ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

ENHANCEMENT OF DISSOLUTION PROPERTIES, PREPARATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF POORLY SOLUBLE DRUG REPAGLINIDE

S.B.Bhanja[1*], P. Ellaiah[1],B.S.Nayak[1],D.K.Mahapatra[1],A.Sahu[1], S.K.Padhy[1]and B.B.Panigrahi [2]
[1]Department of Pharmaceutics, Jeypore College of Pharmacy, Jeypore (K), Odisha.
[2]Hi-tech College of Pharmacy, Bhubaneswar, Odisha.
E-mail: satyabrata_bhanja@rediffmail.com

Received on 30-06-2011 *Accepted on 14-07-2011*

Abstract

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 1:1M ratio 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 evaporation and 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 shown by 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

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and or poor membrane permeability of drug molecule.

The poor solubility and slow dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability especially for class-II substances according to BSC. The bioavailability may be enhanced by increasing solubility and dissolution rate of the drug in the gastro-intestinal fluid [(1)].

Diabetes mellitus is a group of syndrome characterized by hyperglycemia, altered metabolism of lipids, carbohydrates, proteins and an increased risk of complications from the vascular disease[(2)].

Repaglinide is a non-sulfonylurea oral hypoglycemic agent of the meglitinide class, is mainly used in the management of type II diabetes mellitus. Chemically it is **(**S)-2-ethoxy-4-{2-[3-methyl-1-[2-(1-piperidinyl) phenyl] butyl] amino]-2-oxoethyl} benzoic acid. It has short biological half-life of less than one hour and rapidly eliminated from body[(3-5)].Repaglinide is a BCS class II compound and the bioavailability of Repaglinide following oral administration is low (60%)[(6-8)]. BCS class II compounds are poorly soluble but highly permeable, and they exhibit bioavailability that is limited by dissolution rate. The dissolution rate of BCS class II drug substances may be accelerated by improvement of the wetting characteristics of the bulk powder[(9)].

Poloxamer 188 [α-Hydro-w-hydroxy poly(oxyethylene) poly(oxypropylene) poly-(oxyethylene) block copolymers] generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless with molecular weight of 7680–9510. Functionally it can be used as dispersing agent, emulsifying agent, solubilizing agent, tablet lubricant and wetting agent [(10)].

β-Cyclodextrin occur as white, practically odorless, fine amorphous powders, having a slightly sweet taste with a molecular weight of 1135. Functionally it can be used as solubilizing and stabilizing agent[(11)].

Various techniques for the improvement of the dissolution rate of poorly water soluble drugs include Micronization, inclusion complexes with β-Cyclodextrin, amorphous drug, and solid dispersions with

hydrophilic carriers [12]. The solvent evaporation, melt adsorption, fusion, spray drying, spray freezing, spray congealing and kneading methods are the techniques reported for the preparation of solid dispersions. There is report on improvement of solubility of Repaglinide using Cyclodextrin inclusion complex approach. The interaction in the solid state was investigated by Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (X-RD) analysis. Interaction in solution was studied by phase solubility analysis and dissolution experiments.

The main perspective of the present study aims at overcoming these problems by using the technique of solid dispersion and inclusion complex by using carriers like Polaxomer-188 and β-Cyclodextrin in a view to develop fast release formulation of Repaglinide and hence improve its dissolution characteristic. Preparation of inclusion complex as well as dispersion granules in this manner increases the effective surface area of the drug, potentially increasing its rate of dissolution. Further inclusion complex method was developed into a tablet dosage form for immediate release of drug.

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.

PREPARATION OF SOLID DISPERSIONS AND CYCLODEXTRIN INCLUSION COMPLEXES

Various carriers are used to make solid dispersions and inclusion complexs. In the present study Poloxamer 188 was used as a hydrophilic carrier in the preparation of solid dispersions and β-Cyclodextrin was used as a carrier for the preparation of inclusion complexes. These solid dispersions and inclusion complexes were prepared by using different methods *viz.* Physical Mixing, Solvent Evaporation and Kneading Method. These were used in different ratios with respect to plain drug.

Solvent evaporation method[13]

Solid dispersions and inclusion complexes of Repaglinide were prepared by dissolving carriers (Poloxamer 188 / β-Cyclodextrin) and Repaglinide at their corresponding ratio in common volatile solvent like

methanol using a glass mortar. They were mixed by slight pressure for 15 min. Then the solvent was allowed to evaporate in hot air oven at 45 ^{0}C for 2h. The dried mass were passed through 120 # mesh and stored in desiccators at room temperature until further use. The dispersions were made in different ratios with respect to drug and polymers as shown below in Table no. 01 and 02.

Kneading Method[14]

Repaglinide and carriers (Poloxamer 188 / β-Cyclodextrin) were weighed according to their corresponding ratio. Repaglinide and carriers were transferred to a mortar pestle. The mixture was reduced the size by continuous stirring with pestle. Water-methanol mixture (3:1) ratio was added to the above physical mixture and continuously stirred until the slurry mass was formed. Slurry mass was collected and dried in a hot air oven for 2 hrs at 50 °C, dried mass was collected and further dried in desiccators over silica gel for 24 hrs to remove all the excess residual solvents. The dried mass were collected and passed through 120 # mesh, and packed it in a closed container. The dispersions were made in different ratios with respect to drug and polymers as shown below in Table no. 01 and 02

Table 01: Formulation of solid dispersion with Poloxamer-188 as carrier.

Formulation code	Carrier	Drug: Carrier	Method
PM 1	Poloxamer 188	1:1	Physical mixing
SD 1	Poloxamer 188	1:1	Solvent Evaporation
SD 2	Poloxamer 188	1:3	Solvent Evaporation
SD 3	Poloxamer 188	1:5	Solvent Evaporation
SD 4	Poloxamer 188	1:7	Solvent Evaporation
SD 5	Poloxamer 188	1:1	Kneading
SD 6	Poloxamer 188	1:3	Kneading
SD 7	Poloxamer 188	1:5	Kneading
SD 8	Poloxamer 188	1:7	Kneading

Table 02: Formulation of inclusion complexes with β-Cyclodextrin as carrier.

Formulation code	Carrier	Drug: Carrier (Molar ratio)	Method
PM 2	β-Cyclodextrin	1:1	Physical mixing
IC 1	β-Cyclodextrin	1:1	Solvent Evaporation
IC 2	β-Cyclodextrin	1:3	Solvent Evaporation
IC 3	β-Cyclodextrin	1:5	Solvent Evaporation
IC 4	β-Cyclodextrin	1:7	Solvent Evaporation
IC 5	β-Cyclodextrin	1:1	Kneading
IC 6	β-Cyclodextrin	1:3	Kneading
IC 7	β-Cyclodextrin	1:5	Kneading
IC 8	β-Cyclodextrin	1:7	Kneading

Preparation of Physical Mixture[(15)]

Physical mixtures were prepared by homogeneous blending of Repaglinide with carriers (Poloxamer 188 / β-Cyclodextrin) at 1:1, ratio in a mortar and pestle for 10 minutes until a homogenous mixture was obtained and then it was passed through a 120 # mesh and stored in a desiccators at a room temperature until further use.

Solubility Study

A cleaned and dried graduated test tube of 10 ml was taken and 10 ml of 0.1 N HCl (pH1.2) was poured into it. Then small, unknown quantity of Repaglinide was added to it and dissolved properly by shaking with hand. The above procedure of addition of drug and then shaking was continued until the drug went into solution that means until a clear solution was obtained. At the moment when the drug was undissolved in the solution even after shaking with hand that means a supersaturated solution, the test tube containing the drug with solvent was subjected for shaking in a mechanical shaker for 12 hr. The above solution was then filtered, dilutions were

made and absorbance was noted in UV Spectrophotometer at 243 nm. Likewise, solubility was determined in at pH 6.8 and 7.4. The results are given in Table no. 03.

