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DEVELOPMENT OF ORAL CONTROLLED RELEASE TABLET WITH SOLUBILITY ENHANCEMENT OF REPAGLINIDE

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ABSTRACT

The present study was carried out to develop oral controlled release tablets of Repaglinide with a rationale of providing improved solubility and better patient compliance, will serve to provide effective mode of treatment to elderly, impaired and non-cooperative patient suffering from diabetes. The Repaglinide-ß-cyclodextrin complex was prepared in order to increase the solubility of drug. The inclusion efficiency of different ratios of Repaglinide-ß-cyclodextrin complex was calculated, that shows the inclusion efficiency of 1:2 molar ratio complex is highest. The oral tablets of Repaglinide (F1 to F4) were prepared by direct compression method using super disintegrants, for optimization of the diluents. The value of pre-compression of blends and post-compression tablets exhibited satisfactorily results. The formulation F4 complied with all the physical parameters such as hardness, friability and disintegration time, and taken for further studies. Solubility studies revealed that complexing agents contribute to solubility enhancement of the drug.

Keywords: Repaglinide,Beta-cyclodextrin,Simulated gastric fluid,Friability,Drug dispersion

INTRODUCTION

The conventional oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. It remains the preferred route of administration in the discovery and development of new drugs candidates and formulation. The popularity of oral route is attributed to most versatile, convenient, patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods, generally improve shelf life of the product and commonly employed route of drug delivery for systemic action. In fact the development of a pharmaceutical product for oral drug delivery, irrespective of its physical form (solid, semisolid, or liquid dosage form) involves varying contents of optimization of dosage form

characteristics within the inherent constraints of Gastrointestinal physiology. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. Oral solid dosage forms such as tablets has been formulated and developed now-a-days since they are most effective routes of administration of a new drug. Till date oral route ismajor and safest route of administration for majority of drugs. Although these new systems are in fast progression, for many drugs and therapeutic indications, conventional oral solid release drug delivery systems provided satisfactory clinical performance with an appropriate balance of efficacy and safety. Recent advances in novel drugdelivery aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance.[1] Oral drug delivery is still preferred way of administration for most of the active drug molecules due to its several advantages such as greater flexibility in design, high patient compliance, greater stability, accuracy in dose, easy of production, formulation of tablets is preferred oral dosage form. But the poor dissolution of water insoluble drugs is the major problem for pharmaceutical formulators to prepare in the form of tablets.[2] The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption. Since they exhibit poor and erratic dissolution profiles, most water-insoluble drugs are included by the FDA in the list of drugs having a high risk for therapeutic in equivalence due to differences and inconsistencies in bioavailability. Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability. A biopharmaceutical Classification System (BCS) wasintroduced by Amidon et alas a basis for predicting the likelihood of in vitro-in vivo correlations for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to Biopharmaceutical Classification System (BCS) which is incorporated in the guidelines of the Food and Drug Administration (FDA), Class II drugs are with high permeabilityand low solubility. Regulatory agencies have utilized the BCS to allow the use of in-vitro dissolution data for establishing the in-vivo bioequivalence of drug products Recently, the concept of the BCS has been used not onlyfor the bio waiver but also for formulation design from early to clinical stages. The bioavailability of a BCS class II drug is rate-limited by its dissolution, so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability. Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS class II drugs. Poor water soluble drugs are associated to slower rate of absorption from oral route; therefore, it is required to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs. To improve the dissolution rate various techniques have been introduced to enhance the dissolution rate and solubility of the drug. Compounds with poor aqueous solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughputs screenings have a poor solubility. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for poorly water soluble drugs. Solubility is an important parameter for absorption of drugs especially for those which are water insoluble and poorly soluble drugs. Dissolution of such drugslimits their absorption through oral route. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability. According to Noyes-Whitney equation, increase in saturation solubility leads to an increase in dissolution velocity in the lumen and blood, thus accelerating drug diffusion, promoting absorption and therefore enhancing bioavailability of drugs. Due to poor solubility and limited dissolution rate Class II drugs suffer less bioavailability thereby decreased therapeutic effect. Several techniques

