Azhar Int J Pharm Med Sci 2024; Vol 4 (2):125-140.

Open Access

Print ISSN: 2735-4598
Online ISSN: 2735-4601

(Research Article.)

Improvement of Class II Drug Properties by Crystal Agglomeration Design

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Article history: Received 06-09- 2023 **Revised** 04-12-2023 **Accepted** 12-03-2024

Abstract: Repaglinide (RPG) is an antihyperglycemic drug; according to the Biopharmaceutical Classification System (BCS), it is considered a class II drug. It exhibits low oral bioavailability (about 56%) due to its poor water solubility and dissolution rate; also, it has very poor flowability. This study was introduced to design an RPG drug in the form of spherical crystal agglomerates using the spherical agglomeration technique to improve and solve these problems with the drug. Three solvents are used in this technique: a good solvent (acetone), a bad solvent (water), and a bridging liquid (chloroform). Different polymers were added in this process, like HPMC E5, Poloxamer 407, or PEG 6000, in various concentrations as a stabilizer. All developed agglomerates under an optical microscope have a nearly spherical shape with a particle size range of 342.52 to 529.2 µm. The percentage yield was 85.06% to 89.16%, and the drug content was 95.57% to 99.18%. Their flowability considerably improved where angle of repose (23.05º to 29.16º), CI (12.73% to 18.92%), and HR (1.15 to 1.23) compared to pure RPG (49.36º, 36.84%, and 1.58, respectively). The solubility improved by 1.8 to 3 folds compared to the drug, and the dissolution rate was significantly enhanced in all prepared agglomerates, where the complete release (99.89%) was observed in SA8 after 60 minutes. Scanning Electron Microscopy (SEM) confirmed that the crystals became more regular and spherical in shape. These results concluded that spherical crystallization could be an effective alternative method to improve RPG properties and enhance its bioavailability.

Keywords: Repaglinide, Spherical agglomerates, Polymers, Spherical crystallization, Micrometric properties, Solubility, Dissolution.

1. INTRODUCTION

In the pharmaceutical industry, the recent trend is focused on delivering high-quality medicines through a pharmacoeconomic approach. The oral route for drug administration is the most common, accepted, and marketed route for systemic effect. Among all orally administered drugs, solid dosage forms, especially tablets, are the most preferred. This is due to the flexibility in dosage strength, lower cost, least variability of content, easy administration by patients, relative stability, and convenience of manufacture, packaging, storage, handling, and use[1].

It is important that solubility and bioavailability be taken into consideration for the drug molecule to reach its target site and exert its therapeutic effect. Unfortunately, the screening programs in the pharmaceutical industry indicated that > 40% of recent chemical entities had various problems when transferring from formulation to generic development because of their poor solubility[2]. Therefore, solubility or dissolution enhancement techniques are the main challenge for researchers in formulation design and the developmental process. There are many techniques that have been adopted

Cite this article: Marzouk, M., Osman, D., and Abd El-Fattah, A. Improvement of Class II Drug Properties by Crystal Agglomeration Design. Azhar International Journal of Pharmaceutical and Medical Sciences, 2024;4(2):125-140. doi:10.21608/AIJPMS.2024.234758.1236
DOI: 10.21608/AIJPMS.2024.234758.1236

for improving the dissolution characteristics of the drug with poor water solubility, which include complexation, pH adjustment, solid dispersion, hot melt extrusion, lyophilization technique, micronization, nanocrystals, prodrug approach, liquisolid compacts, melt sono-crystallization, and spherical crystallization (agglomeration) technique[3].

The direct compression method is the most efficient technique in tablet preparation because powder blends can be directly compressed into the tablets without resorting to intermediate steps such as granulation. So, the direct compression method helps reduce production time and costs[4]. Drugs that have very poor flowability and micrometric properties of crystal-like compressibility are not suitable for the direct compression process of tablets[5]. Poor flowability of the drug causes a variety of manufacturing problems, including a lack of mixing efficiency, and the flow of powder from the hopper or feed shoe during the tableting process does not occur smoothly; therefore, it leads to great variation in tablet weight and, accordingly, the drug content between tablets[5]. There are numerous methods to enhance the flow characteristics of compression mixtures, including extrusion-spheronization, melt extrusion, melt solidification, melt granulation, melt extrusion, and spherical crystallization[6].

The spherical crystallization technique is a novel agglomeration approach that can convert the fine crystals produced from the crystallization process directly into a spherical shape. This method is a particle engineering technique through which crystallization and agglomeration may be achieved in a single step, simultaneously producing a direct transformation of the crystalline drugs into a compacted spherical form with the objective of improving their solubility, dissolution, flowability, and compactability[7]. There are a number of reports available in the literature for the enhancement of solubility, in-vitro drug release studies and improvement of the bioavailability of the drug. There are a numbers of drugs being reported in the literature that increase the solubility and dissolution profiles of the drugs. Also, their flowability was improved by using the spherical crystal agglomeration technique. These drugs, such as ibuprofen[8,9], indomethacin[10], aceclofenac[11], mebendazole[12], Ramipril[13], gliclazide[14], Simvastatin[15], naproxen[16] etc., and also these reports proved that this technique is a more efficient manufacturing methods that saves time with low cost.

There are four main principle steps involved in the spherical crystallization process: 1) flocculation zone; 2) zero growth zone; 3) fast growth zone; and 4) constant size zone[17,18]. In this process, three solvents are used with the drug: a good solvent, a bad solvent, and a bridging liquid. Good solvent and poor solvent are freely miscible with each other, but the bridging liquid is immiscible with the poor solvent. Bridging liquid is added to induce and promote the formation of agglomerates[19]. The addition of polymers to water during spherical crystallization improved the properties of spherical agglomerates; it slowed down the nucleation process. Since crystals can't spontaneously aggregate as a result of these polymers, spherical agglomerates have plenty of time to be formed. The polymers could change crystal habits, which interfere with the sphericity and particle size of the agglomerates[20].

Repaglinide (RPG) is an antidiabetic drug of the meglitinide class that has a benzoic acid structure and is used in the treatment of type 2 diabetes, where it controls postprandial hyperglycemia. It is a highly favored drug alternative to sulfonylureas, and it is the most commonly used drug of the meglitinide class.

RPG is considered a class II drug based on the BCS due to its low solubility and high permeability, where the dissolution rate is the rate-limiting step for its absorption. It has a low oral bioavailability of about 56%, which is due to poor dissolution, and also has a hepatic first-pass metabolism[21]. It has an intrinsic water solubility of approximately 0.022 mg/ml[22]; it is freely soluble in acetone and soluble in ethanol, methanol, dichloromethane, and chloroform[23].

