ISSN: 2349-5448

International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Vol.7 | Issue 4 | Oct - Dec -2023

www.ijpcr.com

DOI : https://doi.org/10.61096/ijpcr.v7.iss4.2023.264-274

Research

Formulation And *In Vitro* Evaluation Of Sustained Release Matrix Tablets Of Metoprolol

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Published on: 20 Oct 2023

Published by:
DrSriram Publications

Abstract

In the present work, an attempt has been made to develop Sustained release tablets of Metoprolol by selecting natural polymers Tragacanth, Acacia gum, and Xanthan gum as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed good 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 F4 formulation showed maximum % drug release i.e., 99.63 % in 12 hours hence it is considered as optimized formulation F4 which contains Acacia gum (50 mg). Optimized formulation F4 was followed Higuchi release kinetics mechanism.

Keywords: Metoprolol, Tragacanth, Acacia gum, Xanthan gum and sustained release tablets.

INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing

uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Drawbacks of Conventional Dosage Forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Design and formulation of oral suatained release drug delivery system

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion.

MATERIALS AND METHODS

Metoprolol Procured From Ravoos Laboratories Limited (India). Provided by SURA LABS, Dilsukhnagar, Hyderabad, Tragacanth from Loba Chemie Pvt. Ltd Mumbai, India, Acacia gum from Merck Specialities Pvt Ltd, Mumbai, India, Xanthan gum from Aravind Remedies (AR), Chennai, India, PVP-K 30 from Unify chemicals, Jothi Aromas and DK Enterprises, India, Aerosil from S.D. Fine Chemicals. India, Magnesium Stearate from Merck Specialities Pvt Ltd, Mumbai, India, Lactose from S.D. Fine Chemicals, India

Analytical method development

Determination of λ max

100mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 100 ml volumetric flask and made it up to 100ml with the media (Secondary stock solution–100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of calibration curve

100mg of pure drug was dissolved in 10ml methanol (Primary stock solution - 1000 µg/ml). From this primary stock solution 10 ml was pipette out into 100 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Indian Pharmacopoeia.

Formulation development of Tablets

All the formulations were compress by direct compression. The compositions of different formulations are given in Table 7.4.The tablets were prepared as per the procedure given below and aim is to prolong the release of Metoprolol. Total weight of the tablet was considered as 250mg.

Procedure

1) Metoprolol and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 1: Ingredients and Uses

Ingredients	Uses
Metoprolol	API
Tragacant	Binding Agent
Acacia gum	Binding Agent
Xanthan gum	Binding Agent
PVP-K 30	Binding Agent
Aerosil	Diluent
Magnesium Stearate	Lubricant
Lactose	Anticaking agent

Table 2: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol	25	25	25	25	25	25	25	25	25
Tragacanth	50	100	150	-	-	-	-	-	-
Acacia gum	-	-	-	50	100	150	-	-	-
Xanthan gum	-	-	-	-	-	-	50	100	150
PVP-K 30	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Lactose	156	106	56	156	106	56	156	106	56
Total Weight	250	250	250	250	250	250	250	250	250

RESULT AND DISCUSSION

The present study was aimed to developing sustained release tablets of Metoprolol using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release study.

Analytical method

Graphs of Metoprolol were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 675 nm respectively.

Table 3: Observations for graph of Metoprolol in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.165

