materials can decrease tablet strength and increase the capping tendency. Capping is a phenomenon whereby extensive elastic relaxation breaks bonds that were formed during compression, leading to laminar breakage of the upper part of the tablet. Capping increases with increasing compression pressure, tableting speed, and tablet thickness, as well as low powder humidity. Using precompression before the main compression during tableting can lead to lower capping incidence.[4]

Dry granulation is one of the options used to reduce capping tendency. It can be performed using a tablet press or roller compactor for the first compaction, in which primary particles are agglomerated to form slugs or ribbons, which are afterwards treated by milling and sieving. It has been demonstrated that multiple compaction of a material can also lead to changes in compatibility. Lower tensile strength is usually observed, due to a reduction in bonding potential, which is partly spent during the first compression and not completely recovered while breaking the slugs or ribbons.[5]

In the field of pharmaceutical powder compaction, it is often necessary to improve the material flow properties in order to obtain a uniform die-filling in a tablet press. The flow properties can be enhanced by converting fine powders into larger agglomerates. Wet granulation is traditionally applied because the equipment and knowledge are available. In wet granulation, a fluid binder is distributed on a powder blend and subsequently the granules are dried.[6]

Dry granulation, is a widely used process for granulation without water. This method allows the granulation of materials sensitive to moisture and heat.[7]Several researchers have developed methods to use hydroxypropyl methylcellulose (HPMC) as a dissolution rate-enhancing polymer. However, use of HPMC in solid dispersions is complicated by its unique solution properties, non thermoplastic nature, and charring at elevated temperature. There is a need in the pharmaceutical industry for an easily scalable method to combine poorly water-soluble drugs and dissolution rate enhancing polymers without the use of solvent or heat addition.[8] Crystal modifications can also appear during the compaction process. Changes in crystal form may changes the solubility, dissolution and other physicochemical properties.[9]

Indomethacin was discovered in 1963 and it was first approved for use in the U.S. by the Food and Drug Administration in 1965. Its mechanism of action, along with several other NSAIDs that inhibit COX, was described in 1971.Indomethacin is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. Indomethacin is a methylated indole derivative and a member of the arylalkanoic acid class of NSAIDs.



2-{1-[(4-chlorophenylcarbonyl]-5-methoxy-2-methyl-1*H*-in dol-3- yl} acetic Acid

Indomethacin (IM, 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, BCS) along with very poor flowability.

The present aim of the work is to prepared compacted granules of Indomethacin with different polymers by using slugging method. The prepared granules were evaluated for saturation solubility, dissolution rate and other physicochemical properties like density and flow properties. Finally compare the all mentioned physicochemical properties of prepared compacted granules with the raw crystals of Indomethacin.

MATERIALS AND METHOD

MATERIALS:

Indomethacin (98% purity) was obtained from Sun Pharma (Vadodara, Gujarat, India). Hydroxy Propyl Methyl Cellulose (HPMC-E5), Kollicoat IR was obtained as gift samples from Alembic research centre (Vadodara, Gujarat, India). Chitosan was obtained as gift sample

from Central Institute of Fisheries Technology Cochin (Degree of deacetylation 86%).Polyvinyl Pyrrolidone (Povidone-K30) was obtained from Loba Chemicals (Mumbai, India).

METHOD:

Preparation of slugged Physical powder mixtures of different polymers and the poorly water-soluble drugs (Indomethacin) at drug: Polymer ratios mentioned in table: 1 was dry-blended. Slugs were prepared by compression of the resulting physical mixtures on a KBR Press with 30 second dwell time. Round, flat-faced punches with 13-mm diameter were used. A compression force of 1 tone was utilized for all slugs, and the range for slug weight was 500-800 mg. The resulting slugs were milled in mortar and pastel then passed through sieve no # 22 so as to form uniform compacted granules containing drug and polymers. Prepared the physical mixture (Table: 2) of the all compacted formulation by simply mixing the drug and polymer in the mortar and pastel without compaction.

YIELD AND DRUG CONTENT DETERMINATION:

The prepared compacted granules and physical mixtures were weighed after processing and product yield was calculated. Compacted granules (100 mg) were powdered, from which powder equivalent to 20 mg IM was weighed and extracted using three portions of 100mL Phosphate buffer pH 6.8. Each portion was filtered through a G-4 sintered glass filter and volume was adjusted to 100 mL.After sufficient dilutions with Phosphate buffer pH 6.8, samples were analysed spectrophotometrically at 320nm and IM content was calculated.

SATURATION SOLUBILITY STUDY:

Saturation solubility study of Indomethacin and their compacted granules were carried out in distilled water. Each excessive quantity (50 mg) of IM and equivalent prepared compacted granules 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 hr 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 analysed at 320 nm by UV-visible spectrophotometer (Jasco model). The study was performed in triplicate (n = 3).

