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## SIZE ENLARGEMENT OF GRISEOFULVIN BY NOVEL POWDER WETTING SOLVENT CHANGE TECHNIQUE

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### ABSTRACT

The present work describes a novel Power Wetting Solvent Change technique to improve the solubility, dissolution and other physicochemical properties of a poorly water-soluble drug substance. Griseofulvin is an antifungal agent BCS class- II pharmaceutical having poor solubility and other physicochemical properties. The benefit of this technique compared to a conventional granulation is that very small quantity of organic solvents is needed for their preparation and hence minimizes the entrapment of residual solvent in the final prepared granules. The granules are prepared by wetting the powder with the dichloromethane and then dried. The study of different hydrophilic polymers like hydroxyethyl cellulose, hydroxypropyl cellulose, polyethylene glycol and polyvinyl pyrrolidone on the physicochemical properties were also studied. The pure and the prepared granules were characterized in terms of production yield, drug content, solubility, in vitro release profile, flowability, density, particle shape by microscopy and wettability. The size enlarged granules were characterized using powder XRD, FTIR and DSC techniques. A considerable enhancement in the saturation PEG and PVP followed by HEC, HPC, drug excipient physical mixture and pure drug. The prepared granules also exhibited improvement in physicochemical properties like wettability and flowability as compared to the unmodified. XRD data confirmed crystalline drug in the prepared granules. FTIR study revealed that there were no chemical changes in the prepared granules. In conclusion, the result of this work suggest that the powder wetting solvent change Technique is the novel granulation techniques useful to enhance the solubility, dissolution rate and physicochemical properties of poorly water-soluble drug like Griseofulvin.

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### Key Words

Powder Wetting Solvent Change Technique, Wettability, Griseofulvin, Solubility, Dissolution.

## INTRODUCTION

Griseofulvin (GF) is an antifungal agent and is practically insoluble in water. Several gastrointestinal absorption of griseofulvin.<sup>(1-2)</sup> This work is focused primarily on evaluation the Powder Wetting Solvent Change Technique (PWSCT) on a lab scale for improving the solubility, dissolution and other physicochemical properties of GF. Hence the aim of the present study was to improve the solubility, dissolution and other physicochemical properties of GF by novel Powder Wetting Solvent Change granulation Technique with different hydrophilic polymers. The pure GF and the prepared granules were then characterized in terms of production yield, drug content, solubility, in-vitro release profile, flowability, density, particle shape by microscopy and wet- ability. The size enlarged granules were also characterized using powder XRD.

During the last decade there has been a rising development in pharmaceutical research to generate drug substances that exhibit high lipophilicity and poor water solubility. Such physicochemical characteristics direct to problematic biopharmaceutical properties, which may diminish or even prevent success of pharmaceuticals biopharmaceutical properties, which may diminish or even prevent success of pharmaceuticals in the clinic.<sup>(3)</sup>

The poor solubility and low dissolution rate of poorly water soluble active pharmaceutical ingredients in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. While the rate-limiting step for absorption from the gastrointestinal tract is a significantly slower dissolution rate. Nearly about 40% of the new chemical entities currently being discovered are poorly water-soluble drugs. Based upon their permeability characteristics, the Biopharmaceutics classification system (BCS) categorizes such drugs in two major classes, i.e., Class II and IV. The (BCS) class II drugs are poorly water-soluble entities with high permeability. Attempts to enhance drug solubility and dissolution rate of the drug in the gastro-intestinal fluids. Attempts to enhance drug solubility of these therapeutic agents correlate well with enhancement in their bioavailability. Especially for class II substances the bioavailability may be enhanced by increasing the solubility and dissolution

rate of the drug in the gastro-intestinal fluids. Most formulation strategies for such drugs are targeted at enhancing their dissolution rate and/or solubility in-vivo by achieving their fine dispersion at absorption level. A common approach to improve the dissolution rate of poorly water-soluble API were micronization, formation of solvates, adsorbents, complexes, microspheres or more regularly solid dispersion.<sup>(4-8)</sup> The mechanisms involved in solubility and dissolution rate enhancement include transformation of stable modifications into less stable ones or even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wet ability and solubility of the drug by the carrier material.

