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Development and Evaluation of Controlled Release Tablets of Pravastatin for Cardiovascular Disease

Janagam Venkata Rajkumar[1*], V. Vanitha[1], T. Kiran [2], T. Shyam[2]

[1]Department of Pharmacy, KLR College of Pharmacy, Telangana, India; [2]Department of Pharmacy, MRM College of Pharmacy, Telangana, India

[*]***Corresponding Author:*** *Janagam Venkata Rajkumar, Department of Pharmacy, KLR College of Pharmacy, Telangana, India*

E-mail: janagam.raj@gmail.com

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ABSTRACT

Pravastatin is a statin medication, used preventing cardiovascular disease in those at high risk and treating abnormal lipids. It should be used together with diet changes, exercise, and weight loss. It is taken by mouth. In the present work, an attempt has been made to develop controlled release tablets of pravastatin by selecting natural polymers as retarding polymers. All the formulations were prepared by direct compression method using 6 mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release i.e., 98.91% in 8 hours hence it is considered as optimized formulation. Whereas the formulations containing Xanthan gum showed more retarding with increasing concentration of polymer. The formulations with Guar gum were unable to produce the desired rug release pattern.

Keywords: Pravastatin, Polymers, Compression, Direct compression method, Kinetics

INTRODUCTION

The development of oral controlled release system has been a challenge to formulation scientist due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract [1,2]. Matrix type drug delivery system is an interesting and promising option when developing an oral controlled release system. Availability of wide variety of polymers and frequent dosing intervals helps the formulation scientist to develop sustained/controlled release products. Oral Sustained Release (S.R)/Controlled Release (C.R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance [3-5].

MATERIALS AND METHODS

Pravastatin, gum karaya, xanthan gum, guar gum, magnesium stearate, talc, MCC pH 102 all the chemicals used were laboratory grade [6].

Formulation of pravastatin controlled release tablet by direct-compression: Composition of preliminary trials for pravastatin controlled release tablet by direct compression is shown in Table 1. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 12 mm flat punch, B tooling. Each tablet contains 10 mg of pravastatin and other pharmaceutical ingredients.

Table 1: Different formulation of pravastatin controlled release tablets

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Pravastatin	10	10	10	10	10	10	10	10	10	10	10	10
Gum karaya	10	20	30	40	-	-	-	-	-	-	-	-
Xanthan gum	-	-	-	-	10	20	30	40	-	-	-	-
Guar gum	-	-	-	-	-	-	-	-	10	20	30	40
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
MCC pH102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total	100	100	100	100	100	100	100	100	100	100	100	100
Note: All ingredients are expressed in mg only.												

Evaluation of post compression parameters for prepared Tablets: The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

RESULTS AND DISCUSSION

Standard calibration curve of pravastatin:

It was found that the estimation of pravastatin by UV spectrophotometric method at λ_{max} 298 nm in 0.1 N hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2 µg/ml-10 µg/ml. The regression equation generated was y=0.0636 x+0.0751 shown in Table 2 and Figure 1.

Table 2: Concentration and absorbance obtained for calibration curve of pravastatin in 0.1 N hydrochloric acid buffers (pH 1.2)

Concentration (µg/ml)	Absorbance* (at 298 nm)
2	0.193
4	0.34
6	0.461
8	0.579
10	0.709
Note: Correlation coefficient=0.9985 y=0.0636 x+0.0751	

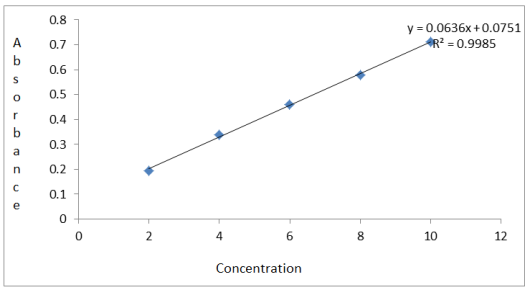

Figure 1: Standard graph of Pravastatin in 0.1 N HCl

It was found that the estimation of pravastatin by UV spectrophotometric method at λ_{max} 299 nm in pH 6.8 phosphate buffer. Had good reproducibility and this method was used in the study? The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2 µg/ml-10 µg/ml. The regression equation generated was y=0.0595 x+0.083 shown in Table 3 and Figure 2.