10	0.312
15	0.449
20	0.586
25	0.728

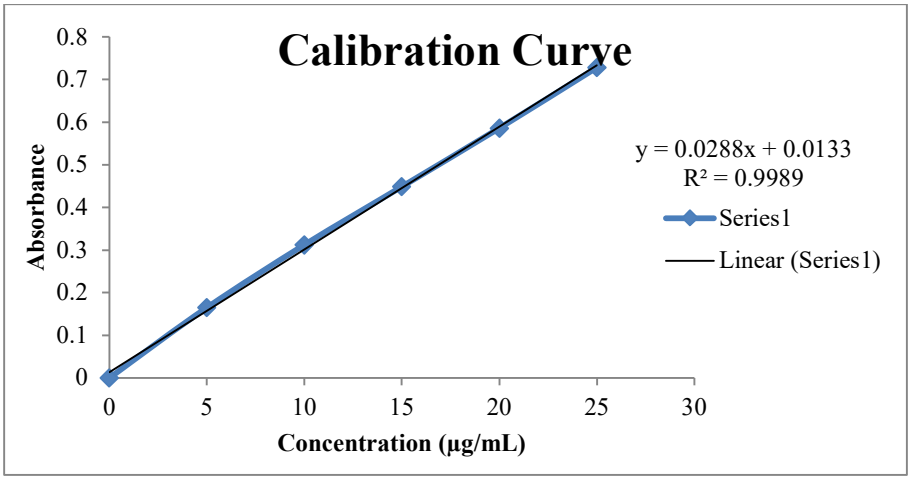

Fig 1: Standard curve of Metoprolol

Table 4: Standard graph values of Metoprolol at 675 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.173
10	0.324
15	0.468
20	0.588
25	0.751

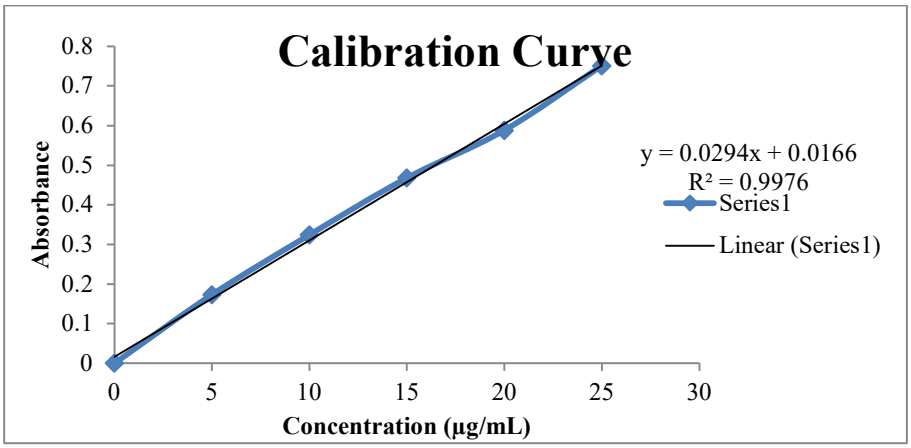

Fig 2: Standard curve of Metoprolol

Preformulation parameters of powder blend

Table 5: Pre-formulation parameters of Core blend

Formulation	Angle of	Bulk density	Tapped density	Carr's index	Hausner's

Code	Repose	(gm/ml)	(gm/ml)	(%)	Ratio
F1	25.76±0.3	0.59±0.01	0.63±0.01	10.19±0.8	1.17±0.02
F2	24.47±0.3	0.56±0.01	0.66±0.03	10.26±0.5	1.14±0.03
F3	25.86±0.2	0.53±0.06	0.64±0.03	10.33±1.0	1.11±0.06
F4	23.50±0.1	0.58±0.21	0.67±0.12	10.23±0.5	1.18±0.06
F5	22.26±0.1	0.69±0.02	0.55±0.02	11.28±0.8	1.12±0.05
F6	23.99±0.2	0.57±0.04	0.68±0.04	11.35±0.6	1.12±0.03
F7	26.64±0.1	0.55±0.04	0.69±0.05	10.12±0.7	1.19±0.09
F8	23.37±0.3	0.54±0.12	0.51±0.04	10.27±1.0	1.16±0.07
F9	24.14±0.4	0.51±0.02	0.52±0.01	10.24±0.8	1.13±0.02

All the values represent n=3

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be 10.12± 0.7 to 11.35±0.6 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio 1.11±0.06 to 1.19±0.09 indicating the powder has good flow properties.

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 6: Quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	252.85	5.7	0.78	3.11	98.22
F2	248.05	5.4	0.42	3.59	99.17
F3	253.61	5.1	0.16	3.97	100.0
F4	254.47	6.1	0.84	3.22	95.84
F5	247.83	5.9	0.59	3.68	96.97
F6	250.02	6.2	0.90	3.45	99.61
F7	246.87	5.8	0.61	3.88	97.34
F8	253.50	5.4	0.32	3.71	98.72
F9	251.75	5.5	0.34	3.32	95.20

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 246.87 to 254.47 mg, so the permissible limit is ±7.5% (>250 mg). The results of the test showed that, the tablet weights were within the limit.

