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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF REPAGLINIDE

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ABSTRACT
The aim of the present work is to design sustained release matrix tablet of repaglinide using polymers like HPMC K4M, HPMC K15M, and HPMC K100M. Croscarmellose was used as swelling agent. Repaglinide is an effective antihyperglycemic drug. But due to its shorter half life patients are required to take the drug several times a day, which compromises its therapeutic effects. Matrix tablet is a compromising approach in extending the release rate of drug. Tablets were prepared by wet granulation method. Granules were prepared and flow properties were evaluated by measuring bulk density, tapped density, compressibility index, angle of repose. The formulated tablets were subjected to post formulation evaluation such as hardness test, thickness, friability, drug content and in- vitro drug release studies. The in-vitro dissolution studies were carried out by using USP Type-II dissolution apparatus for 12hrs. For first 2hrs it is carried out in 0.1N HCl at pH 1.2 followed by phosphate buffer pH 7.4. The results for the dissolution studies indicates that formulation containing HPMC K 100M showed better dissolution than formulations having HPMC K 4M and HPMC K 15 M.

KEYWORDS: Sustained Release Matrix Tablet, Repaglinide, HPMC K15M, HPMC K4M, HPMC K100M.

INTRODUCTION
Oral route is the most preferred route for the drug delivery as it provides maximum active surface area for absorption of various drugs.[1,2] For an effective treatment maintenance of plasma drug concentration within therapeutic index is essential. However conventional oral tablets fail to maintain the same. Oral conventional tablets offer certain limitations like multiple dosing, see-saw fluctuations in plasma drug concentration, unpredictable absorption etc. which lead to the development of oral sustained release tablets.[1,3]

Sustained release tablet is defined as dosage form which is designed to control the drug release profile in order to achieve desired drug concentration at the target site for an extended time period.[4,5]

The most common method to fabricate controlled/sustained release formulation is to develop a matrix tablet containing rate controlling hydrophilic or hydrophobic polymers. Drug release through matrix is governed by various factors like polymer swelling, water penetration, drug dissolution etc.[1,6,7]

Diabetes Mellitus is a metabolic disorder that occurs due to improper secretion of insulin or insulin action or both. The disease is characterized by disturbed carbohydrate, protein and fat metabolism; tissue damage, vascular damage; retinopathy, nephropathy & cardiovascular complications.[8,9]

Repaglinide is an oral hypoglycemic of meglitinide class. It is benzoic acid derivative; short acting antidiabetic drug. It is rapidly absorbed and metabolized; have a short half life of about 1hr & oral bioavailability of 56%.[1,10] It acts by closing the K^+ channels of beta cells of pancreas as a result membrane of beta cells get depolarized and channels get closed causing the release of intracellular Ca^{2+} ions. The elevated level of intracellular calcium ions promotes the release of insulin. Owing to its shorter duration of action & faster onset of action it serves as suitable candidate for sustained release drug delivery system. As this pharmacokinetic modification will not only preserves the fast action but also increases the $T_{max.}$[8,11,12]

MATERIALS AND METHOD
Repaglinide was obtained as free gift sample from Torrent Pharmaceuticals Limited, Gujarat, India. HPMC K 100M, HPMC K4M, HPMC K 15M were purchased from yarrow chemicals products, Mumbai. Talc, PVP K30, Calcium Stearate were purchased from SD Fine chemicals Ltd., Mumbai. Croscarmellose sodium was offered as gift sample from Shreeji pharma International.

Formulation of Sustained Release Matrix Tablets

Tablet formulations were prepared by wet granulation method using non aqueous solvents. Proportion of different excipients with drug was as given in table 1 were weighed individually. All ingredients were sifted through sieve no. 60. Half of the required quantity of all ingredients excluding calcium stearate and talc were mixed together for about 15 minutes. PVP K30 dissolved in isopropyl alcohol was used for the purpose of wet granulation of final blend. The damp wet mass is prepared in mortar and passed through sieve no. 12. The granules are dried in hot air oven at 60 ^{0}C for 30 minutes. The dried granules are then passed through sieve no. 16. Finally rest half quantity of the ingredients were added and mixed in the granules. The blend is then lubricated with calcium stearate and talc. Finally tablets were compressed to net weight of 200 mg by using 10 station mini rotary tablet punching machine.

