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Effect of Different Stabilizers and Polymers on Spherical Agglomerates of Gresiofulvine by Emulsion Solvent Diffusion (ESD) System.

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ABSTARCT: Emulsion Solovent Diffusion (EDS) technique combines crystallization and agglomeration directly to generate spherical agglomerates with improved micromeretic properties, thus obviating need for further processing by granulation and agglomeration. The present study was focused on spherical crystallization of an antifungal drug Gresiofulvine (GRV) using above mentioned ESD technique in which distilled water as an external phase and the internal phase consisted of dichloromethane which acts as good solvent as well as bridging liquid for recrystallization and agglomeration process. Apart from being poorly water-soluble, GRV exhibits poor flow and compressibility owing to its irregular shaped crystal habit and electrostatic charge. The spherical agglomeration was carried out in the presence of different polymers (hydroxyl propyl cellulose (HPC), Eudragit-RLPO) and stabilizers (Beta cyclodextrin, poloxomer-F68 and Polyethylene glycol. The pure GRV and the prepared agglomerates were characterized in terms of production yield, drug content, solubility, in-vitro release profile, flowability,density,packability , thermal behavior (differential scanning calorimetry-DSC), X-ray diffraction (XRD), Fourier transforms infra red spectroscopy (FTIR).The optimized spherical agglomerates exhibited excellent physicochemical and micromeritic properties, solubility, dissolution rate, flowability and packability when compared with pure drug as well as the physical mixture of drug with excipients.The XRD also revealed a characteristic decrease in crystallinity. The dissolution studies demonstrated a marked increase in the dissolution rate in comparison with pure drug and physical mixture. The DSC showed a decrease in the melting enthalpy indicating disorder in the crystalline content. FTIR study reveals there are no chemical changes in prepared recrystallized agglomerates. The considerable improvement in the dissolution rate of GRV from optimized crystal formulation was attributed to the wetting effect of polymers, decreased drug crystallinity, altered surface morphology and micronization.If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed spherical agglomerates with improving the physicochemical and micromeritic properties.

Key Words: Gresiofulvine, Emulsion Solovent Diffusion (EDS), Crystallization, Agglomeration, compressibility, Flowability, Packability.

INTRODUCTION:

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water.[1] In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their high lipophilicity.[2]

As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. One way of improving dissolution involves the reduction of particle size and/or increasing saturation solubility. One of the most common approaches used to reduce particle size is milling, a mechanical micronization process. Milling is a well-established technique which is relatively cheap, fast and easy to scale-up. However, milling has several disadvantages, the main one being the limited opportunity to control important characteristics of the final particle such as size, shape, morphology, surface properties and electrostatic charge. In addition, milling is a high energy process which causes disruptions in the drug's crystal lattice, resulting in the presence of disordered or amorphous regions in the final product.[3] These amorphous regions

are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions.[4]

The alteration of the surface properties also changes the milled product's saturation solubility as well as blending and flow properties, which in turn, have an impact on the formulation process. Furthermore, milled particles often show aggregation and agglomeration which results in poor wettability and thus poor dissolution.[5] An alternative to milling involves growing the particle from a solution to the desired size range under controlled conditions, for example by spray drying, emulsion solvent-diffusion [6] and supercritical fluid technology.[7, 8] One of the advantages of these methods is the possibility of designing in certain beneficial characteristics such as enhancing dissolution rate by incorporating different polymers. The spherical crystallization technique has been successfully applied now days to improve the micromeritic properties of drug substances.[9] In the most common case, this technique is reputed to improve the wettability and dissolution rate of different drugs.[10, 11, 12, 13] Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release .[14,15]

There are two main methods for spherical crystallization: spherical agglomeration (SA method) and emulsion solvent diffusion (ESD method).[16] In the SA method, a quasi-saturated solution of the drug, in a solvent in which it is very soluble, 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. When interaction between the drug and the good solvent is stronger than that of the good and poor solvents, the good solvent drug solution is dispersed in the poor solvent, producing quasi emulsion droplets, even if the solvents are normally miscible. This is due to an increase in the interfacial tension between good and poor solvent. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent. This process is known as the emulsion solvent diffusion (ESD) process.

