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DEVELOPMENT AND EVALUATION OF SOLID DISPERSION OF POORLY WATER SOLUBLE DRUG

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ABSTRACT

The purpose of the present study was to enhance the solubility of poorly water soluble drug, Repaglinide using spray drying based on solid dispersion technique by using the hydrophilic carrier Polyethylene glycol 4000 (PEG 4000) in three different drug: PEG 4000 ratios (1:1, 1:3, 1:5), with the addition of Aerosil 200. The batch with drug-carrier ratio 1:5 was found to be an optimized batch. The formulations were characterized by Fourier transformed infrared spectroscopy (FT-IR Spectroscopy), and X-ray diffractometry (XRD). Dissolution studies were carried out in pH 7.4 Phosphate buffer. SDSD was also evaluated for its Physical characteristics, percentage yield, flow properties and particle size determination. Stability study of selected optimized formulation was carried out by storing at 40˚C /75% RH for 1 month. The FT-IR studies revealed that, no drug- excepient interaction takes place. From powder X-ray diffraction study it was found that crystalline form of Repaglinide has been converted into an amorphous form in the solid dispersion formulations. Rapid burst release (80-82%) from the solid dispersion formulation was observed within 60 min. From the obtained results it was concluded that, developed solid dispersion is an effective approach for enhancing the solubility and hence dissolution rate of the Repaglinide.

KEYWORDS: Diabetes mellitus, Repaglinide, PEG 4000, Solid dispersion, spray drying.

INTRODUCTION

Diabetes mellitus is a life threatening disorder and an important cause of prolonged illness and early death. It is associated with numerous healthcare dangers, such as hyperglycemia unbalanced metabolism of lipids, proteins and carbohydrates and increased risk of complications caused by increasing vascular diseases1, 2. The most important cases of diabetes mellitus are types 1 and 2 in which the first type is corresponding to insulin but the second type is independent and more prevalent. Repagilnide, is generally used in the management of type 2 diabetes mellitus.

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Hence, there will be two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents includes: Enhancing solubility and dissolution rate of poorly water-soluble drugs and Enhancing permeability of poorly permeable drugs. Repaglinide belongs to BCS (biopharmaceutics classification system) class II1. BCS class II compounds are highly permeable but poorly soluble, and their bioavailability depends on extent and rate of dissolution. It has a extremely short half-life of about 1 h, and following oral administration its bioavailability is 56%. Therefore, its oral bioavailability could be increased via solubility enhancement.

There are numerous methods for increasing the solubility of poorly water-soluble drugs, including particle size reduction, solid dispersion, nanosuspension, supercritical fluid technology, inclusion complex formation techniques and floating granules. In the solid dispersion technique, the product is usually composed of a hydrophobic drug which could be dispersed as either molecular or crystalline particles in a hydrophilic matrix. As a result of increased specific surface area of the drug molecule and decreased thickness of the boundary layer, enhancement of the dissolution rate could be achieved. There are various methods to produce solid dispersions which include hot melt extrusion, melt agglomeration, vacuum drying and rotary evaporation, freeze drying, supercritical anti-solvent and spray drying method. The present study was developed based on the spray drying method, which is a common technique in pharmaceutical companies due to its high scalability and advantages such as good uniformity of molecular dispersion, the possibility of continuous manufacturing and large scale production with high recoveries in comparison to other methods. In spray drying, the solution of drug and carrier is transported to a nozzle via a pump system and atomized into fine droplets.

The purpose of the present study was to develop solid dispersion of Repaglinide as a model drug by using a spray drying technique in order to enhance its aqueous solubility and dissolution rate. The Repaglinide microparticles were prepared by using hydrophilic carrier PEG 4000 and Aerosil 200.

MATERIALS AMD METHODS

Materials

Repaglinide was purchased from Yarrow chem. Products, Mumbai. PEG 4000 was received from Research lab fine chem. Industries. (Mumbai). Aerosil 200 (Research lab fine chem. Industries, Mumbai). Methanol (SD Fine chem. Limited, Mumbai). And all other chemicals used were of analytical grade.

