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DEVELOPMENT AND CHARACTERIZATION OF SURFACE SOLID DISPERSION OF CURCUMIN FOR SOLUBILITY ENHANCEMENT

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Surface solid dispersion (SSD) of curcumin was developed and characterized with purview to overcome solubility hurdle in its pharmacokinetic and pharmacodynamic performance. SSDs were prepared by co-evaporation method using polyplasdone XL, croscarmelose sodium, and silicone dioxide and polyethlene glycol 6000 as carrier. The optimized SSD (F9) was characterized using FE-SEM and XRD as an analytical tool. The formulation of modified Curcumin shows better drug release profile as compared to the natural Curcumin. Formulation F9 released more than 90% of the loaded Curcumin within 30 minutes where marketed formulations shows 90% drug only after 60 minutes.

Keywords: Curcumin, surface solid dispersion, fast disintegrating tablet

INTRODUCTION

Many of the discovered chemical entities are lipophilic in nature and suffer from poor aqueous solubility. Because of their low aqueous solubility, dissolution becomes the rate limiting step for their systemic absorption and bioavailability[1, 2]. Consequently, the major number of pre-existing pharmaceutical compounds along with the new discovering bioactive compounds suffers from insufficient dissolution throughout the gastrointestinal tract and therefore achieves inferior systemic exposure after oral administration[3]. There are various generalized approaches of solubility enhancement of poorly soluble active pharmaceutical ingredients (APIs). Among these, solid dispersion is used to be the most popular one and the basic technique. Despite it exhibits certain constraints including poor miscibility of matrix and drug which is due to their different forms of state as crystalline, amorphous or molecular causes segregation, use of the water soluble polymers causes tackiness or wetness of solid mass of SD, amorphous form of the drug produced during solid dispersion is less stable and can be converted into the more stable crystalline form, commercial limitations include laborious and expensive method of its preparation, reproducibility, difficulty in formulation, and poor shelf-life, drug gets entrapped within the polymer structure

There are systems in which the drug is distributed on the surface of a water insoluble carrier to increase solubility and dissolution rate such systems are called as surface solid dispersions[17]. Surface solid dispersion may be considered as a special type of solid dispersion in which the water insoluble drug is weakly bounded onto the surface of the water insoluble carrier polymer[18]. Polymers used for surface solid dispersion also have the property of fast disintegration in aqueous medium. That is due to their hydrophilic nature and extensive swellability in the aqueous medium. This exposes the adsorbed drug to the medium and then drug is readily dissolute into the medium. Curcumin has been reported to have potential anti-inflammatory, antibacterial and anti cancerous activity. Amongst anti cancerous agent, curcumin has been proven efficacious against many cancerous cells. However its activity is limited due to low systemic availability after per oral administration due to low aqueous solubility.

Curcumin has been classified as potential BCS class II drug therefore it has low solubility and high permeability. It is insoluble in aqueous medium and dissolution is the rate limiting step for its oral absorption in the body. Drug was selected on the basis of its limitation of solubility which would be increased by SSD technique. Not only this, its low dose also supports this technique as SSD allows high ratio of polymers/drug for the formulation.

Another intent of the study is to fabricate the C-SSD as fast disintegrating per oral tablet to facilitate rapid clinical effects as an anti-inflammatory and anti cancerous drug.

MATERIALS AND METHODS

Curcumin was obtained as gift sample from Mankind Pharma Ltd. Polyplasdone XL, croscarmelose sodium, polyethylene glycol 6000 and silicone dioxide were purchased from Wacker Chemie, Geramany. Absolute alcohol was obtained from Changshu Yangyuan chemical

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china; all the solvents used during the study were of HPLC grade.

