

Research Article

Effect of Polyethylene Glycol on Physicochemical Properties of Spherical Agglomerates of Antidiabetic Drug.

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ABSTRACT

Spherically agglomerated crystals of Pioglitazone hydrochloride (PGH) with improved flowability and compactibility were successfully prepared by emulsion solvent diffusion method. Plane agglomerates and agglomerates with polyethylene glycol 6000 (PEG) 1% and 2% were prepared using methanol, chloroform and water as good solvent, bridging liquid and poor solvent respectively. Particle size, flowability, compactibility and packability of agglomerates were preferably improved for direct tableting compared with raw PGH. These improved properties of spherically agglomerated crystals were due to their large and spherical shape and enhanced fragmentation during compaction which was well supported by increased tensile strength and less elastic recovery of its compact. X-ray powder diffraction and differential scanning calorimetry study were indicated polymorphic transition of PGH from form II to I during recrystallization but not associated with chemical transition indicated by Fourier transforms infrared spectra.

KEYWORDS

Spherical crystallization, polyethylene glycol 6000, pioglitazone hydrochloride, compatibility, pack ability.

1. INTRODUCTION

Tablet is the most preferred dosage form than any others as it is most stable, readily portable and consumed dosage form. Direct tableting has been renewed a efficient process by mixing and compressing a powder to save time and cost as compared with granule tableting.¹ But it strongly depends on the flowability, compactibility and packability of the drug crystals used otherwise lot of excipients are necessary resulting in bigger sized tablets. Crystal could be generated employing any of the available technique like sublimation, solvent evaporation, vapor diffusion, thermal treatment, crystallization from melt precipitation and growth in presence of additives.² Fine crystals are preferred over large crystals of poorly soluble pharmaceuticals as they provide greater bioavailability. However, micronization of crystals frequently prevents efficient powder processing due to poor flowability, compactibility and packability.³ Thus novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during recrystallization process has been desired. The use of spherical crystallization technique appears to be efficient alternative for obtaining suitable particles for direct compression.⁴ Spherical crystallization is a particle design technique by which recrystallization and agglomeration can be carried out simultaneously in one step which has been successfully utilized for improvement of flowability and compactibility of crystalline drugs.^{5, 6, 7} Two methods are reported in the literature for generating spherical agglomerates: the spherical agglomeration (SA) method and emulsion solvent diffusion (ESD) method.^{8, 9} In SA method nearly saturated solution of the drug in the good solvent is poured into the poor solvent, provided that the poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and good solvent. Under agitation a third solvent called bridging liquid is added. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals.¹⁰ In ESD method the drug is dissolved in the good solvent and bridging liquid and the resultant solution is dispersed into the poor solvent producing emulsion (quasi) droplets, even though the pure solvents are miscible due to an increase in the interfacial tension between the solvents. In this method the affinity between the drug and good solvent is stronger than that of good solvent and poor solvent. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase and the poor solvent diffuses into the droplets by which drug crystallizes inside the droplets.¹¹

Pioglitazone hydrochloride (PGH) is thiazolidinedione oral antidiabetic used in the management of type II diabetes mellitus. It is rapidly absorbed after oral administration; peak plasma concentrations are obtained within two hours.¹² The aim of present investigation was to study the effect of addition of PEG during spherical agglomeration of PGH on physicochemical properties.

2. MATERIALS AND METHODS

2.1. Materials

Pioglitazone hydrochloride (PGH) was kindly provided by Alembic research Centre, Gujarat, India. Polyethylene glycol 6000 (PEG), methanol and chloroform were purchased from Rajesh chemicals, Pune, India.

2.2. Experimental methods

2.2.1. Development of spherically agglomerated crystals of PGH by ESD method

PGH (1g) was dissolved in a mixture of 6ml methanol (good solvent) and 4ml chloroform (bridging liquid). The resultant solution was poured in to distilled water (50ml) containing 500mg, 1gm of PEG, with stirring at 800 revolutions per minute (rpm) for 20 minutes at 25°C. The obtained recrystallized agglomerates were collected by vacuum filtration and dried in oven at 60° C for 4 hours (hrs). The dried crystals were stored in desiccators at room temperature before use. Above process was repeated several times to obtain enough materials for characterization and to observe repeatability.