Experimental work

Preformulation Studies of Repaglinide

a) Organoleptic properties

Repaglinide was tested for organoleptic properties such as appearance, colour, odor, taste etc.

b) Appearance: Transferred approximately 2gm of the sample on a white paper spreaded uniformly and examined visually.

c) Colour: Small quantity of pure repaglinide powder was taken in a butter paper and viewed in well illuminated place.

d) Taste and odor: Repaglinide was tested manually for its taste and odor.

Melting point determination

Melting point of the drug was determined by capillary method using Melting point apparatus. Here, the capillary tube was filled by pressing the open end gently into sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug packed into the bottom of the tube, the tube was placed into the slot behind the eye-piece on the Melt-temperature. Make sure the unit is plugged in and set to zero, and then turn it on. The temperature were noted when the drug start to melt and the drug till complete melt.

Solubility studies

Solubility is important pre-formulation parameter because it affects the dissolution rate of drug and hence, the bio availability of drug. Solubility of repaglinide was determined in methanol, acetone, phosphate buffer (pH 7.4) and distilled water. Solubility studies were performed by taking excess amount of repaglinide in different beakers containing the solvent.

Compatibility study

The compatibility study was done by FT-IR spectroscopy by using FT-IR spectrophotometer (thermo Nicolet). FT-IR spectra were obtained by an FT-IR spectrophotometer using the potassium bromide (KBr) disk method by means of a hydrostatic press. The procedure consisted of dispersing a sample (druf and drug-carrier mixture) in KBr and compressing into disk by applying a pressure by hydraulic press. Data were collected over a spectral region from 4000 to 400cm-1 with a resolution of 2 cm-1.The interaction between drug and excipients was observed IR- spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug .And obtained data spectra are shown in figure no.2.

Spectroscopic studies of Repaglinide

Standard calibration curve of Repaglinide in Phosphate buffer (pH 7.4)-
Method
Calibration curve of Repaglinide was prepared in phosphate buffer (pH 7.4) at different dilutions.

Preparation of stock solution-
Repaglinide (10 mg) was accurately weighed and dissolved in phosphate buffer (pH 7.4). The final volume was made up to 100 ml with phosphate buffer (pH 7.4) to obtain a concentration of 100 ug/ml. This stock solution was used to prepare further standard solutions of drug.

Preparation of standard solution-
Aliquots (0.5-5.0 ml) of stock solutions of Repaglinide were transferred into series of 10 ml volumetric flask and volume was made up to the mark with phosphate buffer (pH 7.4) to give the concentration range from 5 to 50 ug/ml. The absorbance was measured at 247 nm against the reagent blank. From the absorbance, standard curve was plotted.

Preparation of spray dried solid dispersion of Repaglinide

Measured quantities of Repaglinide and PEG 4000 (as per table no. 2) were dissolved in 90 ml methanol. Aerosil 200 (in given concentrations) was dispersed in methanolic solution of drug and carrier and final volume was made up to 100 ml with methanol. The resultant dispersion was constantly stirred on magnetic stirrer while being subjected to spray drying process. Spray drying was carried out using a spray dryer in a co-current mode. Under different set of conditions indicated in table no.1.

Table 1: Spray drying process parameters

Sr. No.	Process parameters	Values
1	Inlet temperature	100 ˚C
2	Outlet temperature	55-75 ˚C
3	Feed flow rate	2 ml/min
4	Pressure	200 kPa.

Table 2: Formulation of Solid Dispersion

Batch No.	Drug: Carrier ratio(w/w)	Drug, Carrier and Aerosil 200	Quantity (gm)
F1	1:1	Repaglinide	1
		PEG 4000	1
		Aerosil 200	1
F2	1:3	Repaglinide	1
		PEG 4000	3
		Aerosil 200	1
F3	1:5	Repaglinide	1
		PEG 4000	5

		Aerosil 200	1

Characterization of solid dispersion of Repaglinide

Percentage yield

The prepared solid dispersions were collected and weighed. Percentage yield was calculated by dividing the measured weight of solid dispersionsby total weight of drug and carrier.
The formula for % yield calculation-

$$\% \text{ yield} = \frac{\text{Weight of spray dried solid dispersion}}{\text{Total weight of drug and polymer}} * 100$$

Micromeritic studies of solid dispersion

The solid dispersions were characterized by their micromeritics properties, such as Carr's compressibility index, Hausner ratio and Angle of repose.