The spherical crystallization technique has already been successfully applied to improve the physicochemical properties of number of pharmaceutical substances. In the most common case, this technique is presumed to improve the wettability and dissolution rate of different drugs and sometimes a number of drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release. There are two methods for spherical crystallization i.e. Solvent change technique (SC Technique) and Emulsion solvent diffusion (ESD method).<sup>(8-10)</sup> In the solvent change technique, a good solvent (a solvent in which it is very soluble) of drug substance is poured into a poor solvent of the drug. Provided that the good and the poor solvents are freely miscible and interaction (binding force) between the solvents is stronger than drug interaction with the good solvent, crystals precipitate immediately. A suitable amount of a third solvent, which is not miscible with the poor solvent and which preferentially wets the precipitated crystals, is added to the system while stirring. This third solvent, which is called a 'bridging liquid', can collect the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid. Main disadvantages of this technique are the use of three solvents and hence increase in chances of entrapment of solvent in crystal lattices i.e. residual solvent entrapment.<sup>(12)</sup> To minimize these disadvantage

present work revealed the novel Powder Wetting Solvent Change Technique (PWSCT) in which the drug powder is just wetted by the organic solvent and then to it as the distilled water during stirring process. Hence this method minimizes the use of organic solvent and reduces the chances of entrapment of residual solvent.

## **MATERIALS AND METHODS**

### **Materials:**

Griseofulvin (99% purity) was obtained from Sun Pharma (Vadodara, Gujarat, India). Hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), polyethylene glycol-6000 (PEG) and polyvinyl pyrrolidone (PVP) were obtained as gift samples from Alembic Limited (Vadodara, Gujarat, India). Dichloromethane was obtained from Lobe Chemicals (Mumbai, India).

### **Power Wetting Solvent Change Technique**

Weigh the accurate quantity of Griseofulvin in a porcelain dish. Wet the taken quantity of Griseofulvin with sufficient quantity of acetone. Add 20mL distilled water along with the different hydrophilic polymers by stirring up to 10 minutes. After stirring for 10 min. the prepared agglomerates were collected by filtration through whatman filter paper no. 42 under vacuum. The spherical crystals were washed with distilled water and placed at 45° for drying in a hot air oven for 24 hr and then stored in desiccators.

### **Yield and drug content**

Prepared granules were weighed after drying, and production yield was weighed and extracted glass filter and volume was adjusted to 100 ml after sufficient dilution with Methanol, samples were analyzed spectrophotometrically (Pharma spec 1700, Shimadzu Corporation, Kyoto, Japan) at 295 nm. Griseofulvin content was calculated by comparison with standard solution.

### **Saturation solubility studies**

Saturation solubility studies were carried out using de-ionized water as a solvent. Excess quantity (250 mg) of samples was taken in six screw capped test tubes with fixed volume (10 ml) of deionized water. The resultant suspension was treated at 37 C with 100 rpm in incubator shaker. After 24 hrs samples were withdrawn

and filtered through 0.2 $\mu$  filters (Multiport® N Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with deionized water and analyzed at 297 nm by UV- visible spectrophotometer

### **Dissolution study**

The in vitro drug release of prepared granules were measured in triplicate by using dissolution apparatus (Lab India Disso 2000, Lab India Pvt. Ltd, India, Mumbai, India) USP type II (paddle) dissolution apparatus. Dissolution studies were carried out using 0.54% SLS at 50 rpm and the temperature of the dissolution medium was maintained at 37  $\pm$ 0.5°C. Samples were withdrawn after suitable interval of 15 min. for 1 hrs. and replaced each time with 5 ml of fresh dissolution medium. The drug concentration in the dissolution medium was assayed spectrophotometrically at 297 nm (Pharma spec 1700, Shimadzu Corporation Kyoto, Japan)

### **Measurement of flowability and density**

The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using Density apparatus (Serwell, Bangalore, India). The Carr's index (%) and the Hauser's ratio were then calculated by using LBD and TBD. The angle of repose of drug powder and the agglomerates were assessed by fixed funnel method. The Car's index reflects the compressibility of the agglomerates, and there is a correlation between the compressibility index and the flowability of the spherical agglomerates

### **Wetability study**

Powder bed hydrophilicity test was carried out to assess the wet ability of the prepared granules by placing the sample (2g) in sintered glass tube to form a bed in the glass tube on which ethylene blue crystals (~100mg) were placed. The tube was brought into contact with the surface of water and the time taken for water to rise by capillary movement to dissolve methylene blue crystals was noted. The shortest time corresponds to the most wet table sample. The test was performed in triplicate.

