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INCLUSION COMPLEXATION OF REPAGLINIDE WITH BETA CYCLODEXTRIN TO IMPROVE SOLUBILITY

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ABSTRACT

Repaglinide is an antidiabetic drug having low solubility due to its crystalline nature. Drug is coming under class II BCS classification. Here it is an attempt to improve solubility by inclusion complexation method. For this research work cyclodextrin was used. Cyclodextrin is derived from starch. It of different types alfa, beta and gamma cyclodextrin. Depending upon number of sugar moiety cyclodextrins are classified. β Cyclodextrine used in research work for complexation with Repaglinide. X ray Diffraction study was conducted for both pure drug and complex .The pure drug shows sharp peaks in graph which reflects nature of crystallinity. Inclusion complexation was done by Physical mixture and kneading method. Volume, temperature and solvent was optimised. After complexation micromeritics and in vitro dissolution tests were conducted. Which gave satisfactory results. Calibration curve was done with distilled water. Phase solubility study was conducted.

KEYWORDS: X Ray Diffraction, Phase solubility, BCS, crystallinity, amorphous.

MANUSCRIPT

INTRODUCTION

Repaglinide is a drug used for type II diabetes. It works on the body by stimulating body to produce insulin. It also helps to prevent nerve problem, blindness, kidney damage. It keeps blood sugar low. It belongs to meglitinide class non-insulin dependent Diabetes mellitus (NIDDM) short acting secretagogues. It acts by binding β cells of pancreas. Its chemical formula is $C_{27}H_{36}N_2O_4$. this meglitinide derivative is more effective in lowering blood sugar levels compared to metformin, sulfonyl urease, thiazolidine dione derivatives. Repaglinide is benzoic acid derivatives which has very rare chances of liver toxicity. 2-ethoxy-4-[2-[[(1S)-3-methyl-1-(2-piperidin-1-ylphenyl) butyl] amino]-2-oxoethyl] benzoic acidis chemical name of the drug. It is excreted 90% as faces and 8% in urine. It acts by inhibiting ATP sensitive potassium channel.it has a biological half-life of one hour. The bio availability of this drug is too poor.

More than 400 million people across the world under the threat of diabetes. Repaglinide is one of the old drugs which is less studied compared to other antidiabetic drugs as metformin and others. The solubility of drug is least in aqueous medium and under BCS class II. Effects of curcumin for diabetic patients are needful and helpful. So combined therapy for diabetes is effective. The study is designed to improve the aqueous solubility by different techniques. both drugs having challenges for formulations. Solid dispersion can improve the solubility of curcumin. The repaglinide can be enhanced its solubility by complexation. It can be formulated by enhancing its dissolution rate. As there as not still studied the combined formulation of complexed formulation with the said techniques, its important to study the comparative study of drug with complexation and non-complexed active ingredients. the successful study may lead to cost effective formulations with an effective formulation for mankind.

MATERIAL AND METHODS

List of equipments used

SL.No.	Apparatus	Sourse
1	Analytical balance	Adair Dutta, AD-50 B, Kolkata
2	Glass wares, beakers, separatory funnel	Borosil
3	Magnetic stirrer	Remi magnetic stirrer
4	Syring	Dispovan
5	Sonicator	Probe Sonicator
6	UV/ VIS. Spectroscopy	Systronic double beam 2203 smart spectrophotometer

7	Powdered – XRD	Phillip analytical X-ray BV (PW3710) X-ray Diffractometer
8	Dissolution Apparatus	USP 8 basket Digital Test Apparatus Lab India (Disso-2000) Mumbai.
9	Sieve set	ASTM Standard Sieves, SISSO, India
10	Distillation apparatus	Borosil
11	Shaker water bath	Remi shaker water bath
12	Incubator	Thermoline laboratory incubator

1. Micromeriticcs study

- DENSITY MEASUREMENT
- Bulk Density.

First 1gm drug is weighed accurately and kept in a clean dry graduated measuring cylinder. Then after pouring the dug in to the cylinder, the granular bed made uniform with out disturbing much. The volume map measured directly from the granulation. Measured volume is called as bulk volume. The density is called as bulk density.

$$\text{Bulk density} = \frac{\text{weight of the drug}}{\text{Bulk volume}}$$

- Tapped density

After measuring bulk volume of the same measuring cylinder is subjected to tapped really 200 times by hand. Then volume was detected. This volume is called as tapped volume.

$$\text{Tapped density} = \frac{\text{Weight of the granules}}{\text{Tapped density}}$$

- FLOW PROPERTIES
- Angle of Repose

A glass funnel having tip cut horizontal to the surface was fixed at constant height around 2 cm with the help of a stand and on the tip one graph paper was placed. 2gm of the drug was weighed and directly poured at a time through the funnel. So the granules formed a conical structure having a height. The weight of the firmed core way measured with the help of scale and the perimeter of the core was marked with the help of marker. From this average radius of the formed circle was measured by drawing various diameter through the center, the angle of repose was calculated by the following formula.