Preparation of SSD by Co-evaporation method

Four carriers sodium starch crosscarmelose sodium, polyplasdone XL, silicone dioxide and polyethylene glycol-6000 in four groups A, B, C and D were used in three different drug: carrier ratios (1:1, 1:5, 1:10) hence, total twelve formulations were prepared as depicted in Table 1 in which the carriers were divided into two broad classes, super disintegrates (group A and B) and adsorbent (group C and D). For F1 formulation 100 mg of the drug was dissolved in 10 ml of ethanol (99.9% v/v) and 100 mg of the carrier was dispersed into it as to render drug: carrier ratio 1:1. The dispersion was magnetically stirred at 100 rpm at 70ºC ± 0.5 to completely evaporate the solvent and to obtain dry product. The procedure was repeated for other formulations with variable amount of carrier in their respective ratios.

Evaluation of prepared SSDs

Equilibrium Solubility study

Accurately 10 mg of pure drug was added to 25 ml conical flask containing 10 ml of distilled water (0.1% w/v) and kept for 72 hr at 37˚C ± 0.5 on water bath shaker. Sample of 5 ml was withdrawn after 72 hr, filtered through nylon filter disc (0.22 µm) and analyzed at 429 nm. Similar study was conducted for each formulated SSD (from F1 to F12) following same procedure and conditions.

Drug content determination

The drug content study was performed taking SSDs theoretically equivalent to 10 mg of drug and extracted with 5 ml quantity of 99.9% v/v ethanol in two successive steps. The solution was filtered through nylon filter disc (0.22 µ) and the volume was rendered up to 10ml with 0.1N HCl buffer pH 1.2. This was diluted 100 times with 0.1N HCl buffer pH 1.2 and analyzed at 429 nm in triplicate and mean value with standard deviation was recorded.

In-vitro adsorption study

Accurately 10 mg of curcumin was added to 100 ml of distilled water and ten folds weight (100mg) of crosscarmelose sodium was added to it. The mixture was magnetically stirred at 100 rpm and temperature was maintained at 37˚C ± 0.5 for 4 days. Five milliliters of sample was withdrawn at 0, 0.5, 1.0, 2.0, 3.0, 4.0 days and analyzed spectrophotometrically at 429 nm to determine the percent drug adsorbed with respect to time. This study was repeated for polyplasdone XL, silicone dioxide and polyethylene glycol-6000.

Characterization studies

For characterization studies, powder samples of SSD F6, F9, silicone dioxide, polyplasdone XL and pure drug were subjected to following analysis.

Scanning electron microscopy

The scanning electron microscopy (SEM) of samples was conducted by using scanning electron microscope operated at an acceleration voltage of 4 kV. Sample particles were coated with a thin gold layer by sputter coater unit (VG Microtech, West Sussex, UK) under an argon atmosphere in order to make them conductive. The coating time was 5-6 min and the surface morphology of samples was studied by observing the photomicrographs at different magnifications ranging between 100 X – 3500 X.

Carrier Class	Group	Carrier Used	Drug : Carrier Ratio		
Super disintegrant	A	Croscarmellose sodium	1:1	1:5	1:10
	B	Polyplasdone XL	1:1	1:5	1:10
Adsorbent	C	Silicone dioxide	1:1	1:5	1:10
	D	Polyethylene glycol-6000	1:1	1:5	1:10

X-ray powder diffraction

X-ray powder diffraction (XRPD) patterns samples of were recorded by x-ray diffractometer. The samples were irradiated with monochromatized Cu-Kα radiation, generated at 1.542 Å wavelength, at 30 kV and 30 mA. The samples were scanned over a range of 20º - 100º at the chart speed of 10 mm/ 2θ. The intensity of the peaks in XPRD patterns was recorded in cps and was studied for crystallinity of the samples.