Hardness test: Hardness of the five tablets of each batch was checked by using Pfizer hardness tester and the data's. The results showed that the hardness of the tablets is in range of 5.1 to 6.2 kg/cm^2, which was within IP limits.

Thickness: Thickness of five tablets of each batch was checked by using Micrometer and data. The result showed that thickness of the tablet is raging from 3.11 to 3.98 mm.

Friability: Tablets of each batch were evaluated for percentage friability and the data . The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content: Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.20 – 100.00 %. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In vitro* drug release studies**

Table 7: Dissolution data of Metoprolol tablets F1-F9

% OF DRUG RELEASE

Time (H)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	37.81	32.14	27.38	25.65	17.31	19.38	18.38	16.21	15.31
2	41.20	35.63	35.79	26.16	25.23	25.43	26.45	20.07	25.03
3	44.39	45.82	42.88	34.98	26.96	36.86	29.59	25.17	28.12
4	57.85	51.40	48.54	45.29	36.35	38.75	38.83	38.56	36.13
5	62.34	55.09	59.17	56.73	41.02	47.46	44.26	41.58	38.09
6	67.13	63.46	66.62	68.22	54.75	56.13	55.15	50.27	49.17
7	79.91	75.02	71.93	75.73	58.13	64.16	66.29	56.68	50.24
8	83.28	78.59	75.87	78.40	68.84	68.77	69.76	64.37	65.36
9	95.96	81.36	83.26	86.01	78.22	76.85	75.27	73.77	69.81
10	96.21	85.11	89.15	89.58	85.09	84.49	76.19	78.42	70.63
11	97.56	90.78	90.02	96.96	87.56	88.88	87.64	81.12	75.43
12		96.19	98.14	99.63	98.75	90.16	93.49	89.28	89.19

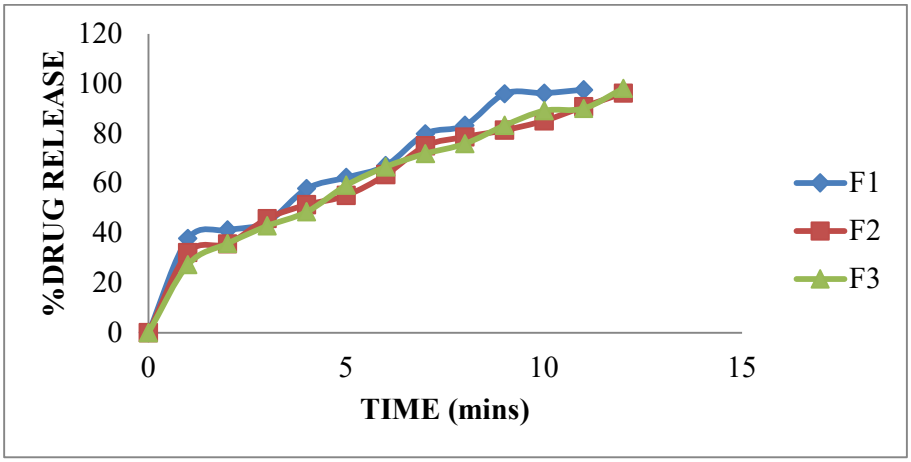

Fig 3: Dissolution profile of Metoprolol (F1, F2 and F3 formulations)