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

Where,

θ = Angle of repose.

h = height of the formed cone.

r = radius of the circular base on the formed cone.

Table no. 6: Flow properties with angle of repose.

Angle of repose in degree	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

- Carr's index

It is one of the most important parameter to characterize the nature of powder and granules.

$$\text{Carr's index}(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 7: Compressibility and flow property relationship.

Carr's index	Types of flow
5-15	Excellent flow
12-16	Good flow
18-21	Fair to passable flow
23-35	Poor flow
33-38	Very poor flow
>40	Extremely poor flow

- Hausner's Ratio

It is an important character to determine the flow property of powder and granules.

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

Value less than 1.25 indicates good flow and greater than 1.25 indicates poor flow.

RESULT AND DISCUSSION

Illuriation on micromeritics study of pure drug.

Experiment	Result
Bulk density	0.1742 gm/ml
Tapped density	0.2632 gm/ml
Carr's index	33.82%
Hausner's ratio	1.51
Angle of repose	33.52^0

SIEVE ANALYSIS

An accurate weighed 2gm quantity of drug was subjected to granulometric study using sieves 22, 30, 44, 60, 80, 100 &120 using a sieve shaker. Drug is sieved nearly around 10 minutes than the sieves are removed from the sieve shaker & powder retained in each sieves was calculated in percentage form using initial weight taken. The results were given below.

Sieve no.	Retained amount of drug (in mg)	Percentage retained (%)
22	0.926	46.3
30	0.330	16.5
44	0.176	8.8
60	0.168	8.4
80	0.016	0.8
100	0.101	5.05
120	0.010	0.5
Total	1.727	86.35

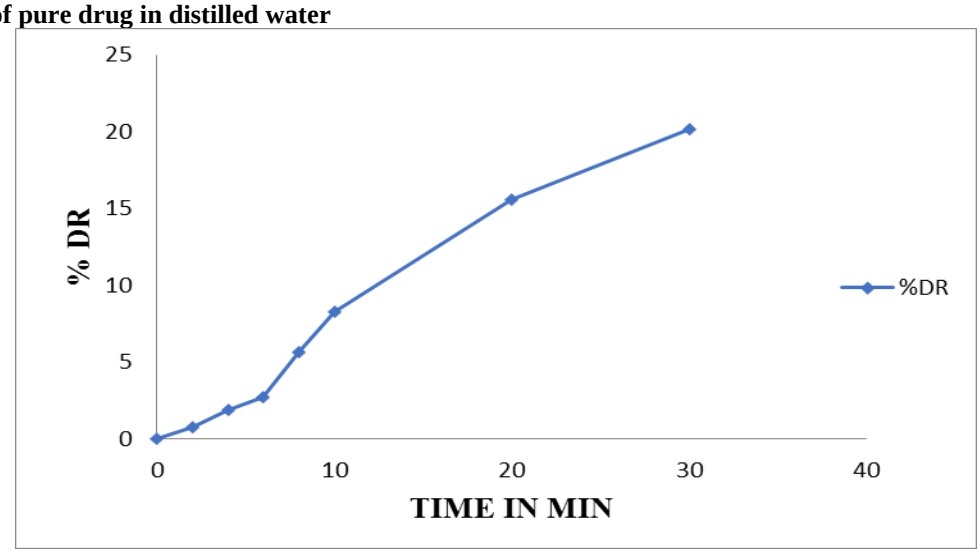
Calibration curve of drug with pH 7.4 buffer solution

Concentration (mcg/ml)	Absorbance
0	0
5	0.076
10	0.191
15	0.298
20	0.396
25	0.492
30	0.611
35	0.728
40	0.836
45	0.939
50	1.043

