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Research Article

Preparation and Characterization of Spherical Crystals of Embelin to Improve the Solubility and Micromeritic Properties

*Gadhave MV[1], Banerjee SK[2]

[1]*Research scholar, Department of Pharmaceutics, Bhagwant University, Ajmer, Rajasthan, India.*
[2]*Department of Pharmaceutics, VJSM's Vishal Institute of Pharmaceutical Education and Research, Ale, Pune - 412411, Maharashtra, India.*

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ABSTRACT

Embelin, a chemical constituent obtained from Embelia ribes Burm. Having several therapeutic activities like anthelmintic, antimicrobial, enzyme inhibitory, hepatoprotective, antihyperlipidemic, etc. The poor water solubility and poor micromeritic properties of Embelin lead to low dissolution rate and poor flow during tabletting. The aim of present study was to enhance solubility, dissolution rate and improvement of micromeritic properties of the poorly soluble drug. The spherical agglomerate of Embelin was prepared by solvent change method in the presence of hydrophilic polymer in different concentration. The solvent system used was acetone, water and dichloromethane as good solvent, anti-solvent and bridging liquid respectively. Spherical agglomerates were subjected for determination of percent drug content and particle size analysis. The agglomerates obtained evaluated using by Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), X-Ray Powder Diffraction (XRD) and Scanning Electron Microscopy (SEM) analysis. The FTIR and DSC study showed no interaction between drug and polymer. XRD studies showed a decrease in crystallinity of agglomerates. Spherical agglomerates showed improvement in solubility, dissolution rate and micromeritic properties in comparison to that of the pure drug. The SEM also showed that the agglomerate possess a good spherical shape.

Key words: Embelin, spherical agglomeration technique, solubility, dissolution, micromeritic properties.

INTRODUCTION

Spherical crystallization is a particle design technique. In this technique crystallization and agglomeration can be carried out Embelin simultaneously in one step. This technique has been successfully utilized to improve flowability and compactibility of crystalline drugs. It is the process that enables to control the type and the size of the crystals[1]. Spherical Crystallization process transforms the fine crystal obtained during crystallization, into spherical agglomerates. Agglomerates formed further improves the flowability and compressibility of pharmaceutical ingredient which enables direct tabletting of drug instead of further processing like mixing, granulation, sieving, drying etc[2]. It was a very effective technique in improving the dissolution behaviour of some drugs that having low water solubility and a slow dissolution profile by using hydrophilic polymer during crystallization process. The technique had been used to improve the powder micromeritic properties (flowability and compressibility) and dissolution of drug. The various parameters were optimized in this such as type, amount and mode of addition of bridging liquid, temperature, and agitation speed and reaction rate to get more practical yield of spherical agglomerates. General methods for Spherical Crystallization are spherical agglomeration, emulsion solvent diffusion, ammonia diffusion and neutralization methods[4, 5].

Embelin is a chemical constituent obtained from Embelia ribes Burm. Having several therapeutics activities like anthelmintic[6], antimicrobial[7], enzyme inhibitory[8], hepatoprotective[9], antihyperlipidemic[10], analgesic[11], anticancer[12], and antifertility activities[13]. Chemically it is 2, 5-dihydroxy-3-undecyl-1, 4-benzoquinone[14].Embelin was stable to aqueous alkali but it was unstable under neutral and acidic condition. Its solubility strongly depends on the pH of the test medium and particle size and hence a suitable candidate for spherical crystallization process to improve the flow properties and compressibility. Also, Embelin shows incomplete and poor oral bioavailability due to low aqueous solubility. Hence, the improvement of aqueous solubility in such a case is essential to improve therapeutic efficacy. This technique as the name indicates, provides crystalline agglomerates that are spherical in shape, which exhibit excellent micromeritic properties of many drugs such as Ascorbic acid[15], Aceclofenac[16], Aspirin[17], Atorvastatin Sodium[18], Benzoic acid[19], Carbamazepine[20], Celecoxib[21], Etoricoxib[22], Felodipine[23], Glipizide[24], Ibuprofen[25], Indomethacin[26], Lornoxicam[27], Meloxicam[28], Nebumetone[29], Naproxen[30].