DENSITY AND FLOWABILITY DETERMINATION:

Flow properties of the drug and prepared compacted granules were studied by determining the bulk density (σb), tap density (σt), 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 (σb) = Mass / Poured volume (1)

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

Carr's Index = [(σt – σb) / σt] x 100 (3)

Hausner ratio = (σt / (σb) (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

IN VITRO DISSOLUTION STUDY:

In vitro dissolution was evaluated using a conventional dissolution test. Powder dissolution studies were carried out first on the pure drug and second on the compacted granules. Each test was carried out in 750 ml dissolution medium at 37°C ±0.5^{0}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 with the dissolution medium and analysed at 320 nm using a UV Vis spectrophotometer (Jasco model).

RESULTS AND DISCUSSION

The different hydrophilic polymers and drug IM were utilized for compaction process: dry blending of drug and polymer to produce a simple physical mixture, and compacting the blends by slugging with single punch compression machine and subsequent milling. The slugging processes resulted in enhanced dissolution rate for the poorly water-soluble IM compared to the drug and the corresponding physical mixture. The slugging methods produced comparable solubility and rate and extent of drug dissolution. The production yield was found satisfactory and ranged from 87% to 92% for the compacted granules. The drug content of compacted granules is also found satisfactory ranged from 92 % to 96%.

Saturation solubility:
The solubility study was carried out in distilled water. The results of the solubility study of compacted granules, physical mixtures were mentioned in table: 3 and figure: 1-2 .The solubility studies revealed that the solubility of IM in distilled water was 9.5 µg/ml. The solubility of the physical mixture were slightly improves (insignificantly) compared to the indomethacin raw drug crystals. There is significant improvement in ($P < 0.01$) the solubility of compacted granules with different polymers mentioned in above table: 3. The solubility of compacted granules with Kollicoat IR (grafted polymer of PEG and PVP) was shows on higher side (90.5 µg/ml) followed by compacted granules with HPMC, PVP and chitosan. This improvement in solubility may be due to changes in the crystal forms, structure, and surface modification during compaction process with different polymers.

Density and flowability:
Indomethacin shows poor flow properties having larger Angle of repose, Carr's Index (CI) and Hausner's ratio mentioned in table: 4. The compacted granules for indomethacin significantly improve 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 spherical shape and a lower static electric charge.

Dissolution study:
In the dissolution study, IM-HPMC showed 97 % cumulative drug releases in 20 min followed by IM-CTS (94%), IM-PVP (92%), and IM-KIR (90%) from compacted granules as compared with IM (56 %) [Figure: 3].The order of improving the dissolution rate is IM-HPMC> IM-CTS> IM-PVP> IM-KIR> IM.The mechanism for how the compaction process enhanced dissolution properties is believed to be a microenvironment surfactant effect of used hydrophilic polymers. The used polymers in compaction process gives enhanced dissolution due their local surfactant concentration in the boundary layer surrounding the drug particles, providing a lower energy pathway for drug dissolution. The compaction processes are believed to be particularly effective at enhancing the rate of drug dissolution because the drug particles are maintained in direct contact with the hydrophilic polymer particles during drug dissolution, in contrast with a physical mixture where the drug and polymer particles may quickly disperse and be separated in the dissolution medium.

Evidence that hydrophilic polymers may act as a surfactant to facilitate drug dissolution is found in and Fig.3 where dissolved polymers in the bulk medium resulted in faster drug dissolution for physical mixtures compared to the drug alone. It was also demonstrated that polymer presence is critical to the dissolution enhancement mechanism. Samples of the drugs alone subjected to the same slugging procedure which did not exhibit faster drug dissolution.

CONCLUSIONS

A readily scalable compaction process requiring no solvent and no heat addition was effective in enhancing drug dissolution of poorly water soluble drug (Indomethacin). Compacting poorly water-soluble drug particles with different hydrophilic polymers like HPMC, kollicoat IR, PVP and Chitosan particles resulted in a granular powder having enhanced drug solubility and dissolution properties. Drug dissolution rates were comparably high for compacted granules then their physical mixture and drug alone, suggesting that compaction processes with hydrophilic polymers improve the drug dissolution rate. The mechanism is believed to be a microenvironment polymer effect facilitated by keeping the polymers and drug particles in close proximity during drug dissolution.

Table: 1 Product code of IM compacted granules with different polymers.

Product Code	Polymer used	Drug: Polymer ratio
IM	Indomethacin (API)	**-----**
IM-HPMC	Hydroxy propyl methyl cellulose	1:0.1
IM-CTS	Chitosan	1:0.1
IM-KIR	Kollicoat IR	1:1
IM-PVP	Polyvinyl Pyrrolidine (Povidone-K30)	1:0.2

Table: 2 Product code of physical mixture of IM with different polymers.

