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Formulation and evaluation of solid matrix tablets of repaglinide

Jitender Joshi, Lata Bhakuni and Sachin Kumar

N K B R College of Pharmacy and Research Centre, Meerut, India

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ABSTRACT

An appropriately designed controlled-release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target tissue. Matrix tablets are an interesting option when developing an oral controlled release formulation. The aim of this study is to develop a once-daily sustained release matrix tablet of Repaglinide using sodium alginate as release controlling factor. In order to achieve required sustained release profile tablets were compressed using sodium CMC, sodium alginate, Magnesium Stearate, and PVP. Six different formulation of Repaglinide were prepared by using different ratio of drug: polymer. The tablet was characterized by hardness, wetting time, weight variation and In Vitro Drug Release which shows the satisfactory result. All batches of solid matrix tablets were satisfactory in terms of dissolution profile. The batches of all formulations, MT5 batch [Sodium CMC With drug (1:3)] showed more release than the other concentration and better results. The MT5 batch of Solid matrix tablets was found to be 96.0 % drug release in 300 minutes.

Keywords: Repaglinide, Matrix tablets, Sodium alginate, Sodium CMC.

INTRODUCTION

The use of controlled-release technology in the formulation of pharmaceutical product is becoming increasingly important. Controlled drug delivery involves the application of physical and polymer chemistry to produce well characterised and reproducible dosage forms, which control drug entry into the body within the specifications of the required drug delivery profile [l].

The matrix form release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials [2].

Rate of drug release is mainly controlled by the delivery system itself, though it may be influenced by external conditions, such as pH, enzymes, ions, motility and physiological conditions [3].

The performance of matrix tablets is strongly dependent on the matrix materials used, which are normally synthetic or semi-synthetic polymer [4]. Drug release also depends on other factors such as pore permeability, shape and size of matrix, drug solubility, polymer molecular weight, drug loading, compression force and hydrodynamic conditions [5, 6].

Matrix Tablets advantages

1. Simplicity of formulation
2. High drug loading
3. Reduction in drug blood level fluctuations

4. Reduction in dosing frequency
5. Reduction in adverse side effects and
6. Reduction in health care costs i.e., economy [7].