The present research work was an attempt to prepare spherical agglomerates of Embelin by solvent change method. The spherical agglomerates obtained were evaluated for determination of percentage yield,

*Author for correspondence: E-mail: manoj2481@rediffmail.com

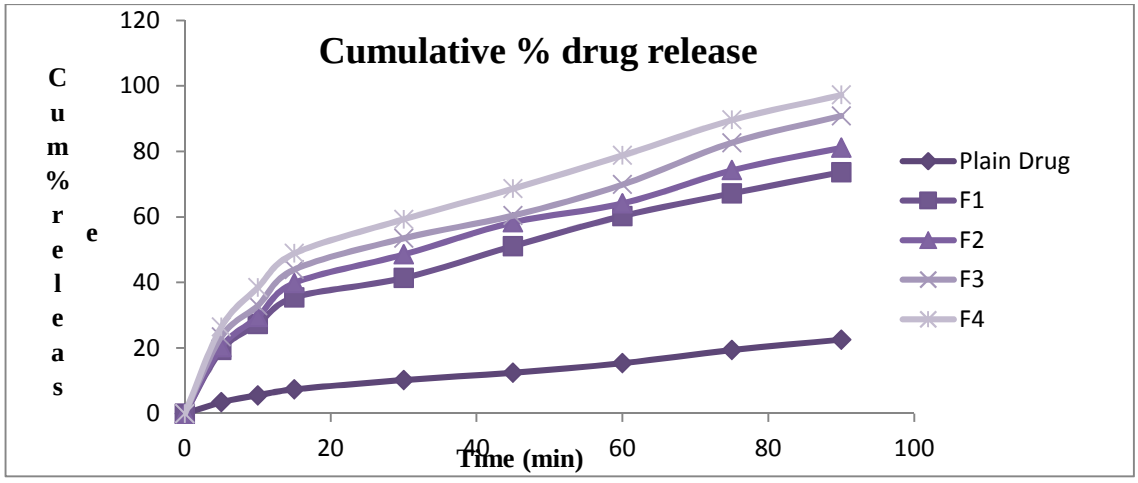

Fig. 1: Dissolution profile of plain drug and spherical agglomerate in phosphate buffer 7.4