The objective of this work was to evaluate the feasibility of the emulsion solvent diffusion technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug, griseofulvin. Griseofulvin is an antifungal agent and is practically insoluble in water. Several literature reports reveal that solid dispersions have increased the dissolution rate and gastrointestinal absorption of griseofulvin.[17, 18, 19] This work is focused primarily on evaluating the solvent diffusion technique on a lab scale for improving the solubility and dissolution characteristics of griseofulvin. In addition, it also evaluates the use of different stabilizers and polymers on the solubility and dissolution rate. The in vitro release of the drug from the prepared agglomerated crystals was investigated and compared to that of the pure. SEM was used to study the surface characteristics of the granules. Furthermore, differential scanning calorimetry and X-ray powder diffraction were utilized to investigate the crystallinity of the system.

MATERIALS AND METHODS:

MATERIALS:

Griseofulvin (99% purity) was obtained from Sun Pharma (Vadodara, Gujarat, India).Poloxomer F68, β-Cyclodextrin (BCD), hydroxy propyl cellulose and Polyethylene Glycol-6000 were obtained as gift samples from Alembic Limited (Vadodara, Gujarat, India). Eudagit RLPO was obtained from Degussa India Pvt.Ltd.research center (Mumbai, India).Dichloromethane (analytical grade) was obtained from Loba Chemicals (Mumbai, India).

METHOD:

Spherical agglomerates were prepared without polymers/stabilizers and with polymers and stabilizers by spherical crystallization technique. The different spherical agglomerates were prepared using the polymers and stabilizers coded in table 1 and polymer/stabilizers composition was given in Table 2. In a crystallization vessel, Griseofulvin (1 g) and with polymers like Hyroxypropyl cellulose (HPC), Eudeagit-RLPO Were dissolved in DCM (10 mL).An aqueous phase (100 mL) containing different stabilizers like PEG, β-Cyclodextrin and Poloxomer- F68 was added, and the contents were stirred at 1000 ± 25 rpm using a constant speed stirrer (Remi motors Ltd, Mumbai, India).The stirring was continued until spherical agglomerates were obtained and the supernatant was clear. At the completion of agglomeration, the whole mass was filtered. The same filtrate was used for subsequent washings of agglomerates. Then agglomerates were dried at 37^0C for 24 hours in a hot air oven.

YIELD AND DRUG CONTENT:

Agglomerates were weighed after drying, and process yield was calculated. Agglomerates (300mg) were powdered, from which powder equivalent to 100 mg Greseofulvin was weighed and extracted using three portions of 20mL methanol. Each portion was filtered

through a G-4 sintered 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. Greseofulvin content was calculated by comparison with standard solution.

SATURATION SOLUBILITY STUDIES:

Saturation solubility studies were carried out using deionized water as a solvent. Each excessive 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^{o} C with 100 rpm in incubator shaker. After 24 hrs samples were withdrawn and filtered through 0.2µ filters (Ultipor®N_{66}, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with deionized water and analyzed at 297 nm by UV-visible spectrophotometer.

DISSOLUTION STUDY:

Dissolution studies were carried out using 0.54%SLS in a Type II (paddle) dissolution apparatus (Lab India Disso 2000, Lab India Pvt. Ltd, Mumbai, India). The stirring speed used was 50 rpm and the temperature of the dissolution medium was maintained at 37±0.5 ◦C. The drug concentration in the dissolution medium was assayed spectrophotometrically at 297 nm (Pharma spec 1700, Shimadzu Corporation, Kyoto, Japan) every 15 min for 1 hr.

MEASUREMENT OF FLOWABILITY AND PACKABILITY:

Measurement of flowability:

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 Hausner's ratio were then calculated by using LBD and TBD [20, 21]. The angle of repose of drug powder and the agglomerates were assessed by fixed funnel method [22].

The Carr index reflects the compressibility of the agglomerates, and there is a correlation between the compressibility index and the flowability of the spherical agglomerates. The angle of repose was measured by a fixed funnel method. The results presented are mean value of three determinations.

