

# Preparation And Evaluation Of Sustained Release Matrix Tablets Of Repaglinide (Usp) Using Natural Polymers

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**Abstract:** The objective of the present work is to develop and characterize oral sustained release matrix tablets of Repaglinide. Repaglinide is practically insoluble in water so it is suitable to develop sustained release matrix tablet using hydrophilic polymers. Repaglinide is anti-diabetic drug used extensively in the treatment of diabetes type II. The natural polymers like carrageenan, chitosan, gum karaya, Bhara gum were utilized in the formulation of matrix tablets containing Repaglinide by wet granulation technique and evaluated for its drug release characteristics. Granules were prepared and evaluated for its physical properties and shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), in vitro drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The in vitro release study of matrix tablets were carried out in phosphate buffer pH 6.8 for 12 hr. Among all the formulations, F2 with shows 100% better controlled release at the end of 12 hrs when compared to other formulations. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero order to evaluate the kinetics and mechanism of the drug release. The drug release of optimized formulations F2 follows zero order kinetics and the mechanism was found to be diffusion coupled with erosion (non-Fickian diffusion). The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

**Keywords:** Repaglinide, chitosan, carrageenan, gum karaya, bhara gum, Matrix tablet, Sustained release, Wet granulation.

## I. INTRODUCTION

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system. Recent trend in development of sustained-release drug delivery systems was the use of gums of plant origin to fulfill the aim of retarding the drug release. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form<sup>2</sup>. Repaglinide is the first member of new class of oral hypoglycemic designed to normalize the meal time glucose excursions. Repaglinide induces rapid onset short lasting insulin release. It is administered before each major meal to control postprandial hyperglycemia the dose may be omitted if

a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycemia. Side effects are mild headache, dyspepsia, arthralgia, and weight gain. After oral administration, Repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C<sub>max</sub>) occurs within 1 hour (T<sub>max</sub>). The present study was designed to formulate matrix tablets using carrageenan, chitosan, gum karaya, bhara gum matrix polymers for controlling release of poorly water soluble drug Repaglinide.

II. AIM AND OBJECTIVE OF PRESENT STUDY

AIM

The main aim of the present investigation is to design, formulate and evaluate the sustained release dosage form of Repaglinide (USP) using natural polymers.

OBJECTIVES

- ✓ Preformulation studies such as API characterization, solubility studies, determination of melting point.
- ✓ To improve its oral bioavailability.
- ✓ To develop the extended release system over a period of time.
- ✓ Increased patient compliance by reducing the dose frequency.
- ✓ Determination of  $\lambda_{max}$  and development of calibration curve of Repaglinide using UV spectrophotometer.
- ✓ To perform various quality control evaluation parameters for the prepared tablets.

III. METHODOLOGY

A. FORMULATION OF EXTENDED RELEASE LAYER

Matrix tablets of were prepared by Wet Granulation method. The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve. Repaglinide, Carrageenan, Chitosan, Bhara gum, gum karaya, Ethyl cellulose, Micro crystalline cellulose were taken in a poly bag according to the formulation table and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug. Weigh Starch accurately and it is mixed with water to form a paste is used as binder solution and kept separately. The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules. Then the wet granules were dried in trays and pass the air for drying .Samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content. The dried materials were passed through the sieve#20. After sieving dry granules were lubricated using Magnesium .stearate and Talc. After lubrication granules were sent to compression. Repaglinide Matrix tablets was compressed using 12mm round punch.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Repaglinide(USP)	4mg							
Carrageenan	15%	30%	-	-	-	-	-	-
Chitosan	-	-	15%	30%	-	-	-	-
Bhara gum	-	-	-	-	15%	30%	-	-
Gum karaya	-	-	-	-	-	-	15%	30%
Starch	5 mg	5mg						
Talc	12mg							
Magnesium Stearate	12mg							
MCC	q.s							
Total wt(mg)	200	200	200	200	200	200	200	200

Table 1: Formulation Table For Extended Release Layer

IV. RESULTS AND DISCUSSION

A. PREFORMULATION STUDIES

a. ORGANOLEPTIC CHARACTERS FOR REPAGLINIDE

DESCRIPTION OF REPAGLINIDE (API)

Test	Description
Colour	white to off-white powder

SOLUBILITY

Table showing the Solubility of Repaglinide (API) in various solvents.