2.2.2. *Thin layer chromatography (TLC):*

PGH and its prepared agglomerates were dissolved in methanol and spotted on reverse-silica gel plate separately, which was developed with a solvent system toluene: methanol: ammonia (7:3:0.1 v/v) and detected by iodine vapor.

2.2.3. *Micrometric properties of raw crystals and spherical agglomerates:*

Mean particle size of PGH and its agglomerates was determined by randomly counting average diameter of 100 particles with optical microscope and their SEM microphotographs were taken. Micrometric properties of raw crystals and spherical agglomerates were determined. Particle size was determined by microscopy method. Bulk density and tap density was determined according to following method. A 50 ml glass cylinder was weighed and filled with 30 ml sample and reweighed. The opening was secured with parafilm. The cylinder was gently reversed once and the powder was carefully leveled without compacting. Bulk volume was determined after one mechanical tap on a tap density tester (Dolphin™). Tap volume was measured after 2000 taps.¹³ Each analysis was repeated thrice. Values of bulk density and tap density were used to calculate Carr's index and Hausners ratio in eq. 1 and 2 respectively.^{14, 15}

$$\text{Carr's index} = [(\text{Tap density} - \text{Bulk density}) / \text{Tap density}] \times 100 \quad (1)$$

$$\text{Hausners ratio} = \text{Tap density} / \text{Bulk density} \quad (2)$$

The flow behavior of raw crystals and spherical agglomerates was determined by Angle of repose using fixed funnel method.¹⁶

2.2.4. *Compaction behavior of raw crystals and spherical agglomerates:*

Compaction behavior of raw crystals and spherical agglomerates were analyzed by Heckel equation, elastic recovery (ER) and crushing strength. The Heckel method was most frequently. It is assumed that the densification of the powdered column follows a first order kinetics. Thus the degree of material densification is correlated to its porosity.^{17, 18} The Heckel equation is widely used to evaluate the volume reduction of the materials when pressure is applied during compression and is as given below.

$$\ln(1/1-D) = KP + A \quad (3)$$

Where D is the relative density of powder for applied pressure P. The slope of the straight-line portion, K, is the reciprocal of the mean yield pressure (MYP), of the material. From the value of the intercept, A, the relative density, D_a and the relative density of powder bed at the point when the applied pressure equals to zero, D_o , can be calculated using following equations.

$$D_a = 1 - e^{-A} \quad (4)$$

$$D_o = 1 - e^{-A_0} \quad (5)$$

$$D_b = D_a - D_o \quad (6)$$

Where A_0 represents the intercept of the line when $P = 0$. The relative density, D_b , describes the phase of rearrangement at low pressure and is the difference between D_a and D_0 .

Heckel study was performed by compressing 500 mg of raw crystals and spherical agglomerates on hydraulic press (Samrudhi Enterprises, Mumbai, India.) using 13 mm flat faced punch and die set, at pressure 20, 30, 40, 60, 80, 100 and 120 kg/cm² and thickness of compacts were determined. True density of the powder was determined by compression at 120 kg/cm². The weight, diameter and thickness were also determined. M.Y.P., D_a , D_0 and D_b were determined as per equation 3, 4, 5 and 6 respectively. For determination of ER thickness of the compact of agglomerates and raw crystal of PGH was determined at compression pressure 60 kg/cm² and at 24 hrs after releasing the tablet. ER was calculated in e. 7.¹⁹

$$ER = [(t_2 - t_1) / t_1] \quad (7)$$

2.2.5. Solubility study

Solubility of raw crystals and spherical agglomerates of PGH were determined in distilled water and in pH 2 KCl buffer. Excess amounts of sample were added in 20 ml of distilled water / pH 2 KCl buffer and were continuously shaken (300 rpm) at $25 \pm 0.5^\circ\text{C}$ for 48 hrs. Samples were filtered through 0.45 μm filter and assayed spectrophotometrically for drug content at 269 nm.

2.2.6. X-ray powder diffraction (XRPD):

X-ray powder diffraction of raw crystals and spherical agglomerates were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu K_α – radiations (1.542 \AA) and analyzed between $2-60^\circ$ (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5×10^3 cycles/s and the chart speed was kept at 100 mm/2 θ .