For these characteristics of RPG, it is used as a model drug in this study to overcome the problems of its poor solubility, in-vitro dissolution rate, and also its poor flow properties.
The present work aims to develop and design spherical crystal agglomerates of RPG using the spherical crystallization (agglomeration) technique, which not only enhances the solubility and dissolution rate of the model drug but also improves the micrometric properties such as flowability of the drug. After that, evaluation and characterization of the prepared spherical agglomerates were carried out.

2. METHODS

2.1. Material:

Repaglinide was supplied by the Egyptian International Pharmaceutical Industries Co (EPICO) (Egypt). HPMC E5, PEG 6000, and Poloxamer 407 were supplied by the Egyptian International Pharmaceutical Industries Co (EPICO), Cairo, Egypt. Disodium hydrogen phosphate and potassium dihydrogen phosphate, El- Nasr Pharmaceutical Co. (Egypt). Methanol, acetone, and chloroform, EL-Gomhouria Co. (Egypt).

2.2. Methods:

2.2.1. Establishment of a calibration curve for RPG in a phosphate buffer solution of pH 6.8

An amount of 10 mg of RPG was accurately weighed and solubilized by 2 ml of methanol in a 100 ml volumetric flask. The volume was completed to 100 ml with a phosphate buffer (PB) solution of pH 6.8 to form a standard stock solution of concentration 100 µg/ml. From this standard stock solution of the drug, serial dilutions were prepared to obtain samples ranging from 20 µg/ml to 100 µg/ml. The diluted solutions were measured with spectrophotometric assay **(Jenway, Model 6405 UV/ visible; England)** at λ_{max} 283 nm. The experiment was repeated in triplicate, and the mean absorption wavelengths were plotted against the corresponding concentrations to establish a calibration curve[24].

2.2.2. Compatibility of RPG with proposed polymers

The possible interactions between the drug and the proposed polymers were characterized by differential scanning calorimetry and Fourier transform infrared.

2.2.2.1. Fourier transform infrared (FTIR):

By an FTIR spectrometer **(Shimadzu Corporation, Model-8400S., Koyto, Japan)**, 1:1 w/w drug and polymer physical mixtures were prepared and compressed in the form of discs using KBr. The disc was placed in the sample holder and preserved in the device to record IR bands. The spectrum within the region, from (4000 to 400 cm^{-1}) was recorded[25].

2.2.2.2. Differential scanning calorimetry (DSC)

Thermograms of pure RPG alone and its physical mixtures with suggested polymers in the ratio of 1:1 (w/w) were determined by using DSC (**Schimadzu, Model DSC-50, Japan**). In this investigation, the mixture (3mg) was crimped in the aluminum pans and then scanned under an N_2 gas atmosphere at a 25 ml/min flow rate and a 10 °C/min heating rate of over 25 – 300 °C temperature range[26].

2.2.3. Preparation of RPG spherical agglomerates using different concentrations of different polymers

Spherical crystal agglomerates were prepared through the spherical crystallization technique using amounts as shown in Table 1. Acetone was used as a good solvent for RPG[27]. An amount of 200 mg RPG was dissolved in 4 ml of acetone until a clear solution was obtained. A hydrophilic polymer solution (10 ml) of HPMC E5, poloxamer 407, or PEG 6000 (as a stabilizer) in various concentrations (0.25% w/v, 0.5% w/v, 0.75% w/v, or 1% w/v) in distilled water, was used as a poor solvent. The drug solution was added to the prepared polymeric solution and maintained with a continuous speed of stirring at 500 rpm using three-blade electric stirrers (Overhead Stirrer DLS **VELP®; SCIENTIFICA, (50-2000 rpm), Italy).** After that, chloroform, which is the bridging liquid (1.5 ml), was added drop-wise to the drug-polymeric mixture and allowed to stir continuously for 25 minutes until spherical agglomerates were settled. After that, the spherical agglomerates were collected on Whatman filter paper through filtration, dried for 24 hours at room temperature, and stored in a desiccator for future study[10,28,29].

2.2.4. Evaluation of RPG spherical agglomerates

2.2.4.1. Percentage practical yield

The percentage yield of all prepared agglomerates was calculated using the following formula[30]:

$$\%\ yield\ = \frac{Practical\ weight}{Theoretical\ weight}\ x\ 100$$

2.2.4.2. Drug content

The drug content in a percentage for all prepared spherical agglomerates was determined by dissolving an amount of spherical agglomerates equivalent to 2 mg of RPG in a minimum quantity of methanol (2 ml), thoroughly mixing by stirring, and then the volume was completed to 50 ml with a PB solution of pH 6.8., filtered through Whatman filter paper, and the filtrate was diluted suitably with a PB solution of pH 6.8 and the absorbance was measured at 283 nm using a UV/visible spectrophotometer[31]. Moreover, % drug content was then calculated using the following equation:

$$\% \, Drug \; content = \frac{Concentration \; of \; drug \; in \; sample \; solution}{Equivalent \; conc. of \; drug \; taken} \times 100.$$

According to USP standard of drug content, the acceptable range is 90-110% [32].

2.2.4.3. Optical microscopy and mean particle size determination

The shape and particle size of RPG particle powder and its agglomerated crystals were studied using an optical microscope **(Model –Euromex. BioBlue.Lab., Holland)** with 10x, 40x, and 100x magnifications; the measurement was determined by taking a small amount of both samples on a slide. About 100 particle sizes were individually measured, and the average was taken. The average particle size was calculated by this formula[31]:

Average particle size = £nd / n

The particles were analyzed by an image analyzing software **(Image Analyzer, S/N - EU 181064)** where the average particle size is defined as the average length of the distance between two lines connecting two points, passing through the particle's center of gravity[29].

2.2.4.4. Evaluation of micromeritic properties

The micrometric properties, such as the flowability of pure RPG powder and all prepared spherical agglomerates, were assessed through the determination of the angle of repose, tapped density, bulk density, Hausner's, ratio and Carr's index. The relationship between the angle of repose, Carr's index, Hausner's ratio ranges, and flow properties were is mentioned in Table 2.

Angle of repose

The angle of repose was determined by using the fixed funnel method, where the funnel was adjusted at a constant height above a horizontal surface and through which both the drug powder and spherical agglomerates were carefully allowed to pass freely until the lower funnel tip became in contact with the tip of the cone-shaped accumulation. This measurement was performed in triplicate. The height and diameter of the powder accumulation were measured to enable the calculation of the angle of repose using the following equation[33]:

$$Tan \; \theta = h / r$$

Where h and r represent the height and radius of the cone-shaped powder accumulation, (θ) represents the angle of repose.

