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Research Paper

FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLET OF RIPAGLINIDE

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In the present investigation an attempt was made to improve the solubility and dissolution rate of poorly soluble drug Repaglinide by solid dispersions(SDs) and inclusion complexs(ICs) technique and hence to formulate the fast-dissolving tablets of Repaglinide by using different Superdisintegrants. The phase solubility studies indicated that the formation of Repaglinide-β-Cyclodextrin and Repaglinide-Poloxamer 188 are in 1:1Mratio in solution. ICs of Repaglinide with β-Cyclodextrin and SDs with Poloxamer 188 were prepared at various proportions (1:1, 1:3, 1:5 and 1:7) by kneading and solvent evaporation method. The drug release profile was carried out in 0.1 N HCl using USP type II paddle dissolution apparatus. From the above studies, it was found that the kneading method shows the better enhancement of dissolution in comparison to the solvent evaporationand physical mixture (PM) method. The IC in the ratio of 1:3 was found to have highest dissolution rate compared to intact Repaglinide, SDs and PMs. The formation of ICs was evident in these formulations as shownby Fourier-transform infrared (FTIR) spectroscopy and X-ray diffraction (X-RD) studies. The fast dissolving tablets were formulated by using different superdisintegrating agents like Crosspovidone, Sodium Starch Glycolate and Croscarmellose sodium from optimized β-Cyclodextrin ICs. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration, drug content and *in- vitro* dissolution studies.The optimized formulation F4 containing Crosspovidone showed the maximum percentage of drug release i.e. 99.46% at the end of 25 minutes. Drug release from all the tablets followed first order release kinetics with Fickian diffusion mechanism.

Key words: β-Cyclodextrin, *in-vitro* drug release, Phase Solubility, Repaglinide, Solid Dispersion.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. The drug may be administered by variety of routes in a variety of dosage forms. Drugs are more frequently taken by oral administration. The solid dosage forms available mostly in unit dosage forms such as tablets, capsules, lozenges etc[1]. When drugs are administered orally in dry state, tablets and capsules are most convenient dosage form[2].All practical purposes only compression tablets are almost universally used while molded tablets being rate commodity. Drugs are more frequently taken by oral administration[3].

Although a few drugs taken orally are intended to be dissolved within the mouth, vast majority of drugs taken oral are swallowed[4]. Compared

with alternate routes, the oral route of drug administration is the most popular and has been successfully used for the conventional delivery of drug[5].

It is considered most natural, uncomplicated, convenient, safe means of administering drugs[6]. Some of its advantages are greater flexibility in dosage design, ease of production and low cost[7].

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non- compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim to enhance the safety and efficacy of drug molecule by formulating a convent dosage form for administration and to achieve better patient compliance[8].

1) Immediate - release dosage forms allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. These dosage forms usually release (dissolve/disperse) the drug in a single action, which means the drug is released initially very quickly and then passes through the mucosal membrane into the body, reaching the highest plasma level in a comparatively short time [(2)]. Their advantages are releases the drug immediately, more flexibility in adjusting the dose, no dose dumping problem and can be used in initial and final stages of disease

Repaginate is a meglinide analogue used in the treatment of type II Diabetes mellitus. It controls high blood sugar levels and helps in preventing kidney damage, blindness, nerve problems, loss of limbs, sexual problems & heart complications. Thisshould not be used in type I Diabetes mellitus. It is a poorly water soluble drug belongs to BCS class II drug with short biological half - life 1hr. Repaglinide was enhanced by solid dispersion techniques like 1) drop melt techniques. Repaglinide dispersion was selected based on dissolution and formulated as tablet dosage form using various diluents and super disintegrates. The final; formulation was selected based on the dissolution profile that is formulation with MCC as a diluents and cross povidone as a super disintegrants.

Materials and Methods

Materials

Repaglinide was a gift sample from Torrent Pvt. Ltd., Mumbai. Poloxamer 188 and β-Cyclodextrin were gift samples from Microlab Pvt. Ltd., Bangalore. Crosspovidone and Croscarmellose sodium were gift samples from Wockhardt Research Centre, Aurangabad. Sodium Starch Glycolate was purchased from Loba chemicals, Mumbai. All other reagents used were of analytical grade.

PRE-FORMULATION STUDIES:

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Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

Organoleptic properties:

Appearance

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

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

Taste and odour: very less quantity of repaglinide was used to get taste with the help of tongue as well as smelled to get the odour.

Angle of repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured.

Angle of repose was then calculated with the use of the following formula:

$\tan\theta = h / r$

Where, θ = angle of repose, h= height of the pile, r = average radius of the powder cone.

TABLE NO. 1: Organoleptic Properties

Angle of repose	Flow property
	Excellent
25-30 o	Good
30-40 o	Passable
>40 o	Very poor

Determination Of Densities

Bulk Density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition as the granule size increases bulk density decreases.

METHODS:

Bulk density of the sample was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

Bulk Density (g/ml) = Weight of sample in grams Volume occupied by the sample.