RESULTS AND DISCUSSION

The pure drug curcumin demonstrated solubility of 2.46 µg/ml in double distilled water that can be consider as a close evidence of indicating poor aqueous solubility of curcumin. *In-vitro* adsorption profile of silicone dioxide depicted sigmoid curve which is similar to type V adsorption isotherms with maximum percent drug absorption of 82.75% w/w at 72 hrs. Cross carmelose sodium was followed by silicon dioxide with 61.68% w/w drug absorption in multilayer as generated curve with multiple inflections, analogous to the type IV isotherm and both became constant after 72 hr. Polyplasdone XL and Polyethylene glycol 6000 adsorbed curcumin to a maximum of 24.07% w/w and 21.88% w/w respectively. In vitro absorption profiles of these two became constant at 24 hr after the single inflection, indicating monolayeric adsorption of curcumin.

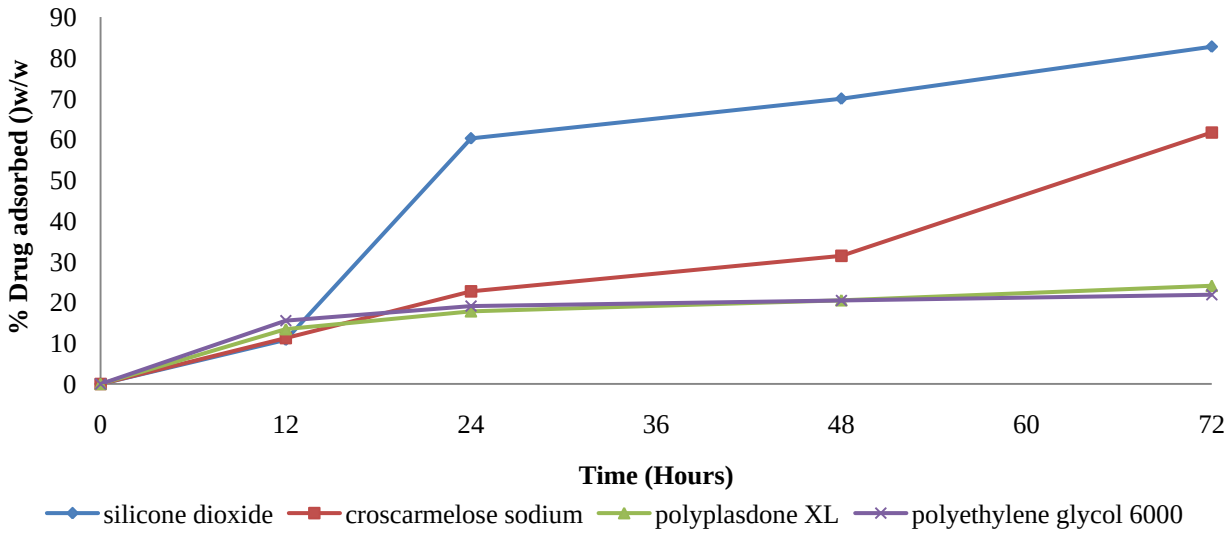

Fig. 1 *In-vitro* adsorption profile of drug on various carriers

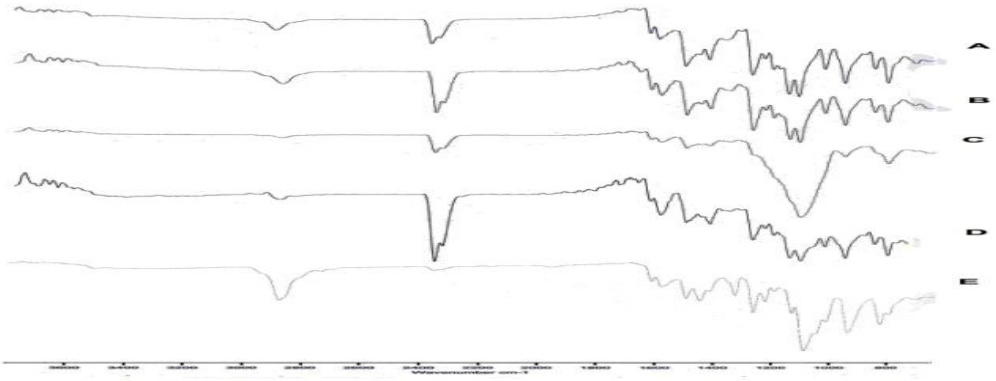

Fig. 2 DRS spectra of pure drug (A), Drug/polyplasdone XL (B), Drug/silicone dioxide (C) drug/croscarmelose sodium (D) and drug/polyethylene glycol 6000 (E)