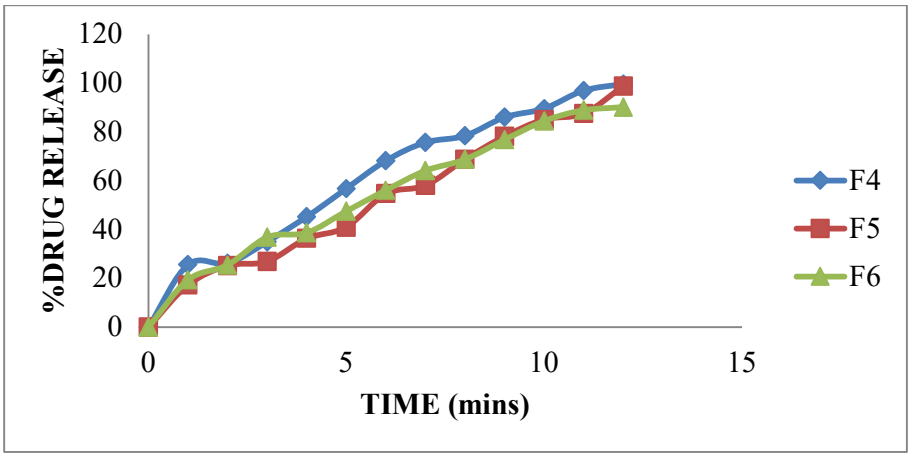

Fig 4: Dissolution prfile of Metoprolol (F4, F5 and F6 formulations)

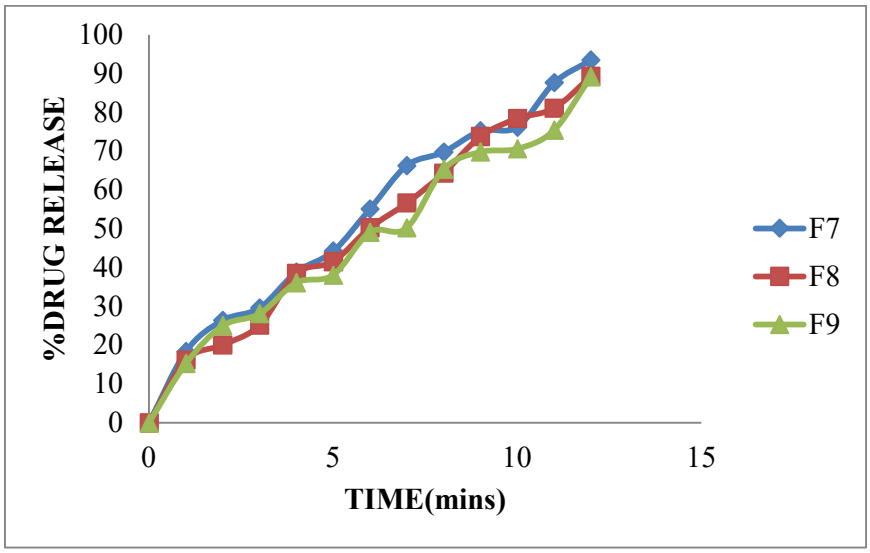

Fig 5: Dissolution profile of Metoprolol (F7, F8 and F9 formulations)

Different formulations (F1-F9) were prepared using different polymers like Tragacanth, Acacia gum and Xanthan gum alone at different ratios. Formulations F1-I3 were prepared using Tragacanth at the ratio of 1:1, 1:2 and 1:3 which showed the drug release about 97.56 % at 11h, 96.19% at 12h and 98.14 at 12h %. Formulations F4-F6 were prepared using Acacia gum at the ratio of 1:1, 1:2 and 1:3 with the drug release of 99.63%, 98.75% and 90.16% and the formulations F7-F9 were prepared by using Xanthan gum polymer at the ratio of 1:1, 1:2 and 1:3 Showed the drug release of 93.49%, 89.28% and 89.19 % at the end of 12 h. Among all these formulations F4 was selected as the best ideal formulation which exhibited 99.63% of drug release in 12 h. Finally Concluded that F4 formulation was considered as optimized formulation.