### **Powder X-ray diffraction study**

Powder X-ray diffraction (PXRD) patterns were traced employing S-X-ray diffractometer (Philips PW 1729, Analytical XRD, Holland) for the samples using Ni filtered Cuk(a) radiation (intensity ratio (  $a_1/a_2$  ): 0.500), a

voltage of 40 KV, a current of 30 mA and receiving slit of 0.2 inches. The samples were analyzed over 20 range of 5.010-39.990° with scanning steps size of 0.020° (20) and scan step time of one second. To minimize the effect particle size on preferred, all the samples were passed through sieve (# 120/240).

#### Fourier transforms infra-red spectroscopy (FT-IR)

FT-IR spectra of prepared size enlarged granules along with the drug and drug with excipients physical mixture 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

**Table: 1** Formulation of Griseofulvin size enlarged granules by compaction, melt granulation technique and their physical mixture.

Product Code	Polymer used	% of polymer used in water
GF	-----	-----
GFHPC	Hydroxyl propyl cellulose	0.2
GFHEC	Hydroxyl ethyl cellulose	0.2
GFPVP	Polyvinylpyrrolidone	0.5
GFPEG	Polyethylene glycol	0.5

**Table: 2** Evaluation parameters of size enlarged granules by powder wetting solvent change technique.

Product Code	Product yield (%)	Drug content* (%)	Solubility* (mg/ml)	Powder bed hydrophilicity study (Water raising time*-hrs)
GF	-----	98±2.356	0.012±0.003	12.0±0.250
GFHPC	95±2.123	96±1.154	0.125±0.023	8.5±0.356
GFHEC	94±3.124	95±1.265	0.223±0.013	6.5±0.258
GFPVP	92±2.568	97±2.389	0.356±0.025	5.0±0.357
GFPEG	93±2.658	96±1.254	0.425±0.065	5.5±0.369

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

#### Fourier transforms infra red spectroscopy (FTIR)

The prominent IR peaks (Wave numbers,  $cm^{-1}$ ) of drug, and prepared granules are given in Table-3. The IR spectra of all the tested samples compaction granules

average scans collected in the region 400 – 4000  $cm^{-1}$  at spectral resolution of 2  $cm^{-2}$  and rationed against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

## RESULTS AND DISCUSSION

### Product yield and drug content

The product yield and the drug content of the prepared granules were mentioned in table- 2. The practical yield of all granules prepared by both methods was found satisfactory and showed above 94%. The drug content was of both melt and compaction granules were also on higher side i.e. above 95%.

with their physical mixture (figure-1) and melt granules with their physical mixture showed the prominent characterizing peaks of pure GF which confirm that no chemical modification of the drug has been taken place.