Measurement of Packability:

The packability of the samples was investigated by tapping them in to a 25-ml measuring cylinder using a tapping machine. Initially, 25 g of substance was weighed and then was gently poured into a measuring cylinder. The volume of 25 g samples was recorded. The poured density (minimum density) was calculated from the powder mass (25 g) and the volume. Then the cylinder was tapped and the volume was recorded after every 100 taps until the volume did not change significantly. The compressibility was evaluated by measuring the tapped density according to the modified Kawakita (I) and Kuno (II) equation

$$N/C = 1/(ab) + N/a \quad \text{.....I}$$

Where as $\{C = (Vo-Vn)/Vo,\ a = (Vo-V\infty)/Vo.\}$

N =Number of tapping, C =Difference in volume (degree of volume reduction.), a and b = constant for packability and flowability, Vo = Initial volume, Vn = Final volume after n^{th} tapping, V∞ = Powder bed volume at equilibrium.

$$\rho_f - \rho_n = (\rho_f - \rho_o) \cdot \exp.(-kn) \quad \text{…II}$$

Where as ρ_f, ρ_o, ρ_n Apparent densities at equilibrium, nth tapped, initial state respectively

The compressibility was assessed by comparing the constants a, 1/b and k in Eqs. I and II, respectively. The constant a represents the proportion of consolidation at the closest packing attained and constant 1/b describes cohesive properties of powders or the apparent packing velocity obtained by tapping. The constant k in Kuno's equation represents the rate of packing process.

CHARACTERIZATION:

Differential scanning calorimetric studies

Differential scanning calorimetric (DSC) analyses of the samples were carried out by using differential scanning calorimeter equipped with computer analyzer (Shimadzu TA –60 differential scanning calorimeter, Shimadzu Corporation, Kyoto, Japan). Samples (of 3-7 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 20-210 ^{o}C.

Powder X-ray diffraction studies

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(α_1/ α_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 2θ range of 5.010-39.990^{o} with scanning step size of 0.020 ^{o} (2θ) 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).

Fourier transforms infra red spectroscopy (FTIR):

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 – 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:

All spherical agglomerates were obtained by the emulsion solvent diffusion method using distilled water as an external phase. The internal phase consisted of Dichloromethane which acts as good solvent as well as bridging liquid for recrystallization and agglomeration process.

The practical yield was found satisfactory and ranged from 90% to 94%. The drug content was decreased as polymer concentration in the agglomerates was increased. The value ranged from 85 % to 90%. The presence of polymers in spherical agglomerates influenced the particle size of resultant agglomerates. As the concentration of the polymers increased, the size of the agglomerates increased. The presence of polymers on the particle surface increases particle–particle interaction, causing faster squeezing out of DCM to the Surface, resulting in increased particle size. The primary particle size was also increased with an increase in polymer content. However, the primary particle size of all the tested agglomerates was lower than that of pure Griseofulvin.Fig:6 represent microscopic observation of raw GRV crystals & the prepared agglomerated crystals. The raw crystals were irregular shaped as compared to the agglomerated crystals, which is spherical in shape.

FTIR study:

The prominent IR peaks (Wave numbers, cm^{-1}) of drug, and prepared spherical agglomerates are given in Table: 3. The IR spectra of all the tested samples showed the prominent characterizing peaks of pure aceclofenac which confirm that no chemical modification of the drug has been taken place.

DSC profile study:

In the DSC studies (Fig.3), pure Griseofulvin showed a sharp endotherm at 216.74^0C corresponding to its melting point. There was no appreciable change in the melting endotherms of spherical agglomerates compared to that of pure drug (GRV-AGG=213.74^0C, GRV-HPC=210.44^0C and GRV-F68=209.13^0C).This observation also confirmed the absence of chemical interaction of drug with additives during agglomeration process, further supporting the results of IR spectroscopy. The DSC results also revealed little amorphization of Griseofulvin when prepared in the form of agglomerates with HPC and ploxomer.This is evident by a decrease, although little, in the enthalpy changes of agglomerates when compared with that of pure.

XRPD scan study:

The XRD scan of plain Griseofulvin showed intense peaks of crystallinity (Fig.4 and 5); whereas the XRD pattern of the agglomerates exhibited halo pattern with less intense and denser peaks compared to plain Griseofulvin indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form. This further supports the DSC results which demonstrated partial amorphization of drug in agglomerates.

Solubility study:

The results of solubility study (Table 2) revealed that the spherical agglomerates with different polymers and stabilizers showed increased solubility compared to the pure drug. This may be due to the improved porosity, decreased primary particle size and partial amorphization of drug in agglomerates as demonstrated by DSC and XRD studies. This may also be due to the improved wettability of spherical agglomerates in the presence of polymers and stabilizers.

