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Original Article

Enhancement of Solubility and Dissolution Rate of Indomethacin by Chitosan Based Solid Dispersion Technique.

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Abstract

Indomethacin is widely used as NSAID and having low aqueous solubility and high permeability (BCS Class II) along with very poor wettability, flowability and dissolution rate. In present investigation solubility and dissolution rate of Indomethacin was improved by solid dispersion (Kneading method) with different diluents (Lactose monohydrate, microcrystalline cellulose), superdisintegrants (croscarmellose sodium, sodium starch glycolate) and water soluble chitosan as polymer. Prepared solid dispersion systems were evaluated for drug content, wettability, saturation solubility, dissolution rate and flowability. Solid dispersion with microcrystalline cellulose and sodium starch glycolate or combination showed significant improvement in solubility and dissolution rate as compare to other dispersion system, physical mixture and drug. Solid state characterization of optimized dispersion system were done by using Thin layer chromatography(TLC),X-ray powder diffraction(XRD), Fourier transform infrared spectroscopy (FTIR) techniques. All prepared solid dispersion systems showed improvement in solubility, wettability, dissolution rate and flowability. The TLC study of optimized dispersion system showed compatibility of used excipients with drug, XRD study shows decrease in crystallinity and FTIR study reveals non significant changes in chemistry of IM in solid dispersion.

Keywords: Indomethacin, Kneading, saturation solubility, superdisintegrants, chitosan.

1. Introduction

Chitosan is a linear cationic polysaccharide obtained by N-deacetylation of chitin, a naturally-occurring structural polysaccharide copious in crab and shrimp shells. It has newly emerged as one of most promising biopolymers for a variety of prospective applications in both biomedical and pharmaceutical fields since it exhibits several desirable biological properties such as non-toxicity, good biocompatibility and biodegradability, accompanied by wide availability in nature, low cost and high flexibility in use. (Felt, Buri, and Gurny, 1998) (Illum, 1998) (Paul and Sharma, 2000) In addition to its use as an additive for direct compression (Upadrashta, Katikaneni and Nuessle, 1992) (Ritthidej, Chomto, Pummangura and Menasveta, 1994), now day's application of chitosan has been examined for its potential in development of a range of drug delivery systems, due to its polymeric cationic character, gel- and film-forming abilities, bioadhesiveness and transmucosalpenetration enhancer properties (Artursson, Lindmark, Davis, Illum, 1994) (Henriksen, Green, Smart, Smistad, and Karlsen, 1996) (Kas,

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1997). Some authors effectively used chitosa n as effectiveness in enhancing dissolution properties and bioavailability of poorly-soluble drugs. (Shete, Yadav and murty, 2012) (Portero, Remunan-Lopez, Vila-Jato, 1998) (Shiraishi, Arahira, Imai, and Otagiri, 1990). During last decade trend in drug discovery has been produces several compounds that exhibit high lipophilicity and poor water solubility.
(Lipinski, Lombardo, Dominy, and Feeney, 1997). Many approaches have been developed to improve solubility and to enhance dissolution rate of poorly water soluble drugs, including both modifications to drug substance itself and creation of specific formulations. Physical modifications often aim to increase surface area, manipulation of crystallanity (Yadav, Shete, Dabake, Kulkarni and Sakhare, 2009) (Yadav, Shete, Dabake, 2010) solubility and wettability of the powder particles and therefore typically focus on particle size reduction or generation of amorphous states. (Hancock and Zografi, 1997) (Grau, Kayser, and Muller 2000)
The poor solubility and dissolution rate of poorly water soluble drug substances in aqueous gastro-intestinal fluids often cause insufficient bioavailability. Especially for class II substances according to Biopharmaceutics Classification System (BCS), bioavailability may be enhanced by increasing solubility and dissolution rate of dru g in gastro-intestinal fluids. (Leuner and Dressman 2000). This may be achieved by incorporating drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on properties of both, drug and carrier, and depending on their ratio, a solid solution of drug in carrier material may be formed. The mechanisms involved in solubility and dissolution rate enhancement include transformation of stable medications into less stable ones or even into amorphous state, reduction of particle size possibly to molecular level as well as enhancement of wettability and solubility of drug by the carrier material.
Indomethacin (IM, γ -indomethacin; 1-(pchlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid), being sparingly soluble in aqueous media is one of 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) along with very poor flowability. (Wu and Benet, 2005). (Watanabe, Wakiyama, Usui, keda, Isobe and Senna 2001).
Based on effectiveness of chitosan in enhancing dissolution of poorly water soluble drug, in present work we investigated influence of several excipients on indomethacin dissolution rate by dispersion method with chitosan. Solid dispersion systems were prepared by using different polymers, drug/polymer ratios and with different techniques (physical mixture of drug with excipients, solid dispersion-kneading) and characterized by Thin Layer Chromatography (TLC), X-ray powder diffractometry and FT-IR spectroscopy.

