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Improvement of Solubility and Dissolution of Indomethacin by Liquisolid and Compaction Granulation Technique

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ABSTRACT:
The purpose of this study was to develop novel techniques to enhance the dissolution rate of poorly water-soluble drugs substance Indomethacin (IM).The granules of IM were prepared by nonaqueous liquisolid and compaction technique by using different excipients. As per the novel formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in appropriate non-volatile liquid vehicles, can be converted into suitably flowing and compressible powders by blending with particular powder excipients. In the liquisolid system, IM was dispersed in Polyethylene glycol-400 (PEG 400) as a non volatile liquid vehicle. Microcrystalline cellulose (Avicel PH 102) and dibasic calcium phosphate (DCP) were used as the carrier, Hydroxypropylmethyl cellulose (HPMC) was used as coating material and sodium starch glycolate (SSG) and crosscarmellose sodium (CCS) were used as disintegrants.The granules were also prepared by compaction technique with the same excipients except non volatile liquid vehicle (PEG 400).The obtained granules from liquisolid compact system display enhanced solubility and invitro release profiles due to the increased wetting properties and surface of drug available for dissolution compared to granules obtained from compaction technique and physical mixture. It was also observed that the drug release rate, water solubility and wettability of liquisolid granules containing super disintergrants were on higher side compared to liquisolid granules without superdisintegrants.

KEY WORDS:
Carrier, Compaction, Dissolution rate, Indomethacin, Liquisolid compacts, Wettability.

INTRODUCTION:

The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of newly developed, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water-insoluble drugs are a major challenge for pharmaceutical formulation scientists. The use of water-soluble salts and polymorphic forms, reducing particle size to increase surface area, the formation of water-soluble molecular complexes, solid dispersion, co-precipitation, lyophilization, microencapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs [1].

The most common method is to increase surface area of the drug by micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted [2-4]. Micronized drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs [5-8].

The technique of 'liquisolid compacts' is a new and promising addition towards such a novel aim for solubility and dissolution improvement. Liquisolid system refers to

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formulations formed by conversion of drug suspensions or solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Various grades of cellulose, starch, lactose, etc., may be used as the carrier, whereas very fine particle size silica powder may be used as the coating material. The advantage of Liquisolid techniques includes simplicity, low cost and capability of industrial production. The compression of these latter systems resulted in a significant 'Liquid Squeezing Out' phenomenon [9-11].It is claimed that if hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained [12-15]. Therefore, it is suggested that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability. According to literature survey the Piroxicam [5], Prednisolone [17], Carbamazepine [17] Propranolol hydrochloride [18], Hydrochlorothiazide [19] liquisolid compacts were prepared for improving the physicochemical properties.

Poorly water-soluble drugs (indomethacin) involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability. It has been established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The rate of absorption of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e., the dissolution rate is often the rate-determining step in drug absorption. Therefore, the solubility and dissolution behaviour of a drug are the key determinants of its oral bioavailability. Indomethacin (IM, γ -indomethacin; 1-(p chlorobenzoyl)-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), and thus the increase in solubility will improve their bioavailability [20-22]. In the present study, the effects of different excipients on the solubility and dissolution profile of indomethacin liquisolid and directly compressible compacted granules were studied.

MATERIALS AND METHOD:

Materials:

Indomethacin (IM) was supplied as a gift sample from Lupin Research Park (Pune, India).Dibasic calcium phosphate, Sodium starch glycolate, Croscarmellose Sodium, Sodium starch glycolate; hydroxy propyl methyl cellulose was procured from Alembic Research Ltd (Vadodara, India). Polyethylene glycol-400 and other raw materials were procured from S. D. Fine (Mumbai, India).

Preparation of granules from liquisolid compact:

Indomethacin (2gm) was dispersed in a nonvolatile vehicle (propylene glycol-PEG 400).Then a binary mixture of carrier-coating materials (microcrystalline

cellulose and dibasic calcium phosphate as the carrier powder and HPMC as the coating material at a ratio of 10:0.5) was added to the mixture containing the drug and propylene glycol under continuous mixing in a mortar. Finally, disintegrants was mixed with the prepared mixture for a period of 5 minutes. The obtained liquisolid system was then compressed using KBR Press (Techno search model-M-15) having 13mm die and flat punches. The obtained liquisolid compact was then beaked and passed through sieve no # 20 to obtain uniform sized granules from liquisolid compact.