Powder density

Bulk density is measured by pouring an accurately weighed quantity of the sample into a graduated cylinder, and then the volume is measured. Bulk density was calculated in gm/cm³ by this formula[34]:

$$Bulk \; Density \; (gm/cm^3) = \frac{Weight \; of \; the \; powder \; (gm)}{Bulk \; volume \; (cm^3)}$$

Tapped density was also determined, where an accurately weighed amount of the sample was poured into a graduated cylinder and the volume was then measured. After that, the measuring cylinder was permitted to 100 tap down its own weight onto a hard surface, and tapping was continued until the stable height was noted. The volume after tapping was used to calculate the tapped density in gm/cm³ by this formula[35]:

$$Tapped \; Density \; (gm/cm^3) = \frac{Weight \; of \; the \; powder \; (gm)}{Tapped \; volume \; (cm^3)}$$

Carr's index and Hausner's ratio calculation[36]

Further evaluation of pure RPG powder and all prepared agglomerated crystals was carried out by the calculation of both Hausner's ratio (HR) and Carr's index (CI). CI was calculated by this equation:

$$CI = \frac{Tapped \; density - Bulkdensity}{Tapped \; density} \; x \; 100$$

Also, HR was calculated using the following equation:

$$HR = \frac{Tapped \; density}{Bulkdensity}$$

2.2.4.5. Saturation Solubility study

Excess amounts of a pure RPG drug powder or RPG spherical agglomerates were dispersed in 10 ml of PB solution (pH 6.8) in screw-capped vials. The dispersion was shaken at 100 rpm in a heated shaker bath at 37±0.5°C for 48 hours to achieve equilibrium. After that, the dispersion was filtered by 0.45 μm syringe filters, followed by dilution with a PB solution of pH 6.8. The sample solutions were subjected to UV spectrophotometric analysis at 283 nm. Three measurements were taken, and then the mean results and the standard deviation were reported[10,38].

2.2.4.6. Evaluation of in-vitro release study

In-vitro release studies of both pure RPG and its prepared spherical agglomerates (equivalent to 2 mg

Table 1. Composition of spherical agglomerates formulations of RPG with different concentrations of polymer solution.

Batch code	RPG (mg)	HPMCE5 (%)	Poloxamer 407 (%)	PEG 6000 (%)	Acetone (ml)	Water (ml)	Chloroform (ml)
SA1	200	0.25	-	-	4	10	1.5
SA2	200	0.5	-	-	4	10	1.5
SA3	200	0.75	-	-	4	10	1.5
SA4	200	1	-	-	4	10	1.5
SA5	200	-	0.25	-	4	10	1.5
SA6	200	-	0.5	-	4	10	1.5
SA7	200	-	0.75	-	4	10	1.5
SA8	200	-	1	-	4	10	1.5
SA9	200	-	-	0.25	4	10	1.5
SA10	200	-	-	0.5	4	10	1.5
SA11	200	-	-	0.75	4	10	1.5
SA12	200	-	-	1	4	10	1.5

Table 2. Relationship between the angle of repose, Carr's index, Hausner's ratio and flowability[37].

Flowability	Angle of repose	Carr's index	Hausner's ratio
Excellent	25 – 30	≤ 10	1.00 – 1.11
Good	31 – 35	11 – 15	1.12 – 1.18
Fair (aid not needed)	36 – 40	16 – 20	1.19 – 1.25
Passable (may hang up)	41 – 45	21 – 25	1.26 – 1.34
Poor (must agitate, vibrate)	46 – 55	26 – 31	1.35 – 1.45
Very poor	56 – 65	32 – 37	1.46 – 1.59
Very very poor	>66	> 38	> 1.60

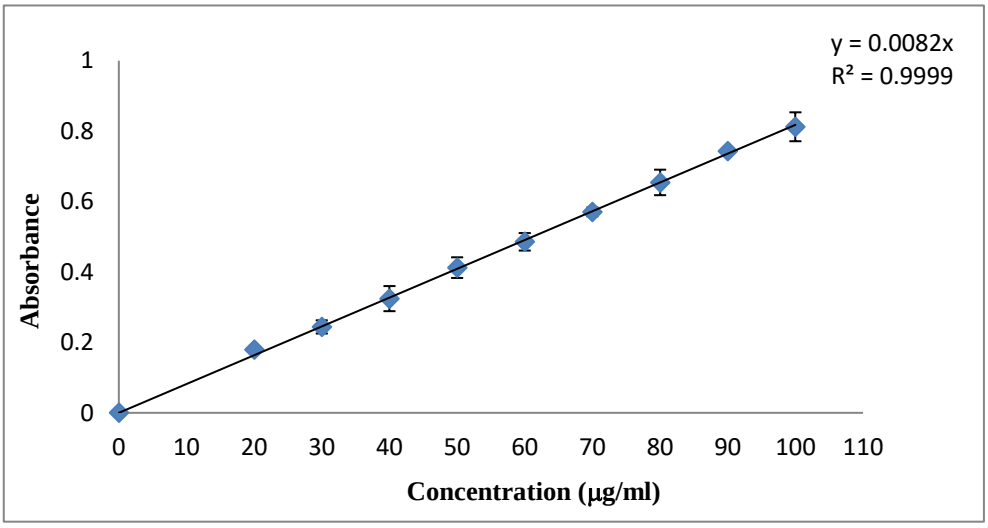

Figure 1. Calibration curve of RPG in PB solution of pH 6.8 at λmax 283 nm.

RPG) were performed by using United States Pharmacopoeia (USP) type II dissolution apparatus **(USP Standard, DA-6D, Bomby 400-069, India)** at 37±0.5 °C and stirring speed at 50 rpm in 300 ml of PB solution of pH 6.8. Samples of volume 3 ml were withdrawn at time intervals of 5, 10, 15, 20, 30, 45, and 60 min from the dissolution medium and replaced with the same volume of fresh PB solution of pH 6.8 for maintaining the sink condition. Samples were suitably filtered through 0.45 µm syringe filters and diluted if necessary.

The absorbance of the samples was estimated using a UV spectrophotometer at λ_{max} (283 nm). The experiment was done in triplicate. From this, the percentage of RPG released was calculated and plotted against the function of time[24,30].

The dissolution profiles of all prepared spherical agglomerates were compared with those of pure RPG using a similarity factor (f_2) to determine whether the difference between the release profiles is significant. The similarity factor is a logarithmic reciprocal square root transformation of the sum of the squared error and was calculated using this equation:

$$f_2 = 50\ log\left\{\left[1+\frac{1}{n}\sum_{n=1}^{n}(Rt-Tt)^2\right]^{-1/2} x\ 100\right\}$$

Where n is the number of time points, R_t is the percentage of drug release of a reference batch at time t and T_t is the percentage of drug released by the comparison batch at time t[39].