Table 3: Relationship between Carr's index, Angle of repose and Hausners ratio

Flow ability	Carr's index	Angle of repose	Hausner's ratio
Excellent	5 – 15	25 – 30	1.00 – 1.11
Good	12 – 16	31 – 35	1.12 – 1.18
Fair to Passable	18 – 21	36 – 40	1.19 – 1.25
Poor	23 – 35	41 – 45	1.26 – 1.34
Very poor	33 – 38	46 – 55	1.35 – 1.45
Extremely Poor	>40	>66	>1.60

a) Angle of repose

Angle of repose was determined by fixed funnel method. In this method, specific amount of sample was allowed to flow from funnel onto a graph paper. The height (h) and radius of the cone formed on graph paper were measured and angle of repose was calculated by following equation-

$$\tan\theta = \frac{h}{r}$$

b) Carr's index

The percentage compressibility of solid dispersion was calculated according to equation given below:

$$\text{Percentage compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

c) Hausner's ratio

The Hausner's ratio of a solid dispersion was calculated according to equation given below:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Particle size measurement

Particle size was determined by microscopic method using calibrated ocular micrometer.

Drug content of solid dispersions

Solid dispersions equivalent to 2 mg drug were taken and dissolved in minimum quantity of methanol and volume was made up to 50 ml. From this solution, 5 ml was taken and again diluted with methanol up to 50 ml. The samples were filtered through Whatman filter paper 0.45µm. The filtrate was analyzed using a UV spectrophotometer at 237 nm against a blank after appropriate dilutions.

In-vitro dissolution studies

Dissolution studies of prepared Spary dried solid dispersion equivalent to 4 mg of Repaglinide were performed using USP type-II apparatus. SDSD weighed and added into the dissolution medium (pH 7.4 phosphate buffer, 900 ml) maintained at rotation speed of 75 rpm at 37±0.5˚C. At the specified times 5 ml samples were withdrawn by using syringe filter and then assayed for Repaglinide content by measuring the absorbance at 247.5 nm using a UV visible spectrophotometer.

Fig. 1: Dissolution test apparatus (USP type-II)

Table 4: Parameters of in-vitro dissolution test for pure drug Repaglinide and its solid dispersion:-

Sr. No.	Parameters	Detail
1	Apparatus	USP Type-II
2	Dissolution medium	Phosphate buffer (pH-7.4)
3	Volume of medium	900ml
4	Temperature	37±0.5˚C
5	Paddle speed	75 rpm
6	Aliquot withdrawn	5 ml

XRD measurement

XRD measurement was carried out using a powder x-ray with Ni-filtered Cu Kα radiation, a tube voltage of 40 kV and a tube current of 40 mA. The scanning rate was 10˚/min a 2ɵ range of 5-40˚ with a step size of 0.02˚.

Stability Studies

The selected optimized formulation was packed in amber colored bottle, which was tightly plugged with cotton and capped with aluminum. Then it is stored at 40ºC/ 75% RH for 1 months and evaluated for their drug content and dissolution study.

RESULTS AND DISCUSSION

Preformulation study of Repaglinide

Table 5: Physical characters of the Repaglinide drug

Sr. No.	Physical characters	Specifications/Limits	Observations
1	Nature	Crystalline powder	Crystalline powder
2	Colour	White to off-white	Off-white
3	Odor	Odorless	Odorless

4	Taste	tasteless	Tasteless

The physical characters of Repaglinide were found to be identical with standards given in analytical profile of drug substance.

Melting point determination

Table 6: Melting point of RPG

Drug	Melting point (˚C)
Repaglinide	130˚C

The melting point of pure Repaglinide was found to be 130˚C. This was found to be identical with the standardas given in analytical profile of drug (130-131˚C).