Dissolution studies of spherical agglomerates

The dissolution profiles of drug and its agglomerates are shown in Fig.7 and 8. The Gresiofulvine agglomerates prepared with polymers like hydoxypropylcellulose, Eudragit-RLPO and stabilizers like betacyclodextrin, polyethylene glycol, poloxomer exhibited better dissolution rate when compared with plain Gresiofulvine, which could be attributed to deposition of polymer and surfactants onto the recrystallized drug surface. Among the formulations prepared, GRV-HPC and GRV-F68 showed highest drug release in 45 minutes. The cumulative percentage of drug released from different agglomerates was increased in the following order:

Agglomerates prepared from polymers: GRV-HPC>GRV-RLPO>GRV-AGG>GRV

Agglomerates prepared from stabilizers: GRV-F68>GRV-PEG>GRV-AGG>GRV

Flowability and packability:

Pure drug GRV exhibited poor flowability and compressibility as indicated by high value of Carr's index (27.93%), Hausner's ratio (1.35) and angle of repose (41.40^0C). 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 agglomerates prepared with polymers and stabilizers showed improved flowability when compared to pure drug. The improved flowability of spherical agglomerates may be due to good sphericity and more size of agglomerates.

The packability profile of agglomerated crystals revealed that from Kawakitas equation the agglomerated crystals showed significantly smaller value (***P<0.01) of parameter **a** and significantly higher value (***P<0.01) of parameter **b, 1/b** as compared to raw crystals of GRV.From Kunos equation agglomerates showed significantly larger value (*** P<0.01) of parameter **k**. From the values of all these parameters it is proved that the agglomerated crystals showed higher packability than that of raw GRV crystals. The increasing packability of agglomerated crystals may be due to lower surface and wider particle size distribution of spherical crystals, during tapping process smaller particle might have infiltrated into the voids between the larger particles and resulted in improved packability.

CONCLUSION:

In this study prepared Greseofulvin agglomerates exhibited excellent physicochemical and micromeritic properties, solubility, dissolution rate, flowability and packability when compared with pure drug as well as the physical mixture of drug with excipients . If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed spherical agglomerates with improving the physicochemical and micromeritic properties.

Table: 1 Codes for recrystallized agglomerated crystals with different stabilizers and polymers.

Sr.No	Polymers /stabilizers used	Agglomerated crystals code
1	Griseofulvin (API)	GRV
2	Without polymers/stabilizers	GRV-AGG
3	Hyroxypropyl cellulose(HPC)	GRV-HPC
4	Eudeagit-RLPO	GRV-RLPO
5	β-Cyclodextrin (BCD)	GRV-BCD
6	Poloxomer- F68	GRV-F68
7	Polyethylene Glycol (PEG)	GRV-PEG

Table 2. Polymers and stabilizers Composition for Greseofulvin agglomeration.

Composition	GRV-AGG	GRV-HPC	GRV-RLPO	GRV-BCD	GRV-F68	GRV-PEG
Greseofulvin (gm)	1	1	1	1	1	1
Hyroxypropyl cellulose(gm)	----	0.25	----	----	----	----
Eudeagit-RLPO(gm)	----	----	0.25	----	----	----
β-Cyclodextrin (gm)	----	----	----	1	----	----
Poloxomer- F68(gm)	----	----	----	----	1	----
Polyethylene Glycol-6000(gm)	----	----	----	----	----	1
Dichloromethane(ml)	10	10	10	10	10	10
Distilled Water (ml)	100	100	100	100	100	100

Table: 3 IR peaks (Wave numbers in cm^{-1}) of drug and prepared spherical agglomerates.

Sr.No	Agglomerated crystals code	Solubility (mg/ml)
1	Griseofulvin (GRV)	1705, 1658,1616,1597,1580,1501,1222,1213.
3	GRV-AGG	1705,1655,1616,1597,1582,1504,1224,1213.
4	GRV-HPC	1705,1656,1614,1598,1584,1506,1224,1215
5	GRV-RLPO	1704,1654,1615,1596,1585,1506,1224,1215.
6	GRV-BCD	1706,1655,1612,1596,1586,1505,1222,1214
7	GRV-F68	1707,1655,1696,1595,1584,1506,1222,1213.
8	GRV-PEG	1705,1654,1615,1596,1585,1506,1224,1215.

Table: 4 Solubility profiles of recrystallized agglomerated crystals with different polymers and stabilizers.