Table 1: Composition of Matrix Tablet of Repaglinide

Ingredients	Formulation Code (in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Repaglinide	10	10	10	10	10	10	10	10	10
HPMC K4M	20	40	60	-	-	-	-	-	-
HPMC K 15M	-	-	-	20	40	60	-	-	-
HPMC K100M	-	-	-	-	-	-	20	40	60
Croscarmellose	144	124	104	144	124	104	144	124	104
PVP K 30	20	20	20	20	20	20	20	20	20
Calcium Stearate	4	4	4	4	4	4	4	4	4
Talc	22	2	2	2	2	2	2	2	2
Iso Propyl Alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total weight	200	200	200	200	200	200	200	200	200

Evaluation of Granules[1, 6]

a. Angle of Repose

To determine angle of repose the granules are allowed to flow freely through funnel on a plain surface. The diameter and height of the heap of the powder is determined & angle of repose of granules was determined by following equation

tanθ = h/r

Where h & r are height and radius of the powder cone respectively.

b. Bulk Density

Loose bulk density & Tapped bulk density were determined using the following formulas.

Loose Bulk Density = Weight of Granules / Bulk Volume of Granules

Tapped Bulk Density = Weight of Granules / Tapped Volume of Granules

c. Compressibility Index

The compressibility index of the granules was determined by using the following formula.

Carr's Index = Tapped Density – Loose Bulk Density/ Tapped Density * 100

The evaluated pre compression parameters of granules are as shown in table 2.

Table 2: Pre compression parameters of granules.

Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Angle of Repose
F1	**0.287±0.003**	**0.308±0.016**	**6.818±1.37**	**25.20±1.31**
F2	**0.262±0.004**	**0.292±0.014**	**10.27±1.39**	**27.21±1.25**
F3	**0.291±0.003**	**0.316±0.011**	**7.911±1.36**	**26.86±1.49**
F4	**0.250±0.005**	**0.285±0.012**	**12.28±1.29**	**25.67±1.84**
F5	**0.272±.0005**	**0.301±0.013**	**9.634±1.34**	**28.47±1.72**
F6	**0.282±0.004**	**0.312±0.011**	**9.615±1.37**	**27.25±1.56**
F7	**0.268±0.006**	**0.304±0.015**	**11.84±1.31**	**25.78±1.54**
F8	**0.278±0.005**	**0.309±0.010**	**11.15±1.34**	**27.35±1.79**
F9	**0.289±0.003**	**0.317±0.012**	**9.779±1.35**	**27.12±1.64**

Evaluation of Tablets[1, 6, 10]

After compression tablets are evaluated for the following parameters.

A. Thickness & Diameter

Physical dimensions of the tablet were evaluated by using vernier caliper. It was measured in mm.

B. Appearance & Texture

Appearance, color, shapes & texture of the tablets was evaluated by visual inspection.

C. Hardness

Hardness of the tablets was evaluated by using Monsanto Hardness Tester & was expressed in kg/cm^2

D. Friability

The test was carried out by using Roche fribilator. Pre weighed tablets were introduced into fribilator. The instrument was set at a speed of 25rpm & was operated for about 4 minutes. Tablets are weighed again & %age weight loss was determined by using following formula.

$$\% \text{ age Weight Loss} = \frac{(\text{Weight})_{\text{initial}} - (\text{Weight})_{\text{final}}}{(\text{Weight})_{\text{initial}}} * 100$$

E. Weight Variation

Twenty Tablets were weighed together and average weight was calculated. Then each tablet was weighed individually and mean weight was calculated. The %age difference between the two was calculated. The tablets pass the test if not more than 2 tablets fall outside the percentage limit and none of the tablet should deviate twice of the percentage limit.