Table 6: Release kinetics

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
25.65	1	1.000	1.409	0.000	1.871	25.650	0.0390	-0.591	74.35	4.642	4.205	0.437
26.16	2	1.414	1.418	0.301	1.868	13.080	0.0382	-0.582	73.84	4.642	4.195	0.446
34.98	3	1.732	1.544	0.477	1.813	11.660	0.0286	-0.456	65.02	4.642	4.021	0.620
45.29	4	2.000	1.656	0.602	1.738	11.323	0.0221	-0.344	54.71	4.642	3.796	0.845
56.73	5	2.236	1.754	0.699	1.636	11.346	0.0176	-0.246	43.27	4.642	3.511	1.131
68.22	6	2.449	1.834	0.778	1.502	11.370	0.0147	-0.166	31.78	4.642	3.168	1.474
75.73	7	2.646	1.879	0.845	1.385	10.819	0.0132	-0.121	24.27	4.642	2.895	1.746
78.4	8	2.828	1.894	0.903	1.334	9.800	0.0128	-0.106	21.6	4.642	2.785	1.857
86.01	9	3.000	1.935	0.954	1.146	9.557	0.0116	-0.065	13.99	4.642	2.410	2.232
89.58	10	3.162	1.952	1.000	1.018	8.958	0.0112	-0.048	10.42	4.642	2.184	2.457
96.96	11	3.317	1.987	1.041	0.483	8.815	0.0103	-0.013	3.04	4.642	1.449	3.193
99.63	12	3.464	1.998	1.079	-0.432	8.303	0.0100	-0.002	0.37	4.642	0.718	3.924