Table 03: Solubility values of Repaglinide in different pH rang.

pH	Solubility(mg/ml)
1.2	3.14
6.8	0.292
7.4	0.147

Phase Solubility Study

The phase-solubility technique permits the evaluation of the affinity between the carrier and drug in aqueous solution. Phase solubility studies were performed according to the method reported by Higuchi and Connors [16]. An excess amount of Repaglinide was taken into screw capped glass vials in which 25 ml of aqueous solution (pH 1.2) containing various concentration of carrier (2-14 %) was added. These flasks were sealed and shaken at 25°C for 48 hours. This amount of time is considered sufficient to reach equilibrium. Then the samples were filtered through a Whattman filter paper no.42. The filtrate was diluted and assayed for Repaglinide content spectrophotometrically (UV-10 Model, Thermo Fisher Scientific) at 243 nm. All solubility measurements were performed in triplicate.

The apparent stability constant (Ks) between drug-carrier combinations were computed from the phase solubility diagrams using the following equation:

$$Ks = \frac{\text{Slope}}{\text{Intercept (1-Slope)}}$$

The results are presented in Tables no. 04 & 05 and Figs 01 & 02**.**

Table 04: Phase solubility study of Repaglinide in Poloxamer 188

Concentration of Poloxamer 188 (% w/v)	Concentration of Repaglinide (mM/L)
2	0.18
4	0.392
6	0.461
8	0.589
10	0.721
12	0.853
14	0.934

Table 05: Phase solubility study of Repaglinide in β –Cyclodextrin

Concentration of β –Cyclodextrin (% w/v)	Concentration of Repaglinide (mM/L)
2	0.237
4	0.439
6	0.591
8	0.716
10	0.805
12	0.911
14	1.065

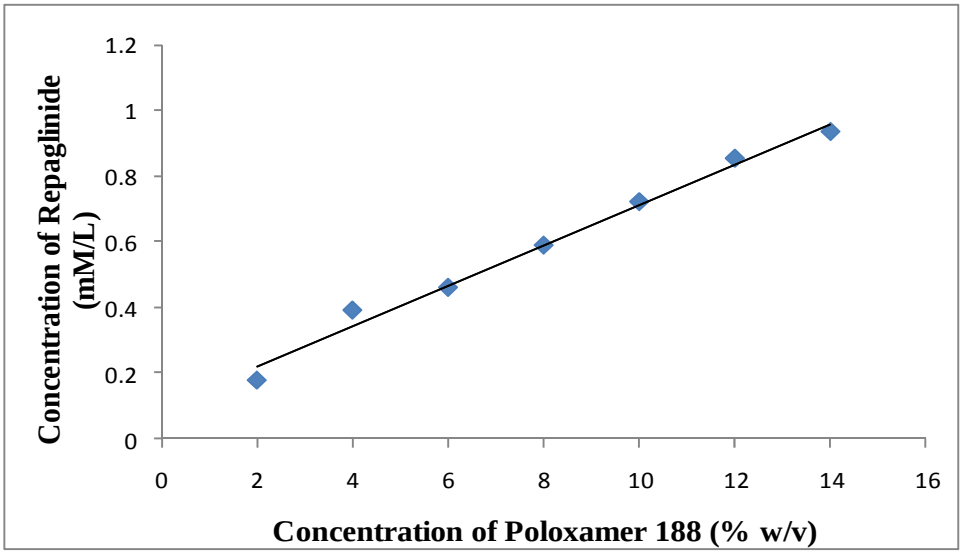

Figure 01: Phase solubility diagram of Repaglinide with Poloxamer 188.

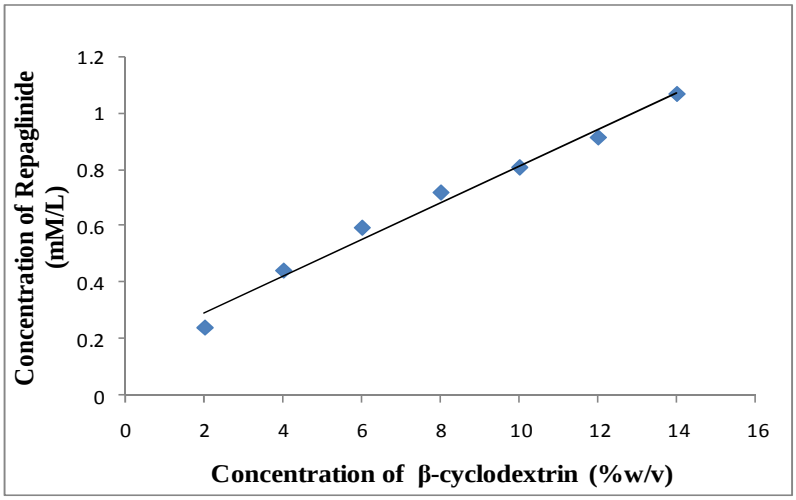

Figure 02: Phase solubility diagram of Repaglinide with β-Cyclodextrin.

Dissolution Studies [17]

Dissolution studies of pure Repaglinide as well as the solid dispersions and physical mixtures were performed using the dissolution apparatus II (USP) with the paddle rotating at 50 rpm in 900 ml of 0.1N HCl as dissolution medium at 37±0.5 ^{o}C. Powders equivalent to 5 mg of Repaglinide were used as samples for the dissolution test. At 5 min intervals, 5 ml of samples were withdrawn periodically and replaced with fresh dissolution medium and assayed for Repaglinide content by measuring the absorbance at 243 nm using UV-Visible spectrophotometer (UV-10 Model, Thermo Fisher Scientific). Dissolution studies were performed in triplicates (n=3).The results are shown in Table no. 07 to 10 and Fig no. 11 to 14.

Table 07: *In-Vitro* drug release profile of solid dispersions prepared by solvent evaporation method.

Time (min.)	Pure drug	Physical mixture (1:1)	Solid dispersion prepared by solvent evaporation method			
			1:1	1:3	1:5	1:7
0	0	0	0	0	0	0
10	14.54	31.32	56.28	58.31	59.71	59.5
20	17.83	36.4	63.7	68.12	70.68	68.9
30	23.59	42.24	68.3	69.9	74.3	72.14
40	28.69	48.38	71.08	74.18	81.4	76.07
50	32.59	53.89	76.6	79.3	85.5	79.93
60	36.76	60.7	80.75	83.5	89.2	84.5
70	43.07	66.74	84.4	86.6	92.87	86.7
80	47.2	72.21	87.7	90.3	96.06	92.9
90	51.02	74.35	90.9	96.18	99.12	97.39

Table 08: *In-Vitro* drug release profile of solid dispersion prepared by kneading method

Time (min.)	Pure drug	Physical mixture (1:1)	Solid dispersion prepared by kneading method			
			1:1	1:3	1:5	1:7

0	0	0	0	0	0	0
10	14.54	31.32	58.3	61.8	64.7	62.32
20	17.83	36.4	67.94	69.04	72.9	66.95
30	23.59	42.24	72.05	74.8	77.19	72.9
40	28.69	48.38	76.82	78.19	81.1	78.19
50	32.59	53.89	78.2	82.08	85.48	82.12
60	36.76	60.7	82.15	86.23	89.9	85.48
70	43.07	66.74	86.5	90.4	94.39	89.91
80	47.2	72.21	89.86	93.3	99.42	96.21
90	51.02	74.35	92.3	98.18	-	-

Table 09: *In-Vitro* drug release profile of ICs prepared by solvent evaporation method

Time (min.)	Pure drug	Physical mixture (1:1)	Inclusion complex prepared by solvent evaporation method			
			1:1	1:3	1:5	1:7
0	0	0	0	0	0	0
10	14.54	32.03	64.21	75.7	68.02	66.8
20	17.83	40.12	74.6	81.9	76.7	74.08
30	23.59	45.38	75.86	85.6	79.88	78.8
40	28.69	51.1	79.93	87.94	83.91	81.4

50	32.59	55.88	82.4	90.8	86.1	84.89
60	36.76	62.4	85.59	93.38	90.8	88.07
70	43.07	66.89	90.78	96.13	93.14	91.32
80	47.2	72.83	94.4	99.78	97.02	96.73
90	51.02	77.68	96.12	-	99.67	98.1

Table10: *In-Vitro* drug release profile of ICs prepared by kneading method.