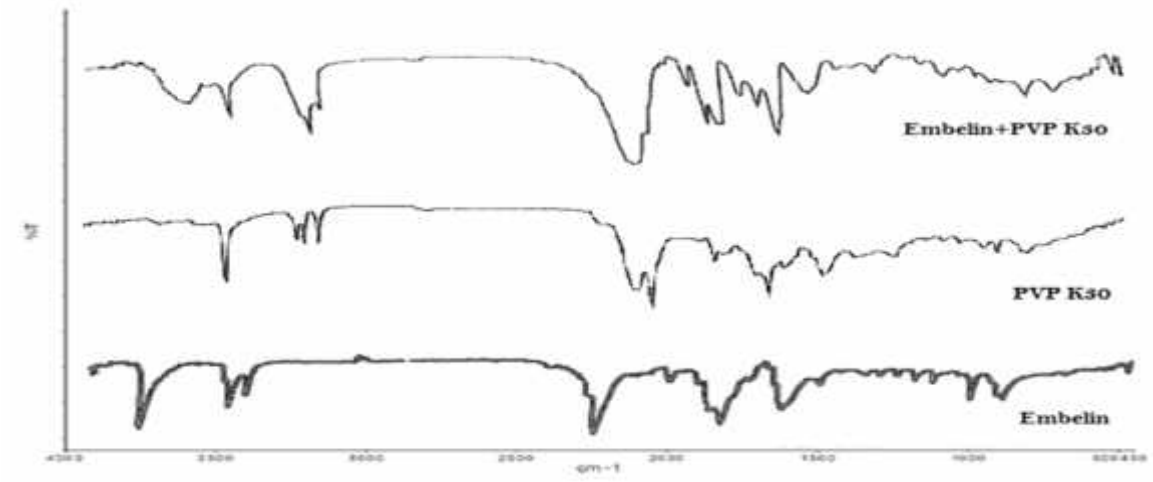

Fig.2: IR spectrum of Embelin, PVP K30 and Embelin + PVP k30

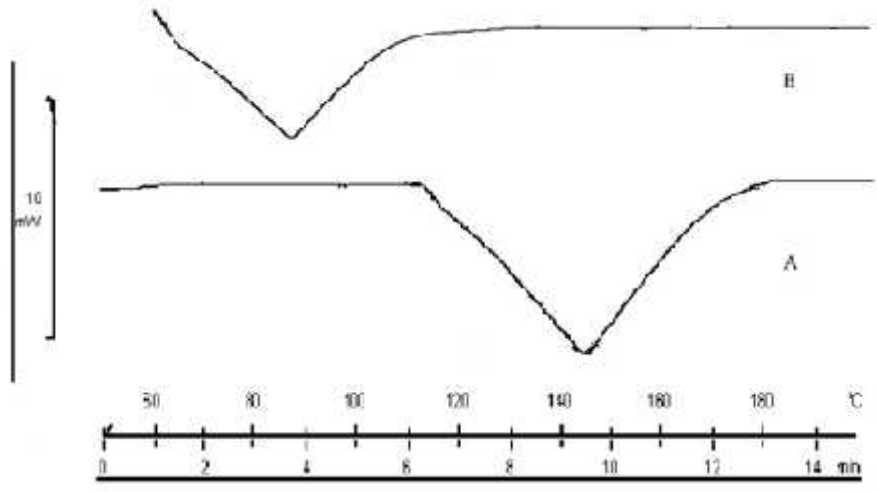

Fig. 3: DSC thermogram of Embelin (A) Plain drug, (B) spherical agglomerates

Table 1: Composition of Spherical Agglomerates of Embelin

ingredients	F1	F2	F3	F4
Embelin (gm)	2	2	2	2
Acetone (ml)	20	20	20	20
PVP K30 solution in water (%)	2.5	5	7.5	10
Dichloromethane (ml)	0.5	0.5	0.5	0.5

percentage drug content, and particle size analysis and micromeritic properties followed by characterization of physicochemical properties such as DSC, FTIR, XRD and SEM analysis. These physicochemical properties of agglomerates were investigated and compared with that of the pure drug.

MATERIALS AND METHODS

Materials: Embelin was purchased from Research Organic, (Chennai, India). PVP K-30 was supply as a gift sample by S. D. Fine chemicals, (Mumbai India). All other chemicals and solvents used were of analytical reagent grade.

Preparation of Spherical Agglomerates of Embelin[31]: The spherical agglomeration was prepared using solvent change method. 2.0 g Embelin was dissolved in a 20 ml acetone to obtained clear solution and added quickly to a 100 ml solution of hydrophilic polymer (PVP-K30) in water at different concentration (2.5- 10.0 w/v). The obtained mixture was stirred continuously at 500 rpm by using a mechanical stirrer. After 15 Min. fine crystals begun to precipitate then bridging liquid i.e. Dichloromethane was added drop wise to obtain spherical agglomerates. The agglomerates were collected by filtration using Whatman filter paper and dried for 24 h at room temperature and store in desiccator for future study.

Micromeritic Properties

Micromeritic Properties[32]: Flowability of Embelin and its spherical agglomerates were determined in terms of the subsequent parameters: Bulk density, Tapped density, Hausner ratio, Carr's index and Angle of repose.

Bulk Density (ρ_b) [33]: It is defined as the mass of a powder divided by the bulk volume. This was Embelin simply determined by the following method. A sample of 25.0 cc of powder from each batch was introduced into a 100 ml graduated cylinder. The cylinder was then dropped at 2-s intervals onto a hard wood surface three times from a height of 1 inch. Thus, bulk density was obtained by dividing the weight of the sample in grams by the final volume in cc of the sample contained in the cylinder. Three replicate determinations were made and the mean calculated (Remi Motors, Bombay, India).

Tap Density (ρ_t): It is defined as the mass of a powder divided by the tap volume. A loosely packed volume of 25 cc of the powder from each batch was poured in a measuring cylinder by means of a funnel, After observing the initial volume, the cylinder was mechanically raised and allowed to fall under its own weight on a hard surface from a height of 2.5 cm at the rate of 120 taps per minute, until no further change in the volume was observed. The tap density was calculated by dividing the weight of the sample in grams by the final volume in c.c. of the sample contained in the cylinder. Three replicate determinations