The values of f_2 may vary between 0 and 100; similar release profiles are considered when the f_2 value is > 50. The value of 100 indicates that the release profiles are identical. When f_2 value < 50, this suggests a significant difference between the compared dissolution profiles[40].

2.2.4.7. Kinetic analysis

Data obtained from the in-vitro release study were fitted to several kinetic equations and models to obtain the best-fitted model (zero-order, first-order, Higuchi diffusion, and Korsmeyer-Peppas models). The highest value of the correlation coefficient (r) was indicated for the best-fitted model[41].

2.2.4.8. DSC for spherical agglomerates

DSC spectra of pure RPG powder and its spherical agglomerate (SA8) were carried out by DSC equipment and compared with each other.

2.2.4.9. Scanning electron microscopy (SEM)

The shape and morphological characteristics of spherical agglomerates were studied by SEM for the agglomerate that showed the highest solubility and percent release (SA8) to confirm with the optical microscopic results that the spherical agglomeration actually occurred. This study was carried out by mounting the samples on double-sided adhesive tape and applying a gold coating before examination on the surface of the particles to make it electroconductive. It was viewed, and photos were taken using an accelerating voltage at suitable magnification[42,43].

3. Results

3.1. Calibration curve construction of RPG in PB solution of pH 6.8.

The relationship between the absorbance and concentration in the calibration curve at the predetermined λ_{max} (283 nm) of RPG in PB solution of pH 6.8 was observed to be linear with the correlation coefficient value (0.9994). This relation was plotted and shown in Figure 1.

3.2. Compatibility of RPG with proposed polymers

3.2.1. FTIR spectral analysis

FTIR spectrum of pure RPG exhibited principal absorption bands at 3305.99 cm^{-1} for N-H stretching, 2850.79 cm^{-1} and 2935.66 cm^{-1} for C-H stretching, 2804.50 cm^{-1} for carboxylic OH stretching, 1635.64 cm^{-1} and 1685.79 cm^{-1} for C=O stretching, 1604.77 and 1566.20 cm^{-1} for aromatic C=C stretching, 1492.90 cm^{-1} for C=C stretching, 1446.61 cm^{-1} for CH bending, 1215.15 cm^{-1} for C-O stretching, 1149.57 cm^{-1} for ether linkage, 1091.71 and 1041.56 cm^{-1} for C-N amine stretching[44,45]. From a comparison of the spectrum of RPG alone with the spectra of all its physical mixtures with the used polymers, it is observed that all principal IR absorption bands of RPG were found, which proved that there was good compatibility between RPG and the proposed polymers (Figure 2).

3.2.2. DSC analysis

A pure RPG thermogram by DSC showed a sharp endothermic peak at 134.74 °C as a result of the melting of the drug, with an enthalpy change (ΔH) of -102.68 J/g that corresponds to its melting[7,45]. The thermal profiles of all RPG-polymer physical mixtures showed the characteristic endothermic peak of RPG, these observations proved the good compatibility of RPG with the proposed polymers (Figure 3).

3.3. Evaluation of RPG spherical agglomerates

3.3.1. Percentage practical yield

The practical percentage yield of the prepared RPG spherical agglomerates was found in the range of

85.06 ± 0.32% to 89.16 ± 0.52%, as observed in Table 3.

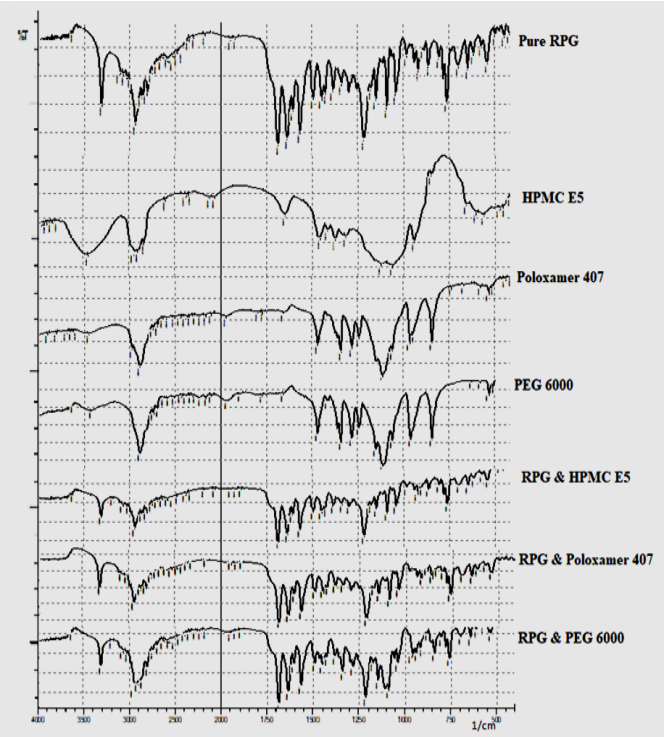

Figure 2. FTIR spectra of pure RPG and physical mixtures with the proposed polymers**.**

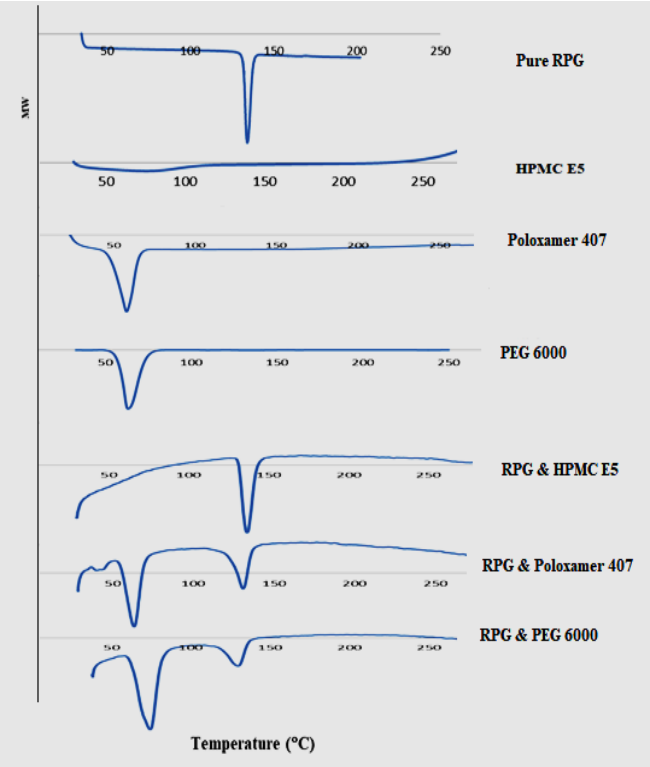

Figure 3. DSC thermograms of RPG and physical mixtures with the proposed polymers.