TAPPED DENSITY:

10 grams of sample was being poured gently

through a glass funnel into a 50ml graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

Tapped Density (grams/ml) = Weight of sample in grams Volume occupied by the sample.

Measurement of Powder Compressibility:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula

TABLE 2: Compressibility index

	Compressibility index	**Flow**
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Verypoor
6	>40	Extremely poor

Compressibility index: $100\frac{(V_0 - Vf)}{V_0}$

$$\text{HausnerRatio: } \frac{V0}{Vf}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume

LOSS ON DRYING:

Determine on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W1). Put the sample inbottle, replace the cover, and accurately weighed the empty bottle with contents (W2). By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator before weighing. Weighed the bottle (W3).The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\% \text{ Loss on drying } = \frac{(W2 - W3) \text{ X } 100}{(W2 - W1)}$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

Solubility Analysis :

Solubility is important pre-formulation parameter because it affects the dissolution of drug, bio availability of drug, less soluble in water, solubility of repaglinide was determined in methanol, ethanol, dimethyl fluoride methylchloride, 0.1NHCl. Solubility studies were performed by taking excess amount of repaglinide in different beakers containing the solvent.

pH:

Weighed and transferred accurately about 1.0 g of sample in 20 ml clean and dried volumetric flask dissolved in methanol free water and made up the volume to 20 ml with the same solvent, mixed. Determined the pH of freshly prepared solution by using recalibrated pH meter.

ASSAY

Weighed accurately 10mg of repaglinide sample and added to 100 ml volumetric flask. Added 1ml of methanol mixed for 10 minutes added 60ml of 0.1 N Hydrochloric acid and dissolved it. Made up the volume to 100ml with 0.1 N Hydrochloric acid. Took 10ml and diluted to 100ml with 0.1 N HCL. Took 1ml and diluted to 10 ml with 0.1 N HCL, absorbance measured at 283nm.

DRUG-EXCIPIENT COMPATIBILITY STUDY BY FTIR

Infra red spectroscopy is one of the most widely used tools for purity analysis of drugs in pharmaceutical Industry. Fourier Transform IR spectra were recorded using bruker Germany. IR spectrophotometer. KBr powder was used to prepare pellet for sampling. The scanning range was 4000- 40cm

Preparation Of Standard Curve

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 283nm.

The Standard solution in repaglinide in pH acetate buffer 10mg of repagilinde is accurately weighed and dissolved in 10ml containing methanol in a volumetricflask. The various concentrations of repaglinide prepared are 10, 20, 30, 40, 50, 60, ug/ml. The absorbance of various solutions of repaglinide are determined spectrophotometricaly at 283nm employing UV double beam spectrophotometer using acetate buffer of pH.

Preparation of solid dispersion and physical mixture :

Solid dispersions prepared by melting the carrier

Solid dispersions (SDs) preparations containing different weight ratios of repaglinide in PEG6000 (1:1, 1:3, 1:5) were prepared by the melting method. repaglinide was added to the melted PEG 6000 at 75oC and the resulting homogenous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in desiccators for 24h.Subsequently, the dispersion was ground in a mortar and sieved through 100#

Physical Mixture

Physical mixture (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of repaglinide and PEG 6000 in a mortar until a homogenous mixture was obtained. The resulting mixture were sieved through a 100# sieve and denoted as PM.

Characterization of solid dispersions of repaglinide with PEG 600064

Drug content

About 10mg of drug equivalent of physical mixture and solid dispersion (theoretical) were weighed accurately and transferred to 50ml volumetric flask to which 10ml methanol was added and sonicated for 15min and volume was made up with methanol. From this stock solution further dilution were done and assayed using ultraviolet spectrophotometer measured at 283nm.

Phase-Solubility Study

Phase-solubility studies were carried out to evaluate the possible solubilizing effect of the carrier by adding an excess amount of drug to flask containing 10ml of aquous solutions containing increasing concentrations of PEG6000.The flask were placed in a mechanical shaker at 75rpm and room temperature for 24hour.After 24 Hours the solutions were filtered and analysed by UV-Spectrophotometer at 283nm..

Dissolution Studies:

Dissolution studies of repaglinide in powder form, SDs, and PMs were performed by using the USP type II paddle apparatus at the paddle rotation speed of 75 rpm in 900ml of pH 5 acetate buffers as a dissolution medium at 37±0.5 °C. The SDs or PMs Equivalent to 2mg of repaglinide was weighed using a digital balance and added into the dissolution medium. At the specified times (every 10 min for 2 hours), 10ml samples were withdrawn by using syringe filter (0.45 µm) and then assayed for repaglinide content by measuring the absorbance at 283 nm using a UV- Visible spectrophotometer. Fresh medium (10ml), which was prewarmed at 37 °C, was added to the dissolution medium after each sampling to maintain its constant volume throughout the test.

Fourier transforms IR spectroscopy:

Fourier-transform infrared (FT-IR) spectra were obtained by using Bruker Germany FTIR. The samples (repaglinide or SDs or PMs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.