2.2.7. Differential Scanning calorimetry (DSC)

Thermal properties of raw crystals and spherical agglomerates of PGH were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (5-10mg) was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 0 to 300°C at a heating rate of $10^\circ\text{C}/\text{min}$.

2.2.8. Fourier transforms Infrared spectroscopy (FT-IR)

Fourier transforms Infrared spectroscopy of raw crystals and spherical agglomerates of PGH was recorded using Jasco V5300 (Jasco, Japan) FT-IR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 4000 to 400 cm^{-1} .

2.2.9. In-Vitro dissolution studies

The dissolution studies were performed by using USP 26 type II dissolution test apparatus (DolphinTM, Mumbai, India). Dissolution medium used were KCl buffer (pH 2) 900 ml, temperature was maintained at $37 \pm 2^\circ\text{C}$ and 100 rpm stirring was provided for each dissolution study. PGH and its spherical agglomerates equivalent to 100 mg of PGH were used for each dissolution study. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41, concentration of PGH was determined spectrophotometrically at 269 nm.

3. RESULTS AND DISCUSSION

3.1. Development of spherically agglomerated crystals of PGH by ESD method

A study started with selection of good solvent, poor solvent and bridging liquid which strongly depends on the miscibility of the solvents and the solubility drug in individual solvents. PGH is soluble in methanol, slightly soluble in chloroform but insoluble in water.²⁰ Thus methanol, chloroform and water were used as good solvent, bridging liquid and poor solvent respectively. Preliminary experiments were performed to optimize the concentration of solvents. It was found that without bridging liquid needle shaped agglomerates were formed. At optimized concentration of good solvent and bridging liquid (3:2) spherical agglomerates of PGH were formed. After optimizing concentration of solvents different stirring rates were tested and an optimum was found to be 800 rpm. Lower stirring rate reduced the possibility of formation of spherical agglomerates while high stirring rate destroyed the agglomerates. When solution of drug in good solvent and bridging liquid was poured into poor solvent the quasi-emulsion droplets of drug solution were produced initially. Successively the crystallization of a drug occurred at the outer surface of the droplet. The spherically agglomerated crystals were produced simultaneously after complete crystallization and the whole process is called as emulsion solvent diffusion. Under stirring the agglomerates were spheronized and compacted.