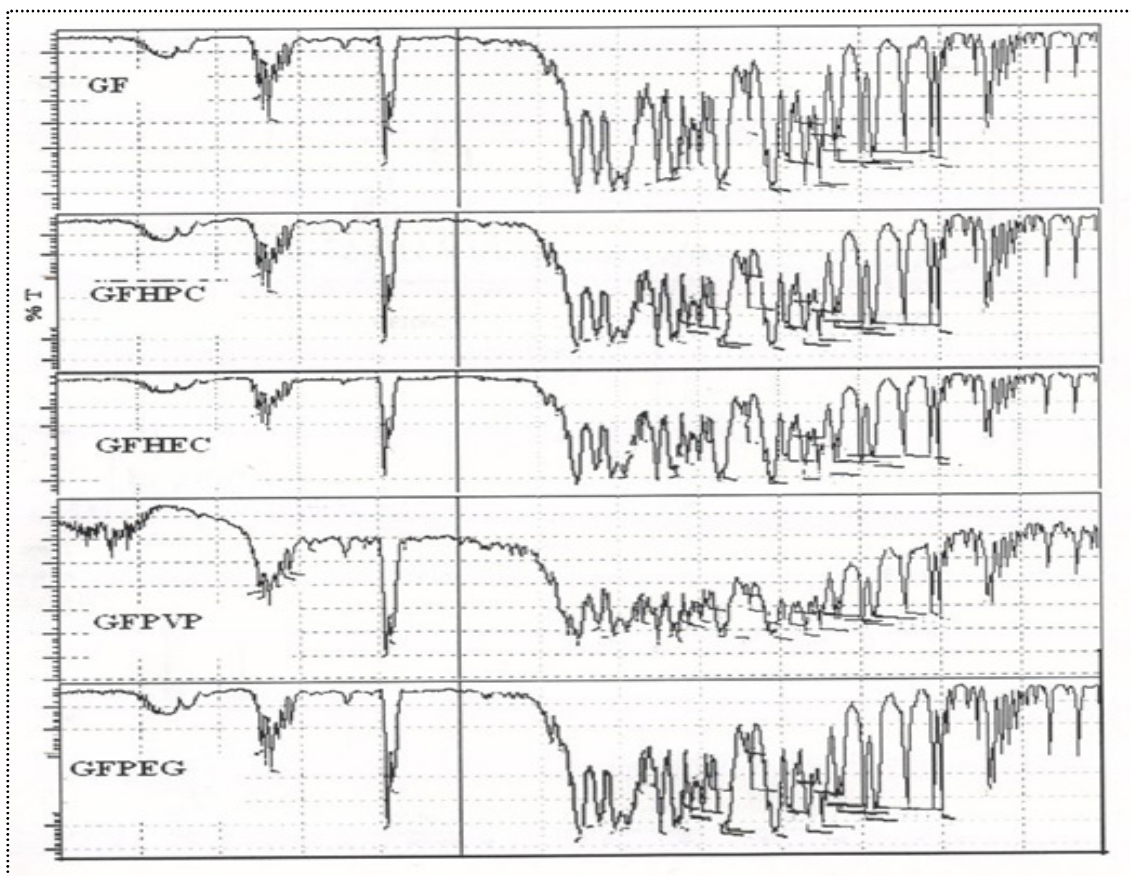
**Table: 3** Flow ability parameters of size enlarged granules by powder wetting solvent change technique

Product Code	Bulk density (mg/ml)*	Tap density (mg/ml)*	Compressibility index*	Hausnar ratio*	Angle of repose*
GF	0.515±0.017	0.655±0.057	21.374±0.075	1.272±0.075	28.08±0.256
GFHPC	0.425±0.026	0.515±0.018	17.476±0.073	1.212±0.015	18.50±0.356
GFHEC	0.435±0.037	0.520±0.023	16.346±0.047	1.195±0.085	17.60±0.456
GFPVP	0.430±0.035	0.525±0.028	18.095±0.087	1.221±0.025	23.56±0.358
GFPEG	0.445±0.048	0.540±0.038	17.590±0.088	1.210±0.019	22.54±0.489

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

**Table: 4** IR peaks (Wave numbers in  $cm^{-1}$ ) of GF and prepared granules

Sr. No.	Prepared granule code	Wave numbers, $cm^{-1}$
01	GF	1705,1658,1616,1597,1580,1501,1222,1213
02	GFHPC	1705,1655,1616,1597,1582,1504,1224,1213
03	GFHEC	1705,1656,1614,1598,1584,1506,1224,1215
04	GFPVP	1704,1654,1615,1596,1585,1506,1224,1215
05	GFPEG	1706,1655,1612,1596,1586,1505,1222,1214