have been reported to improve the solubility and dissolution properties of poorly soluble drugs, which can also improve absorption and bioavailability. Over the years, various techniques have been employed to formulate drug delivery systems which would enhance the dissolution profile and, in turn, the absorption efficiency of water-insoluble solid drugs such as digoxin, digitoxin, prednisolone, hydrocortisone, prednisone, spironolactone, hydrochlorothiazide, polythiazide, and/or liquid lipophilic medications such as clofibrate, chlorpheniramine, water-insoluble vitamins, fish oil, etc. Different approaches have been attempted to increase aqueous solubility of poorly soluble drugs, such as conversion of crystalline molecule to its amorphous state, a particle size reduction via micronization, solubilization in surfactant systems, co-solvency, hydrotropic solubilization, cyclodextrin complexation.

The principles are generally based on the modification of the physicochemical properties of the drug, these includes the conventional approach such as salt formation, pH solubility, micronization, solubilization using co-solvents and micellar solubilization, solid dispersions, oily solutions, complexation with beta-cyclodextrin, self-emulsifying and liquisolid compacts. The methods are not universal suffers from limitations such as large amount of excipients and sophisticated equipment. From the last few years, the pharmaceutical scientists were working to develop patient compliance and safe dosage forms due to enhanced demand in the market for them .As a result developing the new technologies has been increasing annually because the development of new drug molecule requires high cost rather than new technology. So the current trend in most of pharmaceutical industries is development of dosage form with new formulation technology using old drug molecules to improve safety, efficacy and patient compliance[3].

Repaglinide is a meglitinide phenylalanine analogue, which is prescribed as an oral antidiabetic drug for the treatment of type II (non-insulin dependent) diabetes mellitus. It acts primarily by decreasing insulin resistance. Repaglinide is poorly water soluble drug and it belongs to Class II in Biopharmaceutics Classification System. Due to the poor solubility of drug, the dissolution is reduced and hence, it suffers oral bioavailability problems. To overcome this disadvantage, enhancement of solubility of Repaglinide was done through cyclodextrin inclusion complex.

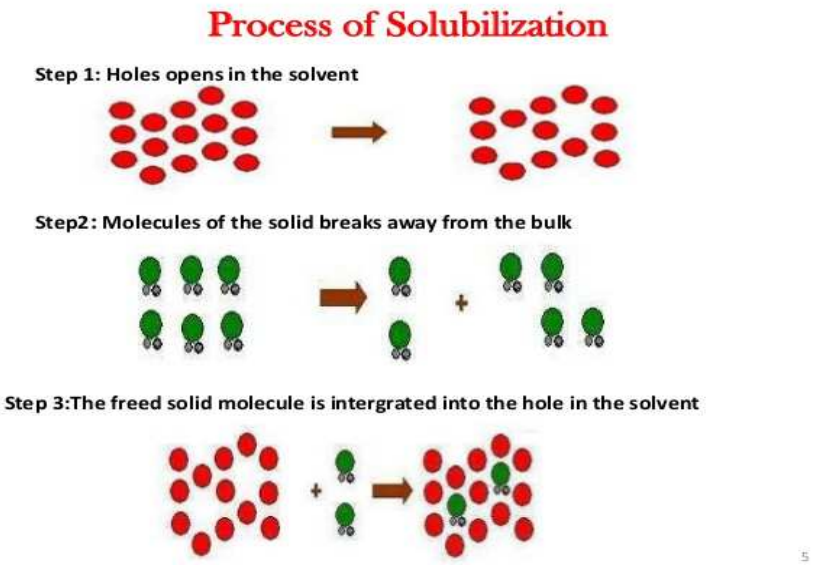


Figure 1: Process of solubilization

MATERIALS AND METHODS

Repaglinidewas obtained as a gift sample from TorrentPharmaceuticals Ahmedabad. Beta cyclodextrins from Gangwal Chemicals Private Limited,Mumbai, sodium hydroxide pellets from Merck Limited, Colorcon,Goa,NaCMC,Qualigens Fine Chemicals,Mumbai,Talc fine powder,PEG 400 Otto, Chemicika-Biochemika reagents,Mumbai.,PVP,M.K Enterprise,Jaipur,Magnesium stearate,Lobachemie private limited,Mumbai,Lactose,Qualigens Fine Chemicals,Mumbai.