Preparation of natural superdisintegrants (plantago ovata seed powder, mucilage and husk powder):

The powder of seeds and husk were prepared by an automatic grinder and sieved (#80). Then it stored in a dedicator until use .For isolation of seed mucilage, the cleaned seeds of Plantago ovata were soaked in distilled water 48 hrs and then boiled few minutes so that mucilage was completely released in to water. This material squeezed through muslin cloth for filtering and separating out the marc.

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volume of acetone was added to the filtrate so as to precipitate the mucilage .The mucilage was dried in oven (less than 60oC), powdered, sieved (# 80) and stored in desiccators until use.

The natural super disintegrants were evaluated for their physicochemical properties. The swelling index is calculated, it is the volume in milliliters that is occupied by 1g of drug or any substance after it has swollen in an aqueous liquid for4 hr. The physical mixture of drug complex with this super disintegrants was allowed to stand for 7 days and the assay of drug was performed for compatability studies.

Preparation of the prepared natural super disintegrants were evaluated for swelling factor, bulk density, tapped density, angle of repose. Angle of reposewere calculated according to the formula procedure in 6.1.4 bulk density and tapped density were found out using the procedure given compressibility and hausner's ratio were found out.

FTIR Studies

The spectral details for the drug and physical mixtures are shown as follows FT-IR Peak Of Various Components.

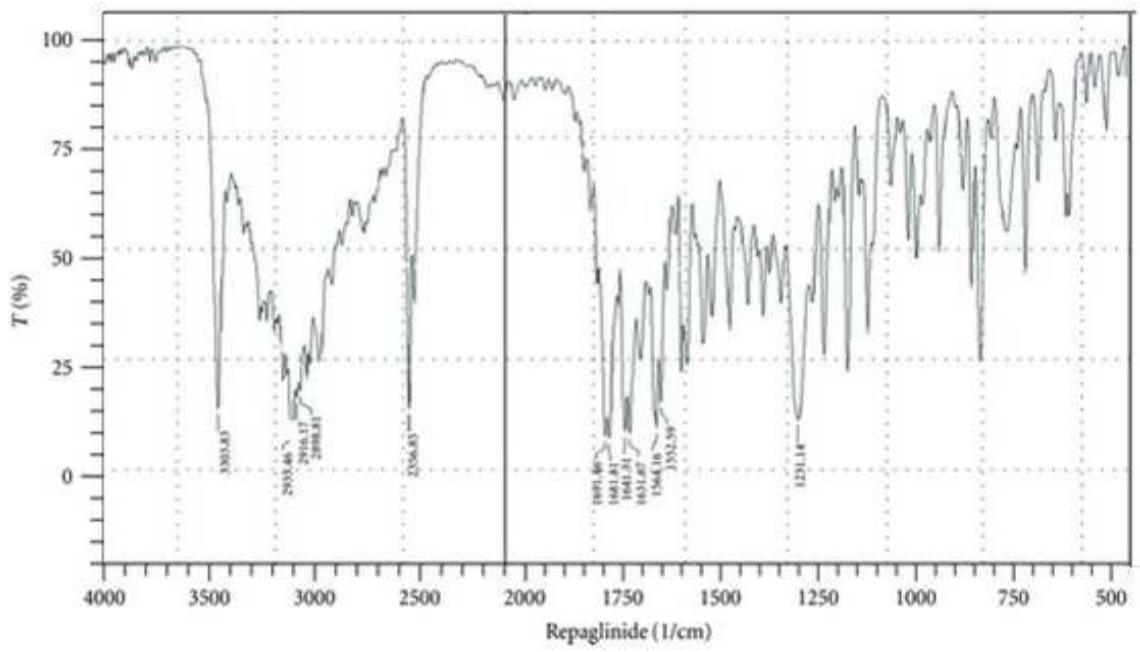

Fig.No. 1: IR spectrum of Repaglinide

Table 3: FORMULATION OF IMMEDIATE RELEASE TABLET

S. No.	Ingredient Name	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	1:5 Solid Dispersion equivalent to 2mg Repaglinide	10	10	10	10	10	10	10	10	10	10	10	10
2	Micro crystalline Cellulose	92	92	92	92	92	92	92	92	92	92	92	92
3	Mannitol	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0
4	Isphagol Mucilage	10	12.0	-	-	-	-	-	-	-	-	-	-
5	IsphagolPowder	-	-	10.0	12.0	-	-	-	-	-	-	-	-
6	Iphagol husk powder	-	-	-	-	10.0	120	-	-	-	-	-	-
7	Cross Povidone	-	-	-	-	-	-	10.0	12.0	-	-	-	-
8	CMC		-	-	-	-	-	-	-	-	-	10.0	12.0
9	SSG	-	-	-	-	-	-	-	-	10.0	12.0	-	-
10	Talc	2	2	2	2	2	2	2	2	2	2	2	2
11	Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
12	Aerosil	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
13	Orange Flavour	1	1	1	1	1	1	1	1	1	1	1	1
	Total weight	200	200	200	200	200	200	200	200	200	200	200	200