Preparation of granules by comp ression technique:

Prepare the slug of Physical powder mixtures of different polymers and Indomethacin at drug: Polymer ratios mentioned in table: 2 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 # 20 so as to form uniform compacted granules containing drug and polymers.

Prepared the physical mixture (Table: 1) 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 liquisolid and compacted granules along with their 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 prepared granules with physical mixtures were carried out in distilled water. Each excessive quantity (50 mg) of IM and equivalent quantity of prepared 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 analyzed 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 IM and secondly on the prepared granules by liquisolid and compaction technique. The dissolution medium used was mixture of one volume of Phosphate buffer pH and four volumes of distilled water. 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. An accurately weighed quantity of each sample equivalent to 50 mg of IM was subjected to the dissolution test. 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 to maintain sink condition. Samples were filtered through a 0.44 m filter, suitably diluted and analysed at 320 nm using a UV Vis spectrophotometer (Jasco model).

RESULTS AND DISCUSSION:

Production yield and drug content:

The production yield (table:2) of the prepared granules by liquisolid technique shows above 90 % which was calculated by measuring the weight of the prepared granules by considering the raw material taken for the granules as 100.0%. The production yield of granules by compaction technique were on lower side in between 80-90%.The content in the prepared granules and their physical mixture shows in range of 94 to 96%.

Saturation solubility:

The solubility of IM in and prepared granules with their physical mixtures in distilled water are given given in Table.2. The table shows that the solubility of IM in distilled water is lower (9.5µg/mL) comparative to the granules prepared by liquisolid and compaction technique and their physical mixtures. The saturation solubility of granules from liquisold system shows on higher side IMLSM2 (170 µg/mL) > IMLSD2 (150 µg/mL) > IMLSM1 (90 µg/mL) > IMLSD1 (80 µg/mL) comparative to granules obtained from compaction system IMDCM2 (95 µg/mL) > IMDCM1 (85 µg/mL) > IMDCD2 (80 µg/mL) > IMDCD1 (60µg/mL).The significantly improvement of solubility of Indomethacin in liquisolid technique may be due to hydrophilic nature of the used non volatile organic solvent (PEG 400) and different excipients which are adhere to the drug particle and make hydrophilic environment when the formulation come in contact with water. The solubility of granules prepared by compaction technique was also improve comparative to physical mixture and IM due to the hydrophilic microenvironment of excipients and superdisintegrants around drug particles.

Powder bed hydrophilicity study:

Table: 2 indicate powder bed hydrophilicity study of IM and prepared granules by liquisolid and compaction technique. The prepared granules showed significantly shortest rising time (** $P<0.01$) of water to its surface as compared to raw IM crystals represent better wattability of prepared granules as compared to raw IM. The order of wettability was IM > IMDCD1 > IMLSD2, IMLSM1 > IMDCM1, IMDCD2, IMLSD1 > IMDCM2 > IMLSM2.The reason for the superior water rising time (wettability) of liquisolid granules followed by compaction granules may due to adsorption of hydrophilic

Table: 1 Product codes of granules prepared by liquisolid and compaction technique along with their physical mixture.

Product Code	Indomethacin (2.0 gm)	Non-volatile solvent(0.5mL)	Carrier (1.5 gm)	Coating material (0.2 gm)	Superdisintegrant (0.3gm)
IMLSD1	IM	PEG-400	DCP	HPMC	-----
IMLSD2	IM	PEG-400	DCP	HPMC	SSG
IMLSM1	IM	PEG-400	MCC	HPMC	-----
IMLSM2	IM	PEG-400	MCC	HPMC	CCS
IMDCD1	IM	-----	DCP	HPMC	-----
IMDCD2	IM	-----	DCP	HPMC	SSG
IMDCM1	IM	-----	MCC	HPMC	-----
IMDCM2	IM	-----	MCC	HPMC	CCS
IMLSD1(pm)	IM	-----	DCP	HPMC	-----
IMLSD2(pm)	IM	-----	DCP	HPMC	SSG
IMLSM1(pm)	IM	-----	MCC	HPMC	-----
IMLSM2(pm)	IM	-----	MCC	HPMC	CCS

a) IM = Indomethacin, b) PEG = Polyethylene glycol, c) DCP = Dibasic calcium phosphate, d) MCC = Microcrystalline cellulose, e) SSG = Sodium starch glycolate, f) CCS = Croscarmellose Sodium

Table: 2 Evaluation parameters of IM and its prepared granules and physical mixtures.