Calibration curve of Repaglinide

Calibration curve of Repaglinide was prepared by using ethanol. The drug was analyzed spectrophotometrically (Elico Double beam UV-Visible Spectrophotometer) at 275 nm.

Figure 2: U-V Double Beam Spectrophotometer

Solubility determination

The solubility of the drug was determined in simulated gastric fluid.

Melting Point:

A small quantity of drug or complexing agents was filled in the capillary tube sealed at one end and kept in melting point apparatus. The melting point was recorded and compared with literature value.

Preparation of the inclusion complexes

1.5 mmol beta cyclodextrin were dissolved in distilled water. A 50% ethanolic solution containing 0.75 mmol Repaglinide was added stepwise to the aqueous solution of beta cyclodextrin. The suspension was stirred for 6 hours in an ultrasonic bath and a temperature of about 30°C was maintained.Different trials of the above solution was prepared by varying the ratios of drug:complexing agent from 1:1 to 1:3 in order to find out the best ratio for solubility enhancement of drug.Later,to the inclusion complex solution of Repaglinide added different ratio of co-polymer sodium CMC to find out the highest Repaglinide solubility complex. Later the highest Repaglinide solubility complex was formulated into an oral tablet.[4]

PREPARATION OF INCLUSION COMPLEX OF REPAGLINIDE

Sl.no	Formulation code	Drug:complexing agent	Repaglinide	Beta cyclodextrin
1	F1	1:1	500mg	500mg
2	F2	1:1.5	500mg	750mg
3	F3	1:2	500mg	1.0gm
4	F4	1:2.5	500mg	1.25gm
5	F5	1:3	500mg	1.50gm

Table 1: Composition of inclusion complex of Repaglinide with beta cyclodextrin

PREPARATION OF INCLUSION COMPLEX OF REPAGLINIDE BETA CYCLODEXTRIN WITH NaCMC

Sl.no	Formulation code	Repaglinide	Beta cyclodextrin	Sodium CMC
1	F6	500mg	1.0gm	300mg
2	F7	500mg	1.0gm	375mg
3	F8	500mg	1.0gm	450mg
4	F9	500mg	1.0gm	520mg

Table 2: composition of inclusion complex of Repaglinide beta cyclodextrin with sodium CMC

Preparation of Repaglinide tablets[7,9]

Uniformly blended all the ingredients of the tablet such as Repaglinide, Betacyclodextrin, sodium CMC,ethyl cellulose, talc and lactose in a glass mortar. Added magnesium stearate after sufficient mixing of the drug complex and compressed the tablets in 5mm punch.

FORMULATION OF INCLUSION COMPLEX REPAGLINIDE TABLETS

INGREDIENTS	F1	F2	F3	F4
Repaglinide	2	2	2	2
Beta cyclodextrin	4	4	4	4
NaCMC	28	28	28	28
Ethyl cellulose	2.4	3.2	4	4.8
Magnesium stearate	4	4	4	4
Talc	4	4	4	4
lactose	35.6	34.8	34	32.2

Table 3: Formulating composition of Repaglinide tablets

Pre-compression studies

All the physical parameters namely, angle of repose, bulk density, compressibility index and Hausner's ratio were performed .

Angle of Repose

It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the given formula.

$\theta = \tan^{-1}(h/r)$

Bulk density :

It is the ratio of total mass of powder to the bulk volume of powder. Required quantity of powder blend was transferred in 50 ml graduated cylinder and the bulk density was calculated by using the formula given below.

Bulk density = weight of powder/ Bulk volume.

Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. Required quantity of powder blend was transferred in 50 ml graduated cylinder which was operated for fixed number of taps until the powder bed volume has reached a minimum Tapped density using the wascalculated by formulagiven below.

Tapped density = Weigh of powder / Tapped volume .

Compressibility Index: [5,6]

It is a simple test to evaluate bulk and tapped density of a powder .