F. Drug content uniformity

20 tablets were weighed and powdered. A quantity equivalent to 100mg of repaglinide was weighed and transferred to 250 ml of volumetric flask. 150 ml of 0.1N HCl was added; shaken well and sonicated for about 25-30 minutes. The final volume was made up to 250ml using 0.1N HCl. The solution was filtered and 10 ml of filtrate was taken in volumetric flask. The final volume was made up to 100 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 242nm using UV Spectrophotometer. The concentration of the drug in the tablet powder was calculated by using the following equation:

$$C_u / C_s = A_u / A_s * \text{Dilution Factor}$$

Where C_u = Concentration of unknown sample
C_s = Concentration of standard sample
A_u = Absorbance of unknown sample
A_s = Absorbance of standard sample

Table 2 Evaluation of Repaglinide Sustained Release Tablets

Formulations	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	1.89±0.10	6.3±0.14	0.32±0.14	99.22
F2	1.87±0.08	6.1±0.13	0.35±0.16	99.74
F3	1.90±0.07	6.0±0.12	0.29±0.20	98.21
F4	1.91±0.11	6.4±0.15	0.32±0.12	99.51
F5	1.88±0.08	6.1±0.13	0.34±0.21	99.01
F6	1.90±0.09	6.1±0.10	0.28±0.12	98.05
F7	1.91±0.11	6.0±0.15	0.31±0.15	99.34
F8	1.88±0.07	6.4±0.12	0.29±0.25	99.12
F9	1.87±0.09	6.2±0.10	0.30±0.17	99.14

G. In- vitro Dissolution studies

In- vitro dissolution studies of the prepared tablets was conducted by using USP Type II Apparatus (Paddle Type) at 37 ± 0.5^{0}C. The paddle was rotated at a speed of 50 rpm. The dissolution studies of prepared tablets of repaglinide was carried out first in 0.1N HCl at pH 1.2 for about 2 hrs, then these tablets are transferred in phosphate buffer (pH 7.4) and dissolution was carried out. 5 ml of dissolution fluid was withdrawn at regular intervals and filtered through 0.45µm filter paper. Content of drug in each sample was determined by using UV spectrophotometer at 242nm for 0.1N HCl & at 278 nm for phosphate buffer. The sample withdrawn was replenished with fresh sample after every withdrawal in the dissolution flask. On the basis of the dissolution studies the formulation that gives the best release profile of the drug was considered as the optimized formulation. The dissolution profiles of the different formulations are as shown in figure 4, 5 & 6.

On the basis of studies it has been concluded that an increase in the concentration of the polymer retards the drug release from the matrices.

H. Stability Studies

The stability studies of the optimized formulation was carried out at 25 ± 2^{0}C / 60 ± 5% RH, 30 ± 2^{0}C / 65 ± 5% RH and 40 ± 2^{0}C / 75 ± 5 % RH for a period of about 90 days. The tablet samples were analyzed each month for physical characteristics and drug release profile.[1,10]

RESULTS AND DISCUSSION

FT-IR Spectroscopy

The FT-IR spectrum of pure drug (Repaglinide) and its physical mixture with different grade of polymers and excipients is as shown in figure

The FT-IR spectrum of pure drug (figure 1) shows amine stretching at 3303.78cm^{-1},2933.83 cm^{-1} CH aromatic stretching, 2850.86 cm^{-1} CH aliphatic stretching, COOH stretching at 2801.6 cm^{-1}, C=O stretching at 1684.52 cm^{-1}, C-N stretching at 1210.51 cm^{-1}, ether linkage stretching at 1147.6 cm^{-1}

The FT IR spectra of the optimized formulation F9 (figure 3) shows OH of CHO stretching and NH of CONH stretching at 3306.694 cm^{-1}, aromatic CH stretching at 2934.529cm^{-1},C=H aliphatic stretching at 2852.200 cm^{-1}, COOH stretching at 2805.11cm^{-1}, C=O

stretching of CONH at 1685.453 cm^{-1}, C-N stretching at 1211.81cm^{-1}, ether linkage stretching at 1148.108cm^{-1}.