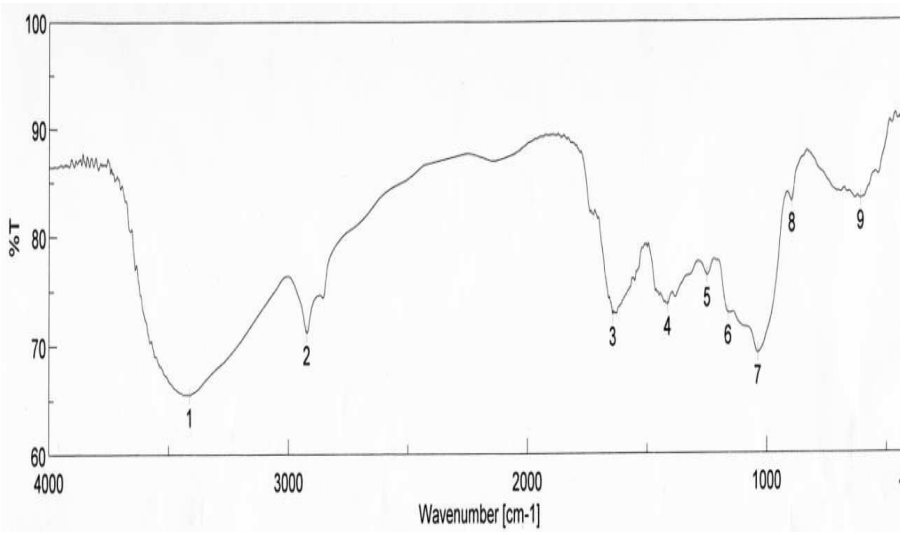

Fig. No. 2: Ispagol Mucilage

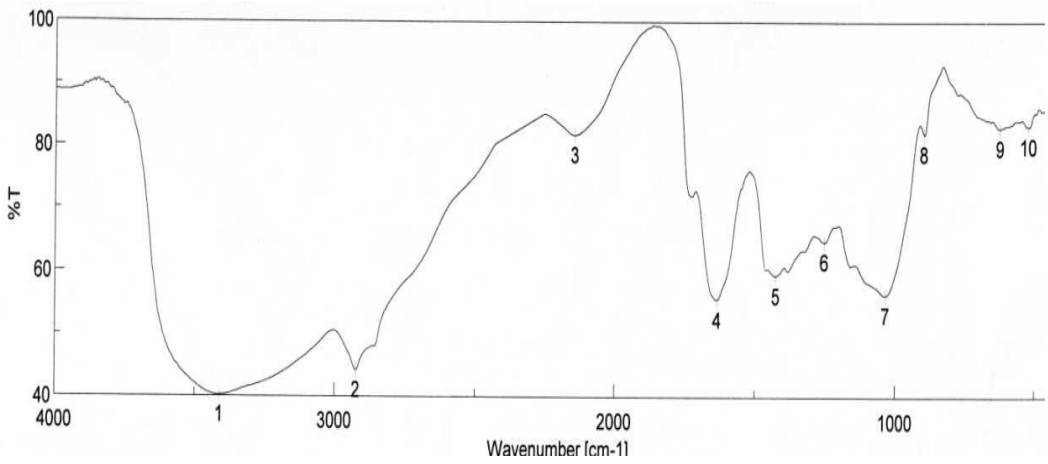

Fig. No. 3: Ispagol Seed Powder

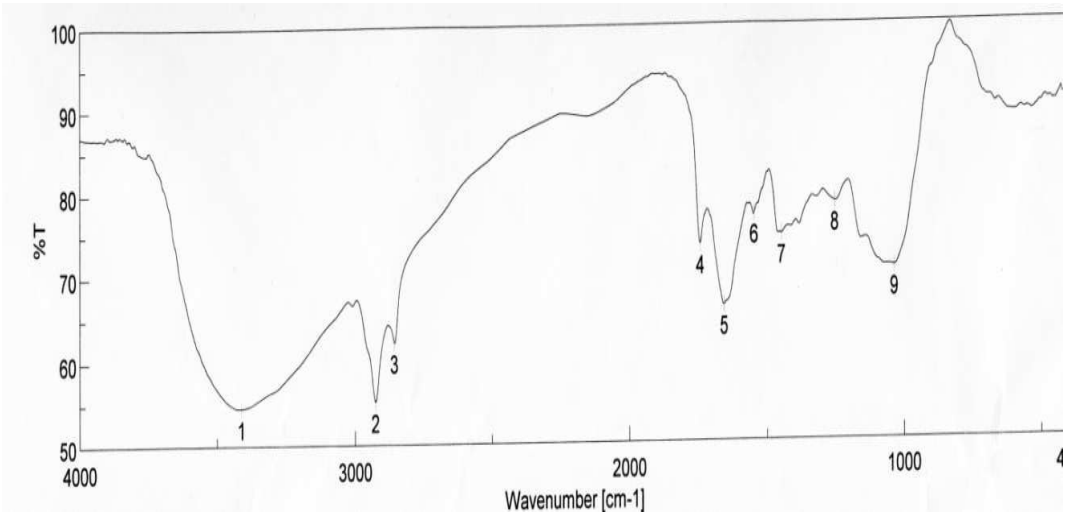

Fig. No. 4: Ispagol Husk Powder

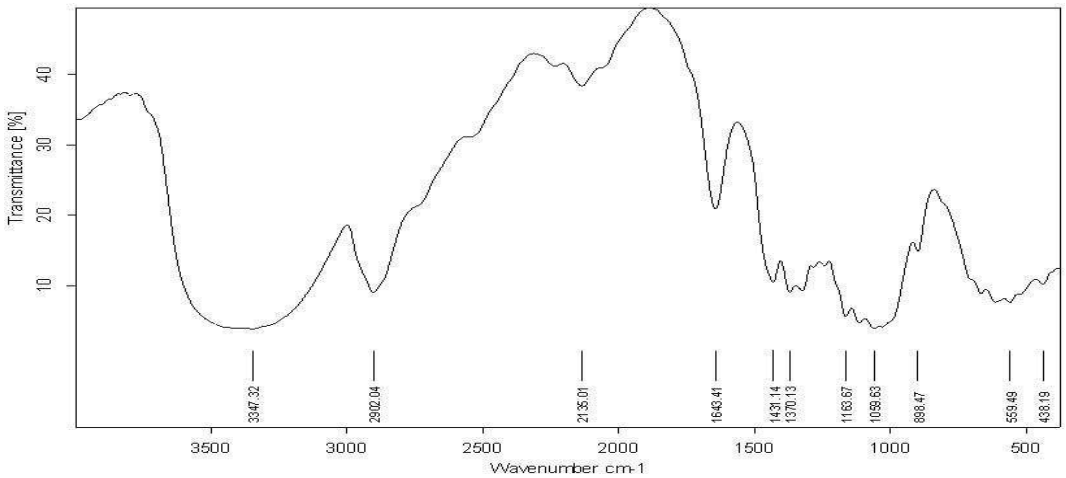

Fig. No. 5: IR Spectra of Microcrystalline Cellulose

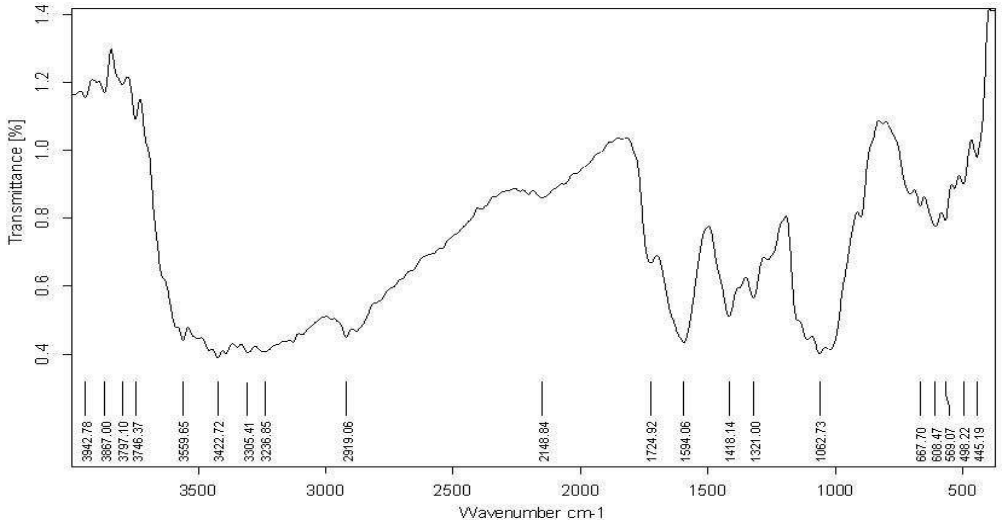

Fig. No. 6: IR Spectra of Crospovidone

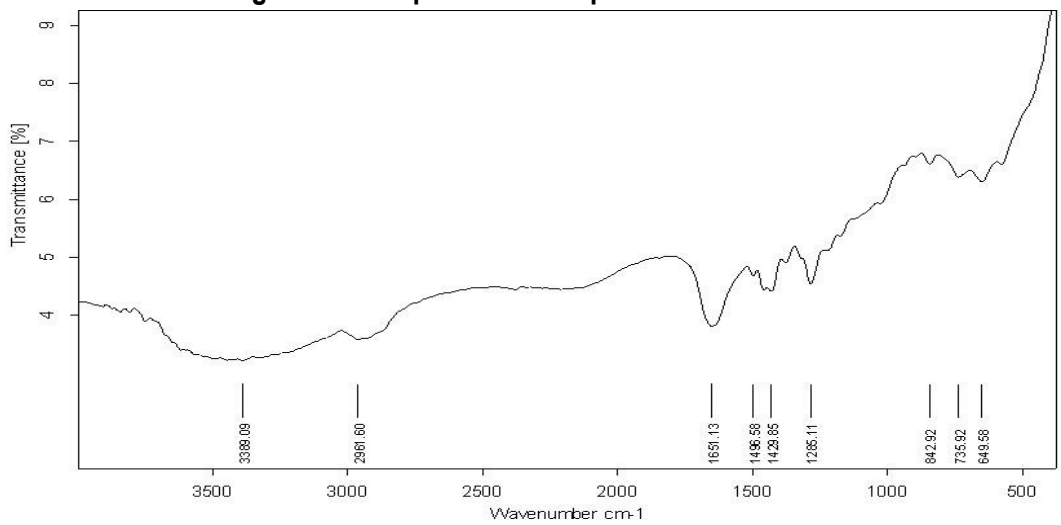

Fig. No. 7: IR Spectra of Croscarmellose Sodium

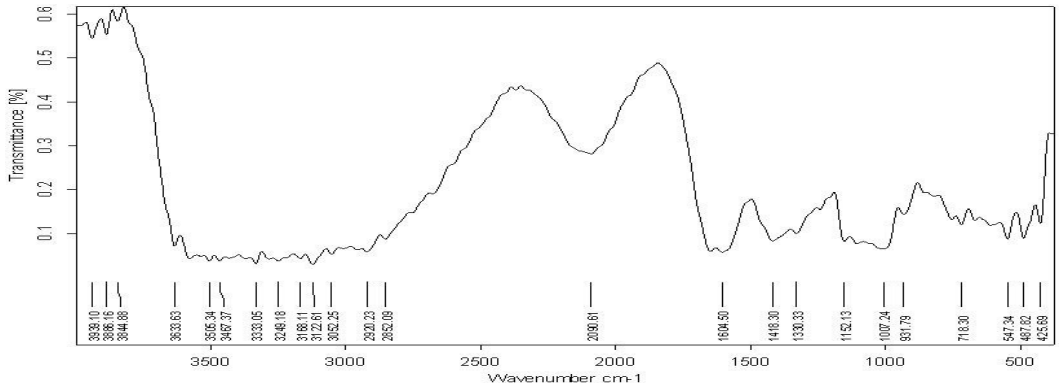

Fig. No. 8: IR Spectra of Sodium Starch Glycolate

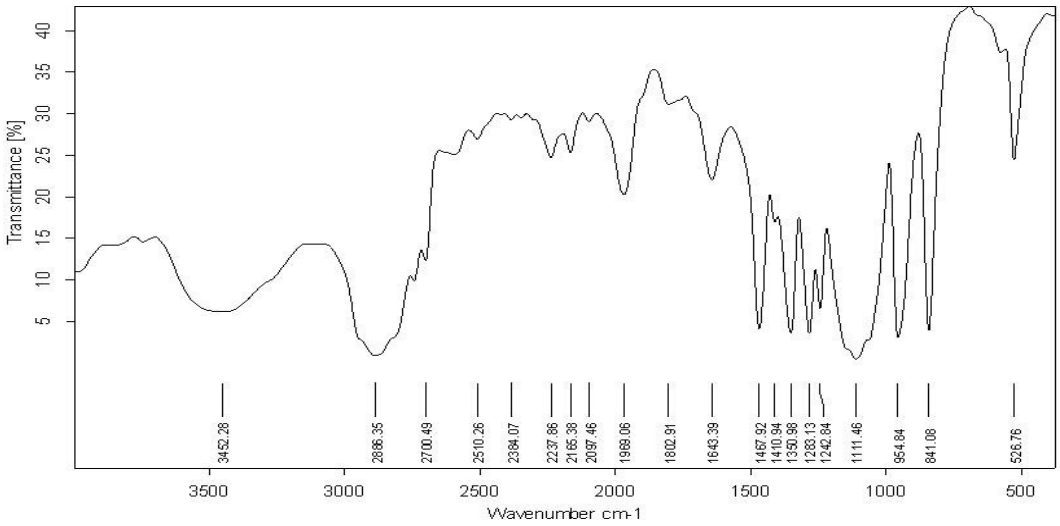

Fig. No. 9: IR Spectra of PEG 6000

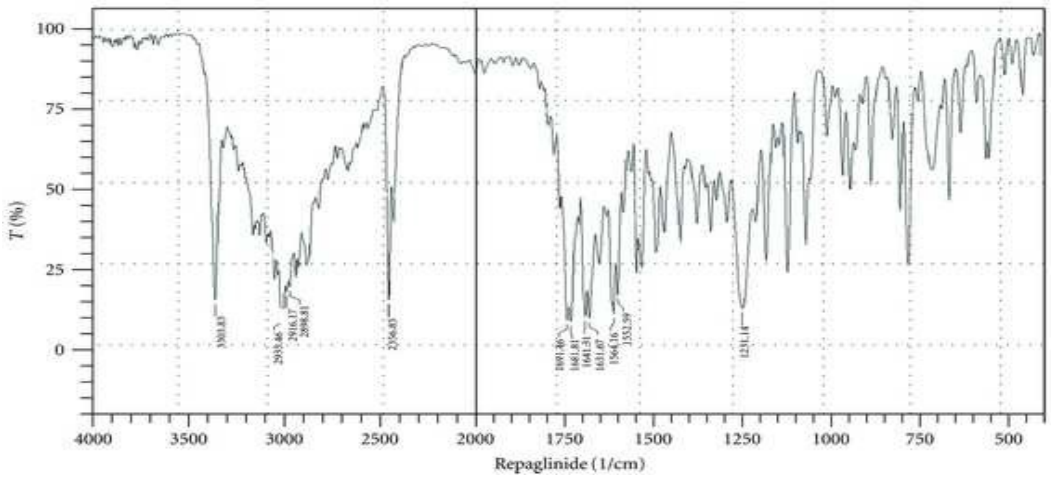

Fig. No. 10: IR Spectra of Repaglinide & Excipient Mixture

Table 4: In-vitro Dissolution Profile of repaglinide Physical Mixture of repaglinide and Solid Dispersion of repaglinide in pH 1.2 Buffers

Sr. No.	Formulation	Percentage drug released after 30 minutes (DR)
A1	Drug	31.23 ± 2.25 %
A2	PM 1:1	41.54 ± 2.58 %