1. Materials and methods

1.1. Materials

Indomethacin (IM) was supplied as a gift sample from Lupine Ltd, (Aurangabad, India).Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate were supplied as gift sample from Alembic Research Center (Vadodara, India). Water-soluble chitosan from Central Institute of Fisheries Technology, Cochin. All other chemicals were obtained from Loba Chemicals, Mumbai, India.

Materials and Methods

Preparation of solid dispersion by kneading method

Indomethacin (IM) and various hydrophilic dilu ents (Lactose monohydrate, microcrystalline cellulose), superdisintegrants (croscarmellose sodium, sodium starch glycolate) or combination of both were weighed in different ratio as shown in table 1 and transferred to mortar for kneading using water soluble chitosan solution in water up to 45 minutes. Sufficient water was being added to maintain paste like consistency. Resulting paste was then dried in hot air oven at 45ºC for 24 hours. Dried dispersions were milled and passed through sieve no. 20.The prepared dispersions were stored in glass vials and used for further studies.

Preparation of physical mixtures

Indomethacin (IM) and various hydrophilic diluents (Lactose monohydrate, microcrystalline cellulose), superdisintegrants (croscarmellose sodium, sodium starch glycolate) or combination of both along with powder of water soluble chitosan were weighed in different ratio as per mentioned in table 1 and transferred to mortar for mixing.

Drug content determination

The prepared solid dispersion systems and their respective physical mixture (≈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 to100mL. After sufficient dilutions with Phosphate buffer pH 6.8, samples were analyzed spectrophotometrically at 320nm and IM content was calculated. The study was performed in triplicate (n = 3).

Saturation solubility study

Saturation solubility study of Indomethacin and prepared solid dispersion systems with their respective physical mixtures were carried out in distilled water. Each excessive quantity (50 mg) of IM and equivalent quantity of prepared solid dispersion systems 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 24hr samples were withdrawn and filtered through 0.2µ filters (Ultipor®N66, 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).

In vitro Dissolution study

The dissolution medium was a mixture of one part of Phosphate buffer pH and four parts of distilled water. 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 dissolution medium was kept constant throughout run by replacing removed samples with an equivalent volume of fresh dissolution medium to maintain sink condition. Samples were filtered through a 0.44 µ filter, suitably diluted and analyzed at 320 nm using a UV Visible spectrophotometer (Jasco V-531, Japan).

Wettability study (Powder bed hydrophilicity test)

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 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.

Flow parameters

Flow properties of the drug and prepared granules were studied by bulk density (σb), tap density (σt), Carr's Index and Hausner ratio and angle of repose.

2.2.8. Thin layer chromatography (TLC)

Qualitative TLC was carried out using 10X10 cm pre coated silica gel 60 aluminium backed TLC sheets with layer thickness of 0.25 mm. A dichloromethane solution of an accurately weighed amount of indomethacin and prepared solid dispersion systems was applied, using a sample applicator, directly onto the TLC sheet, leaving 2 cm from the edge. The sheet was developed with Benzene–Ether–Glacial acetic acid– Methanol (120+60+18+1) system in chamber for 20 min. After development, the sheet was air dried and examined under UV light. The experiment was duplicated under identical conditions.