Solvents	Solubility
Water	Practically insoluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Ethanol	Soluble

MELTING POINT

Melting point of Repaglinide drug was determined by using melting point apparatus and was in the range of 131°C.

B. EVALUATION OF REPAGLINDE TABLETS

a. PRECOMPESSION PARAMETERS

Formulations	Bulk Density (gm/ml)	TAPPED DENSITY (gm/ml)	Carr's Index (%)	Hausner ratio	Angle of repose (°)
F1	0.356	0.400	11.00	1.12	28.16
F2	0.379	0.429	11.66	1.13	24.59
F3	0.344	0.392	12.24	1.14	28.73
F4	0.369	0.425	13.18	1.15	25.14
F5	0.373	0.429	13.05	1.15	27.35
F6	0.349	0.410	14.88	1.17	28.19
F7	0.371	0.426	12.91	1.15	26.31
F8	0.396	0.453	12.58	1.14	25.14

Table: 2

The blends for Matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausners ratio. Angle of repose was less than 30° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flowability and compressibility. Hausner's ratio was less than 1.17 for all the batches indicating excellent flow properties.

b. POST COMPRESSION PARAMETERS

F.Code	Hardness (kg/cm <sup>2</sup> )	Thickness (mm)	Weight (mg)	Friability (%)
F1	5.4±0.44	2.08±0.17	199.8±1.48	0.36
F2	4.5±0.31	2.70±0.25	199.8±1.48	0.36
F3	5.5±0.40	2.81±0.80	200.4±0.54	0.39
F4	5.5±0.55	2.2±0.20	198.6±0.41	0.43
F5	4.6±0.57	2.08±0.66	200.8±1.64	0.12
F6	5.0±0.30	2.91±0.25	205.6±1.14	0.54
F7	4.5±0.57	2.1±0.71	199.2±0.83	0.58

<b>F8</b>	5.4±0.60	2.0±0.89	199.9±0.67	0.64
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Table 3

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in above Table 3

All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 198.6±0.41 and 200.8±1.64mg.

The hardness of the tablets ranged from 4.5±0.31 to 5.5±0.55 kg/cm<sup>2</sup> and the friability values were less than 0.65% indicating that tablets were compact and hard. The thickness of the tablets ranged from 2.0 to 2.91 mm.

All the formulations satisfied the content of the drug as they contained 98 to 100 % of Repaglinide and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control.

**c. INVITRO DISSOLUTION STUDIES FOR MATRIX TABLETS**

**DISSOLUTION STUDY (MATRIX TABLETS)**

**Acidic Stage:**

Medium : 0.1N HCL  
Type of apparatus : USP - II (paddle type)  
RPM : 50  
Volume : 900ml  
Temperature : 37°C± 0.5  
Time : 2hrs

**Buffer Stage:**

Medium : 6.8pH phosphate buffer  
Type of apparatus : USP - II (paddle type)  
RPM : 50  
Volume : 900ml  
Time : 12hrs

In vitro dissolution for matrix tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 12hrs.

**IN-VITRO DRUG RELEASE STUDIES FOR MATRIX TABLETS**

Time (hrs)	F1 %drug release	F2 %drug release	F3 %drug release	F4 %drug release	F5 %drug release	F6 %drug release	F7 %drug release	F8 %drug release
Dissolution medium 0.1N HCL								
0.5	7.2	3.1	4.5	3.1	5.1	4.8	5.8	5.1
1	11.8	6.5	9.2	8.3	7.4	8.7	8.6	9.8
2	20.6	12.4	18.6	10.8	8.7	15.7	12.3	15.4
6.8pH phosphate buffer								
3	29.1	21.8	20.8	21.6	28.0	19.8	17.8	20.9
4	33.8	26.8	33.4	28.7	37.6	23.8	22.8	27.6
5	40.8	30.9	41.8	34.3	43.8	31.7	26.6	30.8
6	45.6	36.8	50.3	46.8	51.4	36.8	31.8	36.4
7	54.3	39.2	58.6	49.2	63.4	43.2	39.3	41.8
8	63.4	48.3	64.5	55.8	75.4	49.6	46.9	49.1
9	71.8	55.8	73.8	61.3	75.4	51.6	51.8	54.6
10	80.6	65.6	81.7	66.8	89.6	57.8	65.3	59.4
11	100	85.6	100.8	100	100.5	83.6	76.6	65.3
12	-	100	-	-	-	89.8	83.6	71.6

Table 4: cumulative percentage drug release from matrix tablets

The Formulation F2 shows 100% drug release at 12 hrs.