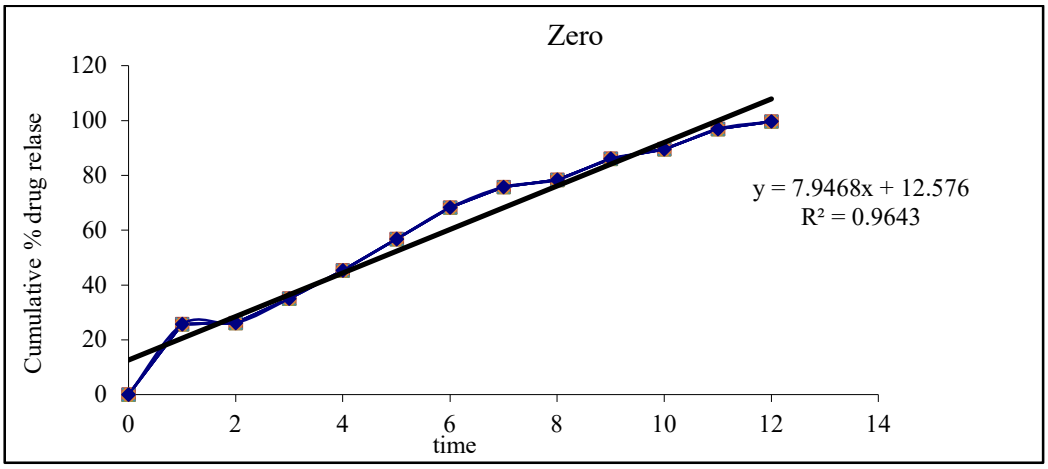

Fig 6: Zero order release kinetics graph

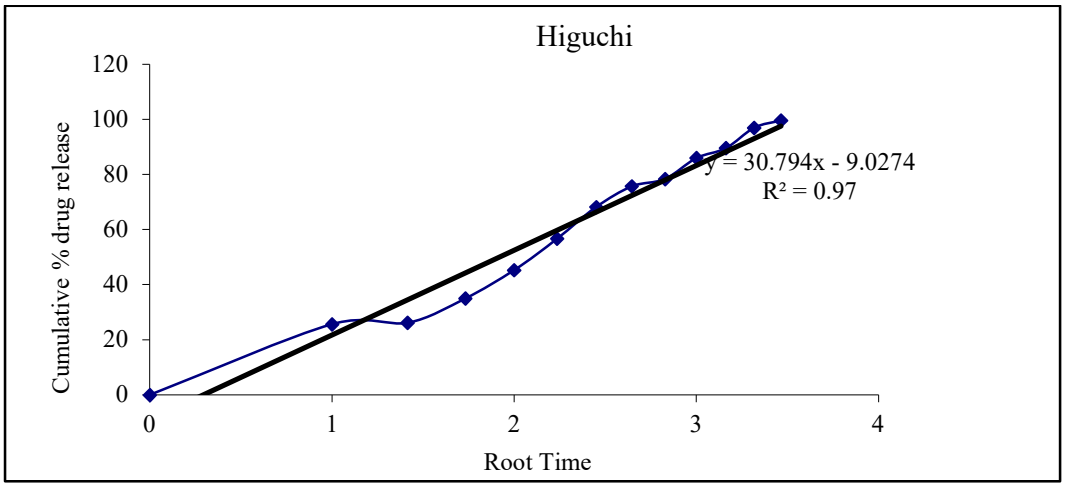

Fig 7: Higuchi release kinetics graph

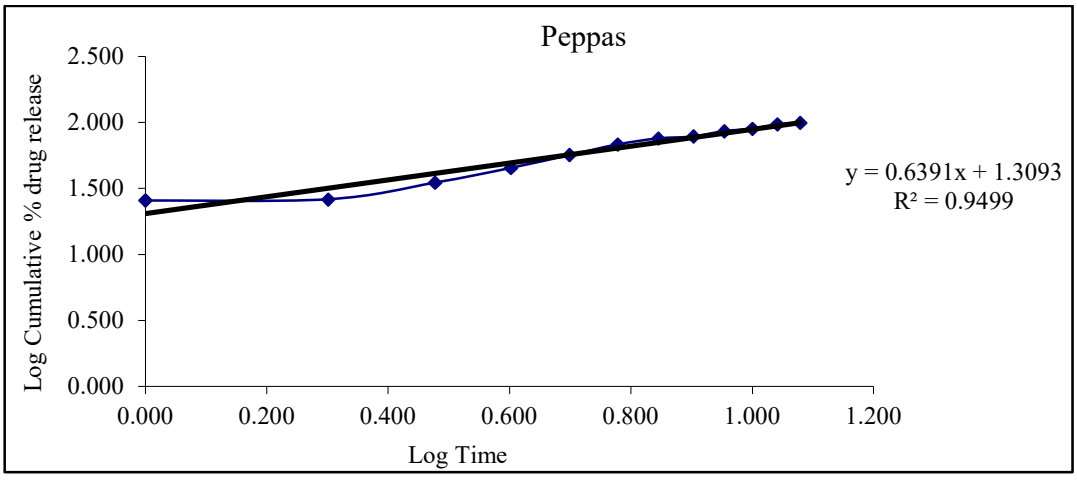

Fig 8: Peppas release kinetics graph

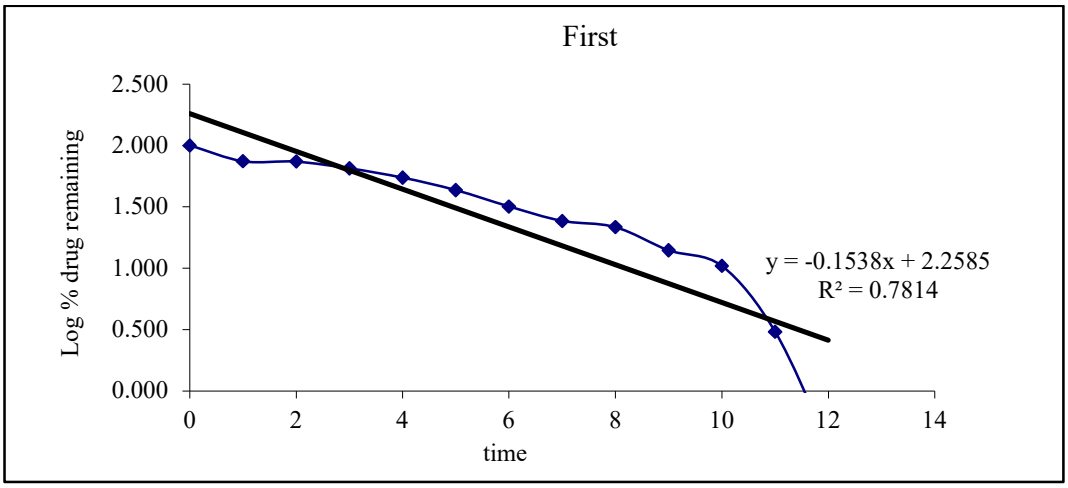

Fig 9: First order release kinetics graph

Table 7: kinetics Correlation coefficient values

Release kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.964$
Higuchi release kinetics	$R^2 = 0.970$
Peppas release kinetics	$R^2 = 0.949$
First order release kinetics	$R^2 = 0.781$

From the above graphs it was evident that the formulation F4 was followed Higuchi release kinetics mechanism.