Solubility determination

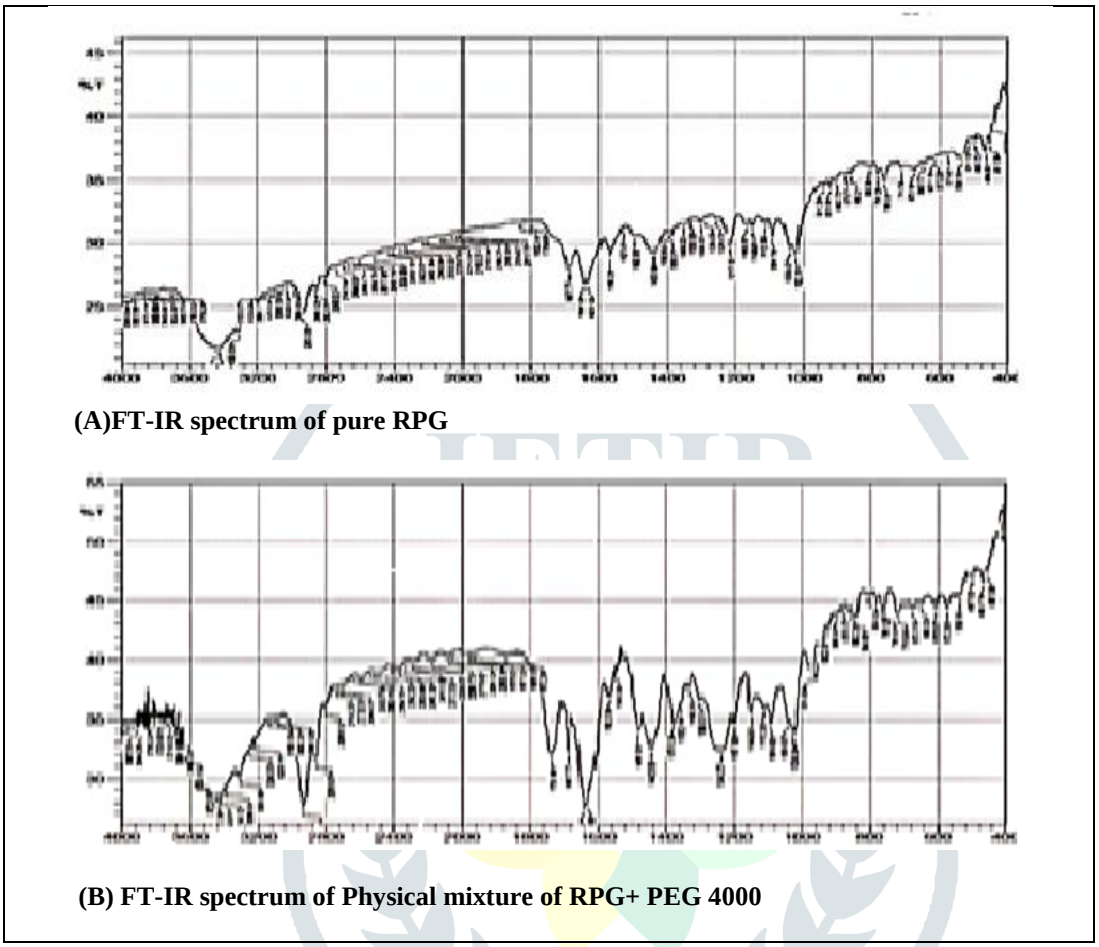
Table 7: Solubility profile of RPG

Sr. No.	Solvent	Solubility (Mean ± S. D.)
1	In distilled water	0.025±0.001mg/ml
2	In Phosphate buffer (pH 7.4)	50.2±5.0 mg/ml
3	In Methanol	120±5.0 mg/ml

n=5

The solubility of repaglinide in distilled water was found to be 0.025±0.001mg/ml, which indicates that repaglinide is practically insoluble in distilled water. 50.2±5.0 mg/ml, solubility of Repaglinide in Phosphate buffer (pH 7.4) indicates that it is Soluble in Phosphate buffer (pH 7.4). And the solubility of RPG in methanol was found to be 120 mg/ml, which indicates that RPG is freely soluble in methanol.

Compatibility study: FT-IR study



(A)FT-IR spectrum of pure RPG

(B) FT-IR spectrum of Physical mixture of RPG+ PEG 4000

Fig.2. FTIR spectrum of pure RPG (A),and physical mixture of RPG+ PEG 4000(B)

All the characteristic peaks of RPG were present in tne spectrum of drug and physical mixture, indicating compatibility between drug and polymer. The spectrum confirmed that there is no significant change in the absorption bands, hence no interaction was observed between them. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers.

Spectroscopic studies.