Sr.No	Agglomerated crystals code	Solubility* (mg/ml)
1	GRV	0.009 ±0.56
3	GRV-AGG	0.023 ±0.75
4	GRV-HPC	0.069 ±0.28
5	GRV-RLPO	0.042 ±0.35
6	GRV-BCD	0.036 ±0.56
7	GRV-F68	0.062 ±0.66
8	GRV-PEG	0.046 ±0.58

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

Table 5: Evaluation Parameters of GRV and optimized spherical agglomerates.

Product code →	CFU	CFU-AGG	CFU-HPC	CFU-F68
Angle of Repose*	41.40 ± 0.28	22 ± 0.33	21.61 ± 0.22	20.39 ± 0.34
Carr's Index*	27.93 ± 0.50	14.75 ± 0.98	12.76 ± 0.37	13.62 ± 0.37
Hauser Ratio*	1.35 ± 0.63	1.12 ± 0.54	1.07 ± 0.29	1.10 ± 0.38
Packability study: (from				
a*	0.39±0.28	0.32±0.30	0.15±0.26	0.17±0.16
b*	0.016±0.34	0.020±0.27	0.022±0.36	0.023±0.29
1/b*	62.5±0.34	50±0.027	45.45±0.36	43.48 ± 0.29
K*	0.019±0.28	0.023±0.30	0.026±0.26	0.022 ± 0.48