2.2.9. PXRD study

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer (Philips PW 1729,Analytical XRD, Holland) for the samples using Ni filtered CuK(α) radiation (intensity ratio(α1/ α2): 0.500), a voltage of 40 KV, a current of 30 mA and receiving slit of 0.2 inches. The samples were analyzed over 2q range of 5.010-39.990^{o} with scanning step size of 0.020^{o} (2q) and scan step time of one second. To minimize the effect particle size on preferred orientation, all the samples were passed through sieve #120 and collected on sieve # 240(# 120/240).

2.2.10. Fourier transform infrared spectroscopy (FTIR) study

FT-IR spectra of prepared spherical agglomerates along with the drug and drug with excipients were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 –of 4000 cm-1 at spectral resolution 2 cm-2 and rationed against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Results and Discussion

Qualitative TLC analyses showed that the Rf value of solid dispersion system was the same as that of the pure drug. Infrared spectroscopy studies revealed that the characteristic absorption bands for different functional groups of indomethacin present in the solid dispersion system were similar to those obtained from the pure drug and to the reported values as shown in table 2.

Investigation of the X-ray diffractograms (figure 1) reveales a number of changes in the location of the peaks (appearance and disappearance) of the different crystal form of solid dispersion systems with respect to IM. There is difference in d-spacing between the XRD spectra of IM and the dispersion system, referring to the habit modification and change in the intensity of the peaks, which indicate a different arrangement. A few diffuse peaks or decrease in crystallinity were observed in the chitosan (CTS) based solid dispersion in which chitosan polymers with others hydrophilic fillers were used, which may indicate a slight physical interaction of the drug with the polymers. From the table 3 it was concluded that all prepared solid dispersions showed product yield and drug content above 94%.

Saturation solubility

With an aqueous solubility of 9.5µg/mL (at 25^0C), IM is clearly poorly soluble. The solubility of IM is therefore expected to limit its absorption from the gastrointestinal tract. The results of solubility study (Table: 3) revealed that the prepared solid dispersions with different polymers and excipients showed increased solubility compared to the pure drug and their respective physical mixture. This may be due to the improved porosity, decreased primary particle size and partial amorphization of drug in dispersed state as compared to raw crystals of indomethacin. This may also be due to the improved wettability of prepared dispersions in the presence of polymers and excipients used. The physical mixture of has also shown higher solubility than the pure drug. The enhancement in aqueous solubility of IM can be explained in terms of wetting property and hydrophilicity of used excipients and polymers with simultaneous reduction in the crystallinity of the drug caused by the kneading process.

Wettability

Table 3 indicates powder bed hydrophilicity study of IM and prepared solid dispersion systems with their respective physical mixture. The prepared solid dispersion showed significantly shortest rising time (**P<0.01) of water to its surface as compared to raw IM crystals represent better wattability of prepared solid dispersion systems as compared to raw IM and physical mixture. The order of wettability was IMLS, IMMS > IMMC, IMLC > IMC > IML, IMS > IMM > IM.The reason for the superior water rising time (wettability) of solid dispersion system may due to adsorption of hydrophilic fillers on the IM crystalline powder in presence of aqueous solution of water soluble chitosan.

Dissolution study:

The *in vitro* dissolution rate of IM and prepared chitosan based solid dispersion systems with hydrophilic fillers and their respective physical mixtures were shown in figure 2, 3 and 4, 5 respectively. For IM there is very low Cumulative percentage drug dissolved in 15 min. higher time required to release 50% and 90% drug. There is significant increase in DC_{15} (Cumulative percentage drug dissolved in 15 min.), $T_{50\%}$ (Time required releasing 50% drug) and $T_{90\%}$(Time required releasing 90% drug.) (Table 4). The significant improvement in dissolution rate of prepared solid dispersion systems by kneading method may be due to higher hydrophilic character of the systems because of the used hydrophilic polymers and carriers and slight reduction of crystallinilty of the raw IM.