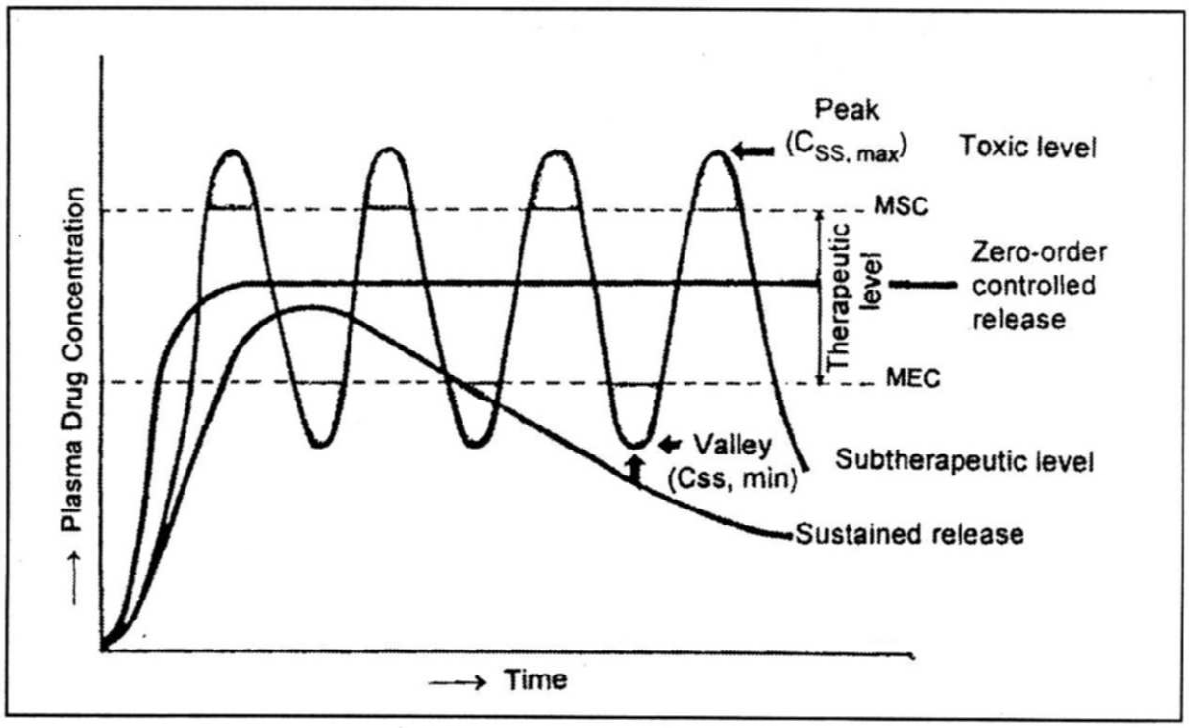


Fig. 1: Plasma level profiles following conventional sustained and controlled release dosing.

Disadvantages of the matrix systems:[7,13]
1. The remaining matrix must be removed after the drug has been released.
2. The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

MATERIALS AND METHODS

Repaglinide was received as gift sample from Torrent Pharmaceuticals Limited, Gujarat, India. Sodium alginate, Sodium CMC, PVP and Magnesium Stearate were supplied by Central Drug House (P) Ltd., New Delhi.

2.1 Calibration Curve of Repaglinide in 6.8 Ph Phosphate Buffer:

2.1.1 Preparation of 6.8 pH phosphate buffer [8]:

- Prepare a 0.2 M solution of potassium dihydrogen phosphate by dissolving 27.218 gm of substance in 1000 ml of distilled Water.
- Prepare a 0.2 M solution of sodium hydroxide solution by dissolving 8 gm of substance in 1000 ml of distilled Water.
- Take 50 ml of above prepared potassium dihydrogen phosphate solution & 22.4 ml of above prepared sodium hydroxide solution. Add both the solution & make the volume of the resultant solution 200 ml. Calibrate the solution for using pH meter & adjust the pH 6.8.

2.1.2 Preparation of stock solution:

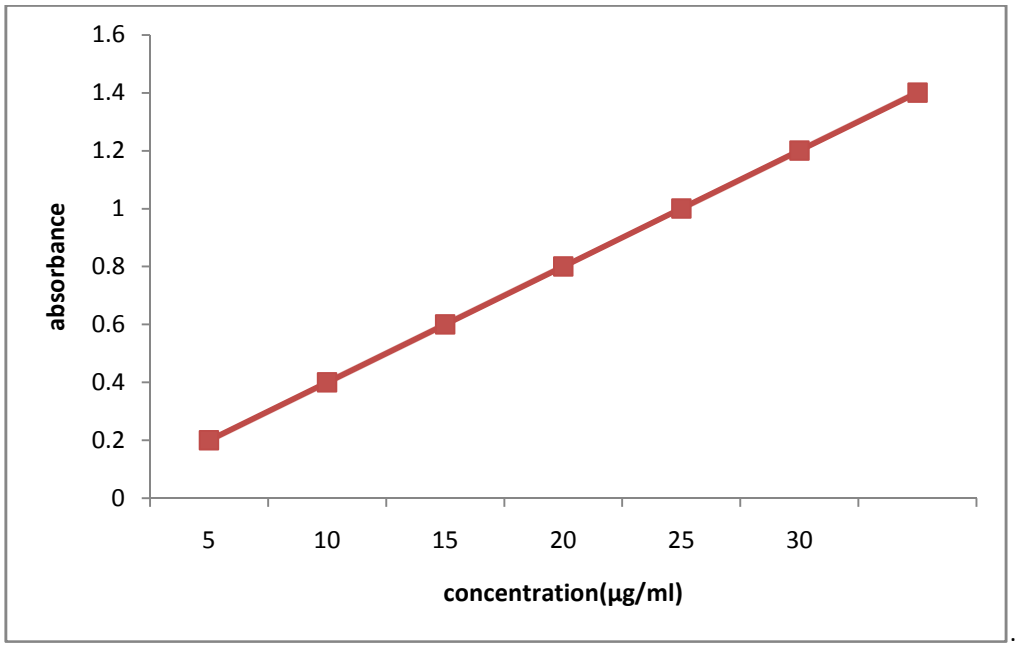
Dissolve 10 mg of Repaglinide in few ml of phosphate buffer by taking 100 ml volumetric flask & make up the volume 100 ml to get a solution of 100 mcg/ml concentration solutions.