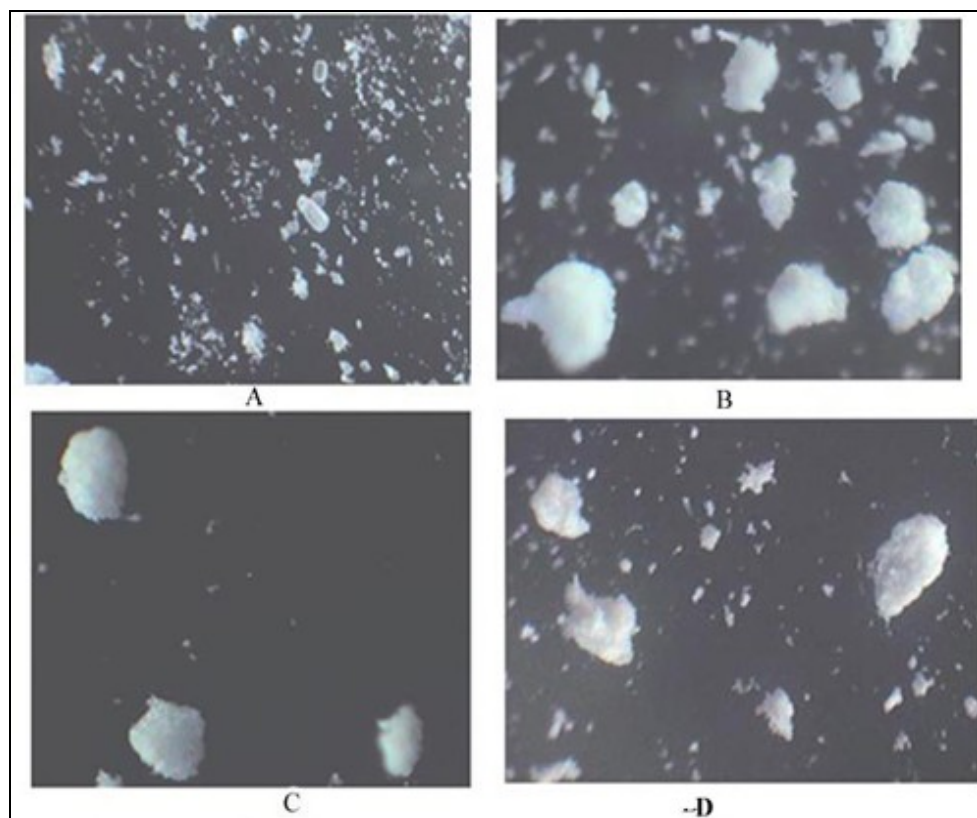


Fig 1: Microphotographs of A: Pioglitazone hydrochloride and Spherical agglomerates of PGH: B: Plane, C: with 1% PEG, D: with 2% PEG.

3.2. Thin layer chromatography (TLC)

The chemical stability of spherical agglomerates was determined using TLC. The TLC of raw crystals and spherical agglomerates of PGH has shown a single spot with R_f value 0.55. It indicated that in spherical agglomerates of PGH drug has not decomposed during recrystallization.

Table 1. Micrometric properties of raw crystals and spherical agglomerates of PGH.

Sample	Average diameter (μm) n=100	Angle of repose ($^\circ$) (n=3)	Bulk density (g/cc) (n=3)	Tap density (g/cc) (n=3)	Carr's Index (%) (n=3)	Hausner's ratio (n=3)
Raw crystals of PGH	16.7 ± 1.05	52.23 ± 0.75	0.322 ± 0.007	0.476 ± 0.006	32.35 ± 0.5	1.42 ± 0.04
PGH spherical agglomerates (Plane)	162.3 ± 1.13	23.14 ± 0.65	0.281 ± 0.006	0.331 ± 0.004	15.01 ± 0.4	1.18 ± 0.05
PGH spherical agglomerates with 1% PEG	152.8 ± 0.81	22.23 ± 0.75	0.279 ± 0.006	0.325 ± 0.003	14.15 ± 0.6	1.16 ± 0.04
PGH spherical agglomerates with 2% PEG	158.7 ± 1.19	23.23 ± 0.29	0.275 ± 0.008	0.320 ± 0.003	14.06 ± 0.7	1.16 ± 0.05

3.3. Micrometric properties of raw crystals and spherical agglomerates

Agglomerates formed were spherical having micrometric properties given in table 1. It was found that particle size of plane agglomerates and agglomerates with PEG (1% and 2%) was increased more than 10 times than original crystals may be due to particle agglomeration in the treated crystals. Microphotographs of drug, plane agglomerates and agglomerates with PEG (1% and 2%) were shown in figure 1 revealed that agglomerates were spherical with smooth surface. The bulk density of plane agglomerates and agglomerates with PEG (1% and 2%) was lower than that of raw crystals of PGH. Reduction in bulk densities of spherical agglomerates indicates

the greater porosity within the agglomerates.²¹ Angle of repose, Carr's index and Hausner's ratio values of the plane agglomerates and agglomerates with PEG (1% and 2%) was lower than raw crystals of PGH, indicates its better flowability might be due to large and spherical shape of agglomerates clearly indicated in microphotographs of agglomerates shown in figure 1. Angle of repose, Carr's index and Hausner's ratio values of agglomerates with PVP has shown its poor flowability. In case of agglomerates with PEG (1% and 2%) average diameter was increased than raw crystals but decreased than plane agglomerates of PGH. These findings suggests that PEG and β -CD were poorly adsorbed at the surface which reduces the interfacial tension between bridging liquid and crystals and decreases the adhesive force acting to agglomerate the crystals.²²