Flow properties

The density and flow property data of IM and prepared solid dispersion systems were mentioned in table 4.According to the literature data, powders with a Compressibility Index (CI) between 5 and 15%, Hausner ratio below 1.25 and angle of repose below 30^0 are suitable for producing tablets which are having good flow property. The raw crystals of IM show higher values of CI (22.14), Hausner ratio (1.252) and angle of repose (38^0) indicating poor flow properties. The prepared solid dispersions had a CI ranging between 9-15, Hausner ratio was below 1.136 and angle of repose in between 24-28^0.Thus as for the rheological properties, the prepared dispersions revealed a good flowability because of their agglomerated size which reduces the surface area and increases the flow rate.

Conclusion

In conclusion, the used chitosan based solid dispersion system has been proved to be a important technique to increase the solubility, dissolution rate and other techniqual characteristics of IM using chitosan as water soluble polymer and different hydrophilic fillers like diluents (lactose, microcrystalline cellulose) and superdisintegrants (croscarmellose sodium, sodium starch glycolate) by using aqueous based kneading technique, without using any organic solvents. Solid-state analysis indicated slightly reduction in crystallinity of the IM and there are no changes in its polymorphic form. The prepared dispersion system displayed a significant improvement in saturation solubility and vitro drug dissolution behavior. The amorphizing effect of chitosan appeared as the main driving force for the enhanced drug dissolution, even though other factors such as improved wettability, reduced aggregation phenomena, increased effective surface area and local solubilization effect played a contribution role. The most effective preparation method was the kneading technique, which not only showed the best dissolution performance but also was the easiest for possible scale-up and industrial applications, without requiring addition of solvents or high temperature for its preparation. Therefore, prepared dispersion system showed that chitosan can favorably affect the IM dissolution properties, yielding a significant improvement in DC_5,$T_{50\%}$ and $T_{90\%}$.

Acknowledgement

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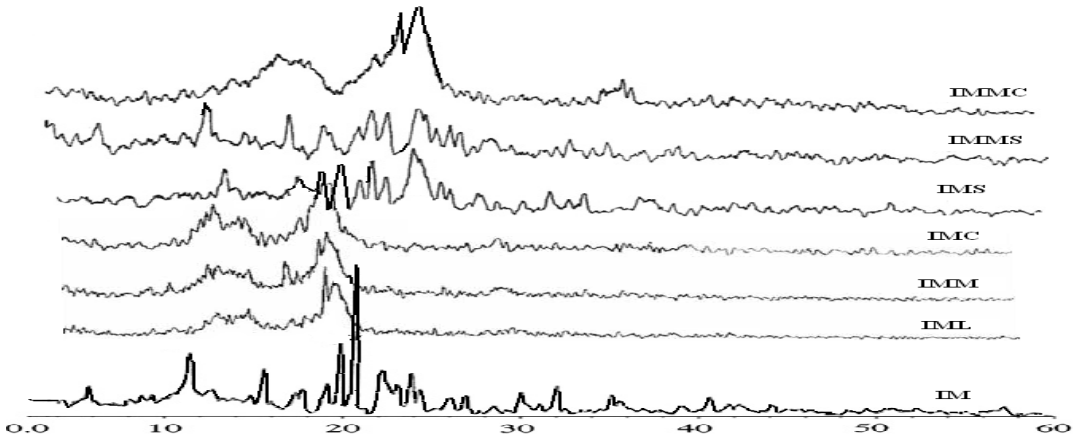

Fig. 1. XRPD spectra of IM and prepared solid dispersion system.