Drug – Excipient compatibility studies

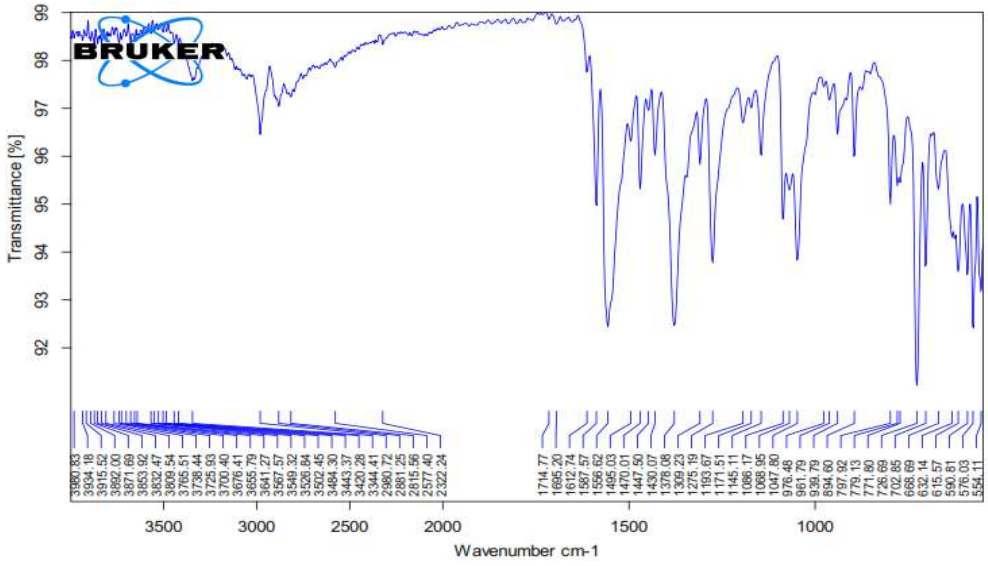

Fig 10: FT-TR Spectrum of Metoprolol pure drug

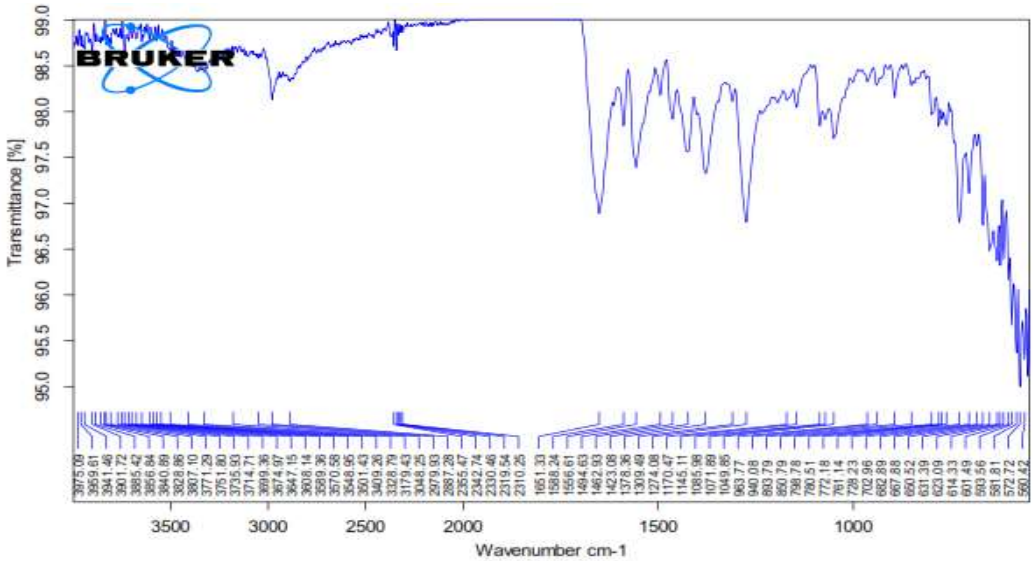

Fig 11: FT-IR Spectrum of Optimized Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Metoprolol and excipients used in the preparation of different Metoprolol Sustained release formulations. Therefore the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Metoprolol and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