Carr's index:

The formula for Carr's index is as below:

Percent compressibility or Carr's index = [(tap - bulk)/tap] × 100

Where bulk is the bulk density (g/mL) and tap is the tap density (g/mL)

Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

Hausner's ratio = $H_R=\rho_t/\rho_b$

Where,ρ_t = tapped density and ρ_b= bulk density

Compressibility index(%)	Hausner ratio	Flow character
<10%	1.00-1.11	Excellent
11-15	1.12-1	Good
16-20	1.19-1.25	Fair
21-25	1.26-1.34	Passable
26-31	1.35-1.45	Poor
32-37	1.46-1.59	Very poor
38	>1.60	Very very poor

Table 4: Flow properties corresponding to compressibility index and Hausner ratio

Friability test

Friability of tablets was determined using Roche friabilator (Electolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of six inches in each revolution. Preweighed sample of 6 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability is given by the formula:

%F = (Loss in weight/initial weight) x 100

Hardness

Hardness or tablet crushing strength (Fc) (the force required to break a tablet in a diametric compression was measured using Monsanto hardness tester.

Drug content

20 tablets were powdered and the blend equivalent to average weight of Repaglinide was weighed and dissolved in 10ml of simulated gastric fluid. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 275 nm. Each sample was analyzed in triplicate.

Uniformity in weight:

20 tablets were randomly selected from each batch and individually weighed. The average weight of 20 tablets was taken.

The batch passes the test for weight variation if not more than 2 of the individual tablet weights deviate from the average weight and if no tablet differs by more than 2 times the % limit as shown in table and none deviate by more than twice the % shown.

Average weight of tablets(mg)	**Maximum % deviation allowed**
130 or less	10%
130-324	7.5%
More than 324	5%

Table 5: Weight variation tolerances for uncoated tablets as per USP standards

***In-vitro* dissolution study**

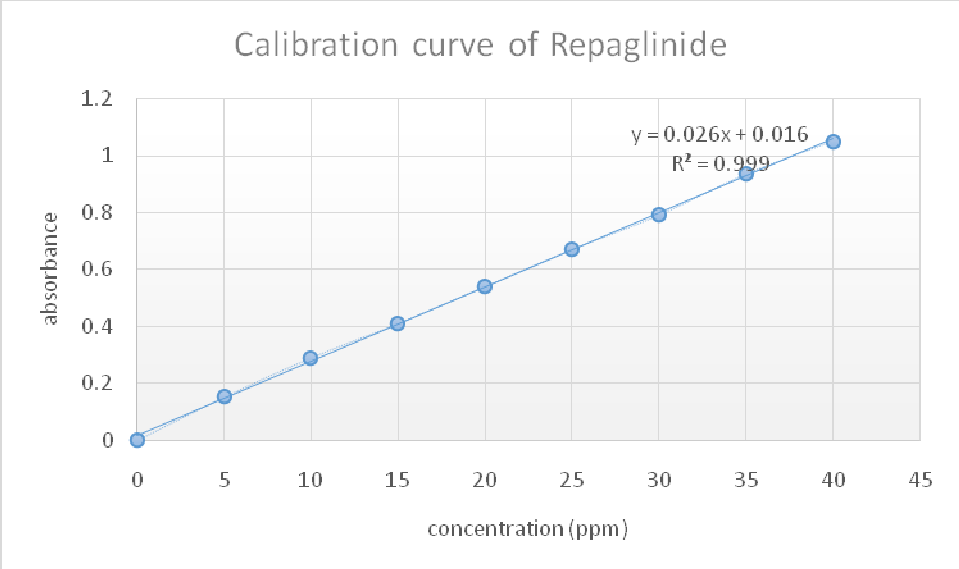
The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus (Dissolution tester USP) type 2 (paddle). The dissolution medium (900 ml, simulated gastric fluid of pH1.2) was taken in a covered vessel and the temperature was maintained at 37±0.5 °C. The speed of the paddle was set at 50 rpm. Sampling was performed at hourly interval for 10hours. For each sample, 5 ml of the dissolution medium was withdrawn and immediately this volume was replaced with the same amount of fresh dissolution medium. The sample was withdrawn and diluted with simulated gastric fluidand analyzed in the UV spectrophotometer (UV-1240 Shimadzu Corporation) at 275 nm. The % cumulative drug release was calculated. All the results were performed in triplicate.[10,11]

Figure 3: USP Dissolution Apparatus

RESULT AND DISCUSSION

Standard calibration graph of Repaglinide in simulated gastric fluid

The standard calibration graph of repaglinide in simulated gastric fluid is depicted in graph.The data of absorbance is shown in table.the data had a correlation coefficient of 0.993.