2.1.3 Procedure:

Prepare different concentrations from 10 mcg/ml to 60 mcg/ml by diluting stock solution as for first concentration 10 mcg/ml, take 1 ml of stock solution & dilute with 10 ml of buffer solution. Similarly other concentrations are prepared .Absorbance are measured at 231nm for each concentration by using UV spectrophotometer (UV-3000, Lab India). Concentration are plotted against absorbance on a graph paper.

TABLE No – 1

S.No	Concentration(µg/ml)	Absorbance
1	2.5	0.115
2	5.0	0.212
3	7.5	0.345
4	10.0	0.482
5	12.5	0.557
6	15.0	0.670
7	17.5	0.798
8	20.0	0.905
9	22.5	1.101
10	25.0	1.215



Calibration curve for: Repaglinide
Solvent / Mobile Phase: Buffer (pH 6.8)
Wavelength (nm): 231 nm

TABLE No- 2

S. NO	INGREDIENT	MT 1	MT 2	MT 3	MT 4	MT 5	MT 6
	Drug : Polymers	1:1	1:1.5	1:2	1:2.5	1:3	1:0
1	Repaglinide	50	50	50	50	50	50
2	Sodium Alginate	50	75	100	125	150	-
3	Sodium CMC	145	115	95	70	45	195
4	PVP	50	50	50	50	50	50
5	Magnesium Stearate (W/W)	1% W/W	1% W/W	1% W/W	1% W/W	1% W/W	1% W/W

2.2 Formulation Development [9]:
Different 6 batches of tablets prepared by wet granulation method. Six different batches of tablets were prepared by taking drug: polymer ratio 1:1, 1:1.5, 1:2, 1:2.5 1:3 1:0. Thus total six batches were prepared (Different combination shown in table 2).

2.2.1 Sieving: Mg. Stearate was sieved through #60 mesh.
2.2.2 Granulation: All the ingredients were mixed in increasing order of weights. The binding solution of PVP in Isopropyl alcohol was used as granulating solvent. The granules were made using #40 mesh. Then granules were dried in oven at 40ºC for 15 min.

2.2.3 Compression: The tablets were compressed on a single punch tableting machine
(Bells India Marketed and Manufactured by Meditron Ing. New Delhi) for 250 mg tablet.

3. Evaluation of Tablets:-
The tablets were evaluated for appearance, hardness, friability and In-vitro drug release.

3.1 Bulk density [9]:
Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight "as it is.

Where, p b =Bulk Density"

M = Weight of sample in gm
V = Final volume of blend in cm 3

3.2 Tapped density [9]:
It was determined by placing known mass of powder in a graduated cylinder & tapping it for fixed number of taps (around 250) until the powder bed volume reached a minimum. Using the weight of the powder in the cylinder and this volume, the tapped density was computed.

3.3 Angle of repose [9]:
The angle of repose was calculated with the formula tan a =H/R, where 'a' is the angle of repose and R is the radius of the conical pile.