Table 3: Concentration and absorbance obtained for calibration curve of pravastatin in pH 6.8 phosphate buffer

Concentration (µg/ml)	**Absorbance* (at 299 nm)**
2	0.193
4	0.331
6	0.446
8	0.553
10	0.677
Note: Correlation coefficient=0.9982 y=0.0595 x+0.083	

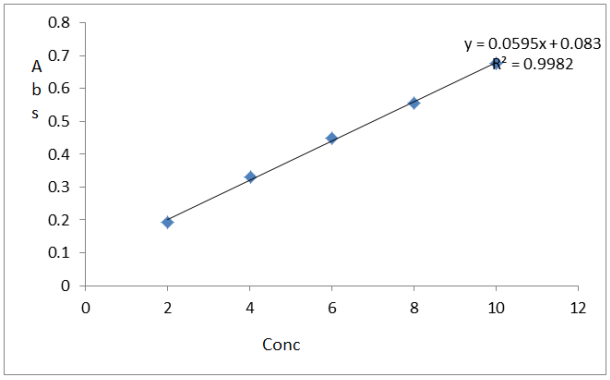

Figure 2: Standard graph of pravastatin in pH 6.8 phosphate buffer

Evaluation parameters for extended release tablets of pravastatin

Pre-compression parameters: The data's were shown in Table 4. The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ratio n fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 4: Pre-compression parameters

Formulations	**Bulk density (gm/cm²)**	**Tap density (gm/cm²)**	**Carr's index (%)**	**Hausner ratio**	**Angle of repose (Ɵ)**
F1	0.45	0.55	18.18	1.22	27.91
F2	0.47	0.55	14.54	1.17	28.23
F3	0.5	0.58	13.79	1.16	29.34
F4	0.46	0.55	16.36	1.19	26.71
F5	0.5	0.58	13.79	1.16	29.34

F6	0.47	0.55	14.54	1.17	28.23
F7	0.5	0.58	13.79	1.16	29.34
F8	0.41	0.5	18	1.21	26.78
F9	0.41	0.5	18	1.21	26.78
F10	0.42	0.51	18.24	1.2	26.68
F11	0.48	0.56	18.12	1.21	26.7
F12	0.41	0.54	18.11	1.22	26.71

Post compression parameters

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 5. The average weight of the tablet is approximately in range of 95 to 105 mg, so the permissible limit is ± 5% (>220 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 5. The results showed that the hardness of the tablets is in range of 4 kg/cm^2 to 4.5 kg/cm^2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table. 5. The result showed that thickness of the tablet is ranging from 1.00 mm to 1.14 mm.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 5. The average friability of all the formulations lies in the range of 0.30% to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23%-99.25%.

Table 5: Post-compression parameters

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	104	4.5	1.5	0.43	97.23
F2	104	4.3	1.5	0.34	98.55
F3	100	4.2	1.5	0.49	98.16
F4	105	4.2	1.4	0.47	99.34
F5	102	4.3	1.5	0.49	98.16
F6	98	4.3	1.5	0.34	98.55
F7	100	4.4	1.4	0.49	98.16
F8	104	4.5	1.5	0.34	99.25
F9	106	4.4	1.5	0.34	99.25
F10	101	4.4	1.5	0.43	98.6
F11	102	4.3	1.5	0.54	98.7
F12	104	4.5	1.5	0.43	98.5

***In vitro* dissolution studies:** *In vitro* dissolution studies were carried out by using 900 ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffers were added to the dissolution medium (900 ml) and the dissolution was carried out for about 6 hours. The samples were withdrawn at regular time intervals of 30 min, 1, 2, 3, 4, 5, 6, 7 and 8 hours respectively (Table 6). The results were displayed in Figures 3-5.