SSD is a drug: carrier dispersion where drug is deposited over carrier and carriers employed for SSD possess hydrophilic character, high aqueous dispersability and large specific surface area. Based on the literature value of specific surface area the carriers can be arranged in the increasing order (Polyethylene glycol 6000 < polyplasdone XL < croscarmelose sodium < silicone dioxide) and extent of in-vitro adsorption are expected to be in same order. The results complied with theory except for Polyethylene glycol 6000 and polyplasdone XL, where polyethylene glycol 6000 and polyplasdone XL showed low adsorption that attributed to its chemical structural (which is further explained in details) and rendered the drug more soluble in the media in spite of its absorption. Rest of the carriers were uniformly dispersed in the test media and provided site for absorption related to their specific surface area.

Consequently, the order of adsorption was Polyethylene glycol 6000 < Polyplasdone XL < croscarmelose sodium < silicone di-oxide but this did not imply the release order. Consequently, SSDs were formulated using various drug-carrier ratios (by a factor of 5) and assessed for solubility enhancement and in-vitro release characteristics.

The identification of compatibility of drug with excipients is one of the primary requisite when designing a dosage form. Since excipients comprise a major portion of dosage form, the possibility for drug excipients interaction that may affect drug stability, dissolution rate and consequently drug adsorption exists. The stored binary samples were analyzed by DRS. The spectral analysis of curcumin (Fig. 2A) showed characteristic bands at wave number 3634, 2885, 2362, 1626, 1594, 1423, 1368, 1232, 1179, 1025 corresponding to O-H stretching, C=O stretching, C=C stretching, Ar-H stretching, C-H deformation, CH_3 deformation, O-H bending, C-O stretching, Ar-H (o,m). These characteristic stretching vibrations were documented in blends: Drug/polyplasdone XL, Drug/silicone dioxide drug/croscarmelose sodium and drug/polyethylene glycol 6000 (Fig 2 B-E) without any petite shift in the wave number of the peaks, however slight changes in intensity of the peaks was due to decreased concentration OD drug in the blend. Slight changes in intensity of the peaks within acceptable limits indicated absence of interaction between drug and excipients used to prepare surface solid dispersion.