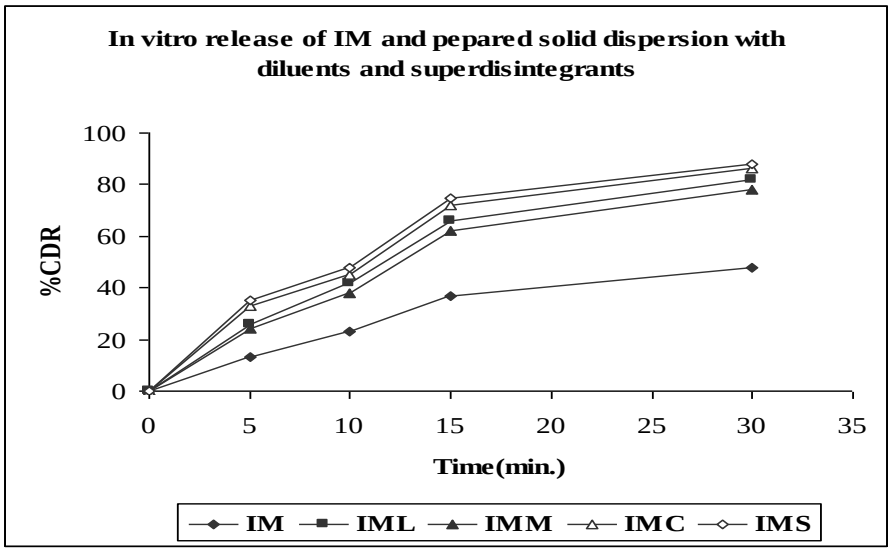

Fig. 2. In vitro release profiles of IM and prepared solid dispersion systems with diluents and superdisintegrants.

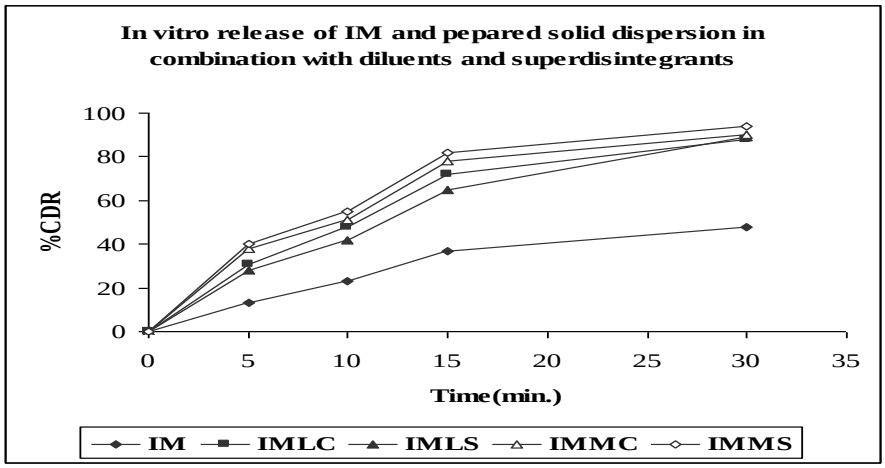

Fig. 3. In vitro release profiles of IM and prepared solid dispersion systems in combination with diluents and superdisintegrants.

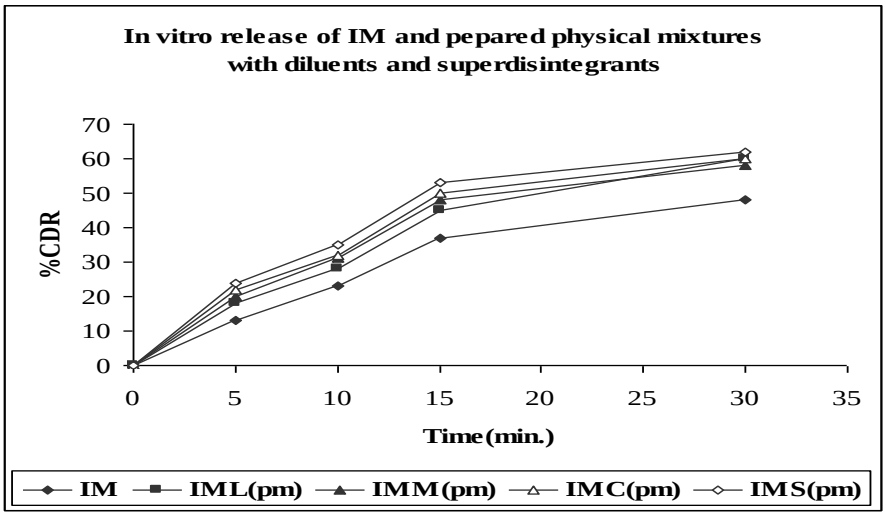

Fig. 4. In vitro release profiles of IM and prepared physical mixtures with diluents and superdisintegrants.