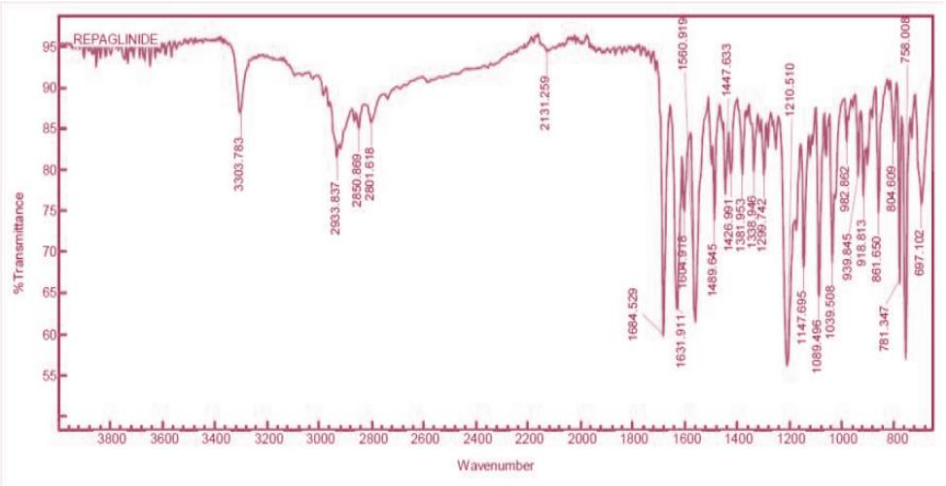

Figure 1 FT-IR spectrum of Pure Repaglinide.

Figure 2 FT IR Spectra of HPMC K 100M

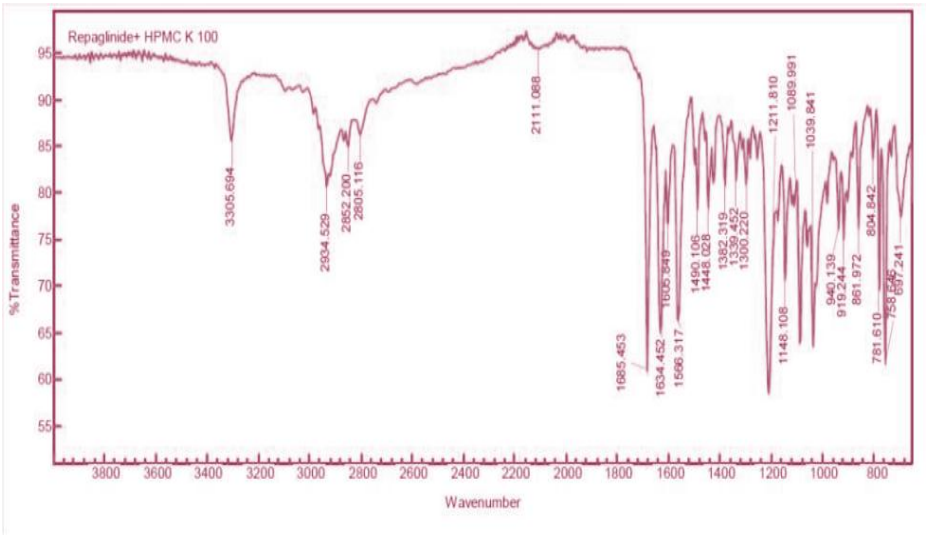

Figure 3 FT IR Spectra of Repaglinide + HPMC K 100M

Table 4 In-Vitro Dissolution profile of Formulations F1-F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	25.21	23.87	21.20	23.21	22.24	21.94	26.24	24.57	22.41
2	38.21	32.58	30.24	39.57	31.20	30.69	40.65	37.24	31.76
3	50.21	48.27	45.21	52.24	49.21	44.69	51.85	49.36	46.25
4	56.25	62.25	51.86	55.64	63.48	51.48	55.34	64.86	54.35
5	60.45	68.25	56.47	60.25	69.54	55.27	61.24	69.45	56.21
6	69.12	74.68	63.24	68.27	75.24	62.37	69.35	75.21	61.58
7	80.16	79.24	70.54	80.57	78.56	69.25	81.25	79.15	70.69
8	88.15	87.15	78.25	89.10	86.94	79.30	88.49	88.36	79.34
9	94.15	92.89	85.45	93.02	93.14	86.35	95.56	93.67	89.78
10	94.25	96.38	92.67	95.14	96.64	92.97	96.12	97.31	94.67
11	97.24	97.68	96.24	97.45	98.01	97.68	97.98	98.12	99.01
12	97.41	98.05	97.01	98.21	98.64	98.37	99.01	99.06	99.15