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

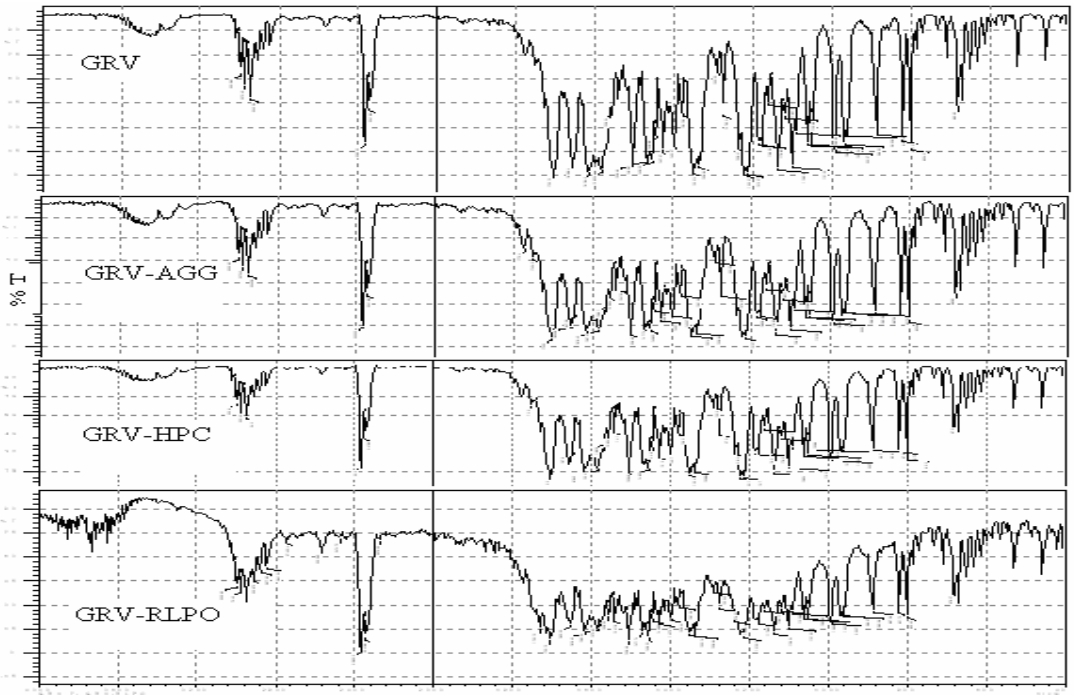


Figure:1 FTIR patterns of griseofulvin (GRV), GRV-AGG, GRV-HPC and GRV-RLPO

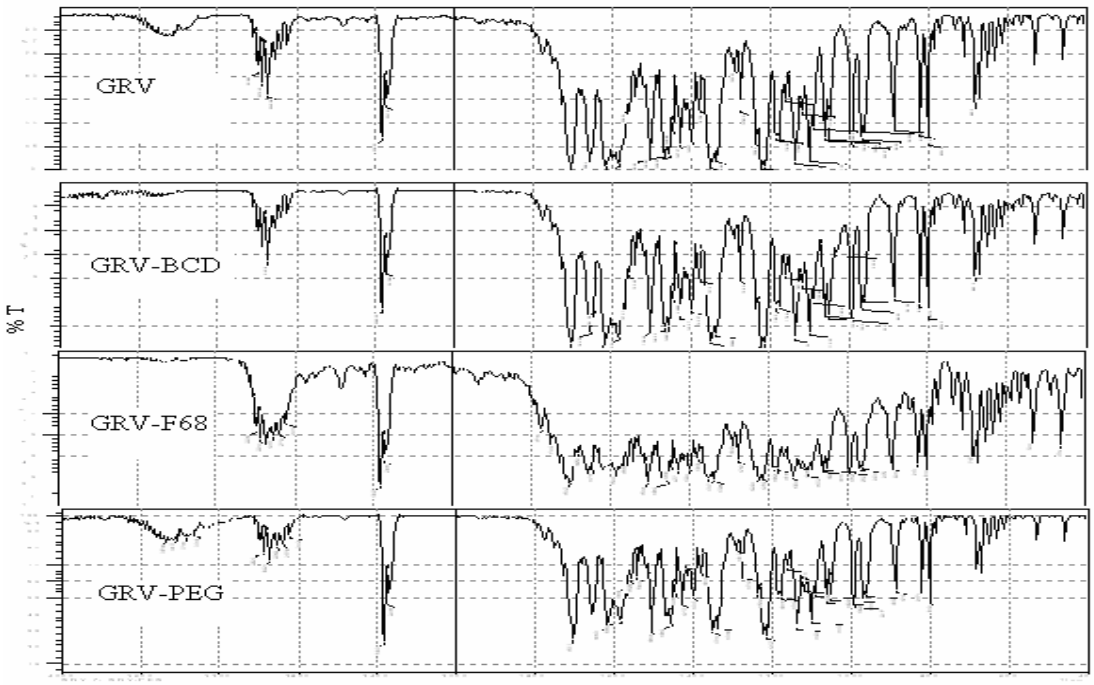


Figure: 2 FTIR patterns of griseofulvin (GRV), GRV-BCD, GRV-F68 and GRV-PEG