A3	PM 1:2	44.86 ± 2.69%
A4	PM 1:5	51.12 ± 2.50%
A5	SD 1;1	87.89 ± 2.25 %
A6	SD 1:2	93.46 ± 2.35 %
A7	SD 1:5	98.35 ± 2.76 %

Table 05 : Preliminary evaluation of natural superdisintegrants

Parameters	Mucilage	Seed Powder	Husk Powder
Bulk Density (gm/cm^3)	0.96	0.50	1.17
Tapped Density (gm/Cm^3)	1.08	0.91	1.35
Hausners Ratio	1.083	1.14	1.11
Compressibility index (%)	6.58	15.37	14.66
Angle of Repose (°)	25.20	40.36	33.15

The IR spectra of SDs and PMs were compared with the standard spectrum of repaglinide. IR spectrum of repaglinide was characterized by the absorption of carbonyl (C-O) group at 1108.83cm^{-1}. In spectra of SDs and PMs, this band was shifted towards higher frequencies at 3005.14 and 2,825.87cm−1 respectively. Also the O-H group which is located at 3,103.54 cm−1 from the IR spectrum of repaglinide, N-H group at1599.09, C=C group at 3005.90, C-N group at 2825.87 It was concluded that there was no well defined chemical interaction between repaglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed.