Time (min.)	Pure Drug	Physical mixture (1:1)	Inclusion complex prepared by kneading method			
			1:1	1:3	1:5	1:7
0	0	0	0	0	0	0
10	14.54	32.03	70.14	79.84	74.4	72.2
20	17.83	40.12	79.3	84.7	82.07	79.14
30	23.59	45.38	79.91	87.4	83.1	80.89
40	28.69	51.1	82.11	89.59	85.19	83.1
50	32.59	55.88	84.02	93.4	88.16	86.29
60	36.76	62.4	86.91	96.7	90.7	88.48
70	43.07	66.89	92.3	99.86	94.5	92.14
80	47.2	72.83	95.14	-	98.91	97.58
90	51.02	77.68	98.28	-	-	-

FTIR spectroscopy:

The FTIR spectra of pure drug (Repaglinide), pure β-CD and the optimized formulation were taken by preparing KBr pellets using 8400S FTIR spectrophotometer (Shimadzu). The condition was used as follows: pressure, 6-8 tons; die size - 13mm; scanning range, 4000-500 cm^{-1}. It was carried out at CIPET, Bhubaneswar. The data are presented in the Figures 03 to 05.

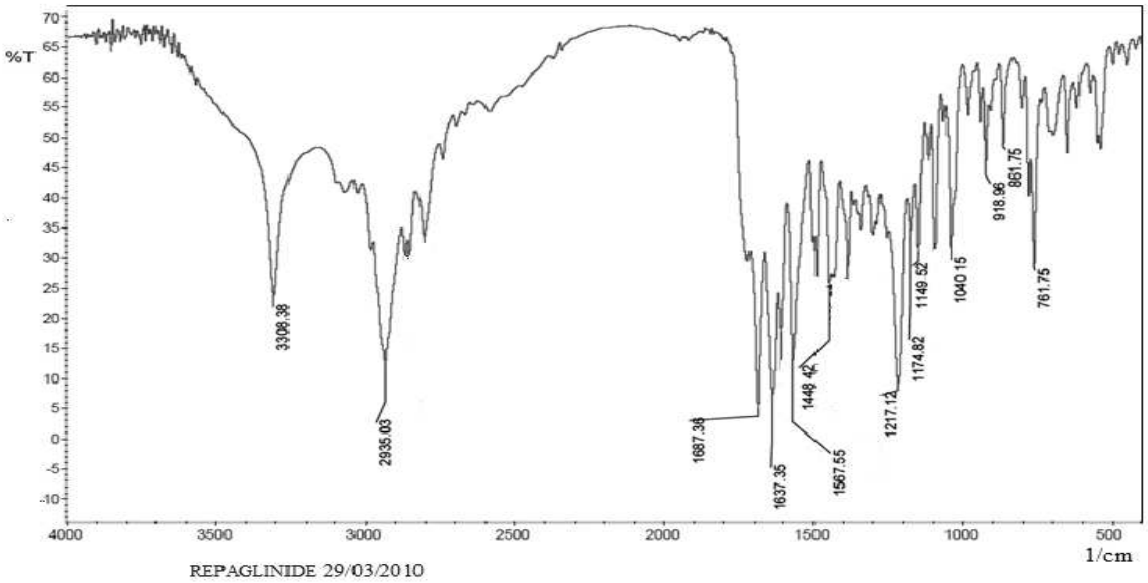

Figure 03: FTIR spectra Repaglinide.

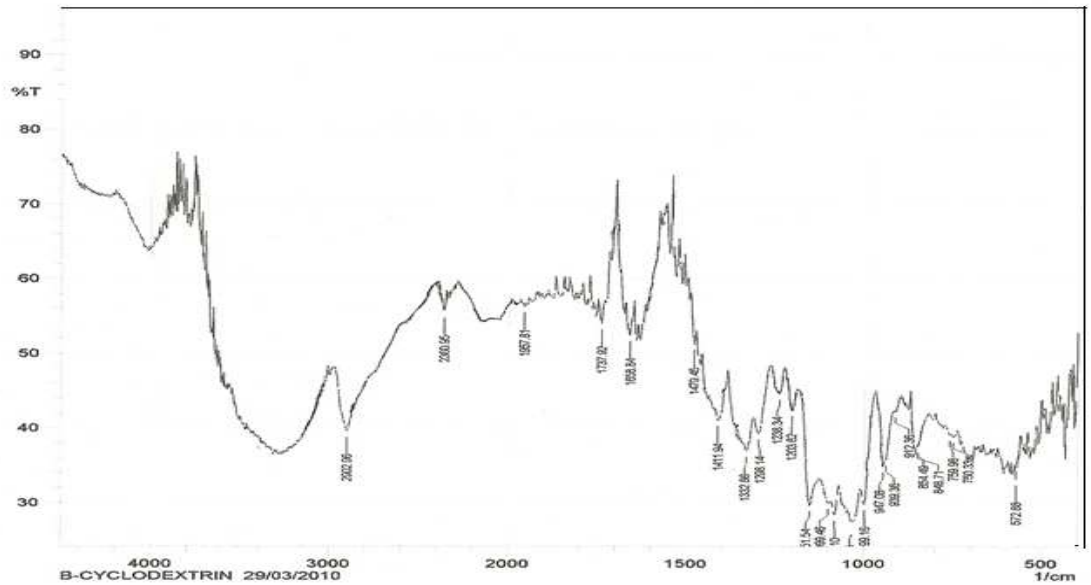

Figure 04: FTIR spectra β-Cyclodextrin

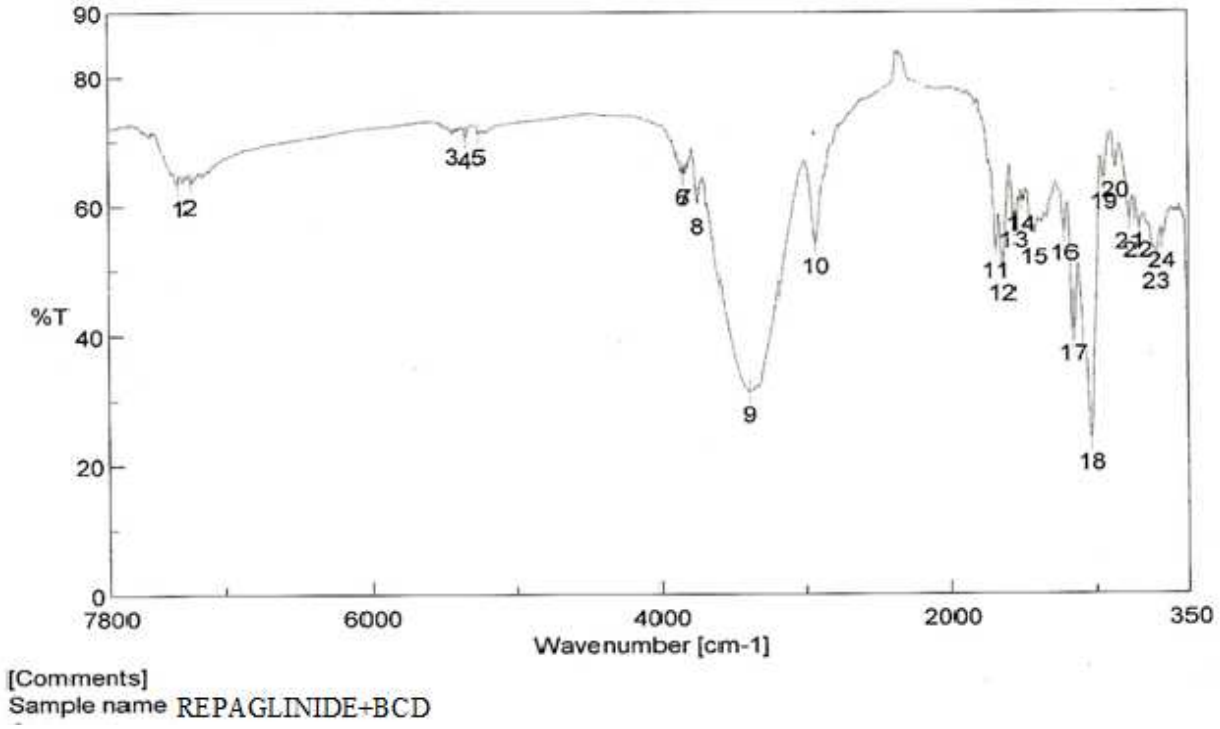

Figure05: FTIR spectra Repaglinide-β-Cyclodextrin inclusion complex (1:3) prepared by kneading method

X-ray powder diffractometry:

To determine the powder characteristics, X-ray powder diffraction studies of solid dispersions were performed. X-ray powder diffraction patterns were recorded at room temperature using PW 1710 X-Ray diffractometer (Philips, Holland) with Cu as anode material and graphite monochromator, operated at a voltage of 35 kV, and 20 mA current. The scanning rate employed was $2°min^{-1}$ over 10 to 30° diffraction angle (2θ) range. It was carried out at CIPET, Bhubaneswar. The data are presented in the Figures 06 to 10.