Table 6: *In vitro* dissolution data of different formulations

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	25.5	20.1	16.4	11.4	15.4	10.4	9.4	8.5	49.5	38.2	26.4	18.9
1	46.7	39.4	26.7	18.6	29.4	16.5	15.6	14.5	78.8	41.9	38.2	28.3

2	76.5	55.3	34.6	29.5	38.5	28.6	21.4	18.4	96.9	62.4	43.4	36.4
3	98.4	75.3	42.4	39.5	55.4	39.5	36.7	23.4	96.1	78.2	59.3	49.5
4		87.3	55.4	49.6	68.4	48.5	42.4	28.2		81.4	76.3	69.3
5		99.4	67.4	57.4	87.1	59.4	49.6	34.8		96.8	88.4	78.1
6			85.4	69.3	98.3	69.2	55.3	40.2			95.4	89.7
7			91.5	78.5		74.5	60.3	44.8			98.5	97.5
8			98.91	82.3		82.3	72.8	50.4				

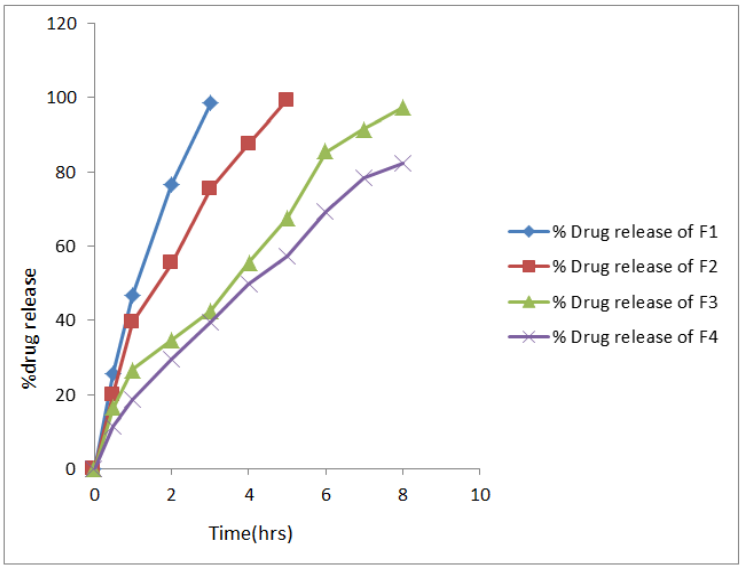

Figure 3: Dissolution profile of formulations prepared with GUM KARAYA polymer

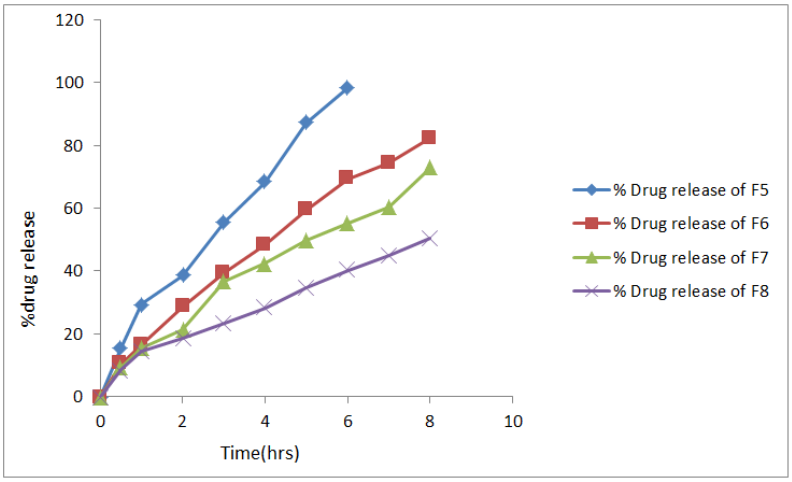

Figure 4: Dissolution profile of formulations prepared with xanthan gum polymer

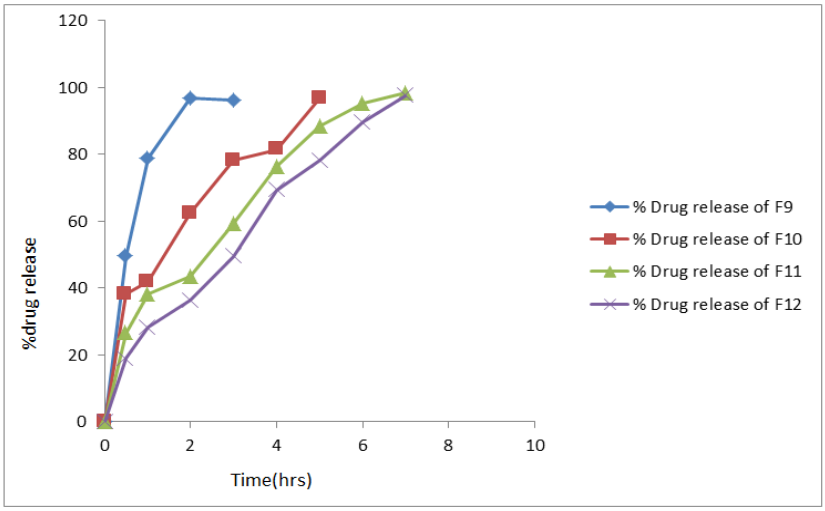

Figure 5: Dissolution profile of formulations prepared with guar gum as polymer

From the tabular column 6 it was evident that the formulations prepared with GUM KARAYA as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. Gum karaya in the concentration of 30 mg showed good % drug release *i.e.