FORMULATION OF REPAGLINIDE

Immediate Release Tablet

According to the formula given in table No. 8, repaglinide immediate relese tablet were formulated and before formulation precompression parameters were evaluated and given in table no. 6.

Table 06: Precompression parameters

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bulk density	0.360	0.370	0.310	0.310	0.32	0.330	0.320	0.350	0.370	0.350	0.330	0.320
Tapped Density	0.450	0.440	0.430	0.420	0.43	0.440	0.410	0.440	0.44	0.45	0.43	0.41
% Compressibility	15.36	15.07	21.64	20.15	20.85	20.47	16.64	16.56	17.35	18.13	18.81	I7.65
Hausners Ratio	1.185	1.11	1.25	1.23	1.24	1.21	1.20	1.43	1.17	1.26	1.36	1.26
Angle of Repose	21.26	20.14	24.38	24.45	23.27	23.17	20.37	20.09	21.15	21.29	25.36	24.19

Table -7: EVALUATION CHART OF TABLET

S.No	Parameter	Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Weight Variation Test	198.66 ±0.23	199.66 ±0.25	197.66 ±0.39	200.66 ±0.43	198.66 ±0.23	196.66 ±0.49	198.66 ±0.39	197.66 ±0.35	199.66 ±0.23	198.66 ±0.23	199.66 ±0.27	199.66 ±0.23