3.4. Compaction behavior of raw crystals and spherical agglomerates

The compressibility of a material is its ability to reduce in volume as a result of an applied pressure. Heckle parameters D_a , D_o , D_b , MYP and elastic recovery of raw crystals and spherical agglomerates of PGH were given in table 2. D_b value represents the particle rearrangement phase in early compression stage and tends to indicate extent of particle fragmentation. The D_b values for plane agglomerates and agglomerates with PEG (1% and 2%) were higher than the raw crystals of PGH indicated that the agglomerates were highly fractured during early stage of compression although fragmentation is followed by plastic deformation. The results were well supported by higher MYP values. The elastic recoveries of the compacts of plane agglomerates and agglomerates with PEG and β -CD were smaller than that of original drug crystals. These findings suggested that the agglomerated crystals were easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression. The improved compactibility of agglomerates might be attributed to characteristic structure responsible for the large relative volume changes during the early stage of the compression process due to their fragmentation. It has been shown that a reduction in bulk density of agglomerates results in an increase in the tensile strength of tablets, similar results were obtained in study by Ali N et.al.²¹

3.5. Solubility study

Solubility of raw crystals and spherical agglomerates of PGH were given in table 3. It was observed that solubility of spherical agglomerates was increased than raw crystals of PGH may be due to increased in wettability and porosity. It was higher for agglomerates with 2% PEG and lower for plane agglomerates.

3.6. X-ray powder diffraction (XRPD)

XRPD of raw crystals and spherical agglomerates of PGH were shown in figure 2. PGH has at least two polymorphic forms that is form I and form II. Diagnostic peaks for form I are at $2\theta=$ 8.7, 12.7, 18.8, 20, 20.1, 22.7, 26.6, 28.3 and for form II are at $2\theta=$ 9.2, 10.4, 15.2, 16.4, 18.6, 21.4. The XRPD of raw crystals of PGH was identical to form II and that of all spherical agglomerates of PGH were identical to form I.²³ It revealed that during spherical crystallization of PGH there was polymorphic transition of PGH from form II to form I and the most providing identification is absence of peaks at 8.7, 20, 22.7 and 26.6 in spherical agglomerates of PGH.

Table 2. Heckel parameters D_a , D_o , D_b , MYP (mean yield pressure) and ER (elastic recovery) of raw crystals and spherical agglomerates of PGH. (n=3)

Sample	D_a	D_o	D_b	MYP	% ER
Raw crystals of PGH	0.617 ± 0.003	0.416 ± 0.011	0.201 ± 0.007	22.54 ± 2.4	8.1 ± 1.2
PGH spherical agglomerates (Plane)	0.411 ± 0.002	0.173 ± 0.003	0.238 ± 0.005	27.41 ± 1.8	4.8 ± 0.3
PGH spherical agglomerates with 1% PEG	0.564 ± 0.003	0.181 ± 0.004	0.383 ± 0.003	25.31 ± 1.6	5.1 ± 0.5
PGH spherical agglomerates with 2% PEG	0.483 ± 0.005	0.161 ± 0.008	0.322 ± 0.003	28.31 ± 2.3	5.0 ± 0.4

Table 3. Solubility study of raw crystals and spherical agglomerates of PGH. (n=3)

Sample	Solubility ($\mu\text{g/ml}$) in	
	Water	pH 2 KCl buffer
Raw crystals of PGH	30.8621 ± 1.2	109.052 ± 2.3
PGH spherical agglomerates (Plane)	76.5086 ± 1.6	227.845 ± 3.1
PGH spherical agglomerates with 1% PEG	82.9741 ± 2.1	268.276 ± 2.1
PGH spherical agglomerates with 2% PEG	92.0603 ± 1.8	369.966 ± 4.3

3.7. Differential Scanning calorimetry (DSC)

DSC thermogram of raw crystals and spherical agglomerates of PGH was shown in figure 3. Crystals of PGH showed melting endotherm at 192.6°C with heat of fusion -120 J/g and all spherical agglomerates of PGH showed melting endotherm at 182°C with heat of fusion -99.24 J/g . These findings indicated that untreated sample has form II which is changed to form I for spherical agglomerates during recrystallization.²³ DSC is generally combined with XRPD to determine polymorphic composition of pharmaceutical powders when polymorphs present different melting points. Thus DSC results were well supported with XRPD indicating polymorphic transitions during recrystallization of PGH might be due to change in crystal habit.

3.8. Fourier transforms Infrared spectroscopy (FT-IR)

Raw crystals of PGH and spherical agglomerates of PGH exhibited identical IR spectra as shown in figure 4,²⁴ which indicated that the altered XRPD spectra and DSC thermogram for these

samples were not associated with any changes at the molecular level. It revealed that no any chemical transition has occurred during recrystallization of PGH.