*, 98.91 in 8 hours. Whereas in the concentration of 40 mg it showed less drug release due to increased retarding nature of polymer. Whereas in case of formulations prepared with xanthan gum as retarding polymer, the formulations with 10 mg concentration of polymer showed complete drug release in 6 hours only, whereas the concentration of polymer increases the retarding nature also increased. The formulation containing xanthan gum in 20 Mg concentration showed good retarding nature with required drug release in 8 hours *i.e.*, 82.3%. Whereas in case formulations prepared with Guar gum as retarding polymer, as the concentration of polymer increases the retarding nature was also increased. When compared with HPMC polymers it was failed to produce desired drug release pattern. From the above results it was evident that the formulation F3 is best formulation with desired drug release pattern extended up to 8 hours as shown in Table 6 and Figures 3-5.

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. From the below graphs it was evident that the formulation F3 was followed Zero order release mechanism as shown in Table 7 and Figures 6-9.

Table 7: Release kinetics data for optimized formulation

Cumulative (%) release q	Time (t)	root (t)	Log (%) release	log (t)	Log (%) remain
0	0	0			2
16.4	0.5	0.458	1.215	1.987	1.922
26.7	1	0.707	1.427	-0.301	1.865
34.6	2	1	1.539	0	1.816
42.4	3	1.414	1.627	0.301	1.76
55.4	4	1.732	1.744	0.477	1.649
67.4	5	2	1.829	0.602	1.513
85.4	6	2.236	1.931	0.699	1.164
91.5	7	2.449	1.961	0.778	0.929
98.91	8	2.646	1.995	0.845	0.037