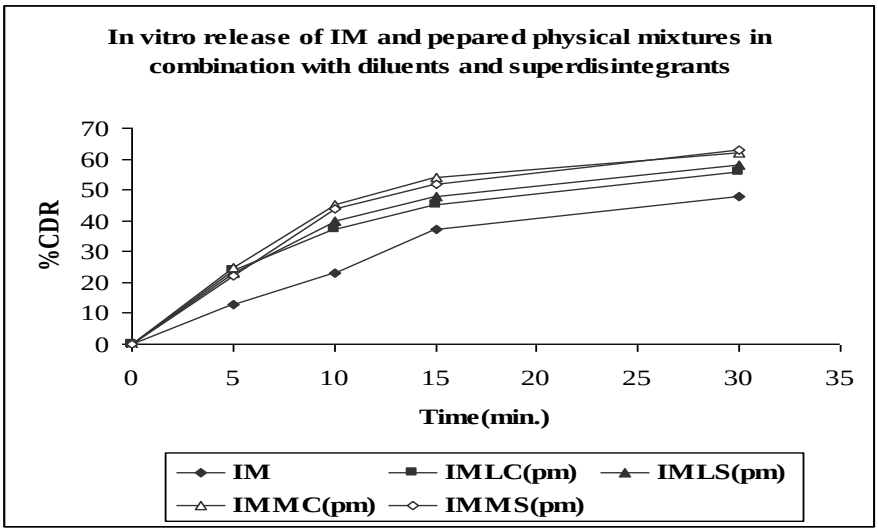

Fig. 5. In vitro release profiles of IM and prepared physical mixtures in combination with diluents and superdisintegrants.

Table 1. Product code of IM solid dispersion systems with different hydrophilic excipients and water soluble chitosan.

Sr. No.	Product Code	Carriers(Diluents/Super Disintegrants) used	Polymer used (Aqueous solution)	Ratio (IM:Carrier: Polymer)
01	**IM**	Indomethacine (API)		
02	**IML**	Lactose monohydrate	Chitosan	1:0.4
03	**IMM**	Microcrystalline cellulose	Chitosan	1:0.4
04	**IMC**	Croscarmellose sodium	Chitosan	1:0.2
05	**IMS**	Sodium starch glycolate	Chitosan	1:0.2
06	**IMLC**	Lactose monohydrate: Croscarmellose sodium	Chitosan	1:0.2:2
07	**IMLS**	Lactose monohydrate: Sodium starch glycolate	Chitosan	1:0.2:2
08	**IMMC**	Microcrystalline cellulose: Croscarmellose sodium	Chitosan	1:0.2:2
09	**IMMS**	Microcrystalline cellulose: Sodium starch glycolate	Chitosan	1:0.2:2

Table 2. Characteristic group absorption frequencies, obtained from infra-red spectroscopy studies, for functional groups of Indomethacin.

Functional group	Bands occurring at wave numbers cm^{-1}						
	IM	**IML**	**IMM**	**IMC**	**IMS**	**IMMS**	**IMMC**
Carboxylic OH deformation	927	925	925	925	927	926	927
C=O stretch (ketone)	1719	1715	1716	1717	1716	1715	1718
Aromatic C=C stretch	1593	1600	1598	1596	1598	1604	1598
C-Cl vibration	755	754	756	758	754	756	757
O-CH3 deformation	1457	1453	1455	1456	1450	1452	1455
Rf value (TLC study)							

Table 3. Evaluation parameters of IM, prepared solid dispersion systems with their physical mixture.