CONCLUSION

The present study was carried out to evaluate the natural polymers for its matrix forming ability due to formation of thick gel structure, so we concluded that Tragacanth, Acacia gum and Xanthan gum formulated tablets were found to be effective in sustaining the drug release up to 12 hrs. During this study, it was also found that polymer concentration influences the drug release behaviour. Drug Excipient Compatibility studies revealed that there was no considerable change. FT-IR studies resulted that all peaks corresponding to different functional groups of pure drug were presents in the drug-excipient mixture no interaction between the drug and excipients. It can be concluded that stable formulation could be developed by incorporating Acacia gum polymer in a definite proportion, so that the sustained released profile is maintained for an sustained release. Release model of sample was found to follow Higuchi release kinetics mechanism with high linearity.

REFERENCES

1. Altaf AS, Friend DR, MASRx and COSRx. Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003; 1: 102-117.
2. Reddy KR., Mutalik S, Reddy S. AAPS Pharm. Sci. Tech.2003; 4: 19. 121-125.
3. Mohammed AD et al. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and Hydroxypropyl methyl cellulose. Pharm Dev Tech.1999; 4: 313-324.
4. Salsa T, Veiga F. Drug Develop. Ind Pharm. 1997; 23: 931.
5. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, inBanker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd Ed, Revised andExpanded, Drugs and the Pharmaceutical Sciences., Marcell Dekker, Inc. NewYork. 1995; 72: 575-609.
6. Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems Modern Pharmaceutics, 4thed; 2003; 121: 501-502.
7. Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind.Pharm.1999; 25: 493-501.
8. Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Ed. Modern Pharmaceutics, 3rdEd Marcel Dekker Inc. New York. 1996; 72: 575.

9. Vidyadhara S, Rao PR, Prasad JA. Indian J Pharm Sci. 2004; 66: 188-192.
10. Bogner RH. Bioavailability and bioequivalence of extended-release oral dosage forms. US Pharmacist. 1997; 22: 3–12.
11. Rogers JD, Kwan KC. Pharmacokinetic requirements for controlled-release dosage forms. In: John Urquhart, ed. Controlled-release Pharmaceuticals. Academy of Pharmaceutical Sciences. American Pharmaceutical Association. 1979: 95–119.
12. Madan PL. Sustained-release drug delivery systems, part II: Preformulation considerations. Pharm Manu fact. 1985; 2: 41–45.
13. Wani MS, Controlled Release System-A Review, 2008; 6 1: 56-62.
14. Banker GS, Anderson NR. The Theory and Practice of Industrial Pharmacy: Tablet,Lachman, (3rded) Varghese Publishing House, Bombay. 1990; 3: 293-303.
15. Lee VHL, Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design, Marcel Dekker, INC, and New York. 1987; 2: 16-29.
16. Manish R, Jayesh P, Siahboomi AR. Hydrophilic Matrices for Oral Extended Release: Influence of Fillers on Drug Release from HPMC Matrices. Pharma Times. 2010; 42(04): 67-73.
17. Kumar KP et al. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. J Chem Pharm Res. 2010; 2 1: 349-360.
18. Brahmankar DM, Sunil B. Jaishwal. “Controlled release medication” chapter 15th in “Bio pharmaceutics and Pharmacokinetics – A Treatise, 1st ed, 2010; 1: 347- 353.
19. Stanley S. Davis, Formulation strategies for abs windows. Drug Discovery Today, 2005; 10: 249-257.
20. Modi SA et al. Sustained Release Drug Delivery System:A Review.Int J Pharma. Res Dev. 2011; 2 (12): 147-160.