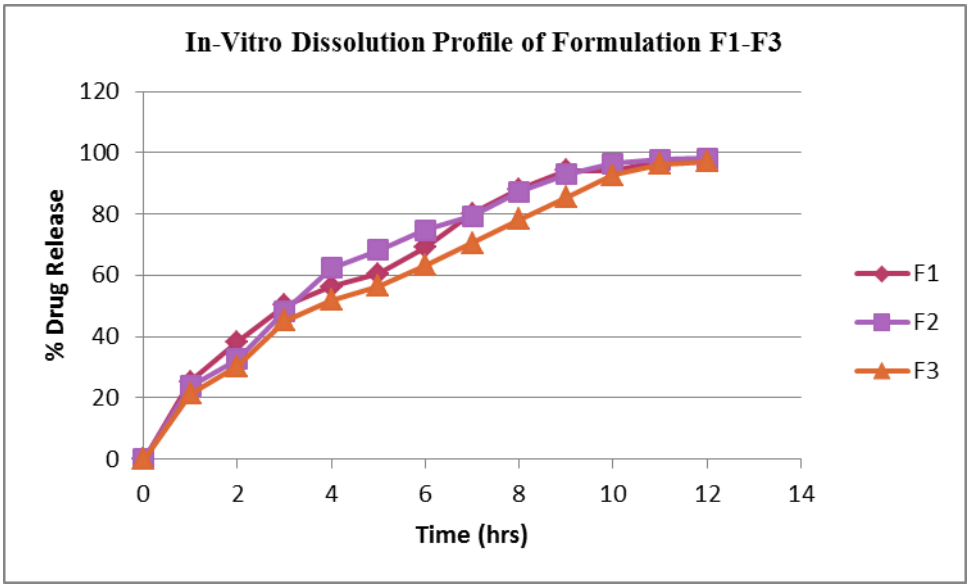

Figure 4 In-Vitro Dissolution Profile of formulation F1-F3

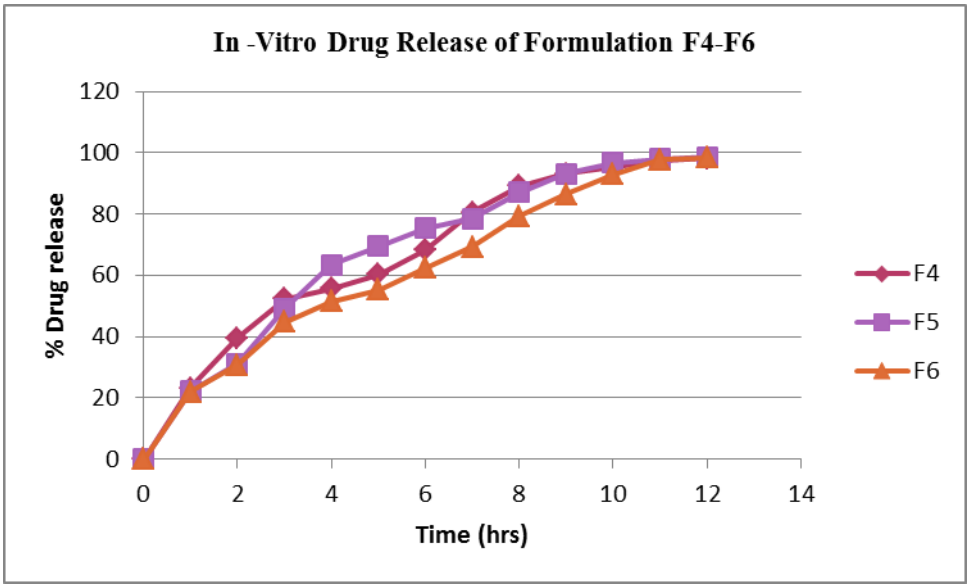

Figure 5 In-Vitro Dissolution Profile of formulation F4-F6

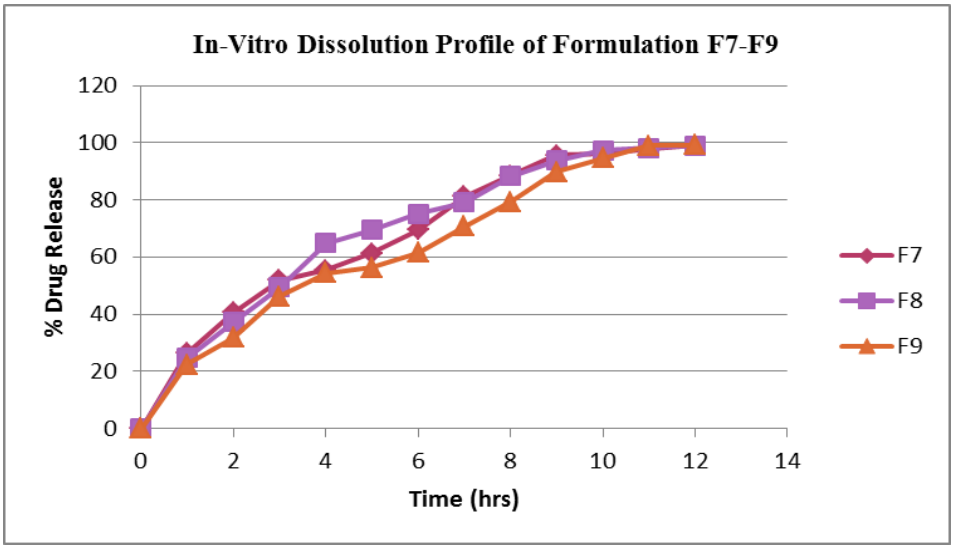

Figure 6 In-Vitro Dissolution Profile of Formulation F7-F9

RESULTS AND DISCUSSION

The formulations F1 to F9 showed acceptable range of different pre-compression & post compression parameters like angle of repose, Carr's index, hardness, thickness, friability, drug content etc.

The matrix tablets of formulations F1 to F3 consist of HPMC K 4M as polymer. The release rate of the formulation was in order F1>F2>F3 up to 3 hrs. Then F2> F1>F3 up to 10-11 hrs. The release rate of formulation F3 was 97.01 at an interval of 12 hrs & of formulation F2 was found to be 98.05 at 12 hrs.

The order of drug release for formulation F4 to F6 containing polymer HPMC K 15M was found to be F4>F5>F6 up to 3 hrs, then F5>F4>F6 up to 11 hrs. The release rate of formulation F6 was found to be 98.37 & of formulation F5 was found to be 98.64 at 12 hrs.

For formulations F7 – F9 containing polymer HPMC K 100M the order of drug release was found to be F7>F8>F9 up to 3hrs. Then F8>F7>F9 up to 10 hrs: F9>F8>F7 for 11-12 hrs.

The formulation F9 shows most significant result in terms of sustained release & in-vitro dissolution rate. Thus Formulations F7-F9 containing polymer HPMC K 100M were found to be the best one.

Stability studies for the optimized batch were conducted as per ICH guidelines. The matrix integrity of the tablets shows not much variation at different temperature & relative humidity conditions. Various parameters like drug content, friability, hardness, physical stability, drug release etc. for the optimized formulation F9 were found to be significant after 90 days.

CONCLUSION

Using polymers HPMC K4M, HPMC K15M, & HPMC K100M; croscarmellose as swelling agent sustained release matrix tablets of repaglinide were successfully prepared. FTIR studies shows that drug & polymer are compatible with each other. On the basis of in-vitro release studies it has been concluded that formulation F9 shows the best drug release for an extended period of 12hrs. It was also concluded that with increase in drug polymer ratio the release rate of drug is decreased thereby sustaining its action. Thus, results suggest that formulated sustained release tablets of repaglinide could overcome their counterparts & lead the market.

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