Fig.4: SEM of Embelin spherical agglomerates

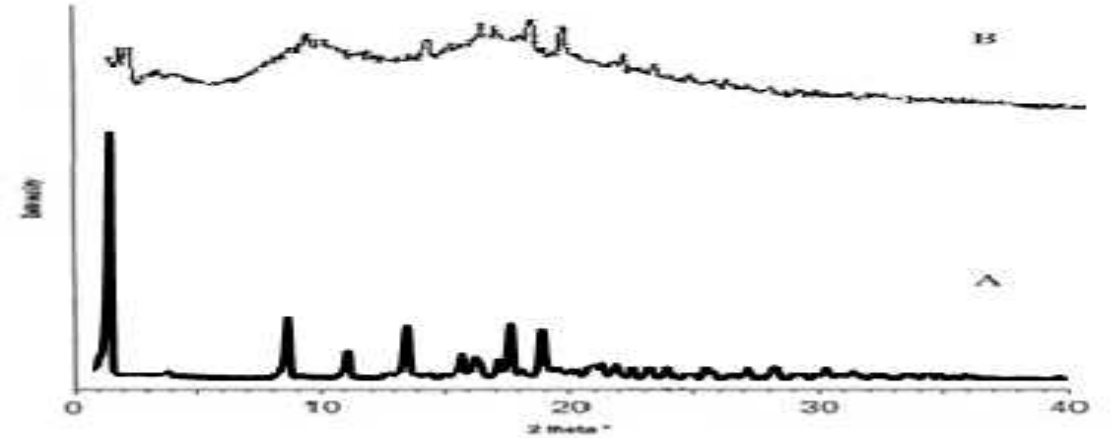

Fig.5: XRD pattern of Embelin (A) Plain drug, (B) Spherical agglomerates

were made and mean calculated (Remi Motors, Bombay,

Table 2: Micromeritic properties of Plain drug and spherical agglomerates

Batch Code	Bulk Density	Tapped Density	Rosin rammler diameter	Carr's Index	Hauser Ratio	Mean yield pressure tone	Angle Of Repose	Shape factor
Plain Drug	0.31	0.46	1200	33.32	1.4	0.520	38.45	-1.204
F1	0.46	0.54	1100	9.35	1.9	0.710	28.48	-1.104
F2	0.44	0.52	845	12.76	1.10	0.910	27.52	-1.079
F3	0.48	0.51	923	9.82	1.13	0.950	26.37	-1.053
F4	0.47	0.52	830	9.80	1.11	1.100	25.58	-1.023

India).

Table 3: Physicochemical Properties of Plain Drug and Spherical Agglomerates

Batch Code	Practical Yield (%)	Drug Content (%)	Solubility (mg/ml)
Plain Drug	-	-	0.076
F1	85.38	92.6	3.62
F2	89.59	93.5	10.35
F3	84.72	93.8	22.83
F4	90.42	97.4	38.79

Carr's Index[34]: Carr derived this dimensionless quantity which proves to be useful to the same degree as that of angle of repose values for predicting the flow behaviour and compressibility behaviour. Compressibility indirectly gives an excellent picture of uniformity in size and shape, cohesion and moisture content. The formula used was,

$$CI = \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}\right] * 100$$

The computed values for the different batches of crystals were expressed in percent.

Particle size[35]: Embelin agglomerates were evaluated for particle size distribution was studied by sieve analysis the weight of agglomerates retained on sieves was subjected to analysis by rosin-rammler distribution

Ln (2-logR) = Ln (aLog) +b Lnd

Where R is cumulative residues percentage by weight D is the particle size and a'&b' are constant

Compressibility studies[36, 37]: Agglomerates (500±10mg) were compressed at compaction pressure of 0.25, 0.75, 1.5, 2.0 and 2.5 tons for one minute using a hydrolic press. The compact alloused to relax for 24 hr pressure (p) relative density (pr) data were analysed using the heekel equation

Ln (1-pr) = KPTA

Where K is heckel constant K=1/360 where 360 is yield strength and mean yield pressure pr is equal to 360. The constant A expresses densification at low pressure

Hausner's Ratio[38]: Particles with high interparticulate friction or cohesiveness have Hausner ratio greater than 1.6 and % compressibility values higher than 40, whereas powder with Hausner ratio less than 1.2 and % compressibility between 5 and 17 can be classified as free flowing powders. Hausner ratio was calculated using following formula.

$$\text{Hausners Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose (Φ) [39]: Angle of repose was determined for all the batches as an index of flow behaviour using basically, the method suggested by Pilpel. The height H and mean radius r measured from five different directions were used to calculate the angle of repose, using the formula,

$$\text{Angle of Repose}(\emptyset) = \tan^{-1}\left(\frac{H}{r}\right)$$

Compatibility Studies:

Fourier transforms infra-red spectroscopy (FTIR): Infra-red spectroscopy was performed on FTIR. The pure drug pvpk-30&spherical agglomerates .obtain embelin and PVP K-30 mix with KBr in mortar and pestle. All above property analysed in FTIR and the range from 400 to 4000nm was selected.