Product Code	Polymer used	Drug: Polymer ratio
IM	Indomethacin (API)	**-----**
IM-HPMC(PM)	Hydroxy propyl methyl cellulose	1:0.1
IM-CTS(PM)	Chitosan	1:0.1
IM-KIR(PM)	Kollicoat IR	1:1
IM-PVP(PM)	Polyvinyl Pyrrolidine (Povidone-K30)	1:0.2

Table 3: Evalvation of IM with its compacted granules and physical mixtures using different polymers.

Product code	Product yield (%)*	Drug content (%)*	Solubility (µg/mL)*
IM	-----	97 ± 2.354	9.5 ± 0.561
IM-HPMC	87 ± 1.326	92 ± 1.896	87.6 ± 1.865
IM-CTS	90 ± 2.365	94 ± 2.987	70.8 ± 2.566
IM-KIR	92 ± 2.356	92 ± 3.568	90.5 ± 1.654
IM-PVP	88 ± 1.897	95 ± 2.567	75.8 ± 1.359
IM-HPMC(PM)	95 ± 2.756	96 ± 2.568	22.5 ± 1.104
IM-CTS(PM)	96 ± 2.359	95 ± 2.759	24.6 ± 0.987
IM-KIR(PM)	96 ± 1.896	96 ± 0.456	28.3 ± 0.866
IM-PVP(PM)	98 ± 2.568	94 ± 0.357	23.9 ± 0.859

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

Table: 4 Densities and flowability determination of Indomethacin and their recrystallized agglomerates.

Sr.No.	Product Code	Bulk Density (gm/mL)	Tap Density (gm/mL)	Angle of repose(^{0})	Carr's Index(CI)	Hausner's ratio
01	**IM**	0.386	0.545	42.76	29.17	1.412
02	**IM-HPMC**	0.286	0.345	22.56	17.10	1.206
03	**IM-CTS**	0.274	0.315	20.36	13.02	1.150
04	**IM-KIR**	0.264	0.308	18.58	14.29	1.167
05	**IM-PVP**	0.257	0.298	21.56	13.76	1.160

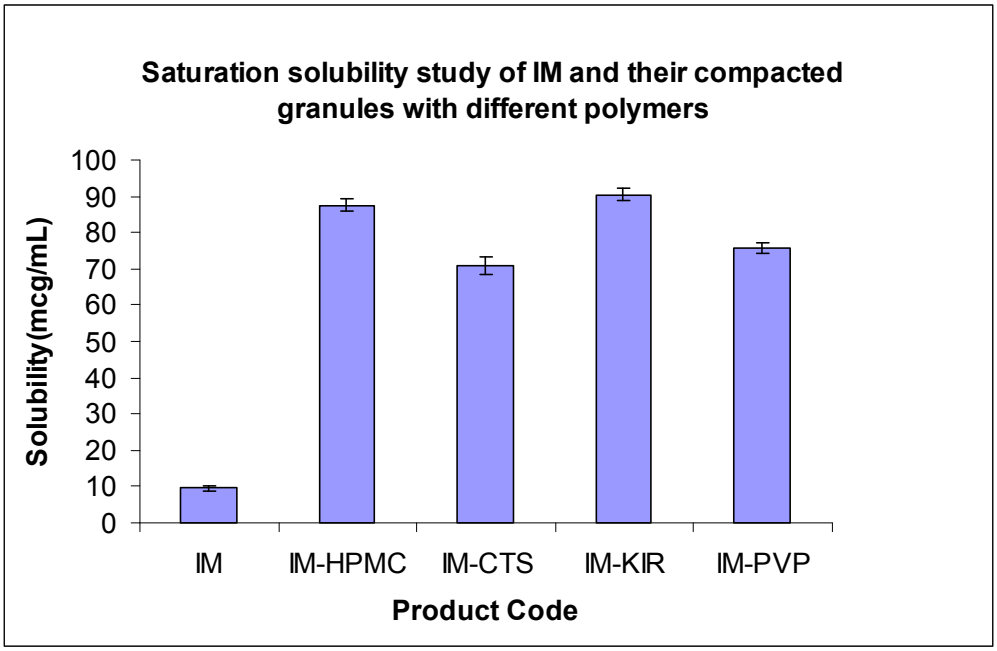


Figure: 1 Saturation solubility of IM and their compacted granules with different polymers.