2	% Friability	0.26	0.20	0.21	0.30	0.28	0.20	0.23	0.21	0.24	0.32	0.25	0.23
3	Thickness (mm)	2.58± 0.01	2.59± 0.03	2.35± 0.05	2.30± 0.02	2.41± 0.05	2.42± 0.06	2.42± 0.02	2.48± 0.06	2.44± 0.04	2.43± 0.05	2.41± 0.04	2.35± 0.06
4	Hardness (Kg / cm^2)	2.06 ±0.10	2.06 ±0.09	2.84 ±0.41	3.17 ±0.15	2.91 ±0.18	2.95 ±0.14	2.74 ±0.14	2.79 ±0.31	2.84 ±0.36	2.90 ±0.37	2.91 ±0.39	2.96 ±0.40
5	Disintegration Time(sec)	23.36 ±2.6	21.05 ±1.5	27.39 ±2.5	23.69 ±2.8	25.63 ±2.4	26.05 ±3.5	22.00 ±2.8	22.05 ±2.5	28.05 ±2.6	26.63 ±3.7	34.68 ±2.9	34.69 ±2.5
6	Wetting time (sec)	50.69 ±1.6	47.69 ±1.9	63.04 ±2.9	66.339 ±2.9	63.36 ±2.6	57.63 ±2.6	54.36 ±1.6	52.69 ±2.7	52.05 ±2.6	53.36 ±2.9	65.39 ±2.5	63.06 ±2.6
7	Uniformity of Dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
8	W.A.Ratio (%)	65.46	65.36	73.85	74.07	66.07	67.35	65.34	65.39	66.15	66.93	74.19	73.69
9	Assay (%)	99.48	100.5	98.34	99.82	99.10	101.41	100.06	100.15	101.21	101.02	100.9	100.4

Table 8: Comparative dissolution study F 1 – F 12 .