Product code	Product yield (%)	Drug Content (%)	Solubility (µg/mL)	Wettability study (water raising time-hrs)
IM	-----	98 ± 2.65	9.5 ± 0.85	9.0 ± 0.26
IMLSD1	92 ± 2.23	95 ± 3.26	80 ±2.69	6.0 ± 0.29
IMLSD2	93 ± 1.25	94 ± 2.45	150 ±3.10	5.0 ± 0.36
IMLSM1	92 ± 2.36	96 ± 2.65	90 ±3.75	5.0 ± 0.12
IMLSM2	92± 3.21	95 ± 2.59	170 ±3.25	4.5 ± 0.24
IMDCD1	87 ± 2.38	95 ± 3.58	65 ±1.25	7.0 ± 0.33
IMDCD2	88 ± 3.48	94 ± 2.57	80 ±2.45	6.0 ± 0.31
IMDCM1	87 ± 2.69	96 ± 2.59	85 ±1.35	6.0 ± 0.36
IMDCM2	89 ± 3.47	95 ± 2.56	95 ±2.35	5.0 ± 0.26
IMLSD1(pm)	97 ± 2.65	96 ± 2.64	17 ±0.79	8.0 ± 0.12
IMLSD2(pm)	98 ± 3.56	97 ± 3.56	25 ±0.65	7.5 ± 0.21
IMLSM1(pm)	96 ± 2.58	95 ± 2.48	22 ±0.95	7.0 ± 0.45
IMLSM2(pm)	98 ± 3.69	96 ± 3.56	30 ±0.87	6.5 ± 0.35

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

Table: 3 Density and flowability parameters of IM and its prepared granules and physical mixtures.

Product code	Bulk density (gm/mL)	Tap density (gm/mL)	Carr's Index	Hasner ratio	Angle of repose (degree)
IM	0.386 ±0.025	0.545 ±0.035	29.17 ±0.986	1.412 ±0.026	42.76 ±1.252
IMLSD1	0.366 ±0.035	0.435 ±0.036	15.86 ±0.056	1.189 ±0.035	27.23 ±1.235
IMLSD2	0.355 ±0.045	0.398 ±0.045	10.80 ±0.058	1.121 ±0.056	25.25 ±1.105
IMLSM1	0.345 ±0.035	0.405 ±0.063	14.81 ±0.059	1.174 ±0.025	26.98 ±2.056
IMLSM2	0.365 ±0.032	0.412 ±0.045	11.41 ±0.025	1.129 ±0.023	27.56 ±1.256
IMDCD1	0.276 ±0.035	0.332 ±0.045	16.87 ±0.897	1.203 ±0.015	25.56 ±1.356
IMDCD2	0.264 ±0.012	0.308 ±0.065	14.29 ±0.789	1.167 ±0.013	26.36 ±1.254
IMDCM1	0.254 ±0.024	0.298 ±0.015	14.77 ±0.578	1.173 ±0.026	28.58 ±1.359
IMDCM2	0.247 ±0.015	0.285 ±0.035	13.33 ±0.856	1.154 ±0.024	26.56 ±1.654
IMLSD1(pm)	0.315 ±0.024	0.395 ±0.085	20.25 ±0.035	1.254 ±0.026	24.58 ±1.235
IMLSD2(pm)	0.295 ±0.039	0.365 ±0.065	19.18 ±0.014	1.237 ±0.045	23.67 ±1.245
IMLSM1(pm)	0.325 ±0.045	0.392 ±0.045	17.09 ±0.025	1.206 ±0.025	25.76 ±1.265
IMLSM2(pm)	0.335 ±0.035	0.415 ±0.095	19.28 ±0.065	1.239 ±0.015	26.49 ±1.456

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

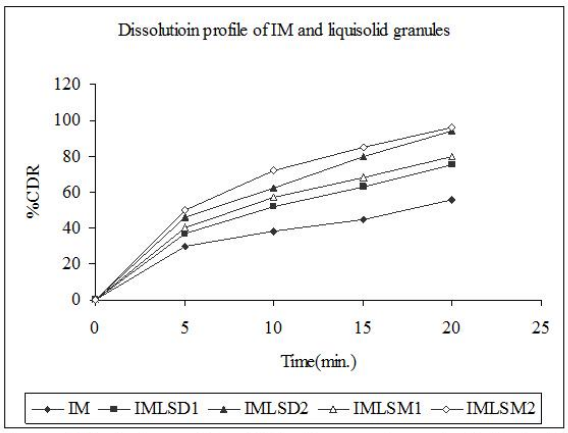

Figure: 1 Dissolution profiles of IM and prepared granules by liquisolid technique.