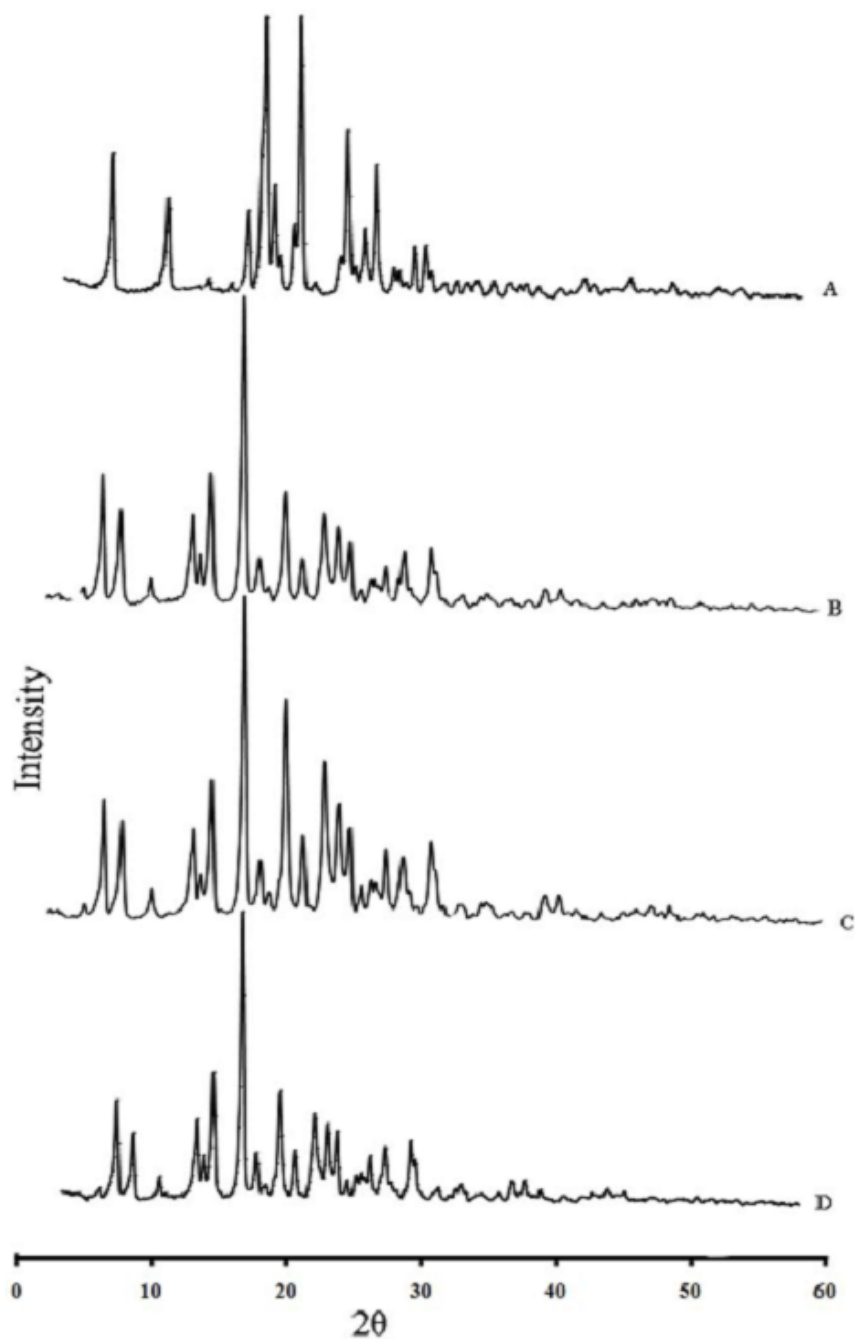


Fig. 2. X-ray powder diffraction pattern of A: Pioglitazone hydrochloride and Spherical agglomerates of PGH: B: Plane, C: with 1% PEG, D: with 2% PEG.