Graph 1: standard calibration curve of Repaglinide in S.G.F

Concentration(ppm)	Absorbance
0	0
5	0.152
10	0.29
15	0.41
20	0.54
25	0.67
30	0.79
35	0.935
40	1.05

Table 6: Standard calibration curve of Repaglinide in S.G.F at 275nm

Solubility determination

Solubility of Repaglinide was found out to be 30.315mg/ml while solubility of drug in presence of complexing agent beta cyclodextrin to be 0.6758mg/ml and in the presence of betacyclodextrin and NaCMC to be 0.8768mg/ml.This shows that the presence of complexing agents enhances the solubility of drug in low pH and is therefore expected to improve the dissolution of drug.

FLOW PROPERTIES:

CODE	ANGLE OF REPOSE (θ)	BULK DENSITY (gm/cm^3)	TAPPED DENSITY (gm/cm^3)	HAUSNER RATIO (H_R)	CARR INDEX (I_C)
F1	29.758	0.523	0.670	1.080	3.82
F2	30.052	0.515	0.678	1.094	3.97
F3	29.944	0.505	0.656	1.091	4.04
F4	29.991	0.522	0.657	1.104	4.09

Table 7: Flow property parameters of different formulated inclusion complexes of Repaglinide Beta Cyclodextrin-NaCMC

The above data revealed that the formed complex is free flowing.

POST COMPRESSION PARAMETERS:

A)Hardness:

The hardness of all formulations were kept between 3 and 5 kg/cm^2.

B)Uniformity of weight:

All the prepared batches comply with the USP standards.

FORMULATION	AVERAGE WEIGHT	%WEIGHT VARIATION
F1	78.5	±1.87
F2	80.2	±0.25
F3	79.2	±1
F4	80.4	±0.5

Table 8: weight variation of different batches of tablet formulation

C)Drug content:

CODE	DRUG CONTENT				
	I	II	III	AVERAGE	S.D
F1	50.45	43.85	50.51	50.60	0.226
F2	49.34	49.57	49.72	49.20	0.438
F3	50.51	50.64	50.85	50.46	0.429
F4	51.61	60.65	50.25	40.77	0.451

Table 9: drug content of different batches of tablet formulations

D)Friability

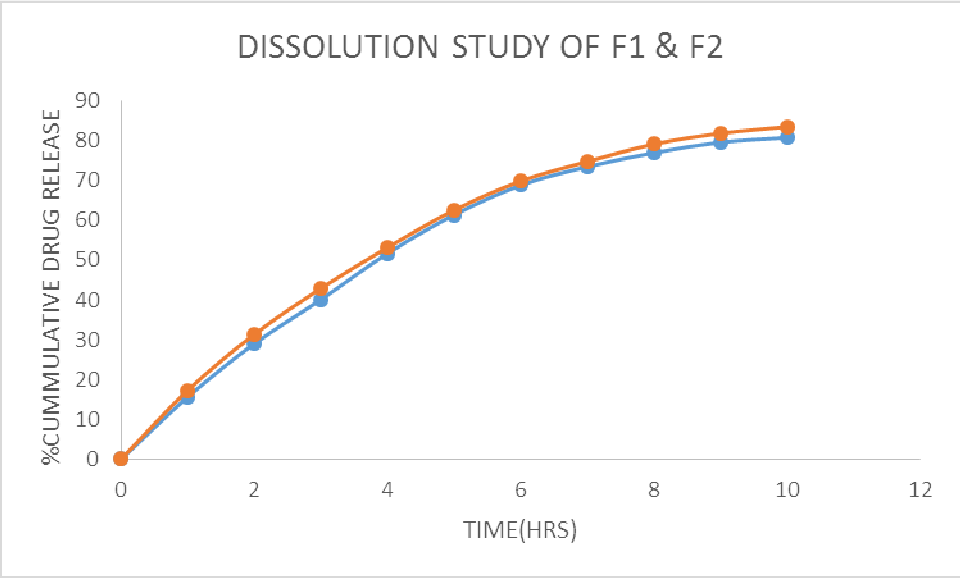
The percentage friability of different batches of tablets was found to be less than 1%.All the batches of tablets were found to pass the friability test.