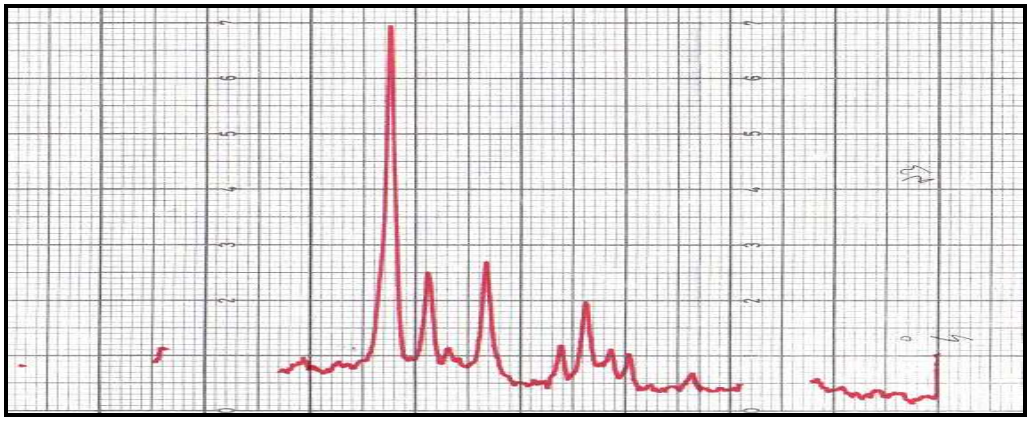

Figure 06: X-ray diffractogram of Repaglinide.

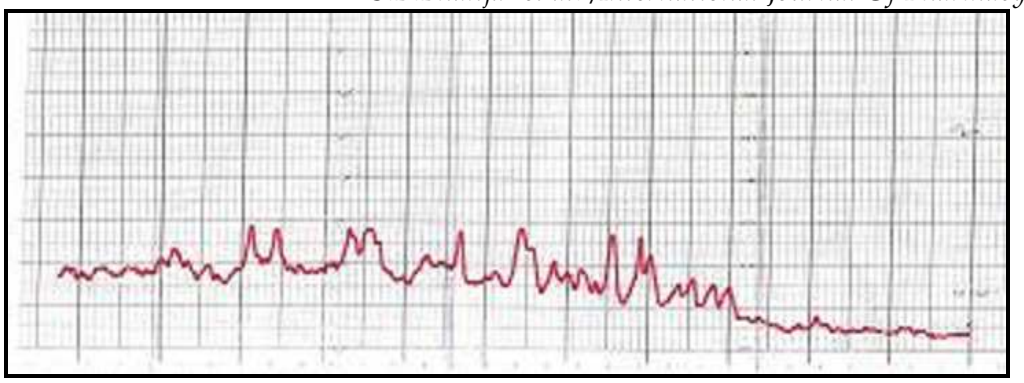

Figure 07: X-ray diffractogram of β-Cyclodextrin

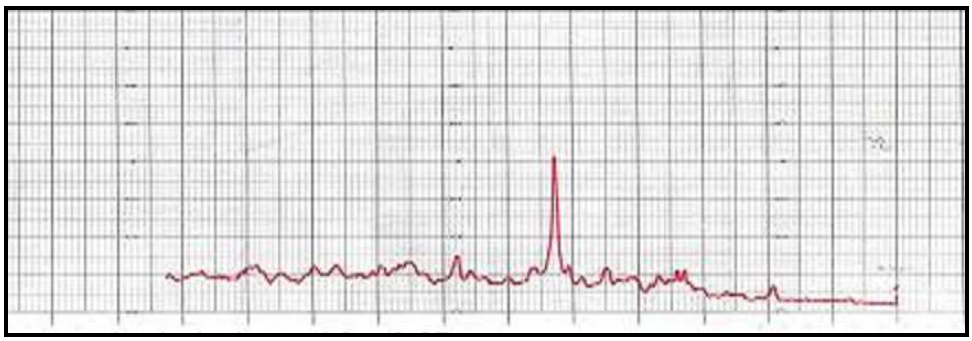

Figure 08: X-ray diffractogram of physical mixture (Repaglinide-β- cyclodextrin).

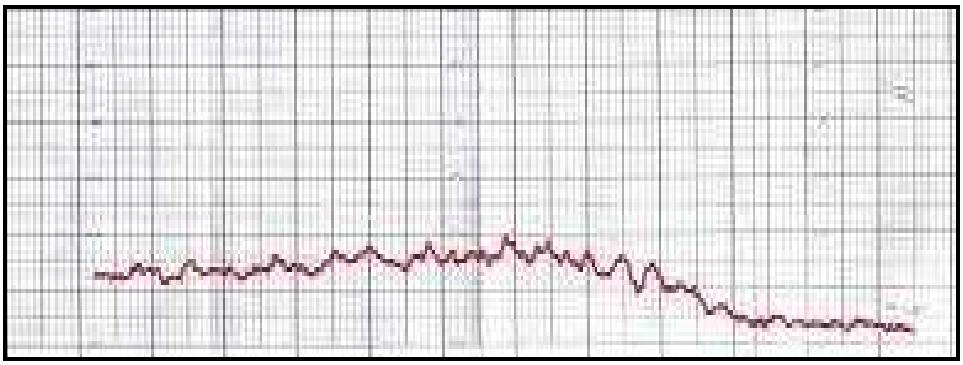

Figure 09: X-ray diffractogram of Repaglinide-β-Cyclodextrin inclusion complex by Solvent evaporation method.

Figure 10: X-ray diffractogram of Repaglinide-β-Cyclodextrin inclusion complex by Kneading method

Estimation of Drug Content [18,19]

About 5mg drug equivalent of solid dispersions, physical mixtures and inclusion complexes were weighed accurately and transferred into a volumetric flask (50 ml) containing few amount of methanol and the flask was shaken for 15 min and final volume was made up to the mark with using 0.1N HCl. The sample was filtered through Whattman filter paper and assayed for Repaglinide content spectrophotometrically (UV-10 Model, Thermo Fisher Scientific) at 243nm. Three replicates were prepared and the average drug contents were estimated in the prepared solid dispersions, inclusion complexes and physical mixtures. The results were presented in Table no. 06.

Actual drug content was calculated for all batches using the equation

$$\text{Drug Content (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Selection of most satisfactory formulation

From all the above formulations, inclusion complex of Repaglinide- β-Cyclodextrin (1:3) showing maximum *in-vitro* drug release. Hence this inclusion complex showing maximum dissolution rate was converted to cost effective tablet formulations.

Formulation and Preparation of Fast Dissolving Tablets

The fast dissolving tablet formulations were developed from Repaglinide β-Cyclodextrin Inclusion complex by using various super disintegrating agents. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have effect of dissolution characteristics as well.

Three different superdisintegrants, Croscarmellose sodium, Crosspovidone and Sodium Starch Glycolate were tried to achieve fast disintegration of tablets. The tablets prepared with different compositions and formulations are shown in Table no. 11.

Table 11: Formulation of fast dissolving tablets.

FORMULATION CODE / INGREDIENTS (In mg)	F 1	F 2	F 3	F 4	F 5	F 6
Solid dispersion equivalent to 4 mg of Repaglinide	16.03	16.03	16.03	16.03	16.03	16.03
Crosscarmelose Sodium	4	8	-	-	-	-
Crosspovidone	-	-	4	8	-	-
Sodium Starch Glycolate	-	-	-	-	4	8
Manitol	25	21	25	21	25	21
Avicel PH 101	80	80	80	80	80	80
Magnesium Stearate	2.97	2.97	2.97	2.97	2.97	2.97
Talc	2	2	2	2	2	2
Total	130	130	130	130	130	130

Inclusion complex (1:3) containing 4 mg equivalent of Repaglinide and excipients were mixed homogeneously (quantities shown in Table-11) in a glass mortar. The mixture was then compressed using an 8 mm, biconcave punch in a single-stroke using 8-station rotary machine (The Rimek Mini Press-1).