3.3.2. Drug content.

The determined % drug contents of RPG in all batches of the prepared spherical agglomerates ranged from 95.57 ± 0.67% to 99.18 ± 0.25%, as shown in Table 3.

3.3.3. Optical microscopy and Mean particle size determination

All prepared spherical agglomerate photos were taken by the optical microscope, as displayed in Figures 4 and 5. It showed that the agglomerated crystals are spherical to nearly spherical in shape, while the crystals of pure RPG are irregular (rods or cubes) in shape. The geometric mean diameters were calculated, and then the results are shown in Table 3, where the mean diameters of the prepared RPG agglomerates ranged from 342.52 ± 17.48 to 529.2 ± 17.15 µm, which are approximately 7.8 to 12.1 times larger than those of the pure RPG powder (43.8 ± 10.20 µm).

Table 3. Physicochemical properties of pure RPG and its prepared spherical agglomerates.

Batch Code	Drug content (%) ± SD	Practical yield (%) ± SD	Particle size (µm) ± SD
RPG	-	-	43.82±10.20
SA1	96.43±0.81	87.65±0.30	384.97±14.54
SA2	95.73±0.85	88.47±0.65	392.89±17.4
SA3	98.80±0.95	86.98±0.48	441.60±19.80
SA4	97.50±0.50	85.06±0.32	529.21±17.15
SA5	99.18±0.25	85.32 ± 0.55	342.52±17.48
SA6	98.50±0.66	86.63± 0.45	344.63±14.70
SA7	96.83±0.93	87.85 ± 0.96	368.57±15.30
SA8	97.27±0.72	89.16 ± 0.52	387.39±20.84
SA9	97.80±0.66	85.77±0.44	436.36 ±16.48
SA10	97.63±0.42	86.43±0.57	473.92±15.66
SA11	95.57±0.67	86.88±0.41	480.62±20.05
SA12	99.04±0.53	88.47±0.76	491.03±13.49

3.3.4 Evaluation of micromeritic properties

Micromeritic properties such as flowability in terms of angle of repose, bulk density, tapped density, CI, and HR were determined for pure RPG powder and prepared RPG spherical crystal agglomerates and shown in Table 4.

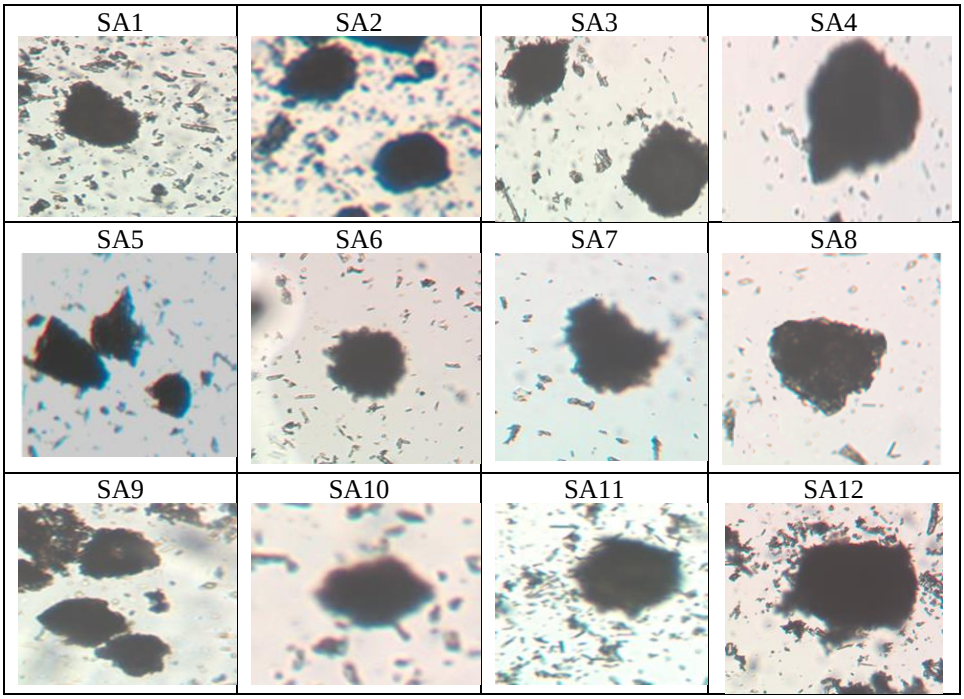

Figure 4. Optical microscopic images of RPG spherical agglomerates prepared with different concentrations of polymers.

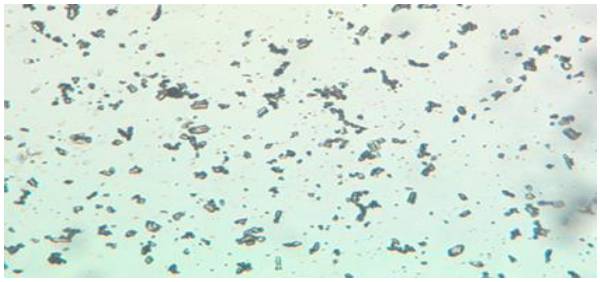

Figure 5. Optical microscopic image of pure RPG powder.

Table 4. Micromeritic properties of pure RPG powder and prepared RPG spherical agglomerates**.**

Batch code	Angle of repose (θ°) ± SD	Bulk density (gm/cm^3) ± SD	Tapped density (gm/ cm^3) ± SD	Carr's index (CI) %	Hausner ratio (HR)
RPG	49.36±0.63	0.260±0.002	0.412±0.004	36.84	1.58
SA1	24.80±0.58	0.471±0.001	0.550±0.002	14.29	1.17
SA2	23.29±0.48	0.362±0.003	0.415±0.002	12.73	1.15
SA3	24.77±0.72	0.343±0.006	0.396±0.003	13.46	1.16
SA4	26.83±0.47	0.385±0.002	0.465±0.005	17.24	1.21
SA5	26.33±0.62	0.429±0.006	0.524±0.002	18.18	1.22
SA6	25.80±0.10	0.408±0.003	0.489±0.001	16.67	1.20
SA7	24.96±0.36	0.283±0.004	0.333±0.002	14.89	1.18
SA8	23.05±0.70	0.376±0.002	0.432±0.003	13.04	1.15
SA9	28.37±0.42	0.314±0.002	0.387±0.001	18.92	1.23
SA10	28.83±0.30	0.374±0.004	0.454±0.003	17.65	1.21
SA11	26.99±0.85	0.377±0.003	0.444±0.002	15.15	1.18
SA12	29.16±0.54	0.340±0.001	0.412±0.005	17.39	1.21

the angle of repose of all prepared RPG spherical agglomerates was noted to be in the range of 23.05° to 29.16°, indicating excellent flowability. Also, it was observed that all prepared RPG spherical agglomerates exhibited values of CI in the range of 12.73% to 18.92%, indicating good to fair flowability. However, the CI of pure RPG powder showed a value of 36.84% indicating very poor flowability. All the prepared RPG spherical agglomerates exhibited HR values in the range of 1.15 to 1.23, indicating good to fair flowability. However, the HR of pure RPG powder showed a value of 1.58, indicating very poor flowability. From these results, it is evident that all the prepared agglomerates displayed a considerable improvement in their flow properties when compared to the pure drug alone.