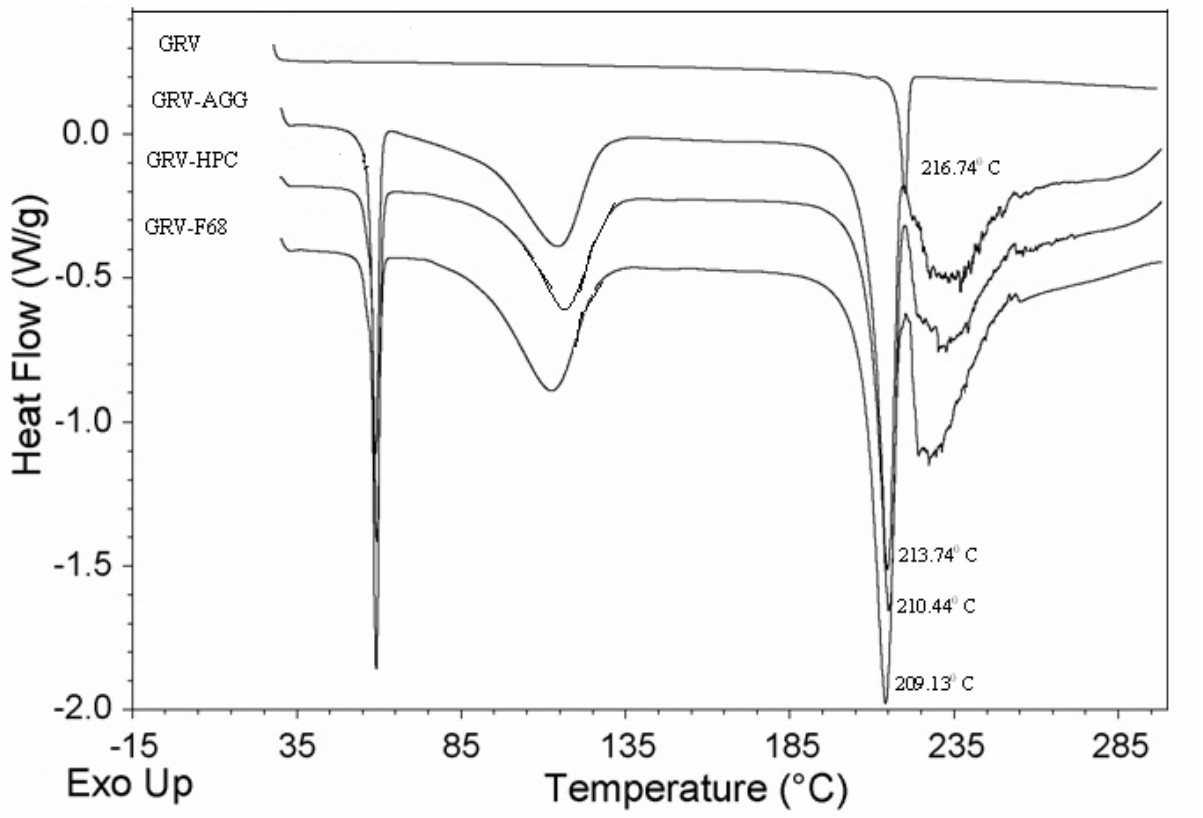


Figure: 3 Differential scanning calorimetry curves of griseofulvin (GRV), GRV-AGG, GRV-HPC and GRV-F68

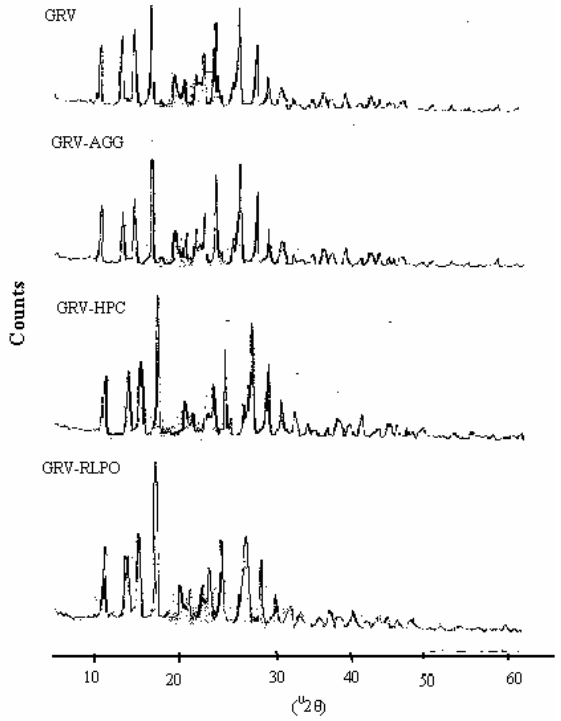


Figure: 4 X-ray diffraction patterns of griseofulvin (GRV), GRV-AGG, GRV-HPC and GRV-RLPO.