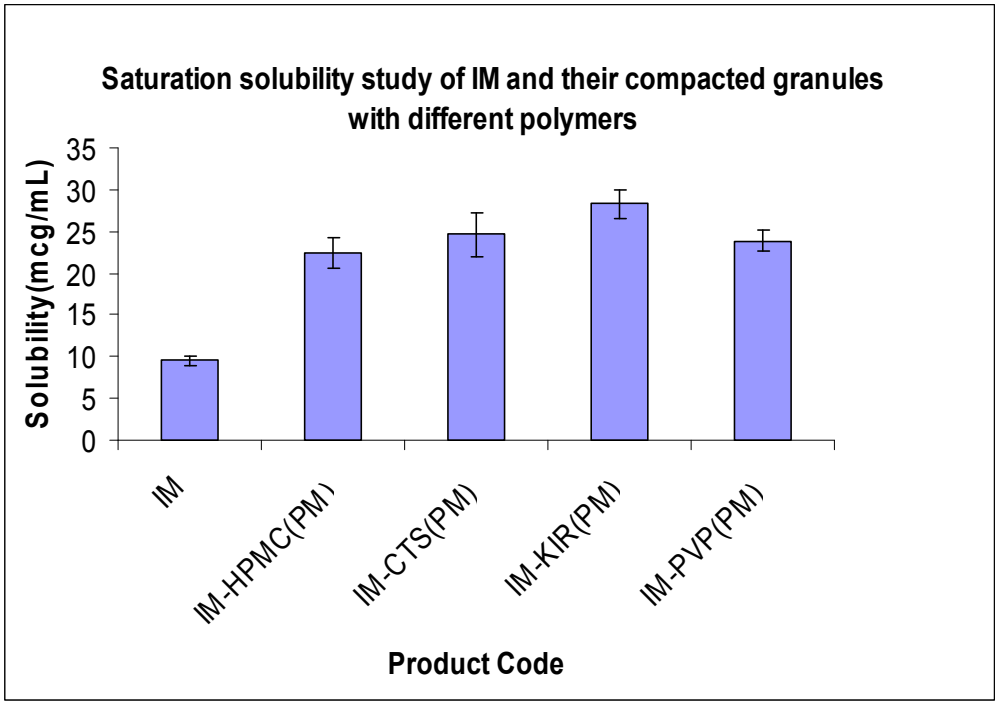


Figure: 2 Saturation solubility of IM and their compacted granules with different polymers.

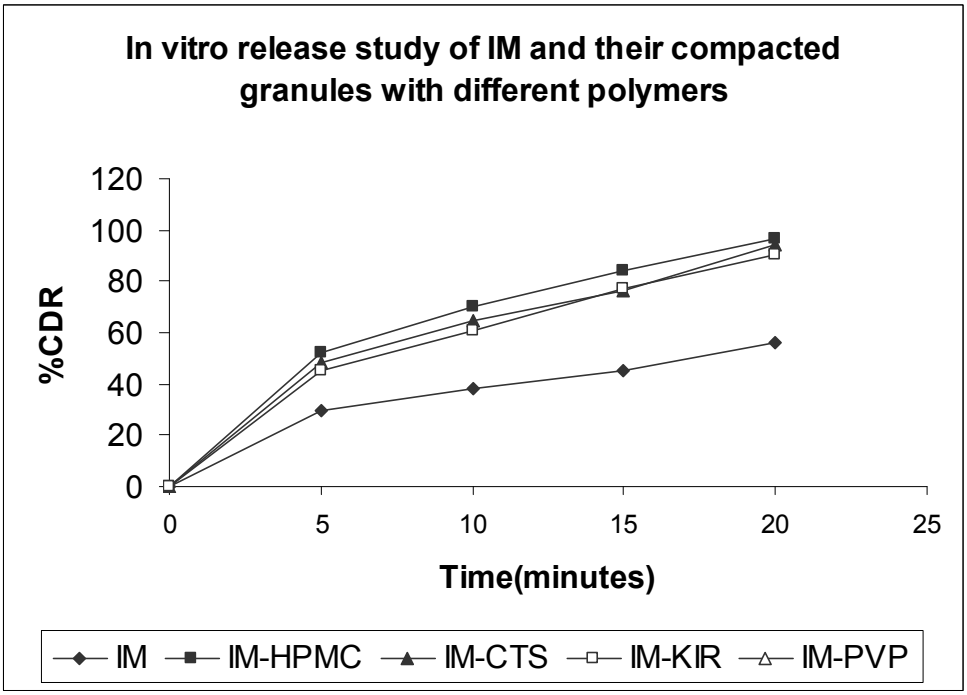


Figure: 3 In vitro dissolution studies of IM and their compacted granules with different polymers.

ACKNOWLEDGEMENTS

The authors wish to thank Sun Pharmaceutical Ltd. Gujarat (India) for providing Indomethacin as gift sample for this research work.

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