Product Code	Evaluation parameters		
	Drug content (%)	Saturation solubility(µg/mL)	Wettability (Water raising time-hrs)
IM	97 ±2.156	9.5 ± 0.561	9.0 ±0.568
IML	96 ±1.268	72 ±1.456	6.5 ±0.654
IMM	97 ±3.256	75 ±1.689	7.5 ±0.489
IMC	95 ±2.568	88 ±1.159	6.0 ±0.597
IMS	96 ±2.578	85 ±1.598	6.5 ±0.576
IMLC	95 ±2.654	95 ±2.568	5.5 ±0.358
IMLS	96 ±2.456	112 ±2.489	5.0 ±0.485
IMMC	95 ±1.987	115 ±2.657	5.5 ±0.658
IMMS	96 ±1.789	110 ±2.591	5.0 ±0.785
IML(pm)	96 ±1.879	18 ±2.356	8.5 ±0.589
IMM(pm)	95 ±1.897	22 ±2.568	8.0 ±0.563
IMC(pm)	94 ±2.564	25 ±2.548	8.5 ±0.365
IMS(pm)	96 ±2.487	23 ±1.556	8.0 ±0.145
IMLC(pm)	95 ±2.456	21 ± 1.456	7.5 ±0.658
IMLS(pm)	96 ±2.687	20 ±1.689	8.0 ±0.521
IMMC(pm)	97 ±2.489	25 ±1.987	8.5 ±0.523
IMMS(pm)	95 ±2.586	27 ±1.789	8.0 ±0.658

Table 4. Dissolution studies of prepared granules by melt and compaction technique. DC_5 (Cumulative percentage drug dissolved in 05 min.),$T_{50\%}$ (Time required to release 50% drug.),$T_{90\,\%}$ (Time required releasing 90% drug.)

Product Code	Bulk density (gm/mL)	Tap density (gm/mL)	Carrs Index	Hausnar ratio	Angle of repose(^{0})
IM	0.555	0.695	20.14	1.252	38
IML	0.515	0.585	11.97	1.136	24
IMM	0.485	0.565	14.16	1.165	25
IMC	0.475	0.555	14.41	1.168	24
IMS	0.485	0.575	15.65	1.186	26
IMLC	0.495	0.552	10.33	1.115	24
IMLS	0.495	0.545	9.17	1.101	27
IMMC	0.475	0.565	15.93	1.189	28
IMMS	0.495	0.548	9.67	1.107	26
IML(pm)	0.535	0.655	18.32	1.224	30
IMM(pm)	0.535	0.665	19.55	1.243	31
IMC(pm)	0.532	0.645	17.52	1.212	32
IMS(pm)	0.545	0.638	14.58	1.171	32
IMLC(pm)	0.535	0.648	17.44	1.211	33
IMLS(pm)	0.525	0.658	20.21	1.253	32
IMMC(pm)	0.525	0.652	19.48	1.242	31
IMMS(pm)	0.535	0.648	17.44	1.211	29

Table 5. Flowability parameters of IM, prepared solid dispersion systems with their physical mixture.

Product Code	Bulk density (gm/mL)	Tap density (gm/mL)	Carrs Index	Hausnar ratio	Angle of repose(^{0})
IM	0.555	0.695	20.14	1.252	38
IML	0.515	0.585	11.97	1.136	24
IMM	0.485	0.565	14.16	1.165	25
IMC	0.475	0.555	14.41	1.168	24
IMS	0.485	0.575	15.65	1.186	26
IMLC	0.495	0.552	10.33	1.115	24
IMLS	0.495	0.545	9.17	1.101	27
IMMC	0.475	0.565	15.93	1.189	28
IMMS	0.495	0.548	9.67	1.107	26
IML(pm)	0.535	0.655	18.32	1.224	30
IMM(pm)	0.535	0.665	19.55	1.243	31
IMC(pm)	0.532	0.645	17.52	1.212	32
IMS(pm)	0.545	0.638	14.58	1.171	32
IMLC(pm)	0.535	0.648	17.44	1.211	33
IMLS(pm)	0.525	0.658	20.21	1.253	32
IMMC(pm)	0.525	0.652	19.48	1.242	31
IMMS(pm)	0.535	0.648	17.44	1.211	29

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