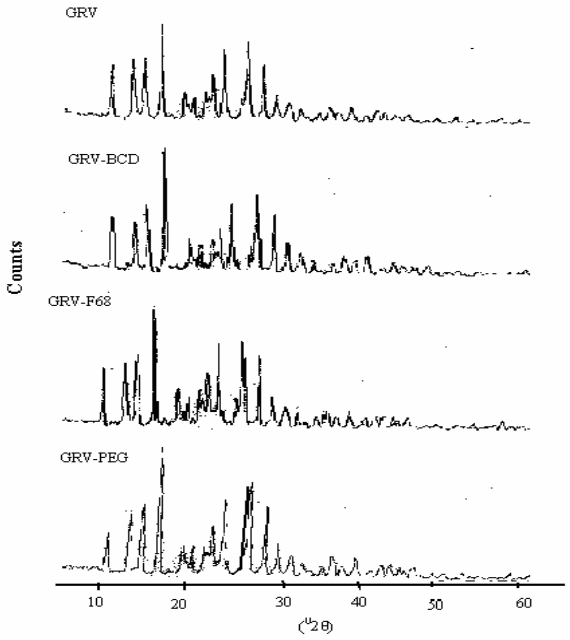
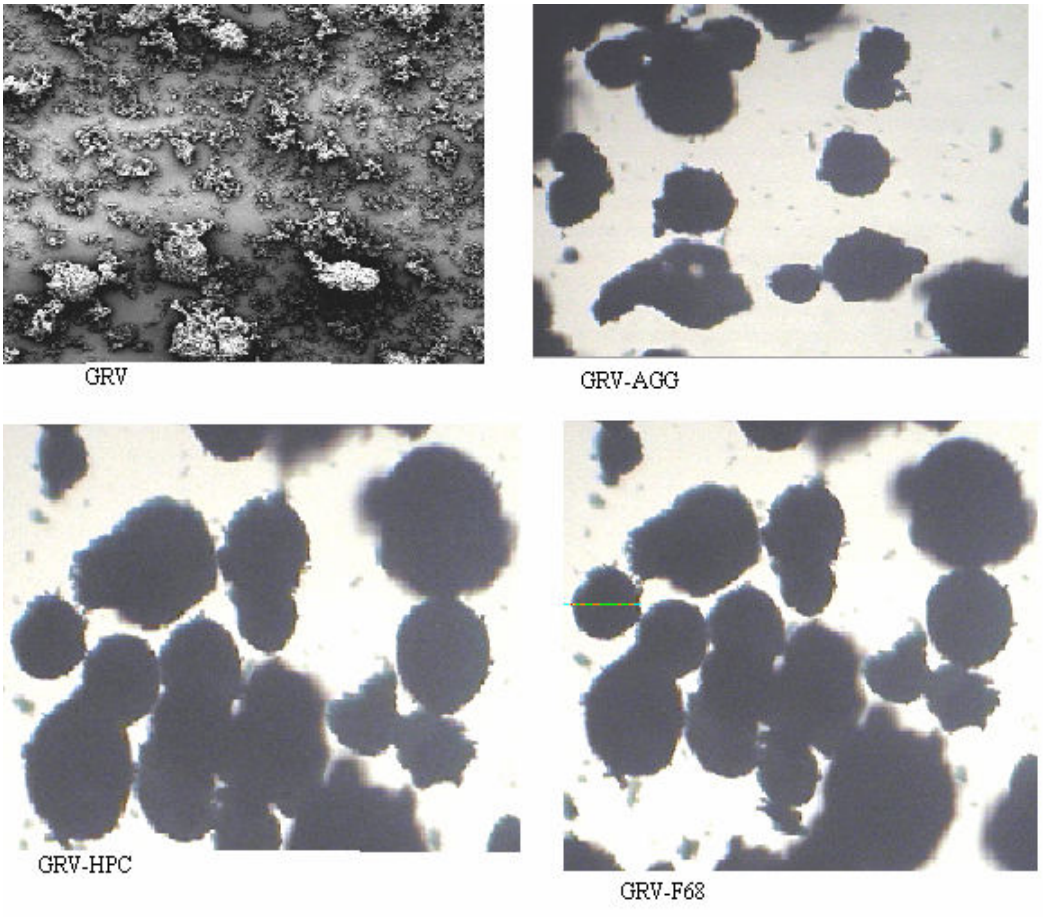


Figure: 5 X-ray diffraction patterns of griseofulvin (GRV), GRV-BCD, GRV-F68 and GRV-PEG



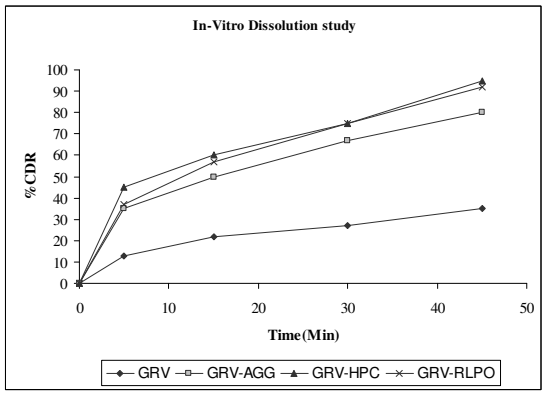


Figure: 7 In vitro release profile of GRV, GRV-AGG, GRV-HPC and GRV-RLPO.

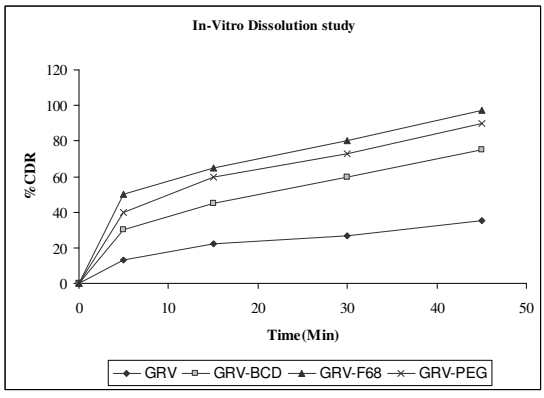


Figure: 8 In vitro release profile of GRV, GRV-BCD, GRV-F68 and GRV-PEG.

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