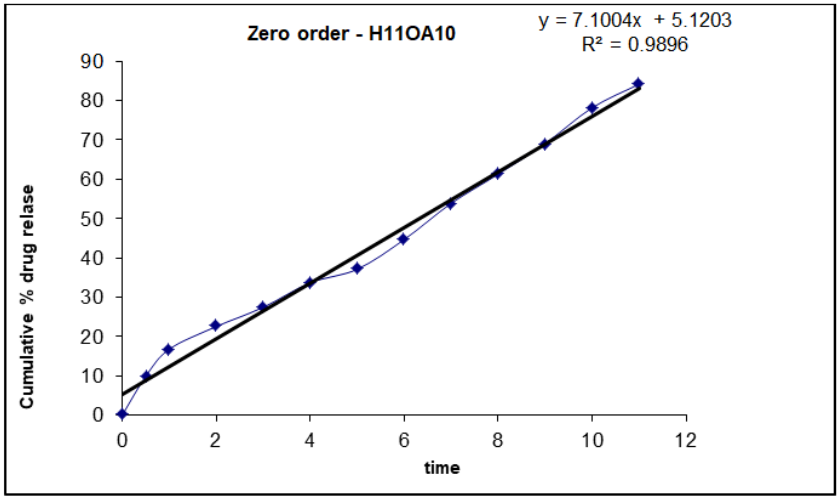

Figure 6: Zero order release kinetics graph

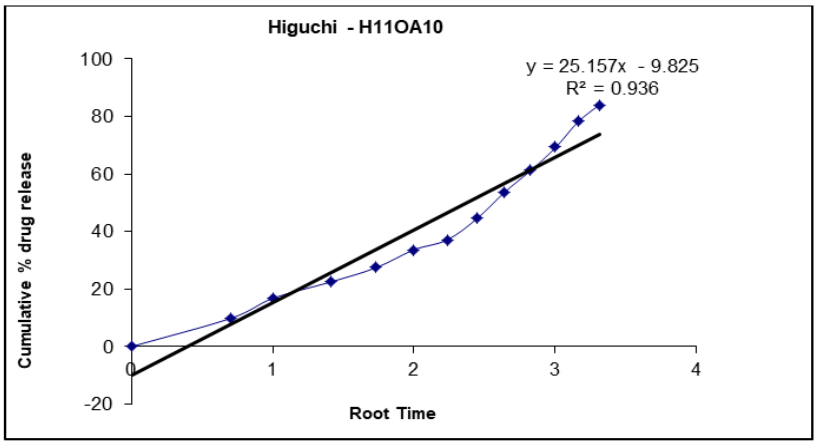

Figure 7: Higuchi release kinetics graph

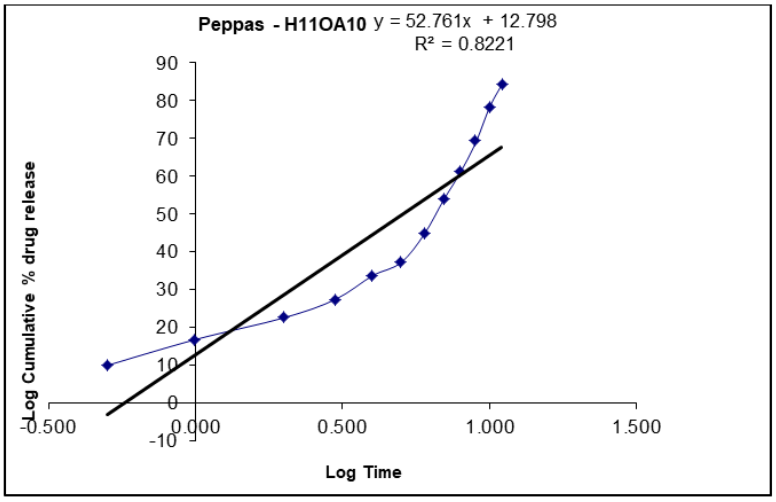

Figure 8: Kars mayer peppas graph

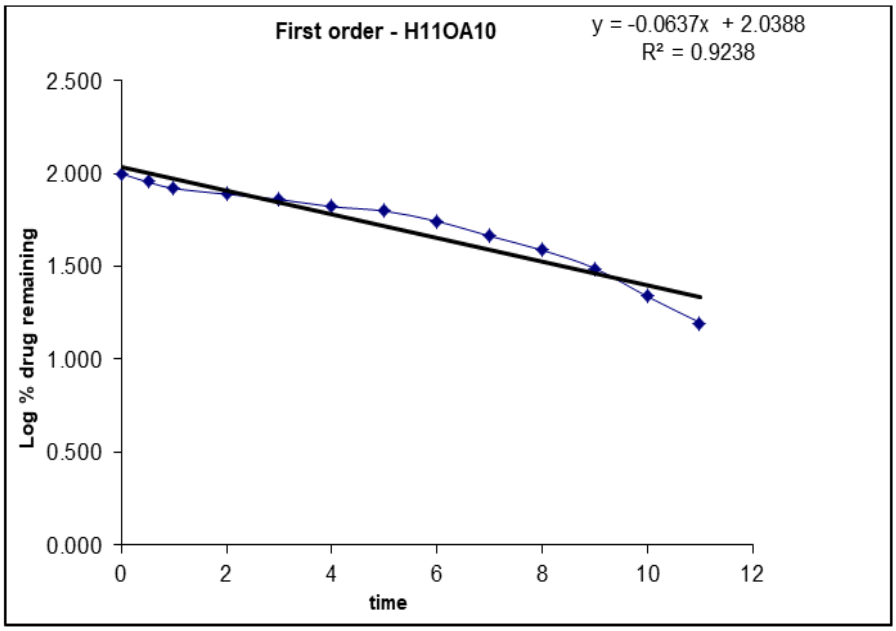

Figure 9: First order release kinetics graph.

CONCLUSION

In the present work, an attempt has been made to develop Controlled release tablets of Pravastatin by selecting natural polymers as retarding polymers. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release *i.e.,* 98.91 % in 8 hours hence it is considered as optimized formulation. Whereas the formulations containing Xanthan gum showed more retarding with increasing concentration of polymer. The formulations with Guar gum were unable to produce the desired rug release pattern.

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