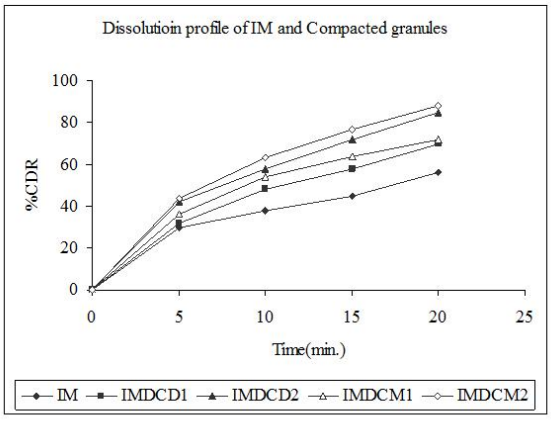

Figure: 2 Dissolution profiles of IM and prepared granules by compaction technique.

excipients on the raw crystals of IM during granules preparation.

Flowability parameter:

Table: 3 represent flowability parameters of the IM and prepared granules in term of Angle of repose, Carr index and Hausnar ratio. The prepared granules by both technique were found to have significantly lower angle of repose (** $P<0.01$) in comparison to the raw crystals of IM ,which could be due to the irregular shaped crystals of IM, which hindered in the uniform flow of crystals from funnel. The reason for the excellent flowability of prepared was due to significant reduction in interparticle fraction because of their agglomerated spherical shape with reduction in the surface area. The Carr index revealed that the flowability of the IM was significantly poor (** $P<0.01$) then that of the granules i.e. these granules were lower Carr index then raw crystals. Hausnar ratio of granules was less then a raw crystal indicates improvement in flowability of the prepared granules.

Dissolution:

In the dissolution study, the granules prepared from liquisolid system IMLSM2 showed 96 % cumulative drug releases in 20 min followed by IMLSD2 (94%), IMLSM1 (80%), and IMLSD1 (75%) as compared with IM (56 %).The order of improving the dissolution rate is IMLSM2> IMLSD2> IMLSM1> IMLSD1> IM.Similarly the granules prepared from compaction system IMDCM2 showed 88 % cumulative drug releases in 20 min followed by IMDCD2 (85%), IMDCM1 (72%) and IMDCD1 (70%) as compared with IM (56 %).The order of improving the dissolution rate is IMDCM2 > IMDCD2 > IMDCM1 > IMDCD1 > IM.

To evaluate the effect of type of carrier on dissolution profile, several formulations were prepared using different carrier and dissolution test were performed. Microcrystalline cellulose has disintegration property, which could facilitate disintegration of granules and improve the dissolution of IM. Because of the presence of a non-volatile solvent acting as a binding agent in the liquisolid formulation, delayed disintegration time is expected. However, in the liquisolid granules containing microcrystalline cellulose, a fast disintegration of granules occurred which can be explained by the disintegrating property of microcrystalline cellulose as compared to granules containing DCP.Here in this study HPMC (2.5%) was used as coating material, if the quantity was increased (5% and above) in formulation they showed low dissolution rate. This could be due to the formation of gel around the disintegrated particles by HPMC, which builds a barrier against diffusion of the dissolved drug into dissolution medium. The use of super disintegrants in the liquisolid technique decreases the disintegration time and increaseas the dissolution rate comparative to without disintegrants.

CONCLUSION:

The granules preparation by compaction and liquisolid process requiring no solvent and no heat addition was effective in enhancing drug dissolution of poorly water-soluble drug Indomethacin. Granules of Indomethacin drug particles by liquisolid and compaction with different diluents, superdisintergratns and polymers resulted in a granular powder having enhanced solubility and dissolution properties. The results showed that the liquisolid technique could be a promising alternative technique to increase the solubility and dissolution of water insoluble drugs. There may be changes in crystallinity of the drug or any interaction between the drug and exipients during the formulation process. The prepared granules also shows improvement in flowability, wettability compared to IM and their physical mixture with different excipientys.The mechanism for solubility

and dissolution improvement of prepared granules may be due to hydrophilic microenvironment around the drug during dissolution process.

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