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	78.45	78.72	79.82	80.37	81.47	84.75	82.58	80.37	83.23	84.76	83.85	83.81
10	80.92	81.45	82.02	82.30	84.50	86.69	85.05	82.15	86.17	86.70	86.05	87.17
15	84.76	84.50	85.03	85.85	86.14	89.15	87.24	85.46	88.55	89.19	89.24	88.65
20	89.15	90.00	90.52	91.90	90.10	93.25	90.53	89.11	92.70	93.29	91.55	92.60
25	93.82	94.37	94.91	94.35	94.15	97.39	95.73	94.15	96.05	96.40	95.75	96.15
30	97.92	99.50	98.75	98.23	98.05	98.87	99.35	99.65	98.41	97.50	98.35	98.99

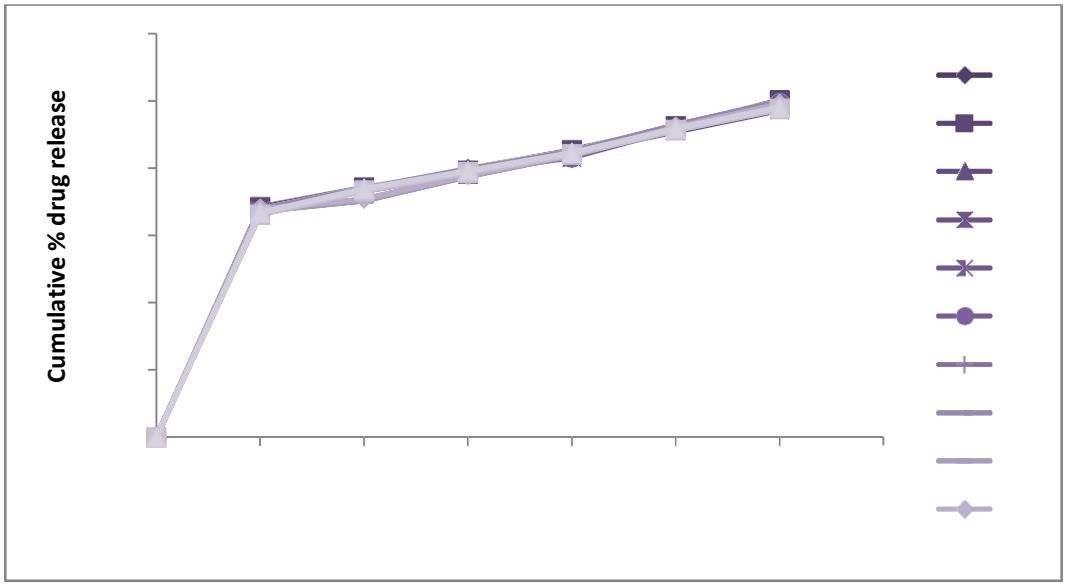

Fig.No. 11. Comparison of *In-vitro* dissolution profile of formulation F1-F12

SUMMARY

In the present study immediate release drug delivery system of repaglinide were successfully developed in the form of mouth dissolving tablets with improved dissolution characteristic by forming solid dispersion with PEG 6000, which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Immediate release tablets of repaglinide were prepared by using natural superintegrants like microcrystalline cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate and their combination as superdisintegrants.

Superdisintegrants work as an auxiliary or as a facilitator of the flowability and compressibility of the mixture and contribute to the immediate release of the tablet, due to its high solubility in water.

For the repaglinide formulation, batch No. 2 was chosen as it has disintegration time around 5-35 seconds and hardness3.5 Kg/Cm^2. IR spectra of drug with other excipients has not shown any interaction and also selected formulation was stable after stability studies.

CONCLUSION

The solubility and dissolution rate of repaglinide can be enhanced by formulating SDs of repaglinide with PEG 6000.The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wetability and dispersibility, and alteration of

the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of repaglinide from its SD and to some extent in PMs. No endothermic peak of repaglinide was present in of SDs with PEG 6000 suggesting the absence of crystalline repaglinide. From FTIR spectroscopy, it was concluded that there was no well defined chemical interaction between repaglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed.

The identical composition of Superdisintegrants showed that a substantial shorter time require for disintegration can be obtained and immediate release tablet were prepared. The repaglinide immediate release tablet (F2) showed 78.72% drug release within first 5 min. and 99.50% drug release with in 30 min.

The results showed that the formulation satisfied the objective of fast disintegration, dissolution, % friability, hardness, wetting time, water absorption ratio, ease of administration and safety.Success of the present study recommends a detailed investigation in to *in-vivo* studies for its effective use in clinical practice.

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Conflict of Interest

The authors declare that they have no conflict of interest