Evaluation of Tablets

The parameters viz. weight variation, thickness, hardness, friability, drug content and tablet disintegration were evaluated as per I.P. specifications[20,21]. The results are shown in Table no 12.

Table 12: Evaluation of direct compressible fast dissolving tablets

Formulation Code	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (%)	Drug Content (%)	Disintegration Time (sec.)
F1	3.5	0.38	129 ±0.41	98.13	35±2.0
F2	3.0	0.40	128±0.44	98.96	41±4.0
F3	3.0	0.36	130±0.40	98.55	31±1.0
F4	3.0	0.31	129±0.51	99.4	27±.2.0

F5	3.5	0.43	127 ±0.49	95.23	39±4.0
F6	3.5	0.47	129±0.43	96.05	46±5.0

In-vitro Dissolution Studies [22,23]

In- vitro release studies were carried out using tablet USP XX Apparatus II (paddle) dissolution test apparatus at the rotation speed of 100 rpm in 900 ml 0.1 N HCl as dissolution medium at 37±0.5°C . Dissolution studies were performed in triplicate (n=3) and calculated mean values of cumulative drug release were used while plotting the release curves**.** The results are shown in table no. 13 and fig no 14.

Table 13: Cumulative % amount of drug released from the formulations

Time (min.)	% Cumulative drug release					
	F1	*F2*	*F3*	*F4*	*F5*	*F6*
0	0	0	0	0	0	0
5	44.3	52.1	50.5	54.87	35.3	40.9
10	64.12	67.3	71.5	74.06	42.6	51.89
15	72.29	77.52	80.09	86.7	59.4	64.96
20	83.7	89.2	87.37	93.8	72.13	81.89
25	89.4	93.78	94.2	99.46	86.53	88.54
30	96.79	97.68	98.68		94.27	95.49

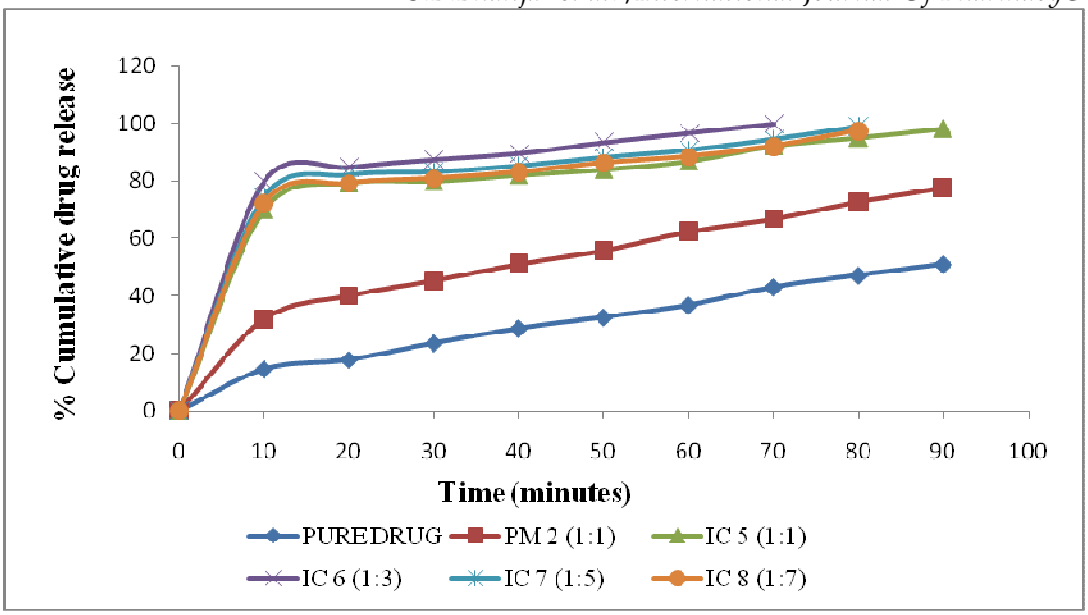

Figure 14: *In Vitro* drug release profile of ICs prepared by kneading method

Drug release kinetics [24,25]

To examine the release mechanism of Repaglinide from the prepared fast dissolving tablets, the results were analyzed according to the following equation.

$$\frac{M_t}{M_\infty} = k.t^n$$

Where M_t / M_∞ is the fractional drug released at time *t*, *k* is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system [device], and *n* is the diffusional exponent that characterizes the mechanism of drug release. It is known that for non-swelling tablets, drug release can generally be expressed by the Fickian diffusion mechanism, for which n = 0.5, whereas for most erodible matrices, a zero-order release rate kinetics is followed, for which n = 1. For non-Fickian release, the n value falls between 0.5 and 1.0 [0.5 < n < 1.0]; whereas in the case of super case II transport, n > 1.

Data of the in-vitro release was fit into different equations and kinetic models to explain the release kinetics of Repaglinide fast dissolving tablets. The kinetic models used were zero-order equation (eq. 1), first-order equation (eq. 2), matrix equation (eq. 3), Korsemeyer-Peppas equation (eq. 5), and Hixon-Crowell equation (eq. 4).

$Q_t = K_0 t$ ---------- (1)

$Q_t = Q_0 (1- e^{-k1}t)$ -------- (2)

$Q_t = K_H.t^{1/2}$ ---------- (3)

$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$ ----- (4)

$Q_t / Q_\infty = K_k\, t^n$ ---------- (5)

Where,

Q_t -------- Is the amount of drug release in time t

Q_0 -------- Is the initial amount of the drug

F --------- Is the fraction of drug release in time t

n --------- Exponent value

And K_0, K_1, K_H, K_{HC}, and K_k are release rate constants for Zero-order, First-order, Higuchi, Hixon-Crowell, and Korsemeyer-Peppas model respectively. Zero order represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs. First order is applicable to study of hydrolysis Kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. Matrix (Higuchi Matrix) is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water-soluble drug.

Hixson-Crowell Equation applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. Korsemeyer-Peppas Equation is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved. Data of the in-vitro release was fit into different equations and kinetic models to explain the release kinetics of Repaglinide fast dissolving tablets. The data are presented in Table 14.

Table 14: Drug Release Kinetic Studies from different formulations

Formulations	R^2 Values			n- value
	Zero order	First order	Korsemeyer- Peppas	
F1	0.858	0.956	0.991	0.427
F2	0.815	0.980	0.994	0.360
F3	0.803	0.947	0.981	0.366
F4	0.820	0.983	0.988	0.371
F5	0.933	0.958	0.963	0.432
F6	0.916	0.964	0.981	0.476

Results and Discussions

Solubility determination.

The solubility of pure Repaglinide at pH 1.2, 6.8 and 7.4 was found to be 3.14, 0.292 and 0.147 mg/ml respectively. The study shows that solubility of Repaglinide decreases as pH increases. The maximum solubility was observed at pH 1.2. The results are shown in table no: 03.

Phase Solubility.

Phase solubility experiments showed that the concentration of Repaglinide in 0.1N HCl (pH 1.2) is notably affected by the presence carriers. The phase-solubility diagram showed a linear increase in solubility of Repaglinide with an increase in concentrations of carriers. All the phase solubility diagrams were classified as type A_L according to Higuchi and Connors because the straight line had a slope less than unity in each case. So it indicates the formation of complex. The apparent stability constant (*K*s) was estimated from the slope of the straight line of the phase-solubility diagram using the equation. The stability constant, *K*s were found to be 662

M^{-1} in case of Poloxamer 188 and 434 M^{-1} in case of β-cyclodextrins, which are within the range (200-5000m^{-1}). This indicates that complexes are quite stable. The data are presented in Tables no-04 & 05 and Figs no 01 & 02.

These results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poor water soluble drugs.

Drug content uniformity study.

The solid dispersions, inclusion complexes and physical mixtures were subjected for evaluation of drug content and the data are presented in Table 06.

Table 06: Percentage of drug content.