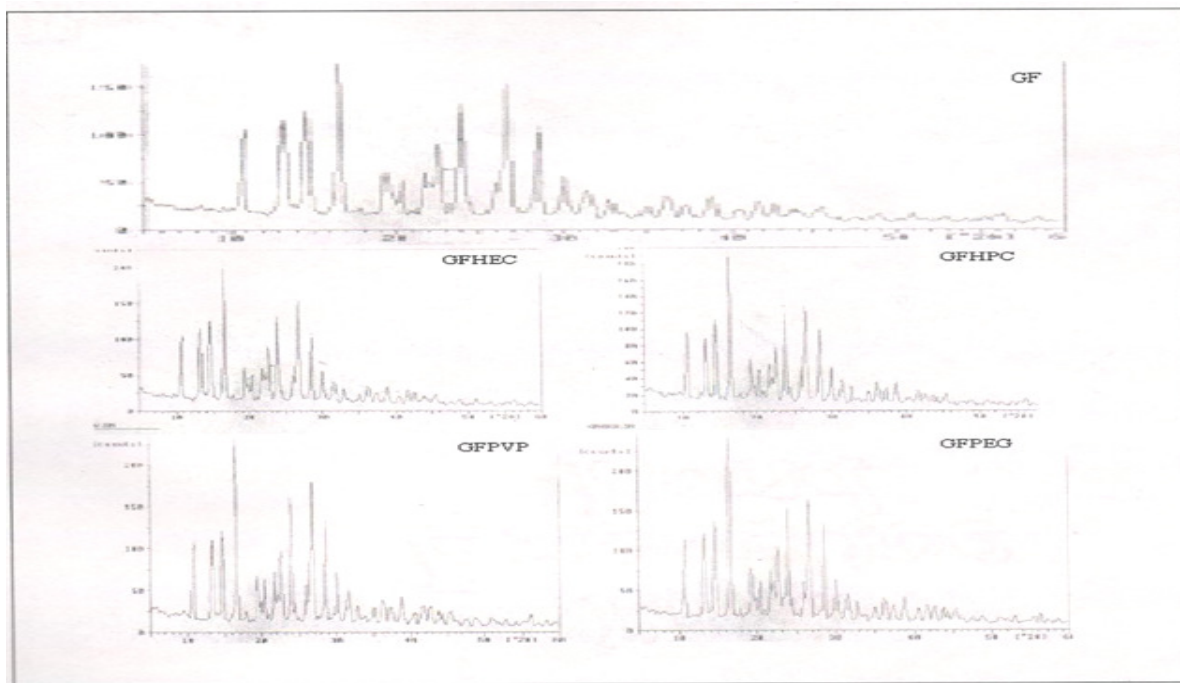
**Figure 1:** FT-IR spectra of GF and size enlarged granules with different polymers

### Powder X-ray diffraction

The XRD scan of plain GF showed intense peaks of crystalline (Figure-2); whereas the XRD pattern of the prepared granules exhibited halo pattern with less

intense and denser peaks compared to plain GF indicating the decrease in crystallinity or partial amorphization of the drug in its prepared granules by both techniques.

**Figure 2:** X ray powder diffraction pattern of GF and size enlarged granules with different polymers



### Solubility study

The results of solubility study (Table-2) revealed that the prepared granules with different polymers and excipient by both compaction and melt granulation technique showed improvement in solubility compared to the pure GF. The saturation solubility all prepared granulates was increased compared to the corresponding physical mixtures and the drug alone because of the higher hydrophilic character of the systems due to the carriers and the slight reduction of crystallinity and Partial amorphization of drug GF in prepared granules as demonstrated by DSC and XRD studies. This may also be due to the improved wettability of prepared granules in the presence of polymers and different excipients.