3.3.5. Saturation solubility study

The histogram of solubility values (mg/ml) of pure RPG and spherical agglomerates of RPG is given in Figure 6. It was observed that the solubility of RPG spherical agglomerates prepared by using different concentrations of different polymers in PB solution of pH 6.8 has increased by 1.8 to 3 folds (from 0.065 to 0.110 mg/ml) compared to the solubility of pure RPG, whose solubility value was 0.037 mg/ml.

3.3.6. Evaluation of in-vitro release study

The results of the in-vitro dissolution study for the drug release data of RPG into PB solution of pH 6.8 from pure RPG powder and all spherical agglomerate preparations that were prepared using different concentrations of different polymers within 60 minutes are graphically illustrated in Figure 7. It was observed that the percentage release of the drug from pure RPG powder was found to be 32.63 ± 0.24 % after 60 minutes, whereas all prepared RPG spherical agglomerates displayed a significant increase in RPG release than pure RPG powder after this time of release, where the percentage release from the agglomerates ranged from 67.42 ± 0.53% for SA9 to 99.89 ± 0.29% (the maximum release), which was observed from the agglomerates prepared by the addition of 1% w/v of poloxamer 407 (SA8).

These results explained that there was a good improvement in the dissolution rate in all prepared crystal agglomerates compared to pure RPG powder, and the increase in the concentration of hydrophilic polymers added in the agglomeration process led to an increase in the dissolution rate. In the results, it was also noted that increasing the polymer concentration in the agglomeration process led to an increase in the dissolution rate of the RPG drug, but in the case of the agglomerates prepared by the addition of HPMC E5 polymer, it was found that the highest percentage release (92.73 ± 0.35%) resulted at a concentration of 0.5% w/v (SA2). After that, the percentage release was decreased gradually with an increase in the HPMC E5 concentration above 0.5% w/v.

The calculated similarity factor (f_2) confirmed that the release profile of all prepared RPG spherical agglomerates was significantly different than that of pure RPG powder, where all the values ranged between 13 - 28% as shown in Table 5.

3.3.7. Kinetic analysis

According to the highest values of the regression coefficients of determination (r), it was found that the in-vitro release of RPG from all prepared spherical agglomerates followed the Higuchi diffusion order. According to the values of (n) resulting from the Korsmeyer-Peppas equation, all prepared spherical agglomerates indicated Fickian transport, except SA1, SA4, SA5, and SA9, which indicated non-Fickian transport.

3.3.8. DSC for spherical agglomerates

The DSC results in Figure 8 showed a sharp endotherm at 134.74 °C for pure RPG that corresponded to the RPG melting point. In the melting endotherm of RPG spherical agglomerate, the change in the endotherm was not appreciable, which was observed at 134.35 °C when compared with that of pure RPG, but there was a decrease in the enthalpy changes (ΔH) of the agglomerate (-49.653 J/g) when compared with that of the pure drug (-201.68 J/g).

3.3.9. Scanning Electron Microscopy (SEM)

The comparative SEM photos of RPG powder and spherical crystal agglomerates of RPG are shown in Figure 9. It was found that the pure RPG powder appeared in the form of small crystals with an irregular rod and cube shapes with visible, sharp edges. In contrast, the spherical crystals showed a more improved surface, regular and spherical shape, and an increase in the particle size of the formed crystal agglomerates than that of the standard drug, as seen from SEM images

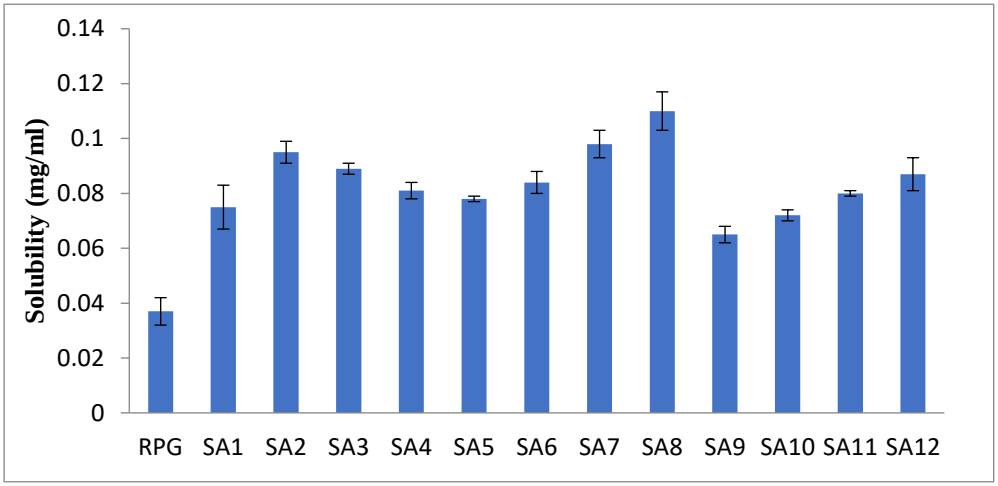

Figure 6. Solubility profile of prepared RPG spherical agglomerates and pure RPG powder**.**