Differential scanning Calorimetry (DSC): The DSC measurements were performed using METLer Toledo DSC 821e module controlled by STARe software (METLer Toledo GmbH, Switzerland). The sample size was 5-10mg, for each measurement was placed in sealed aluminium pans, before heating under nitrogen flow (20mL/min) at a scanning rate of 100C/min, over the temperature range of 50 to 2500C. An empty aluminium pan was used as reference.

Powder X-ray diffraction studies: The powder X-ray diffraction patterns were recorded using an X-ray Diffractometer (PW 1729, Philips, Netherland), with Cu as anode material and crystal graphite monochromator operated at a voltage of 30 kV and a current of 30mA. The samples were analysed in the 2θ angle range of 5 to 800. The range and the chart speed were 2 x 103 CPS and 10mm/ 02θ, respectively.

Scanning electron microscopy (SEM): Small samples were mounted directly on Scotsch double adhesive tape. Samples were coated with gold to a thickness of 100A0 using Hitachi Vacuum Evaporator, Model, and HUS 5GB. Coated samples were analysed in a Hitachi Scanning Electron Microscope Model- S450 operated at 15kV and photograph.

Yield and drug content: Embelin spherical agglomerates where weight after drying and process yield was calculated equivalent to 100 mg of Embelin were accurately weighed, crushed and transferred to a 100 ml volumetric flask. Add 100 ml methanol in it and sample was sonicated for 20 min so as to dissolve the drug and the polymer. The volume was made up to 100 ml with methanol and filtered through a 0.45 µm filters. The filtrate was further diluted with methanol such that the absorbance falls within the range of

Table 4: Drug Release Pattern for Plain Drug and Spherical Agglomerates

Time (min)	Plain Drug	F1	F2	F3	F4
0	0	0	0	0	0
5	3.45	19.37	20.31	23.44	26.41
10	5.57	27.32	29.49	32.92	38.47
15	7.39	35.48	39.87	43.95	48.89
30	10.23	41.39	48.59	53.49	59.33
45	12.47	51.11	58.39	60.44	68.68
60	15.38	60.29	64.19	69.89	78.86
75	19.38	67.22	74.29	82.68	89.63
90	22.57	73.68	81.16	90.87	97.29

standard curve and analyzed at 330 nm by UV-spectrophotometer. (Shimadzu 1800, Japan) and Embelin content was calculated by comparison with standard solution

Solubility study[40]: Solubility studies were carried out using Phosphate buffer pH 7.4 as a solvent. Excessive quantity of Embelin and its spherical agglomerates were taken in separate closed containers (vials) with a fixed volume (10 ml) of Phosphate buffer pH 7.4. The resulting suspension was stirred for 24 hours. After 24 h, the saturated solutions of drug were filtered through 0.45 µm filters. The filtrate was diluted with Phosphate buffer pH 7.4 and the concentration of Embelin was determined by UV-spectrophotometer at 330 nm. (Shimadzu 1800, Japan)

Dissolution study of spherical agglomerates[41]: In-vitro dissolution studies were carried out with Embelin and its spherical agglomerates. The dissolution was perfumed in United States Pharmacopoeia dissolution apparatus I (Basket) dissolution medium was 900 ml Phosphate buffer pH 7.4 maintained at $37.^{0c} \pm 0.5$°C the basket speed was 50 rpm. An accurately weighed quantity of each sample equivalent to 100 mg of Embelin was subjected to the test. Samples 5 ml were withdrawn at predetermined time interval (5, 10, 15, 20, 30 up to 90 minutes) and immediately replace with the equal volumes of dissolution medium. Samples were filtered and appropriately diluted with methanol. Diluted samples were analysed by UV-spectrophotometer at 330nm. (Shimadzu 1800, Japan)

RESULT AND DISCUSSION

Spherical agglomerates were obtained by solvent change method using three solvents (acetone, dichloromethane, water). Acetone a good solvent for Embelin, dichloromethane was used as a bridging liquid and water was anti-solvent. Agglomeration was initiated by the addition of dichloromethane as it acts as bridging liquid. Moreover bridging liquid bring together into the dispersing medium after saturation point was immiscible and only coalescence of bridging liquid occurred, causing an increase in agglomerates. Generally hydrophilic materials are used to impart strength and sphericity to the agglomerates.