Therefore $\theta = \text{Tan-1 } h/r$

Where θ = Angle of repose
h = height of the cone
r= Radius of the cone base
Angle of Repose less than 30 ° shows the free flowing of the material

3.4 Compressibility Index [9]:
The compressibility index of the granules was determined by Carr's compressibility index.

Pb=M/Vp

$\text{Tan } \theta = h/r$

Where, TBD= Tapped bulk density
LBD= Lowest bulk density
%Carr Index= (TBD-LBD) ×100/TBD

3.5 Hardness [6, 8]:
Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of tablets was measured using a Monsanto hardness Tester.

3.6 Friability [8, 9]:
It is a measure of mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure: Preweighed tablets were placed in the Roche friabilator (Electro lab EFL Friabilator, Mumbai, India) and expressed in the percentage by using this formula.

$$\text{Friability}(\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

3.7 Weight variation study [6, 8, and 10]:
With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of a tablet being made is routinely measured to ensure that a tablet contains proper amount of drug. 20 Tablets were taken from each batch. The tablets were weighed and the mean was calculated. The following formula was applied for checking deviation from normal range as per U.S.P. standards.

3.8 Water absorption ratio and wetting time [8]:
A piece of tissue paper folded twice was placed in a Petridish containing 5ml of water. A pre weighed tablet was placed on the paper and the time for complete wetting was measured which is characterized by coloring of tablet. The wetted tablet was then weighed. Water absorption ration
R was determined according to the following formula.

R = (Wa- Wb/ Wb) 100

Where, Wa = weight of tablet after absorption of water
Wb= weight of tablet before absorption of water

3.9 In vitro Dissolution studies [7, 8 and 12]:
In vitro dissolution studies of solid matrix tablets were performed by using (type 2 USP dissolution) apparatus as specified in at 50 rpm; and Sorenson's buffer (pH,6.8), 900 ml, was used as dissolution medium, temperature of dissolution medium was maintained at 370C±0.50C.

Sample of dissolution medium was withdrawn at a specific time interval and was filtered. Absorption of filtered solution was checked by UV spectroscopy (Lab India UV 3000), and drug content was determined from standard calibration curve. Dissolution rate was studied for all designed formulation.

Six formulations of solid matrix tablets of Repaglinide were prepared with varying concentration of Sodium alginate, Sodium CMC, Magnesium stearate and PVP were used as diluents (Table. No.2). For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique.

Table no. 3- Evaluation data of Micromeritic property of bulk powder blend

	MT1	MT2	MT3	MT4	MT5	MT6
Bulk Density (gm/cm3)	0.780	0.550	0.654	0.530	0.721	0.731
Tapped Density (gm/cm3)	0.890	0.690	0.831	0.673	0.819	0.847
Angle of Repose (0)	25.34	25.34	25.66	26.47	25.98	24.64
Compressibility Index (%)	12.98	11.65	12.26	11.72	13.60	12.14

Bulk density, was found in the range of (0.53-0.78 gm/cm^3) and the tapped density between (0.69-0.89 g/cm3). The compressibility index was found between (11.65-13.60) which indicates a fairly good flowability of the powder blend. The good flowability of the powder blend was also evidenced with angle of repose in the range of (24.64-26.47) which is below 40 indicating good flow properties of the granules (Table no.3)