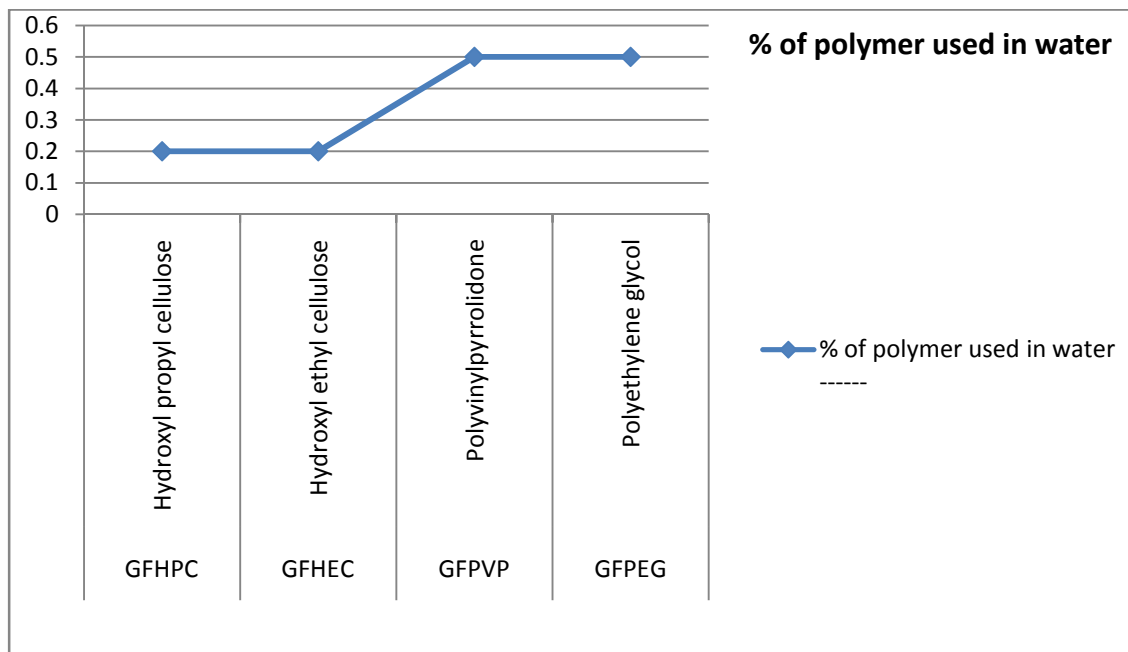
### Dissolution studies of spherical granules

The dissolution profiles of drug and its granules with compaction and melt granulation technique (figure-3). The in vitro dissolution rate of all prepared granulates (figure-3) was significantly increased as

compared to the drug alone, because of the higher hydrophilic character of the systems due to the carriers and the slight reduction of drug crystallinity. The mechanism for enhanced dissolution rate of prepared granules by powder wetting solvent change technique microenvironment due to used hydrophilic polymers like PEG, PVP During dissolution the used polymers creates a local surfactant concentration in the boundary layer surrounding the drug particles , providing a lower energy pathway for drug dissolution. The powder wetting solvent change technique are believed to be particularly effective at enhancing the rate of drug dissolution because the drug particles are maintained in direct contact with the used hydrophilic polymeric particles are maintained in direct contact with the drug and polymer particles may quickly disperse and be separated in the dissolution medium and there might be possibility of partial recrystallization of griseofulvin in

acetone and that will be responsible for change in crystal habit.

**Figure 3:** Dissolution profile of GF, prepared agglomerates by powder wetting solvent change technique:



### Flow ability study

Pure drug GF exhibited poor flow ability as indicated by high value of Carr's index (21.374%), Hausner's ratio (1.272) and angle of repose (28.08°) as per mentioned in table 3. This could be due to the irregular shape and small size of powder, which put hurdles in the uniform flow of powder from the funnel. The prepared granules showed significantly lower values of Carr's index, Hausner's ratio and angle of repose as compared to GF. Thus the prepared granules by both techniques with different hydrophilic polymers and excipients showed improved flow ability compared to pure drug GF. The improved flow ability of spherical granules may be due to good sphericity and more size of granules.

### Wet ability (Powder bed hydrophilicity) study

Table 2 indicates powder bed hydrophilicity study of GF and prepared granules by compaction and melt granulation technique. The granules showed significantly shortest rising time (\*\*P < 0.01) of water to its surface as compared to raw GF. The order of wet ability GFPEG > GFPVP > GFHPC > GFHEC > GF. The reason for the superior wettability with PEG is due to

adsorption of polymers on the raw crystals of GF during preparation.

### CONCLUSION

Prepared size enlarged GF granules exhibited excellent physicochemical and micromeritic properties like solubility, dissolution rate, flow ability and wet ability compared with pure drug as well as the physical mixture of drug with the used excipients. The agglomerates displayed a significant improvement of in vitro drug dissolution behavior. The increase in the dissolution rate can be attributed to the hydrophilic character of the system due to the presence of water-soluble carriers like PEG, PVP, and hydroxyl propyl cellulose in this technique. If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed size enlarged granules with improving the physicochemical and micromeritic properties of GF bypass the granulation step hence the used techniques is less consuming in terms and energy as compared to wet granulation.

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