FORMULATIONS	DRUG CONTENT (%)
PM 1 (1:1)	100.21
SD 1 (1:1)	98.96
SD 2 (1:3)	98.55
SD 3 (1:5)	99.38
SD 4 (1:7)	97.30
SD 5 (1:1)	98.13
SD 6 (1:3)	96.89
SD 7 (1:5)	98.54
SD 8 (1:7)	97.30
PM 2 (1:1)	99.79
IC 1 (1:1)	97.3
IC 2 (1:3)	99.8
IC 3 (1:5)	98.13
IC 4 (1:7)	98.96
IC 5 (1:1)	96.9
IC 6 (1:3)	98.55
IC 7 (1:5)	99.37
IC 8 (1:7)	97.71

From the data it was observed that assayed drug content in the formulated solid dispersions, inclusion complexes and physical mixtures were found to be within the range of 96.89% to 100.21% which indicates that the drug is uniformly dispersed in the powder formulation.

FTIR spectroscopy study.

The FTIR spectra of pure Repaglinide showed characteristics peaks at 1687.36 cm^{-1} which indicates **C=O** stretching vibration. 2935.03 cm^{-1} indicates that **C–H** group is present, 3308.38 cm^{-1} indicates **N-H** bond is present, 1217.12 cm^{-1} indicates **--CH_3** group is present.

X-Ray diffractometry study.

X-RD patterns of pure Repaglinide, β-Cyclodextrin, physical mixture and inclusion complexes (1:3) prepared by solvent evaporation and kneading method. The results are shown in Figure 8.9 to 8.13. The peaks of Repaglinide molecule observed at 0.5, 0.6, 0.7, 2.0, 2.5, 2.7, 6.9°**.** However, the X-RD patterns of the inclusion complexes with β-Cyclodextrins were found to be diffused and different from that of pure Repaglinide, confirming formation of new solid phase. The peaks of Repaglinide molecule are not seen in the physical mixture and inclusion complexes. The X-RD pattern of kneaded and solvent evaporation complex is totally diffused; indicating the formation of complex has an amorphous nature. Inclusion complexes prepared by solvent evaporation method shows peaks near about 2° and complexes prepared by kneading method shows peaks below 1.5°.

***In- vitro* Dissolution studies.**

Dissolution testing of each of the complex was carried out to observe the release pattern of the drug from the complex. The dissolution studies were carried out using the dissolution apparatus II (USP) with the paddle rotating at 50 rpm in 900 ml of 0.1N HCl as dissolution medium at 37±0.5^o. Dissolution profile of pure drug, SDs, and PMs were determined. The cumulative percentages of drug release were shown in Tables no 07 and 08 and Figs no 11 and 12 for both solvent evaporation and kneading method respectively.

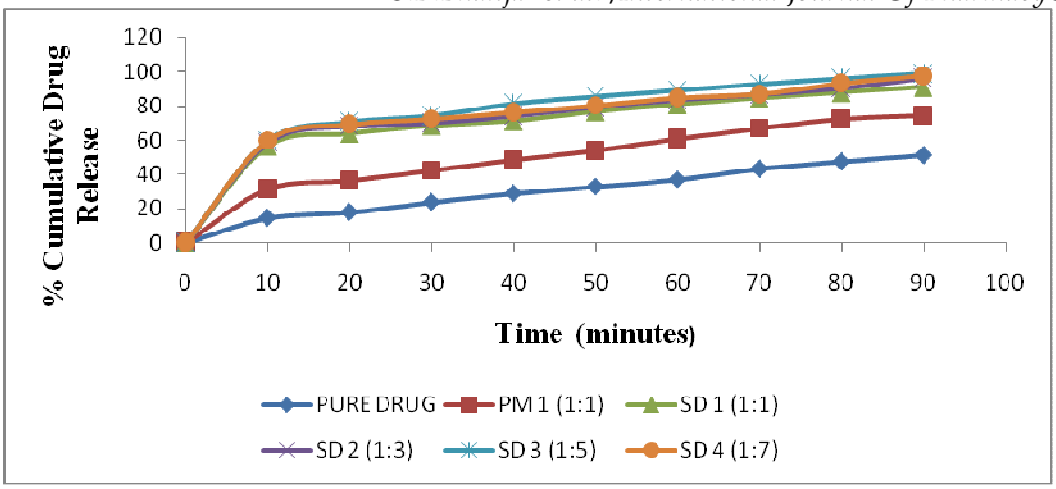

Figure 11: *In Vitro* drug release profile of SDs prepared by solvent evaporation method

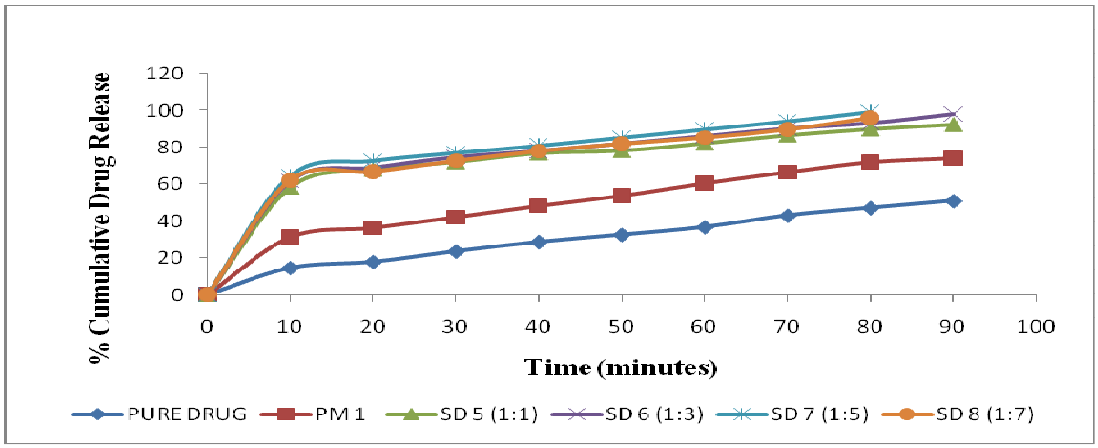

Figure 12: *In Vitro* drug release profile of SDs prepared by kneading method

The average percentage of drug release of pure Repaglinide was found to be 51.02% in 90 minutes. The solid dispersion formulation prepared by solvent evaporation method using Poloxamer 188 as carrier in the ratio of 1:1, 1:3, 1:5 and 1:7 were showed 90.9%, 96.18%, 99.12% and 97.39% drug release respectively in 90 minutes. In case of physical mixture (1:1) the percentage of drug release was found to be 74.35% in 90 minutes.

The increased dissolution rate may be due to the higher solubility of Poloxamer 188 in dissolution medium and better wettability of Repaglinide in formulation. On further increasing the amount of Poloxamer 188 (1:7), the dissolution rate slightly decreased that may be due to the higher amount of carrier itself takes time to dissolution.

The average percentage of drug release of pure Repaglinide was found to be 51.02% in 90 minutes. The solid dispersion formulations prepared by kneading method using Poloxamer 188 as carrier in the ratio of 1:1

and 1:3 were showed 92.3% and 98.18% drug release respectively in 90 minutes, whereas the formulation at ratio 1:5 and 1:7 showed 99.42% and 96.21% of drug release respectively at the end of 80 minutes. The increased dissolution rate may be due to the higher solubility of Poloxamer 188 in dissolution medium and better wettability of Repaglinide in formulation.

On further increasing the amount of Poloxamer 188 (1:7), the dissolution rate slightly decreased that may be due to the higher amount of carrier itself takes time to dissolution.

From the above studies, It was observed that after 10 minutes only 14.54 % of Pure drug was dissolved and even after 90 minutes only 51.02 % of drug goes into solution where as in case of Repaglinide-Poloxamer 188 prepared by kneading method at ratio of 1:5 showed 64.7 % drug release within 10 minutes and almost 99.42 % was released after 90 minute. Physical mixture of Poloxamer 188 (1:1) also improves the dissolution profile of Repaglinide due to its hydrophilic nature but not such an extent as prepared by Kneading method and Solvent evaporation method. The dissolution rate of Repaglinide was strongly dependant on the relative concentration of the drug to Poloxamer 188 ratio. The dissolution rate of Repaglinide from Poloxamer 188 solid dispersions was increased with increase in Poloxamer 188 in solid dispersion up to drug: carrier ratio 1:5. The further increase in amount of Poloxamer 188 in solid dispersion decreased the dissolution rate. The decreased in dissolution rate of the solid dispersions containing higher polymer proportions might be caused by leaching out of the carrier during dissolution which could form a concentrated layer of solution around the drug particles there by reducing the migration of the released drug particles to the bulk of the solution.