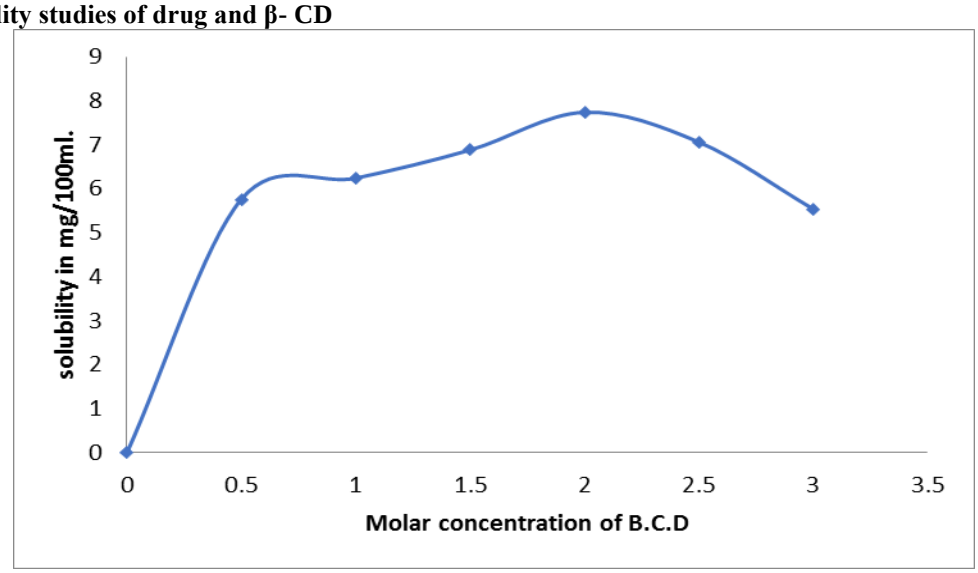
Dissolution data of pure drug in distilled water

Sl.NO.	Time	%DR
1	0	0
2	2	0.76
3	4	1.9
4	6	2.75
5	8	5.63
6	10	8.25
7	20	15.6
8	30	20.18

Dissolution of pure drug in distilled water



Phase solubility studies of drug and β- CD



Methodology optimization

- Selection of Method

Physical mixture method

Drug and beta-cyclodextrin in the ratio 1:2 was taken and were mixed thoroughly with constant trituration, passed through sieve no. 100 and stored in a desicator.

Kneading Method

Drug and beta-cyclodextrin in the ratio 1:2 was taken and to it 20 ml methanol was added and were mixed till a thick slurry was obtained with constant trituration, then it was dried at 45^0 C, passed through sieve no.100 and stored in a desicator.

Drug content in pH 7.4 buffer

Method	% drug content
Physical mixture method	83.82
Kneading method	85.62

Estimation of drug content of drug complex in pH 7.4 buffer

Sample	Volume of methanol	Percentage
A	25	55.12
B	20	85.62
C	15	85.05

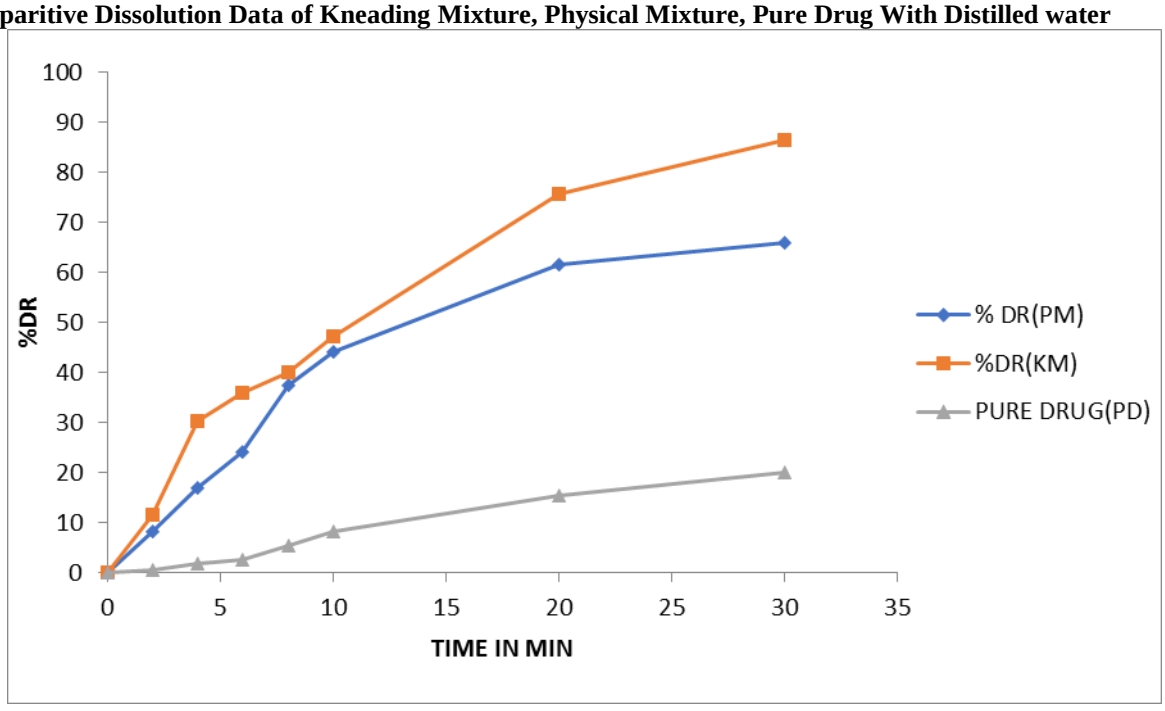
Physicochemical characterization of complex