Preparation of standard calibration curve of Repaglinide in phosphate buffer (pH 7.4)

Table 8: Calibration curve of Repaglinide pure drug

Sr. No.	Concentration(ug/ml)	Absorbance
1	0	0
2	5	0.0391
3	10	0.0874
4	15	0.1313
5	20	0.1735
6	25	0.2541
7	30	0.3239

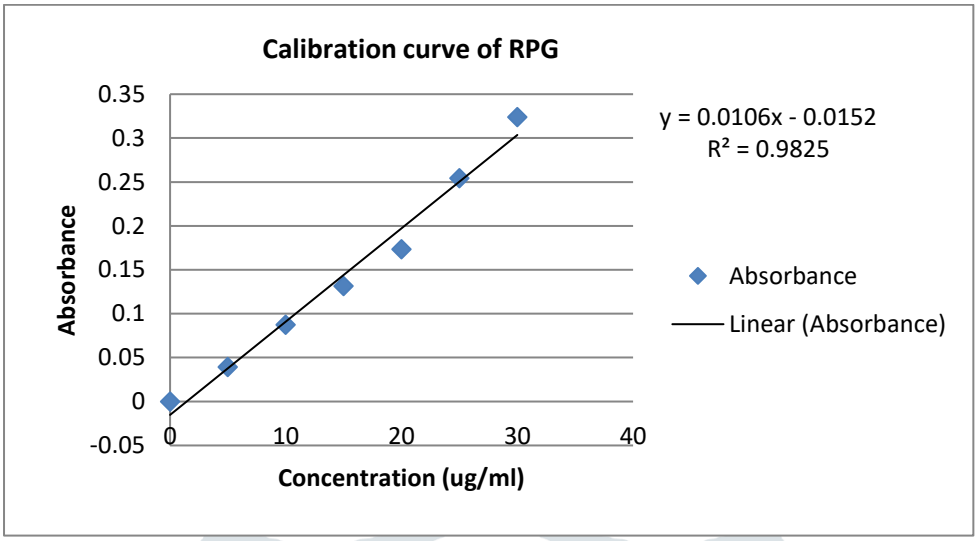


Fig. 3. Calibration curve of Repaglinide pure drug

From the calibration curve equation of regression line is given as-

$$Y=mx+c$$

Where,

Y= Absorbance

m = Slope

c = intercept

Y= 0.01x- 0.015

From the equation of line of calibration curve of repaglinide in phosphate buffer (pH 7.4), the slope was found to be 0.01 with 0.015 intercept. And correlation coefficient (R^2) was found to be = 0.98. The value indicates that the calibration curve of pure RPG was found to be linear.

Table 9: Percentage yield, Particle size measurement values and Dug content of solid dispersion formulations

Batch No.	Percentage yield	Particle size (um) (Mean ± S. D.) n=100	Drug content (%) (Mean ± S. D.)
F1	59.5%	3.2±0.52	93.45±0.32
F2	64.5%	5.1±0.61	93.98±0.45
F3	71.52%	6.0±0.63	94.45±0.57

Percentage yield

It was found that as drug: polymer ratio and aerosol 200 concentrations increased, the % yield was found to increase (Table no.9). This may be because increasing drug: polymer ratio increases bulk of SDSD and aerosol 200 decreases stickiness of the product which aids in collection of SDSD from the spray dryer. It has been reported that aerosol 200 minimizes electrostatic charge produced in spray dried material, allowing increased yield as well as improved flow properties of the powder. There for F3 batch shows high % yield i.e. 71.52%.

Micromeritic studies

Table 10: Micromeritic studies of solid dispersion formulations

Batch No.	Carr's index (%)	Hausner's ratio	Angle of repose
F1	12.2%	1.00	25.60˚
F2	12.5%	1.05	27.42˚
F3	14.90%	1.10	29.11˚

Commonly reported methods for testing powder flow are angle of repose, compressibility index and hausner's ratio. If the angle of repose is between 25-30˚ and the values of compressibility index and Hausner ratio are 12-15% and 1.00-1.11 respectively, then powder is considered to have excellent flow properties. The results of this test are recorded in table 10; indicate the SDSD have excellent flow properties.

Particle size measurement

The particle size of SDSD was found to be in the range of 3.2±0.52 to 6.0±0.63 um (Table 9).

Drug content

The drug content ranged between 93.45±0.32% to 94.45±0.57%. The results indicate that processes employed to prepare solid dispersion in this study was capable of producing formulation with uniform drug content (Table 9).