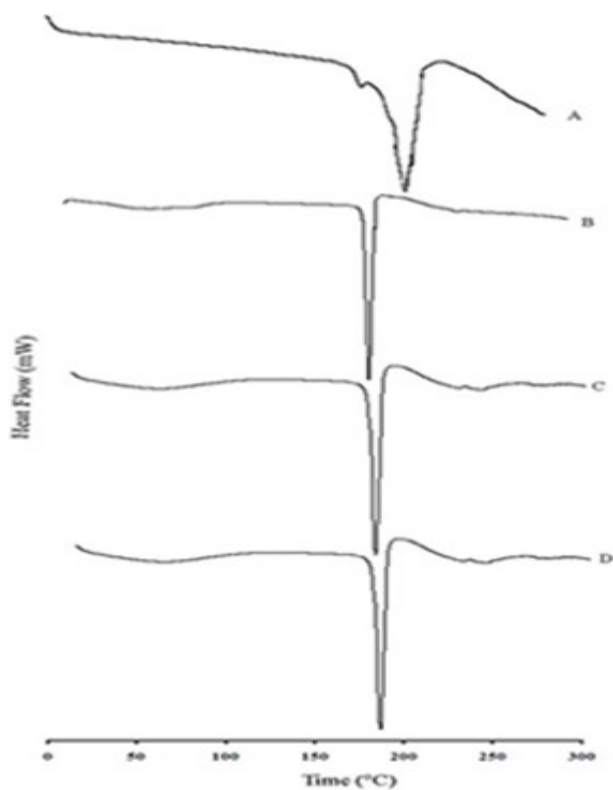


Fig. 3. DSC thermograms of A: Pioglitazone hydrochloride and Spherical agglomerates of PGH: B: Plane, C: with 1% PEG, D: with 2% PEG.

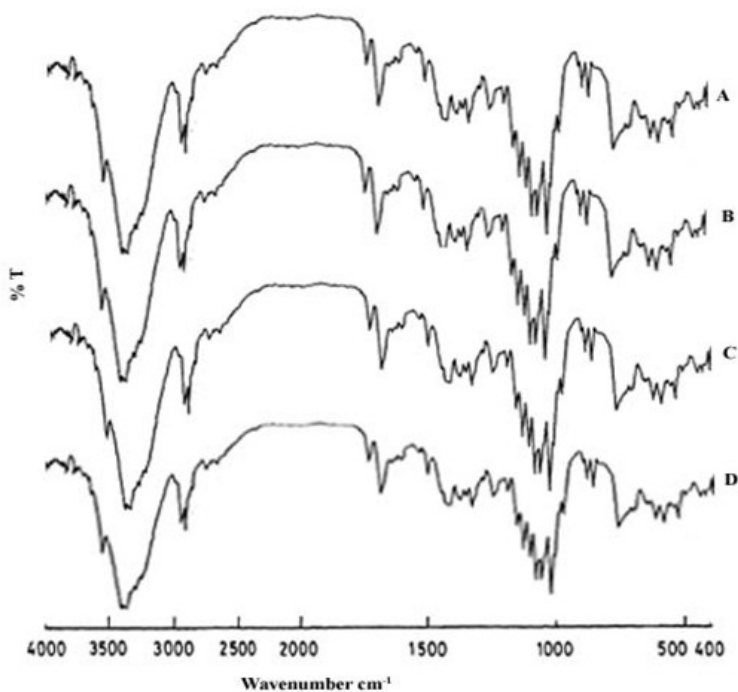


Fig. 4. IR Spectra of A: Pioglitazone hydrochloride and Spherical agglomerates PGH: B: Plane, C: with 1% PEG, D: with 2% PEG.

3.9. In-Vitro dissolution studies

Rate of dissolution of raw crystals and spherical agglomerates of PGH were shown in figure 5. It was observed that for raw crystals of PGH up to 67 % drug was release in 30 min while for agglomerates of PGH drug release was increased with the order > 2% PEG > 1%PEG > plane > raw crystals. The results were well correlated with solubility data.