Parameters	Complex	Pure drug
Bulk density	0.294 gm/ml	0.1742 gm/ml
Tapped density	0.384 gm/ml	0.2632 gm/ml
Compressibility index	23.43%	33.82%
Angle of repose	30.068^0	33.52^0
Hausner's ratio	1.306	1.51

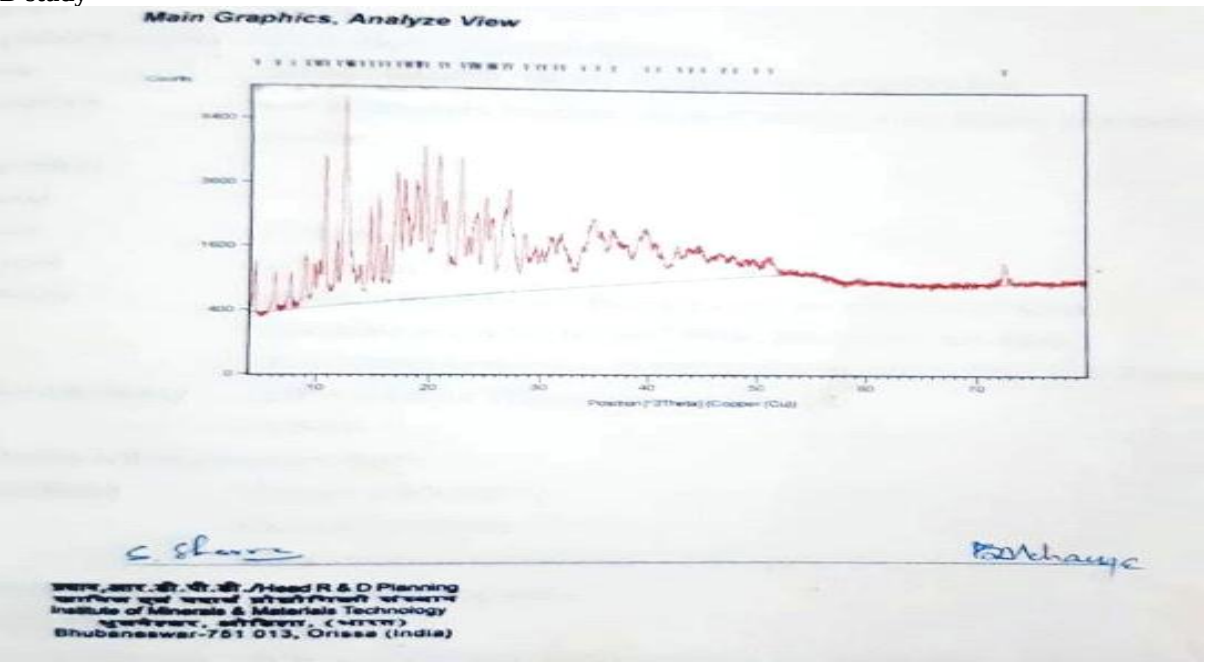
Comparative dissolution data of Kneading mixture, physical mixture, pure drug with distilled water

Time (min)	%DR (PM)	%DR (KM)	Pure Drug(PD)
0	0	0	0
2	8.3	11.58	0.76
4	17	30.29	1.9
6	24.1	35.89	2.75
8	37.5	40.09	5.63
10	44.21	47.2	8.25
20	61.48	75.74	15.6
30	65.94	86.43	20.18

Comparitive Dissolution Data of Kneading Mixture, Physical Mixture, Pure Drug With Distilled water



XRD study



CONCLUSION

According to world health organization (WHO) report from 1980 to 2016 the people of diabetes rose from 108 million to 422 million. Between 2000 to 2016 death rates below the age of 18 increased to 5%. Diabetes plays an important role in failure of kidney, blindness, heart attack. According to WHO diabetes is the seventh leading cause of death. The potent drug repaglinide may plays an important role if it will more soluble. The result is satisfactory and it can be formulated in new dosage form.

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