E)Dissolution study

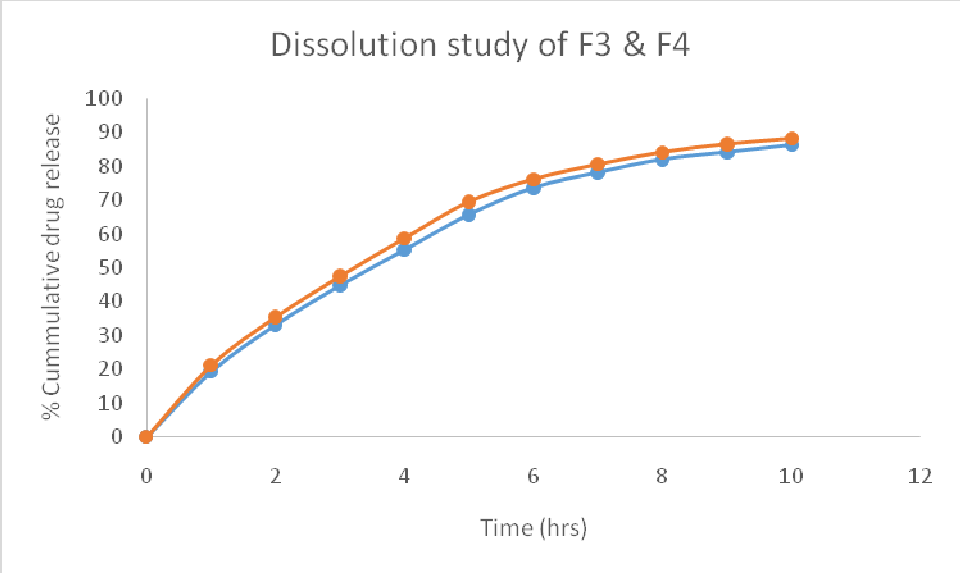
The invitro release data of different batches of tablet formulations are shown in table.The plots of % cumulative drug release Vs time for tablets of different batches are depicted in graphs.

TIME(HR)	FORMULATION CODE							
	F1		F2		F3		F4	
	%CR	SD	%CR	SD	%CR	SD	%CR	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	15.63	0.26	17.31	0.30	19.28	0.59	21.18	0.24
2	29	1.86	31.34	0.90	33.13	0.88	35.43	0.68
3	40.06	0.69	42.88	0.32	44.81	1.17	47.51	0.70
4	51.63	1.27	53.13	1.30	55.31	1.30	58.74	0.60
5	61.31	1.12	62.5	0.78	65.75	0.83	69.55	0.64
6	68.75	0.96	69.79	1.30	73.69	0.62	76.23	0.44
7	73.38	1.95	74.68	1.28	78.23	0.31	80.61	0.71
8	76.89	1.58	79.06	1.08	82.12	1.02	84.23	0.69
9	79.51	0.94	81.79	1.60	84.25	0.95	86.64	0.76
10	80.71	1.23	83.43	1.42	86.34	1.04	88.23	0.65

TABLE 10: Percentage cumulative drug release from the formulations F1-F4.



Graph 2: Comparitiveinvitro release of Repaglinide from F1 & F2



Graph 3: Comparitiveinvitro release of Repaglinide from F3 & F4

The formulation F4 gives maximum cumulative drug release.So it is selected to make oral controlled release tablet of Repaglinide.

CONCLUSION

The major problem of Repaglinide is poor bioavailability and its limited aqueous solubility, which may hinder dissolution. Results revealed that it is possible to enhance the dissolution rate and the bioavailability by preparing complex with β- cyclodextrin and sodium CMC.Different ratios of repaglinide: β- cyclodextrin and repaglinide: β- cyclodextrin:sodium CMC were prepared inorder to find out the better solubility enhancement of drug.The prepared complexex were formulated in tablet forms.Tablet evaluation parameters were performed and finally these were subjected to dissolution study to find out the maximum drug release which was ultimately shown by formulation

F4 containing maximum ethyl cellulose for oral controlled release of repaglinide.

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