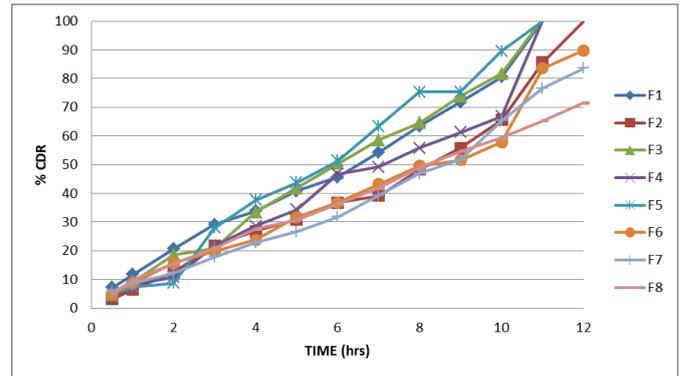


Figure 1: In-Vitro Drug Release Studies for matrix tablets F1 - F8

**d. RELEASE KINETICS**

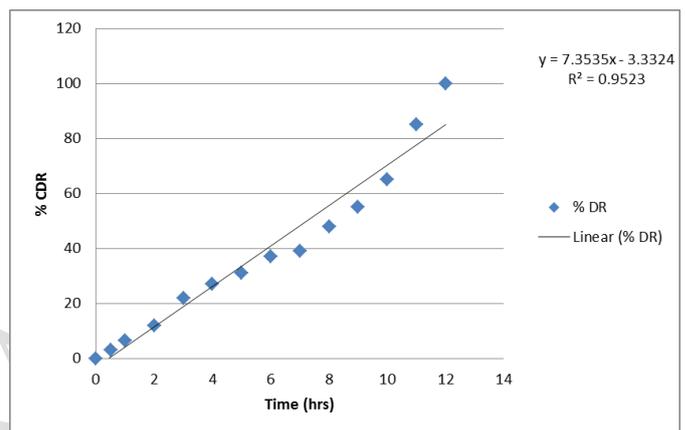


Figure 2: Zero order graph for F2 Formulation

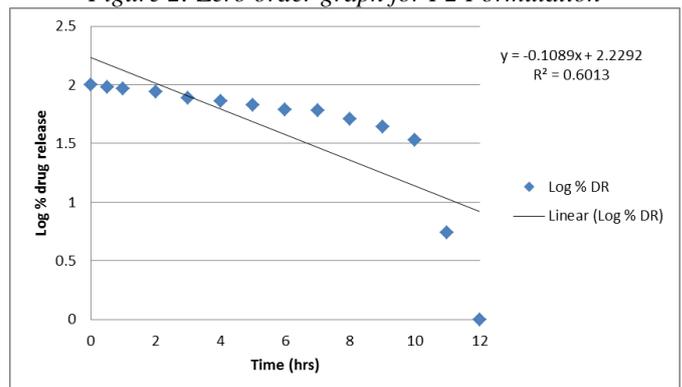


Figure 3: First order graph for F2 Formulation

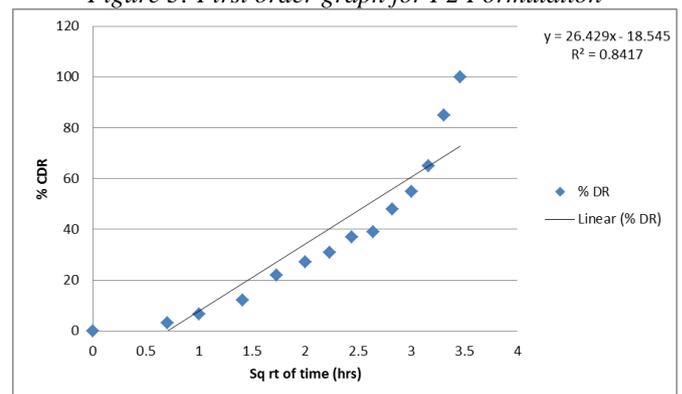


Figure 4: HIGUCHI graph for F2 Formulation

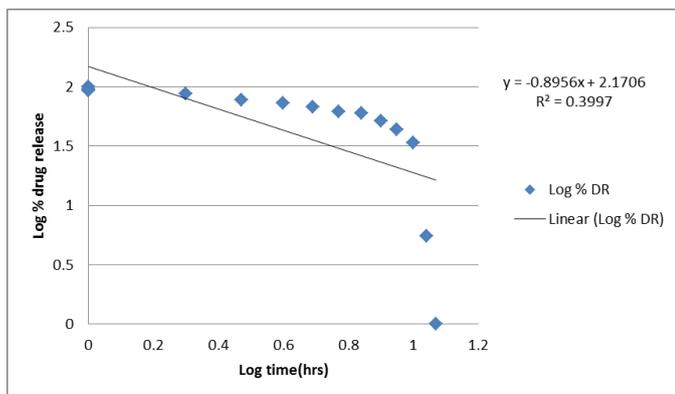


Figure 5: Korsmeyer-Peppas graph for F2 Formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.353	0.108	26.42	0.895
R 2	0.952	0.601	0.841	0.399

Table 5: Release kinetics for F2 formulation for sustained release tablets

e. STABILITY STUDIES

Cumulative% drug release			
Sampling interval	25 <sup>o</sup> C/60%RH	30 <sup>o</sup> C/65%RH	40 <sup>o</sup> C/75%RH
0 Days	100.1	99.8	99.9
15 Days	98.5	98.6	98.2
30 Days	97.82	97.75	97.70
90 Days	96.45	97.32	97.26

Table 6

Stability studies of the formulation F2 of Repaglinide (USP) matrix tablets were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25<sup>o</sup> C/60%RH, 30 °C/65% RH and 40 °C/75% RH for 90 days. There was no significant change in the physical property and percent of drug release was within the limits ±4 during 8hour during the stability period.

V. DISCUSSION

The release profile of formulations F<sub>1</sub>, F<sub>2</sub>, F<sub>3</sub>, F<sub>4</sub> F<sub>5</sub>,F<sub>6</sub>, F<sub>7</sub> and F<sub>8</sub> comprising various polymers like carrageenan, chitosan, bhara gum, gum karaya with varying concentrations. Formulations F<sub>1</sub>, F<sub>2</sub>, F<sub>3</sub>, F<sub>4</sub> F<sub>5</sub>,F<sub>6</sub>, F<sub>7</sub> and F<sub>8</sub> exhibits release rates of 91%, 100% 94.2%, 91%, 97%, 89.8%, 83.6, 71.6% at various time intervals as shown in the table. Among all of these 8 formulations F<sub>2</sub> contains carrageenan shows maximum drug release at the end of 12hrs. Hence it was optimized and decided to develop further formulations.

VI. CONCLUSION

In this study matrix tablet of Repaglinide was prepared by wet granulation technique, using carrageenan, chitosan, bhara gum, gum karaya Polymers used as release retardant. It was found that increase in the concentration of excipients in

polymeric ratio decreases the drug release. Carrageenan is non-carcinogenic, biocompatible and has high drug holding capacity. These led to its application as excipients in hydrophilic drug delivery system. The formulation F2 containing 30% carrageenan respectively showed good drug release with good matrix integrity. From the above result, it has been found that the optimized formula F2 containing 30% of carrageenan as drug retarding polymer shows better sustained effect for 12 hr when compared to other formulations. Different parameters like hardness, friability, weight variation, drug content uniformity, in-vitro drug release were evaluated for these formulations. Based on these results, formulation F2 was found to be the most promising formulations. The optimized formulation F8 follows zero order plot since the regression coefficient is 0.952 and plot was also found to be linear. The regression coefficient (R2) values of zero order in the optimized formulation F2 was greater than the R2 values of First order. Thus, the drug release follows zero order kinetics. The results suggest that the developed sustained release matrix tablets of Repaglinide could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus, the aim of this study was achieved.

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