In-vitro dissolution study

Table 11: Percent drug release of pure drug and its solid dispersion formulations

Time (min)	Percentage of drug release (%)			
	Pure drug	F1	F2	F3
0	0	0	0	0
5	5.2	30.51	61.15	72.45
10	10.15	45.25	65.29	72.92
15	15.4	51.58	66.55	74.15
20	22.15	55.25	67.54	76.61
25	27.62	61.24	70.38	78.32
30	30.51	63.45	70.87	79.83
45	34.61	65.84	73.45	81.05
60	38.71	66.95	75.68	82.51

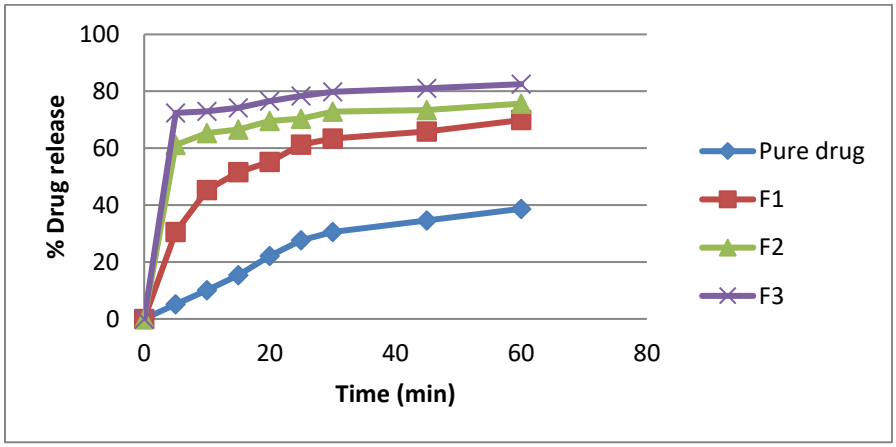


Fig. 4: In-vitro dissolution profile of Repaglinide pure drug and its SD formulations

Figure no.4. shows dissolution profiles of repaglinide and its solid dispersions with PEG 4000.These three formulations exhibited wide difference in dissolution pattern. The fastest one was solid dispersion batch F3, followed by F2, F1 and pure RPG. The rapid burst release (80 -82 %) was observed within 60 min. in case of SD batch F3, than the pure drug which was found to be about 38% . It clearly indicated the ideal complexation between the RPG and PEG 4000.

XRD measurement

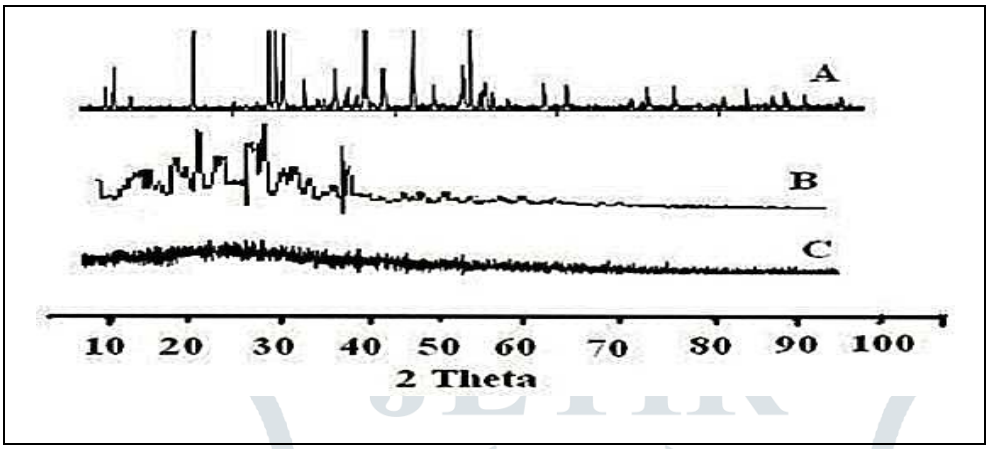


Fig. 5. Diffractogram of drug (A), PEG 4000 (B) and Solid dispersion (C).