Similarly dissolution profile of pure drug, ICs, and PMs were determined. The cumulative percentage of drug released was shown in Tables no 09 and 10 and Figs no 13 and14 for both solvent evaporation and kneading method respectively.

The average percentage of drug release of pure Repaglinide was found to be 51.02% in 90 minutes. In case of physical mixture (1:1) the percentage of drug release was found to be 77.68% in 90 minutes. The inclusion complex formulation prepared by solvent evaporation method using β-Cyclodextrins as carrier in the ratio of 1:1, 1:5 and 1:7 were showed 96.12%, 99.67%, and 98.1% drug release respectively in 90 minutes, whereas the formulation at the ratio of 1:3 showed 99.78% of drug release within 80 minutes. The increased

dissolution rate may be due to the higher solubility of β-Cyclodextrin in dissolution medium and better wettability of Repaglinide in formulation.

On further increasing the amount of β-Cyclodextrins i.e. formulations at 1:5 and 1:7 ratio showed slightly decrease in dissolution rate, that may be due to the higher amount of carrier itself takes time to dissolution.

The average percentage release of pure Repaglinide was found to be 51.02% in 90 minutes. The inclusion complex formulations prepared by kneading method using β-Cyclodextrin as carrier in the ratio of 1:1 was showed 98.28% drug release in 90 minutes. Where as the formulation in the ratio of 1:3 showed 99.86% of drug release within 70 minutes, but in the ratio of 1:5 and 1:7 showed 98.91% and 97.58% drug release in 80 minutes. The increased dissolution rate may be due to the higher solubility of β-Cyclodextrin in dissolution medium and better wettability of Repaglinide in formulation.

On further increasing the amount of β-Cyclodextrin i.e. formulations at 1:5 and 1:7 ratio showed slightly decrease in dissolution rate, that may be due to the higher amount of carrier itself takes time to dissolution.

From the above studies, It was observed that after 10 minutes only 14.54 % of pure drug was dissolved and even after 90 minutes only 51.02 % of drug goes into solution where as in case of Repaglinide- ß -Cyclodextrins complex prepared by Kneading method at 1:3 molar ratio showed 79.84 % drug release within 10 minutes and almost complete release i.e. 99.86 % drug release at the end of 70 minute. In the case of the physical mixtures, the rise in solubility when compared to pure Repaglinide is due to the rapid formation of inclusion complexes in the dissolution medium or to the wetting effect of ß-Cyclodextrin.

Incidentally, ß-Cyclodextrin has surfactant-like properties owing to the hydrophilicity of its exterior surface which can lower the interfacial tension between poorly soluble drugs and the dissolution medium, resulting in higher dissolution as compared other formulations.

Hence it can be said that inclusion complexes (1:3) shows higher dissolution than pure drug, solid dispersions and physical mixtures.

Solid inclusion complex of Repaglinide- ß-CD (1:3) showed higher dissolution than the Repaglinide-Poloxamer 188 solid dispersions. So, this inclusion complex showed maximum percentage of drug release was considered for the formulation of fast dissolving tablets Repaglinide for immediate drug release.

Evaluation of Tablets.

The prepared fast dissolving tablets of Repaglinide were tested for weight variation, hardness, friability, drug content uniformity, disintegration time and *in- vitro* dissolution study as per standard procedure. The results were shown in Table no 12.

The maximum and minimum average hardness of tablets were found to be 3.5 and 3.0 kg/cm^2 respectively. Hence all the formulations comply with hardness test.

The maximum and minimum average friability of fast dissolving Repaglinide tablets were found to be 0.47% and 0.31% respectively. None of the formulations showed deviation (I.P. limit ≤1%) for any of tablets tested.

The maximum and minimum average weights of fast dissolving Repaglinide tablets were found to be 130±0.40 mg and 127± 0.49 mg respectively. None of the formulations showed deviation (I.P. limit ±10) for any of the tablets tested.

The maximum and minimum percentages of drug content from all the formulations were found to be 99.4% and 95.23% which are within acceptable range.

The results of disintegration test of all the formulations (F1 to F6) revealed that faster disintegration time was found within 27±2.0 seconds and larger disintegration time was found within 46± 5.0 seconds. The order was found to be Crosspovidone < Croscarmellose sodium < Sodium Starch Glycolate.

So, from the above study of all the formulations F1to F6, it was observed that the formulation, F4 was suitable for the all evaluation parameters.

***In- vitro* Dissolution study of directly compressible fast dissolving tablets:**

Dissolution study of each of the complex was carried out to observe the release pattern of the drug from the complex. Dissolution of drug was also carried out to compare with release pattern of the drug with the complex. The dissolution studies were carried out in 0.1N HCl, to simulate the gastric pH conditions. The results are presented in Table no 13 and Figure no 15.

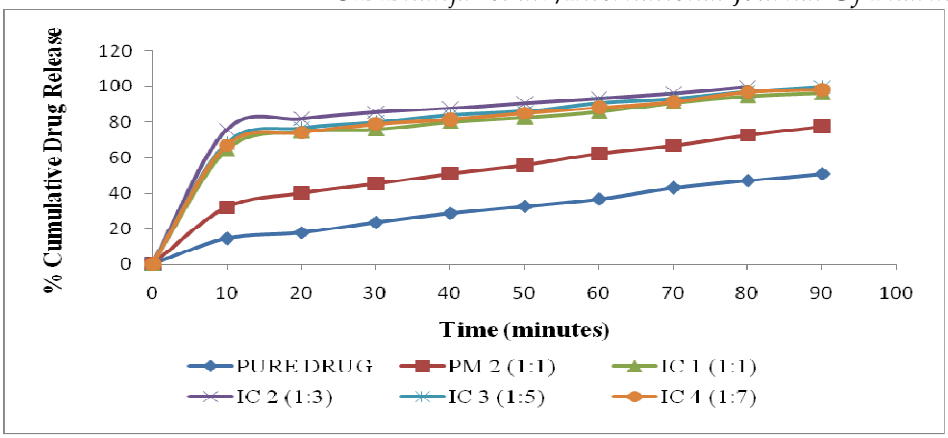

Figure 13: *In Vitro* drug release profile of ICs prepared by solvent evaporation method

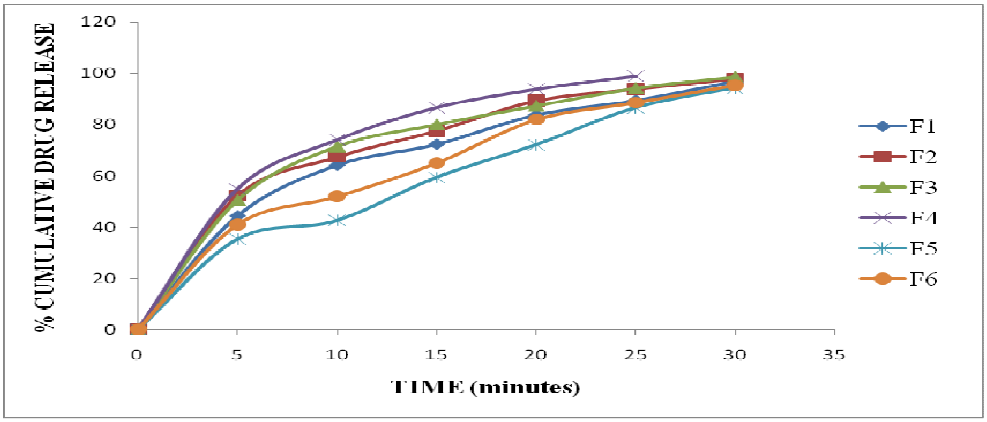

Figure 15: Cumulative % amount of drug released from the formulations F1 to F6

Formulations F1 and F2 containing 3.07% and 6.14% of Croscarmellose sodium showed 44.3 % and 52.1 % of drug release at the end of 5 minutes and 96.79 % and 97.68 % drug release at the end of 30 minutes respectively. In the above two formulations, formulation F2 showed maximum percentage of drug release than the formulation F1. This is due to higher percentage of Croscarmellose sodium in the formulation F2, which hydrates quickly and releases the drug.