Micromeritic Properties: The results of Carr's index, Hausner's ratio, angle of repose particle size distribution are presented in Table 2. These parameters were used to assess the packability, flow and compressibility properties of the agglomerates. The Carr's index, Hausner's ratio, Angle of repose value values for pure drug of Embelin was 36.73%, 1.58, 34.85° respectively, indicating poor flow and packability properties. On the other hand, all prepared spherical agglomerates exhibited higher Carr's index, Hausner's ratio and Angle of repose as compared to pure drug. It also has good compressibility which indicates good packability. The saturation solubility studies indicate that the pure drug having the least solubility while as the formulations have the higher solubility.

Drug Content: Drug content and percentage yield was conceded to know the any loss of drug during formulation; the results were represented in Table.3. Yield for the formulations were within the range of (84.72- 90.42 %) and drug content was (92.6 - 97.4 %). These values indicated that the crystal yield is rises as increase in PVP K-30 concentration during crystallization. The outcomes of in vitro dissolution studies are shown in Table.4 and Figure.1. Pure drug solubility and dissolution rate of spherical agglomerates.

In-vitro dissolution study: The results of in vitro dissolution studies are shown in Table.4 and Figure.1. Pure drug solubility and dissolution rate of spherical agglomerates.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectroscopy was used to investigate the likely interactions between Embelin and PVP-K 30 in the Spherical agglomerates. There is no significant difference in the FTIR spectra of pure drug, and Spherical agglomerates (Figure 2). All basic peaks of Embelin observed at wavenumbers at 3315.93 cm^{-1} (O=H stretching vibration), 2924.35 cm^{-1} (C=H stretching vibration),1750.24 cm^{-1} (C=O stretching vibration), 1614.56 cm^{-1} (C=Cstretching vibration) ,1462.17 $cm^{-1(}$ CH bending in $–CH_2$) , 1375.37 cm^{-1} (CH bending in $–CH_3$), 1219.12 cm^{-1} (C=O stretching vibration) were retained in Spherical agglomerates, which clearly designate that no interaction occurs between pure drug and PVP-K 30 in Spherical agglomerates

Differential Scanning Calorimetry (DSC): The DSC thermo gram of Embelin shows a sharp melting endotherm at 143°C (Figure 3B). In Spherical agglomerates prepared with PVP-K-30, the melting endotherm of is marked in the temperature range of 48.24–99.70 °C and Embelin in the temperature range of 141.53–144.35°C (Figure 3A), predicting that there was no physical or chemical interaction in between and PVP-K-30, Embelin Spherical agglomerates.

Scanning Electron Microscopy (SEM): SEM photomicrographs that predict the surface morphology of the samples are shown in (Figure 4).Characteristic needle-shaped crystals of Embelin were observed in the

photomicrograph of pure drug Embelin (Figure 4). SEM of the Spherical agglomerates (Figure 4) disclose unequal particles with numerous microscopic cracks and crevices, which deliver additional surface for deposition of the drug particles. There is no indication of drug crystals, which confirms the previous findings based on PXRD patterns.

Powder X-Ray Diffractometry (PXRD): The PXRD arrangements of pure drug and solid dispersions are defined in Figure 5. The diffraction arrangements of the Embelin and Spherical agglomerate designate changes in the crystalline nature of the drug. The diffraction pattern of the pure drug Embelin displays a highly crystalline nature, specified by various distinct peaks at a diffraction angle of 2θ ((4.6,9.04, 10.69, 12.61, 13.53, 14.75, 15.45, 16.07, 17.11,17.82, 19.57, 21.32, 22.57, 25.79, 26.97, 30.39, 32.00,34.65, 35.87°) during the scanning range; on the other hand, PXRD of Spherical agglomerate shows a significant slightly change in the degree of crystallinity, as evident by the slightly fading of sharp distinctive peaks. It can be expected that a larger proportion of Embelin has been transformed to the amorphous form. The comparative decrease in the diffraction intensities in the surface Spherical agglomerates can be attributed to the change in orientation during the crystal growth phase. Additionally, as the solution turn into supersaturated; the turbulence generated by the stirrer interferes with the nucleation and crystal-growth phases, leading to development of imperfect crystals or amorphization.

CONCLUSION

This techniques can significantly improves the dissolution rate and flow properties of Embelin without changing crystal forms thus the spherical crystallization technology will provide the directly compressible spherical agglomerates with improved properties. The spherically agglomerates crystals of Embelin with PVP K30 were successfully prepared for enhanced dissolution rate properties of this drug by spherical crystallization technique. The micromeritic properties and also the dissolution profile of the drug were dramatically affected by this technique.

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