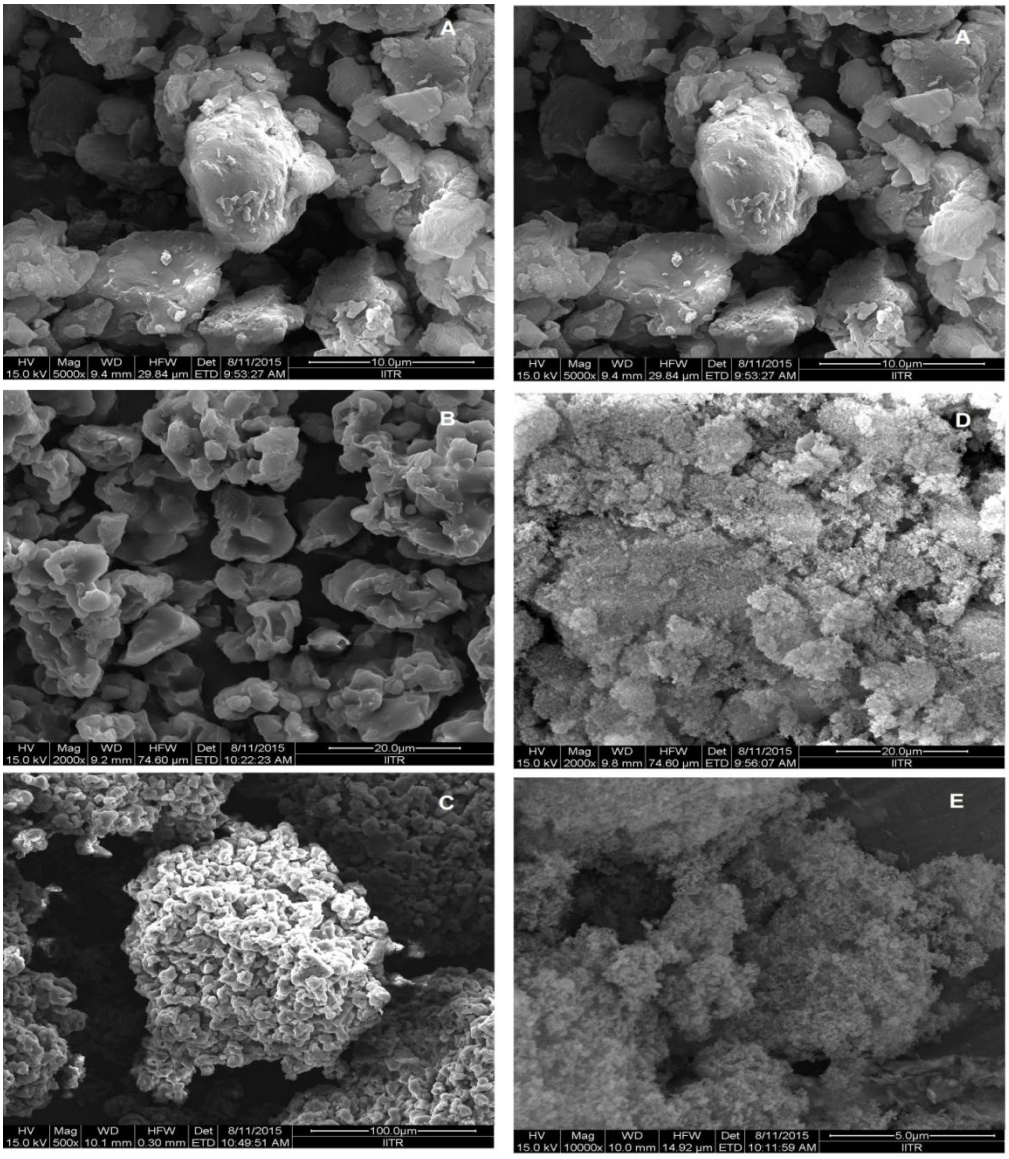

Fig.5 : SEM micrographs of Drug (A), polyplasdone XL(B), SSD F6 (C) , silicone dioxide (D), SSD F9 (E) at 500X magnification.

Relative to pure drug, SSDs displayed better solubility enhancements. Solubility of silicone dioxide and polyplasdone XL was enhanced with increasing drug: carrier ratios as 1:1<1:5<1:10. On the contrary croscarmelose sodium showed solubility enhancement in the order 1:1<1:5>1:10. In this study croscarmelose sodium displayed enhanced drug solubility at drug:carrier concentration of 1:5 which might be attributed to the gel forming ability of croscarmelose sodium. The drug must first diffuse through gel layer before being released into medium. Polyplasdone XL swells rapidly without gel formation because of high cross linking density and increased drug solubility at higher drug:polymer ratio i.e 1:10.

Analytically, carriers can be classified into swellable and non-swellable adsorbent groups. Swellable carriers, croscarmelose sodium and polyplasdone XL are reported to increase the solubility of poorly soluble drugs. Possible mechanism for increasing drug solubility is better being explained on the basis of their chemical structures. Polyplasdone XL is insoluble synthetically crosslinked homopolymer of N-vinyl-2-pyrrolidone. These repeating units in Polyplasdone XL are responsible for the crystallization inhibition due to its anti plasticizing effect and often produce efficient steric hindrance for nucleation and crystal growth. Chemically, these units are similar to N-methylpyrrolidone (NMP), which is water miscible, aprotic polar solvent with high interfacial activity used as solubilising agent .Thus, polyplasdone XL with porous and granular particles that generates high specific surface area combined with unique solvent-like chemistry results in high interfacial activity that serves to enhance the solubility of hydrophobic drugs.