Figure no.5. shows the diffractogram of pure RPG(A), PEG 4000 (B) and SD of RPG (C). RPG showed the characteristic intense peaks at 2θ of 20, 30, 33, 44 and 56.50. These peaks clearly indicated crystalline nature of the pure RPG. Also, the characteristic intense peaks for PEG 4000 were observed at 2θ of 22.5, 29 and 37.50. The intensity of these peaks from RPG and PEG 4000 disappeared in diffractogram of the SD as observed in C. This pattern indicates the amorphous nature of RPG in SD.

Stability studies

The formulation batch F3 analyzed for drug content and in- vitro release studies. The results are given below-

a) Drug content after stability study

The drug content of optimized batch after stability study was found to be 93.67±0.23%.

Table 12: Drug content after stability study

Optimized batch	Drug content before stability	Drug content after stability
F3	94.45±0.57	93.67±0.23%.

b) In-vitro drug release study after stability

Table 13: Percent drug release of optimized batch after stability study

Time (min)	Percent drug release (%)	
	Before stability F3	After stability (30 days) F3
0	0	0
5	72.45	69.54
10	72.92	70.41
15	74.15	71.26
20	76.61	73.58
25	78.32	75.12
30	79.83	77.61
45	81.05	79.43
60	82.51	80.5

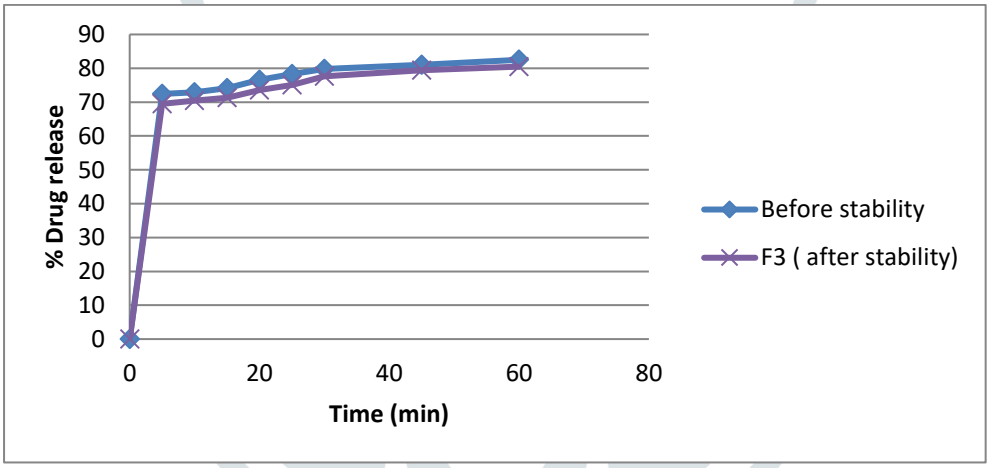


Fig. 6: In-vitro drug release profile of Repaglinide pure drug and its solid dispersion formulations after stability study.

There were no physical changes in appearance and flexibility. After subjecting formulations to the Stability Studies, the results were shown that there were no major changes in Drug Content and In *vitro* Drug Release. Hence the formulation was found to be stable.

SUMMERY AND CONCLUSION

Repaglinide is an anti diabetic drug belongs to the class of Meglitinide analogues. As it is BCS class II drug, due to its poor aqueous solubility, oral bioavailability of RPG is less about 56%. In order to improve its solubility solid dispersion was prepared. In the present research study solid dispersion of RPG was prepared by Spray drying method, by using PEG 4000 as a carrier in presence of Aerosil 200. The preformulation studies were carried out for its colour, odor, taste and melting point determination and were found to be identical with standards given in analytical profile of drug substance. The prepared formulation was then evaluated for different parameters like practical yield, Micromeritic study, particle size measurement, drug content, In-vitro drug release, X-ray diffraction study and stability studies. The F3 batch with drug-carrier ratio 1:5 was found to be an optimized batch with best results. Hence, from the above study it was concluded that the formation of solid dispersion of RPG with PEG 4000 carrier in presence of Aerosil 200 resulted in significant enhancement in the dissolution rate of the drug. Enhancement of solubility and dissolution rate will likely to increase bioavailability which would be beneficial for the better glucose control in diabetic patients.

FUTURE PROSPECTS

The present formulation can be tested for the in-vivo study.The optimized solid dispersion formulation can also be given as capsule, tablet dosage form. And can also used for the development of controlled release preparation.

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