However formulations F3 and F4 containing 3.07% and 6.14% Crosspovidone showed 50.5 % and 54.87% at the end of 5 minutes. The formulation F3 showed 98.68% at the end of 30 minutes, whereas the formulation F4 showed almost complete drug release i.e. 99.46 % at the end of 25 minutes which was faster than other formulations. This is due to increase in percentage of Crosspovidone because Crosspovidone quickly wicks water and readily get hydrated which caused sudden release of drug.

Formulations F5 and F6 containing 3.07% and 6.14% of Sodium Starch Glycolate showed 35.3 % and 40.9% of drug release at the end of 5 minutes and 94.27 % and 95.49 % drug release at the end of 30 minutes respectively which was lowest than other formulations. Since Sodium Starch Glycolate swells with more gelling than Croscarmellose sodium and Crosspovidone which extend dissolution time as a result of which the dissolution time was found to decrease as the concentration of Sodium Starch Glycolate in the formulations increased.

From the overall data of the *in-vitro* dissolution studies among all formulations, F1 to F6, formulation F4 showed the maximum percentage of drug release i.e. 99.46% at the end of 25 minutes.

From the above studies it was observed that as the concentration of superdisintegrants increased the drug release also increased. With reference to the type of superdisintegrants, the release rate was found to following in the order: Crosspovidone > Croscarmellose sodium > Sodium Starch Glycolate.

Drug release kinetic studies from different formulations.

In- vitro drug release data for all the formulations, F1 to F6 were subjected to release kinetic study according to zero order, first order equation and Korsemeyer-Peppas models to ascertain the mechanism of drug release. The R^2 and n values were given in Table no14.

Among the zero order and first order equations the value of regression correlation coefficient (R^2) were found to be higher in first order equation. Hence the drug release from all the formulations followed first order release kinetics. In case of Korsemeyer- Peppas model, the results indicated that release exponent 'n' values are less than 0.5 ($n < 0.5$). This indicates that Fickian type diffusion is the predetermining mechanism of drug release.

So, overall data showed that all the formulations followed first order release kinetics with Fickian diffusion mechanism.

Conclusion

The phase solubility study indicated that the aqueous solubility of drug was increased linearly as a function of the concentration of poloxamer 188 and ß-CD. The apparent stability constants Ks were 662 M^{-1} and 434 M^{-1} which were within the range (200-5000 M^{-1}) indicating that the complexes are quite stable. The inclusion complexes of Repaglinide (1:3M ratio) prepared by kneading method exhibited significantly higher dissolution

in comparison with pure drug, solid dispersions and physical mixtures. Hence Repaglinide-ß-Cyclodextrin (1:3) binary systems along with use of superdisintegrants could be considered for formulation of fast dissolving tablets Repaglinide. The formulation F4 showed the maximum percentage of drug release i.e. 99.46% at the end of 25 minutes.The characterizations of fast dissolving tablets of Repaglinide formulation (F4) that containing Crospovidone (6.14%) is considered as most acceptable. The release kinetics of all formulations was fitted to different kinetic model from the above studies it was observed that all the formulations followed first order kinetics.

Acknowledgements

Authors wish to give thanks to Jeypore College of Pharmacy, Jeypore, Odisha and authority for providing suitable research laboratory to carry out this project work and also my deep greatness to M/S. Torrent Pvt. Ltd., Mumbai for providing repaglinide as a gift sample.

References

1. Dhirendra K, Lewis S, Udupa N, Atin K. Solid Dispersions, A Review. Pak J Pharm Sci. 2009,vol 22(2),pp234-246.
2. *Reynolds JEF, Martindale: The Extra Pharmacopoeia, 30th ed. The Pharmaceutical Press,London,1993.*
3. *The Merck Index, In: An Encyclopedia of Chemicals, Drugs and Biologicals, Published by- Merck Research Laborateries Division of Year NJ-2001 Merck & Co.,Inc:Article no-8297,*
4. *Wilson and Gisvolds, Textbook of organic medicinal and pharmaceutical chemistry,10thedition,1998, pp: 209.*
5. *Kathleen P., Martindale. The Complete drug reference. Thirty-third edition, Pharmaceutical press, 2002.*
6. Culy C, Jarvis B. Repaglinide, a review of its therapeutic use in Type 2 diabetes mellitus. Drugs, 2001,vol61,pp1625-1660.
7. Malaisse W. Repaglinide, a new oral antidiabetic agent: a review of recent preclinical studies, Eur J Clin Invest. 1999,vol29,pp21-29.
8. Wang FEI. Focus on Repaglinide: an oral hypoglycemic agent with a more rapid onset and shorter duration of action than the sulfonylureas. Formulary, 1998,vol33,pp25-30..

9. Amidon GL. A theoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res. 1995,vol12,pp413-420.
10. *Raymond CR, Paul JS, Sion CO. In: Hand book of pharmaceutical excipients, 5th Edition, Pharmaceutical press,Great Britain, 2006.*
11. *Raymond CR, Paul JS, Sion CO. In: Hand book of pharmaceutical excipients, 5th Edition, Pharmaceutical press, Great Britain,2006.*
12. Gopal VS, Averiseni RK, Yogendra NU, Udupa N. Enhanced Dissolution and Bioavailability of Gliclazide using Solid Dispersion Techniques. Int J Drug Delivery 2010,vol2,pp49-57.
13. Prasanthe NL, RamaRao N, Manikiran SS. Studies on Dissolution Enhancement of Poorly Water Soluble Drug using water soluble carrier. Asian J Pharm Clin Research. 2010,vol3(2),pp95-97
14. Najmuddin M, Tousif K, Mohsin A A, Shelar S, Patel V. Enhancement of dissolution rate of Ketoconazole by Solid Dispersion Technique, Int J Pharmacy Pharm Sci. 2010,vol2(3),pp132-136.
15. Gupta S, Srivastav S, Vajpai M. Comparative study of solubility enhancement of poorly soluble drug by Solid Dispersion and Inclusion Complex. J. Pharm Res. 2010,vol3(4),pp692-696.
16. Higuchi T, Connors K, Phase solubility techniques, Adv. Anal. Chem. Instrum. 1965,vol4,pp117-123.
17. Venkatesh K, Arunkumar N, Verma PRP, Rani C. Preparation and in-vitro characterization of Valsartan Solid Dispersion using Skimmed Milk Powder as Carrier. Ind J Pharm Tech Res. 2009,vol1(3),pp431-437.
18. Heo MY, Piao Z, Kim TW, Cao QR, Kim A, Lee BJ. Effect of Solubilizing and Microemulsifying Excipients in Polyethylene Glycol 6000 Solid Dispersion on Enhanced Dissolution and Bioavailability of Ketoconazole, Arch Pharm Res, 2005,vol28,pp604-611.
19. Sapkal NP, Kilor VA, Bhusari KP, Daud AS, Evaluation of some Methods for Preparing Gliclazide- ß-Cyclodextrin Inclusion Complexes, Tropical J. Pharm. Res., 2007,vol 6, pp833-840.
20. *Lachman L, Lieberman A, Kinig JL, The Theory and Practice of Industrial Pharmacy, 4th ed. Varghese Publishing House: Bombay; 1991*.
21. Shashikant DB, Gaurav AS, Sharma AS, Prashant DN. Formulation of Fast Dissolving Tablets of Meloxicam. J Pharm Res. 2009,vol2(4),pp646-650.
22. *United State Phamacopeia Convention, NF Ashian edition, 2004.*

23. Chaulang G, Patil K, Ghodke D, Khan S, Pramod Y. Preparation and Characterization of Solid Dispersion Tablets of Furosemide with Crosspovidone. Res J Pharm Tech. 2008, vol1(4),pp386-389.

24. Gibaldi M, Feldman S, Preparation *in- vitro* evaluation of controlled release doses form of indomethacine., J Pharm Sci. 1967,vol56**,**pp1268.

25. Korsmeyer RW, Gurny R, Doelker EM, Bury P., Peppas NA., Factor influencing drug dissolution characteristics from hydrophilic polymer matrix tablets., Int J Pharm. 1983,vol15,pp25.

Corresponding author
Satyabrata Bhanja*
Email: *satyabrata_bhanja@rediffmail.com*