In contrast, croscarmelose sodium is the sodium salt of cross-linked carboxymethyl ether of starch and its backbone is composed mostly of glucose repeat units. Hydrophilic carboxymethyl groups disturb hydrogen bonding within polymer but many free hydroxyl groups of glucose residue present on the polymer surface are reportedly responsible to enhance the solubility of hydrophobic drugs. Hydrophilic surface interacts with water molecules after their rapid intake from aqueous medium and increase the water molecule interactions on its surface microenvironments. In this way, hydrophilic carriers increase wetting and reduce interfacial tension between hydrophobic drug and water. According to the literature, particles are spherical and non porous that form gel on complete hydration.

Non swellable, adsorbent carriers, aerosil and polyethylene glycol 6000 insoluble with highly porous nature which provides high specific surface area. According to the literature, pores of the adsorbent restrict the nucleation during re-crystallization of drug and as mentioned in adsorption results, a large amount of curcumin was homogeneously distributed in a mono-layer on adsorbents. In the case of a monolayer no work is needed to break the bonds between drug molecules, as reported by which results in higher apparent solubility of the drug. Apart from this, surface adsorption for water by silicone dioxide was reportedly attributed to high silicone dioxide group ($Si\text{-}O_2$) density on the surface which is responsible for similar mechanism of drug wetting and enhancing its solubility.

Polyethylene glycol 1000 considered here to analyze the role of adsorption property on the solubility enhancement without a hydrophilic surface and results showed no prominent solubility enhancements with carrier's hydrophobic surface. Due to its hydrophobic surface, polyethylene glycol 6000 adsorbed the drug strongly and consequently did not release it readily. That proved, for increasing wet ability of drug, carrier with hydrophilic surface is required which also possess good adsorption characteristics and aerosil fitted in this domain

The SEM photomicrograph (Fig. 2A) of pure drug revealed irregular crystals with plain surfaces. The SEM images of polyplasdone XL-10 (Fig. 2B) depicted flaky non uniform sized amorphous particles. The SEM micrograph of silicone dioxide (Fig. 2D) displayed round edged non uniform sized amorphous particles. The amorphous surface probably played an important role in providing larger surface area for drug deposition[9]. Porous and amorphous surface allowed the deep penetration and restricted the drug re-crystallization during the processing of SSD[10] SEM image of Fig. 2E revealed deposition of very fine microcrystals of curcumin on the silicon dioxide

particles which rendered roughness to the smooth surfaces of aerosil and was indicative of SSD formation. The deposition led to major crystal destruction marked by faint evidence of drug crystals further proved by the XRPD results.

Diffraction pattern of curcumin was co-relatable with SEM images. The pure drug was highly crystalline as X-rays diffracted at sharp angles from well defined crystalline surface. Generation of halo areas in the silicone dioxide and SSD spectra was due to amorphous surface of aerosil and amorphization of crystalline drug in SSD, as X-rays were diffracted from the irregular and rough surface of SSD Drug crystallinity calculation provided a quantitative revelation about the reduction in crystallinity after SSD formation as amorphization led to solubility enhancement in comparison to pure crystalline drug

CONCLUSION

The optimize formulation displayed highest solubility of 35.11+- 0.34 micro gram/ml in double distilled water silicon dioxide in 1: 10 ratio with the drug resulted in maximum % cumulative drug release (% CDR) of 93.46 % which was due to fine agreement of the solubility study as improve drug dissolution was a result of increased solubility.