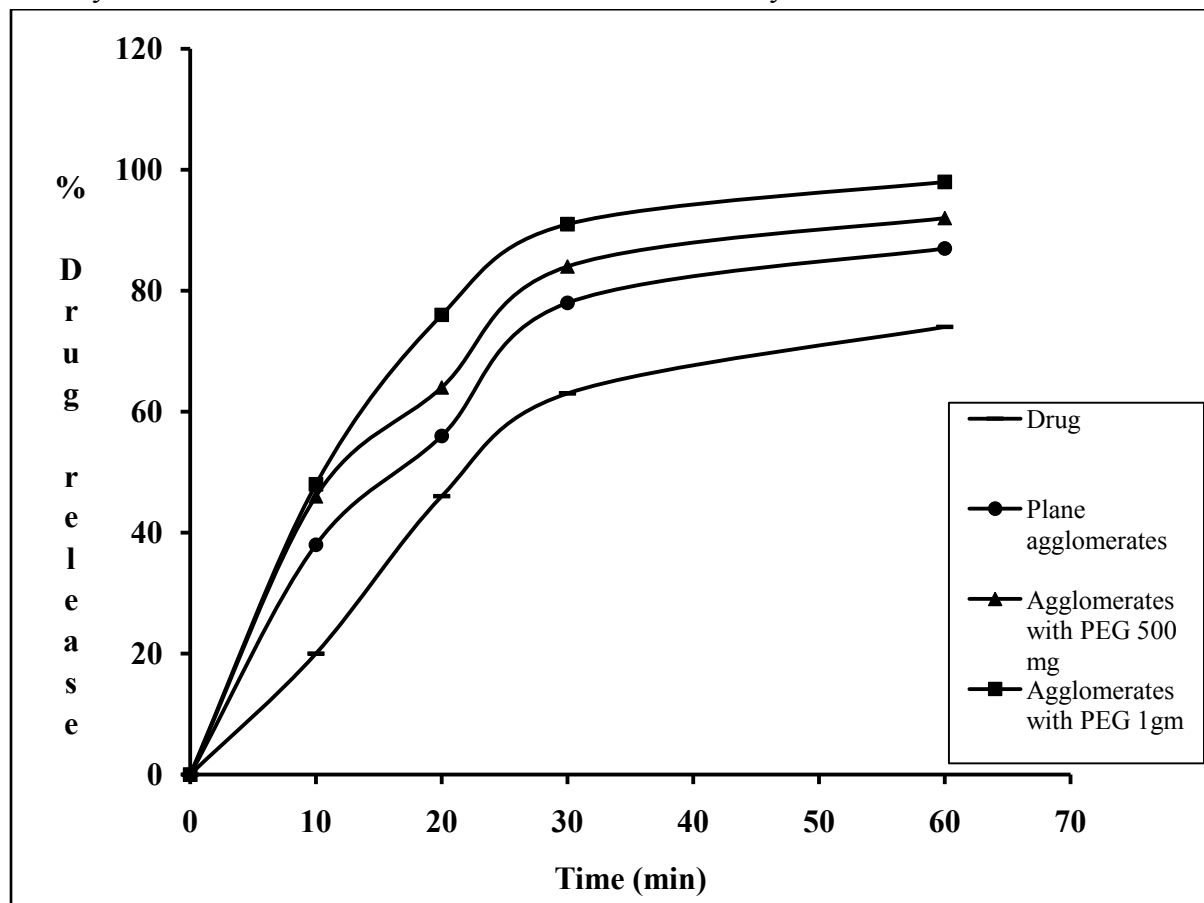


Fig. 5. Dissolution study of A: Pioglitazone hydrochloride and Spherical agglomerates of PGH: B: Plane, C: with 1% PEG, D: with 2% PEG

4. CONCLUSION

Spherical crystals of PGH were successfully prepared by emulsion solvent diffusion method. Flowability, compactibility and packability were dramatically improved for plane agglomerates and agglomerates with 1% and 2% PEG compared with raw crystals of PGH resulting in successful direct tableting without capping. Also remarkable fragmentation, increased tensile strength of plane agglomerates and agglomerates with PEG indicates improved compactibility. Improved solubility and dissolution of plane and agglomerates with PEG than raw crystal of PGH has shown their improved wettability. During agglomeration polymeric transition has occurred but not associated with changes at molecular level. It concludes that spherical crystallization of PGH with polyethylene glycol is a satisfactory method to improve flowability, compactibility and packability for direct tableting.

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