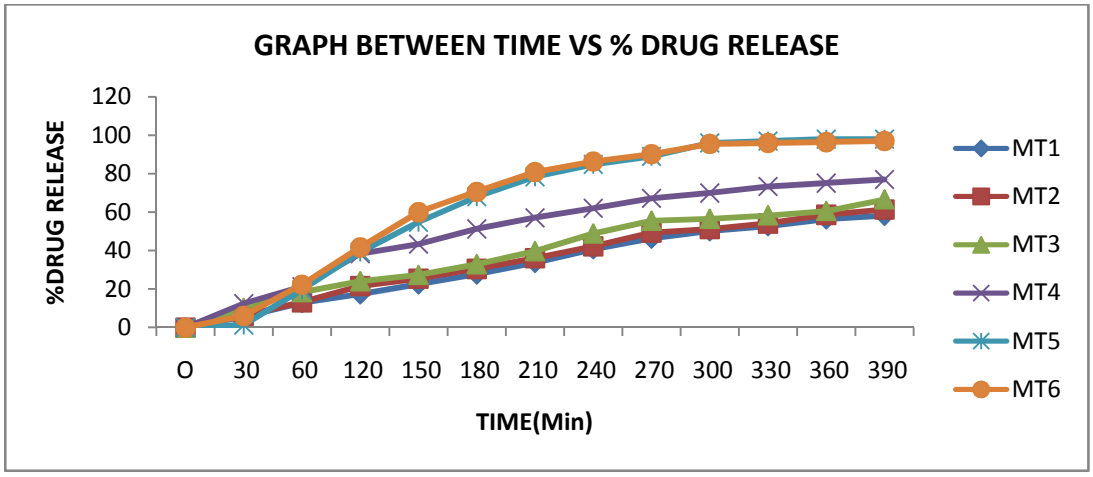
Table no. 4- Evaluation data of compressed tablets of different formulations

	MT1	MT2	MT3	MT4	MT5	MT6
Hardness (kg/cm2)	**4.2**	**3.5**	**3.9**	**4.3**	**4.2**	**3.9**
Friability (%)	**0.44**	**0.51**	**.53**	**0.42**	**0.43**	**0.57**
Weight variation(mg)	**250.2**	**251.6**	**250.4**	**251.0**	**249.5**	**251.3**

(Table no.4).

S. No	Time (Minute)	% Cumulative Release					
		MT1	MT2	MT3	MT4	MT5	MT6
1	0	0	0	0	0	0	0
2	30	5.526	6.227	10.23	12.419	1.325	6.043
3	60	12.819	13.207	18.434	21.169	19.726	22.245
4	120	17.254	21.558	24.108	38.386	39.215	41.658
5	150	22.402	25.421	27.354	43.351	54.784	59.964
6	180	27.623	30.493	32.943	51.328	68.074	70.572
7	210	33.669	36.084	39.732	57.073	78.354	80.843
8	240	40.684	42.258	48.864	62.011	84.849	86.324
9	270	46.224	49.366	55.485	67.194	89.064	90.128
10	300	50.106	51.233	56.515	69.969	96.006	95.458
11	330	52.637	54.134	58.297	73.351	97.043	96.023
12	360	56.265	58.658	60.579	75.086	97.988	96.389
13	390	58.104	61.359	66.573	76.981	98.001	96.945

Tablets were prepared using wet and direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P. The average weight of the prepared tablet was found 249 to 252 mg. All the tablets were exhibit in white colour, odourless, smooth surface with zero defects. A tablet requires certain amount of hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The friability of all the formulation was found to be less than 1.0 %. The hardness of the prepared tablet varied from 3.5 to 4.3 Kg/cm2 which have satisfactory strength to withstand the mechanical shocks.



The % drug release of different batches with time shown in (Table no.5) and shown 98 % show more release with drug polymer ratio 1:3. All the formulations showed no significant variation in all the parameters under the test per guideline.

CONCLUSION

The Solid Matrix Tablets have potential advantages over conventional dosage forms, with their improved patient compliance; convenience bioavailability and reduction in health care cost had drawn the attention of many manufacturers over a decade. The preparation process of direct compression tablets includes co-grinding of all the excipients before compression, resulting the increase in the solubility due to the reduction in the effective particle size of the drug following increase in the wetting of drug particle by the excipients and improved dissolution of drugs.

Solid Matrix Tablet formulation obtained by some of these technologies has sufficient Sustained action in plasma and maintain therapeutic concentration.

In conclusion, overall results suggests that the SMTs containing sodium CMC and Sodium alginate in which Sodium alginate with drug the ratio of 1:3 (MT5) shows best results in terms of percent drug release, compressibility index, hardness and disintegration time. Thus SMTs may be developed for sustained release, for maintaining therapeutic concentration and provide better patient compliance. However further studies are investigations are needed to confirm the in vivo efficiency and for the development of Matrix Tablet.

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