REFERENCES

1. Serajuddin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. Journal of Pharmaceutical Sciences. Vol. 88(10), pp. 1058-1066.
2. Bahl, D. and Bogner, R.H., 2006. Amorphization of indomethacin by co-grinding with neusilin US2: amorphization kinetics, physical stability and mechanism. Pharmaceutical Research. Vol. 23(1), pp. 2317-2325.
3. Randy, M., Moles, R., and Mooter, V.G., 2008. Ordered mesoporous silica induces pH independent supersaturation of basic low solubility compound itraconazol resulting in enhanced transepithellial transport. International Journal of Pharmaceutics, Vol. 357, pp. 169-179.
4. Lalitha Y. and Lakshmi P. K. 2011. Enhancement of dissolution of nifedipine by surface solid dispersion technique. Indian Journal of Pharmaceutical Sciences. Vol. 3(3), pp. 41-46.
5. Balasubramaniam, J. and Bee, T., 2009. Influence of superdisintegrants on the drug dissolution from oral solid-dosage forms. Pharmaceutical Technology and Excipient Supplement. pp. S4-S14.
6. Balasubramaniam, J. and Bee, T., 2008. Effect of superdisintegrants on dissolution of cationic drugs. Dissolution Technology. Vol. 15, Issue 2, pp. 18-25.
7. Yoshioka, M., Hancock, B.C. and Zografi. G., 1995. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitates. Journal of Pharmaceutical Sciences. Vol. 84, pp. 983-986.
8. Planinsek, O., Kovacic, B. and Vrecer, F., 2011. Carvedilol dissolution improvement by preparation of solid dispersions with porous silica. International Journal of Pharmaceutics. Vol. 406, Issue 1-2, pp. 41-48.
9. Eerdenbrugh, B.V., Speybroeck, M.V., Mols, R., Houthoofd, K., Martens, J.A., Froyen, L., Humbeeck, J.V., Augustijns, P. and Mooter, G.V., 2009. Itraconazole/ TPGS/aerosil®200 solid dispersion: characterization, physical stability and in vivo performance. European Journal of Pharmaceutical Sciences. Vol. 38, Issue 3, pp. 270-278.
10. Takeuchi, H., Nagira, S., Yamamoto, H. and Kawashima, Y., 2005. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. International Journal of Pharmaceutics. Vol. 293, pp. 155-164.
11. Hancock, B.C. and Parks, M., 2000. What is the true solubility advantage for amorphous pharmaceuticals?. Pharmaceutical Research. Vol. 17, pp. 397-404.
12. Indian Pharmacopoeia 2007. Government of India, Ministry of Health & Family Welfare, Controller of Publication, New Delhi, India, Vol. 1-2.

13. United State Pharmacopoeia 27/National Formulary 22., 2004. Asian Ed., United state Pharmacopoeial Convention Inc., Rockville.
14. Gennaro, A.R., 2000. Remington: The Science and Practice of Pharmacy. New Delhi, Lippincott Williams and Wilkins.
15. Rowe, R.C., Sheskey, J.P. and Owen, S.C., 2006. Handbook of Pharmaceutical Excipients. London, Pharmaceutical Press.
16. Mellaerts, R., Mols, R., Jammaer, J.A.G., Aerts, C.A., Annaert, P., Van, H.J., Van, D.M.G., Augustijns, P. and Martens, J.A., 2008. Increasing the oral bioavailability of the poorly water soluble drug itraconazole with ordered mesoporous silica. European Journal of Pharmaceutics and Biopharmaceutics. Vol. 69, pp. 223-230.
17. Kiran, T., Shastri, N., Ramkrishna, S. and Sadanandam, M., 2009. Surface sold dispersion of glimepride for enhancement of dissolution rate. International Journal of PharmTech Research. Vol. 1(3), pp. 822-831.
18. Miyahara, M., Watanabe, S. and Higashitani, A., 2006. Modeling adsorption and order formation by colloidal particles on a solid surface: A Brownian dynamics study. Chemical Engineering Sciences. Vol. 61, pp. 2142-2149.

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