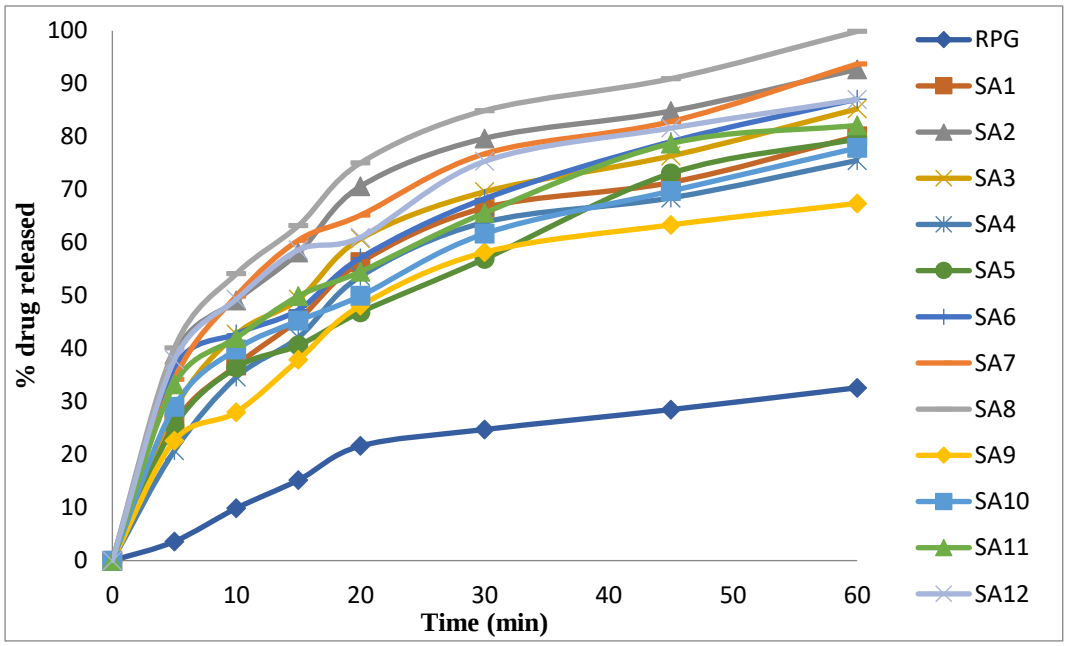

Figure 7. percentage drug released from pure RPG powder and their prepared spherical agglomerates.

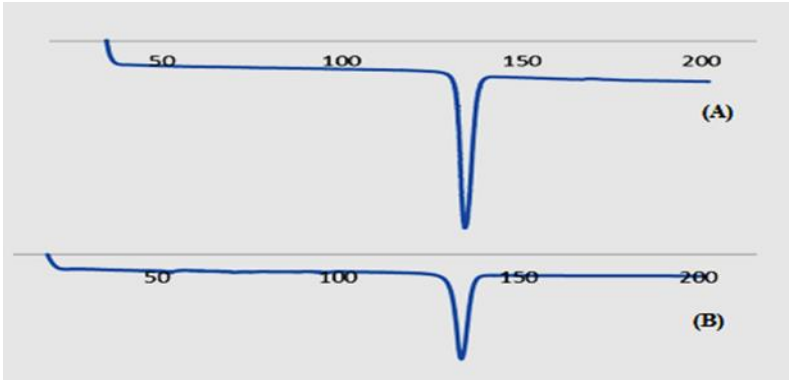

Figure 8. DSC thermograms of (A) Pure RPG powder and (B) RPG spherical agglomerate SA8.

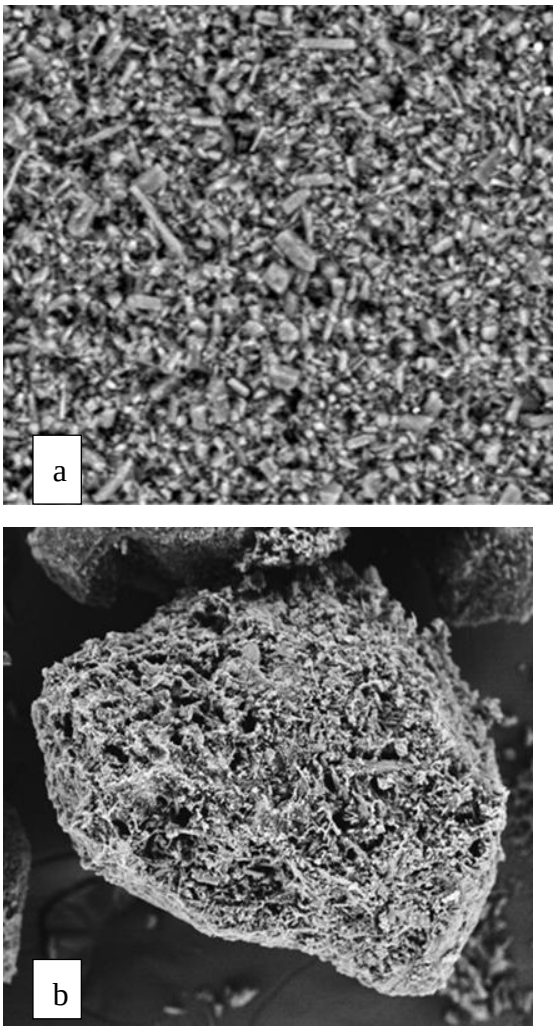

Figure 9. SEM images of (a) Pure RPG powder, (b) RPG spherical agglomerate SA8

Table 5. Dissolution profile similarity factor of prepared repaglinide spherical agglomerates compared with pure RPG powder.

Batch code	Similarity factor (%)	Batch code	Similarity factor (%)
SA1	22	SA7	16
SA2	15	SA8	13
SA3	20	SA9	28
SA4	24	SA10	23
SA5	24	SA11	20
SA6	19	SA12	17

4. DISCUSSION

The standard curve for calibration of RPG indicated that there is good linearity and that it obeys Beer's Lambert law within the concentrations in the assay. The results of FTIR and DSC for the drug and its physical mixtures with polymers suggested for use in the agglomeration process indicated good compatibility without chemical or physical interaction between RPG and the suggested polymers.

The spherical crystallization technique for developing RPG was applied. In this process, three different solvents were used. The drug solution was added directly to the aqueous polymeric solution, where the emulsion droplets were created. Then, the drug crystallizes from the outer surfaces of the droplets because of the back-diffusion that occurs between the two solvents through the emulsion droplet interface. After that, the bridging liquid was added to the previous solution in a drop-wise manner. This liquid is not miscible with the poor solvent, but it makes substantial wetting for the precipitated crystals. The bridging liquid allows the formation of liquid bridges between the formed crystals, which is due to the force of capillary negative pressure and the interfacial tension at the liquid-solid interface. These bridges facilitate the collection and adhesion of crystals to each other, and then the spherical agglomerates are well formed[46].

From the practical yield results, it was noted that the yield increased at higher polymer concentrations (1% w/v) as evidence of the role of hydrophilic polymers in crystal agglomeration by enhancing the formation of bridging and attachment between the agglomerated crystals[47]. In case of HPMC E5 polymer, it was observed that the yield was higher at a concentration of 0.5% w/v, but there was some decrease in the yield at concentrations higher than 0.5% w/v, which may be caused by the formation of viscous gel surrounding the particles by the polymer and the formation of large sticky agglomerates that stick to the vessel walls and the impeller, which leads to the loss of drug and polymers during the process of agglomeration at a higher concentration of HPMC and therefore contribute to lowering the yield[48,49].

Optical microscopic images proved that the agglomerated crystals actually formed in a spherical to nearly spherical shape. From the particle size data results, it was found that the size of agglomerates (342.52 μm to 529.2 μm) was higher than that of the drug (43.8 μm), which indicated that the original single crystals of RPG uniformly agglomerated (growth of particles) through the spherical

crystallization process[50]. It was observed that the size of the formed agglomerates increased with an increase in the polymer concentration; this may be due to the ability of the polymer to bind the crystal during the agglomeration process. It acts as a stabilizer (to stabilize the agglomerates) that prevents the crystals from spontaneous aggregation, thereby supplying sufficient time for the spherical agglomerates to be developed. Also, the polymers in the agglomeration process can alter the crystal habits (form, surface, and size, as well as particle size distribution) of the drug, which causes them to interfere with sphericity and particle size[19]. So, it facilitates the adhesion of crystals to each other in a good manner, and the spherical crystal agglomerates well formed[38,49]. The results of drug content for all of the prepared spherical agglomerated crystals comply with the theoretical values (95.57% to 99.18%).

From the results of angle of repose, CI, and HR in Table 4, it is evident that all the prepared agglomerates showed more a considerable improvement in their flow properties, where all of them were fell within the acceptable limits of flowability (mentioned in Table 2), when compared to the pure RPG powder alone, which showed very poor flowability. This improvement can be attributed to the formation of drug agglomerated crystals with a characteristic spherical shape. Also, the improvement observed in the flow properties may be related to a marked difference in their crystal habits, which leads to a difference in contact points, cohesiveness, and frictional forces between the crystals[51]. So, the obtained RPG spherical agglomerate products became suitable for direct compression of tablets and capsule filling without the need for further granulation processes. Thereby, it proved that spherical crystal agglomeration is an effective method for improving the compressibility and packability of poorly compressible drug powders[52,53].

The improvement in solubility of RPG spherical agglomerates was due to the partial amorphization of the drug during the process of agglomeration. The process of recrystallization may be producing an alteration in the crystal habits, surface modification, hydrophilic properties, and surfactant characteristics of polymers which contributed to the increase in drug solubility and release. Occasionally, solvents may contribute to the change in the crystal form of drug particles surface properties, reactivity, and internal energy, which may play a role in the solubility enhancement of the drug[49,54]. The results of in-vitro release and f_2 values showed a significant increase in RPG dissolution from all the prepared spherical agglomerates compared to its dissolution from pure RPG powder. This fast increase in drug dissolution from spherical agglomerates was due to an improvement in their wettability along with a decrease in the crystallinity of the drug. The good wettability of RPG agglomerates is due to an improvement in micrometric properties by spherical agglomerates formation, resulting in faster dissolution[51,55]. Also, the addition of polymers with a hydrophilic nature could refer to the adsorption of a specified polymer onto the drug surface, thus improving the wettability of the prepared samples. The hydrogen bond interaction between the drug and the added polymers might be another enhancing factor for the drug's dissolution from the agglomerated crystals. Therefore, when the concentration of hydrophilic polymers added in the agglomeration process was increased, there was an increase in the dissolution rate[56]. It was observed that increasing the concentration of all used hydrophilic polymers from 0.25% w/v to 1% w/v led to an increase in the dissolution rate, where the maximum release (99.89%) within 60 minutes was displayed from SA8 agglomerates, which was prepared by the addition of poloxamer 407 (1% w/v). But in case of the agglomerates prepared by the addition of HPMC E5 polymer, it was found that the highest percentage release resulted at the concentration of 0.5% w/v, but beyond 0.75% w/v to 1% w/v, the dissolution decreased gradually. This may be attributed to the addition of HPMC polymer in higher concentrations during the agglomeration process, which may cause excessive sticking to the container, leading to the improper formation of crystal agglomerates. Therefore, the agglomerates that formed using a 0.5% w/v concentration of HPMC were more efficient[49].

The non-considerable change obtained with DSC results indicated that there was no degradation of the drug or interaction with polymers during the crystalline change in the agglomeration process. Although it revealed a few amorphization of RPG powder when it was prepared in the form of spherical agglomerates, this was evident by a noted decrease in the enthalpy change (ΔH) of the agglomerate (-49.653 J/g) when compared with that of pure RPG (-201.68 J/g), referring to the loss of the strong crystalline nature of the RPG drug within the spherical agglomerate[57]. This is also certified by the results of SEM.

Based on the analysis results of SEM, the irregular shape of RPG particles that appeared in the SEM image led to its very poor flowability and difficulties in the compression process, whereas the image of the prepared crystal agglomerate of RPG appeared spherical in shape and had an improved

surface with a larger particle size for the formed crystal agglomerates than that of the standard drug, which indicates that the spherical crystals are formed from very small crystals that are closely compacted into a spherical shape that enables them to flow easily[49, 58].

5. CONCLUSION

The study presented in this research showed that the RPG drug was successfully prepared by spherical crystallization technique through the incorporation of different hydrophilic polymers such as HPMC E5, poloxamer 407, or PEG 6000 for improvement of the formation and characteristics of the produced spherical crystal agglomerates. An evaluation of the prepared RPG spherical crystal agglomerates properties in comparison with the pure RPG powder was carried out. Optical microscopy, particle size, SEM, and DSC analysis displayed that RPG crystal agglomerates showed a regular and spherical shape with an improved surface, particle size enlargement, and reduction in crystallinity of RPG powder. Also, they showed solubility enhancement and significant improvement in the dissolution profile, where SA8 agglomerates displayed the maximum release within 60 minutes. Considerable improvement in the micromeritic properties of all prepared RPG spherical crystal agglomerates has been achieved. These fruitful results indicate that further study can be done to prepare direct compression tablets from RPG spherical crystal agglomerates to improve the solubility, dissolution rate, and bioavailability of RPG drug without any compressibility problems.

Funding: This research received no specific grant from any funding agency. It is on our own credit..

Acknowledgments: We are very thankful to Pharmaceutics and Pharmaceutical Technology Dept. at Faculty of Pharmacy (Girls), Al-Azhar University. We wish to express our appreciation to Pharmaceutical Company (EIPICO), Egypt; for their generous gift of repaglinide, HPMC E5, PEG 6000 and Poloxamer 407.

Conflicts of Interest: There is no Conflict of interest.

Ethical Statement: None applicable

Author Contribution: methodology -writing, Amany I. Abd El-Fattah; review and editing, Maha A. Marzouk and Dina A. Osman. All authors have read and agreed to the published version of the manuscript

List of Abbreviations: RPG: Repaglinide, **BCS** Biopharmaceutical Classification System.

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