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Research

Formulation and *in vitro* evaluation of controlled release matrix tablets of metoprolol

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Abstract

The present study involves in the formulation and evaluation of Controlled release tablets of Metoprolol (25mg). The objective of the present study was to formulate Metoprolol Controlled release tablets by direct compression method by using Eudragit S 100, HPMC K4 M and HPMC K15 M. MCC was used as diluting agent, Magnesium stearate was used as a lubricant and Talc was used as a glident. This Controlled release the drug up to 12 hours in predetermined rate. The formulated powder blend was evaluated for bulk density, tapped density, compressibility index and angle of repose. The formulated tablets were evaluated for physical characteristics of Controlled release tablets such as thickness, hardness, friability, weight variation and drug content. The results of the formulations found to be within the limits specified in official books. The tablets were evaluated for *In-vitro* drug release studies by using USP type II dissolution test apparatus. The dissolution test was performed in 0.1 N HCL for 2 hr and phosphate buffer pH 6.8 for 12hrs. The *in-vitro* cumulative drug release profile of all formulations F1-F12 hours showed good drug release. Hence, Formulation F7 was the most promising formulation as it gives satisfactory release (98.29 %) for 12 hours and F7 found to be the best formulation.

Keywords: Metoprolol, Eudragit S 100, HPMC K4 M, HPMC K15 M and Controlled release tablets.

INTRODUCTION

Drug delivery is a technique of delivering medication to a patient in such a manner that specifically increases the drug concentration in some parts of the body as compared to others. The ultimate goal of any delivery system is to extend, confine and target the drug in the diseased tissue with a protected interaction. Every Dosage form is a combination of drug/active pharmaceutical ingredients (APIs) and the non-drug component called excipients/additives. APIs are the actual chemical components used to treat diseases.[1]

Administration of drugs into the body cavities (rectal, vaginal) can be impractical and unfeasible as they can be degraded at the site of administration (e.g., low pH in the stomach) and may cause local irritations or injury

when the drug concentration is high at the site of administration. Some APIs are sensitive to the environment and can benefit from reducing the exposure to environmental factors (light, moisture, temperature and pH), or they need to be chemically stabilized due to the inherent chemical instability. APIs mostly have unpleasant organoleptic qualities (taste, smell and compliance), which reduce patient compliance.[2,3] The glidants prevent lump formation by reducing the friction between particles and improve the flowability of the tablet granules or powder. Anti-adherents stop the powder from sticking to the machines during manufacturing. Lubricants ensure the smooth surface of dosage form, by reducing the friction between the walls of the tablets and the die cavity during ejection. Flavouring agents help to mask the unpleasant odour and colourants are added to aid in recognition and aesthetics.[4] The most common dosage forms comprise tablets, capsules, pills, ointments, syrups and injections. Various routes of drug administration are tabulated in Table 1 and Figure 3. The preferred route of drug administration depends on three main factors: The part of the body being treated, the way the drug works within the body and the solubility and permeability of the drug. For example, certain drugs are prone to destruction by stomach acids after oral administration resulting in poor bioavailability. Hence, they need to be given by the parenteral route instead. Intravenous administration of drugs gives 100% bioavailability.[5]

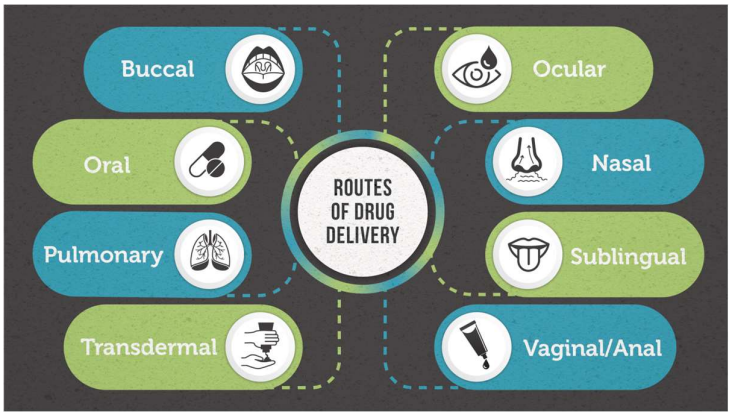
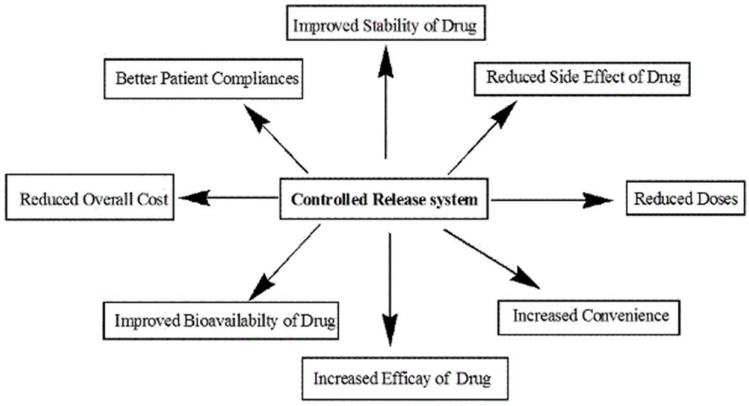


Fig 1: Drug delivery system

Drawback of conventional dosage form

- Poor patient compliance: Chances of missing of the dose of a drug.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.
- The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.[6, 7, 8]

Advantages



1] Therapeutic advantage: Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability: Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance: Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost: The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration. Avoid night time dosing: It also good for patients to avoid the at night time.

5] Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[9,10]

Disadvantages of sustained release dosage form:

1. *Dose dumping:* Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.
2. *Less flexibility in accurate dose adjustment:* In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.
3. *Poor In-vitro In-vivo correlation:* In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.
4. *Increased potential for first pass clearance*: Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating an enzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.
5. *Patient variation:* The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patients.
6. Administration of controlled release medication does not permit prompt termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if significant adverse effects are noted, cannot be accommodated.
7. There is danger of an ineffective action or even absence of it if the therapeutic substance is poorly absorbed from GIT.
8. Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make product very difficult or sometimes impossible to prepare.
9. Therapeutical agents which absorbed by active transport are not good candidates for controlled release dosage form e. g. Riboflavin.
10. Economic factors must also be taken into account, since more costly processes and equipments are involved in manufacturing of many controlled release dosage forms.[11]

MATERIALS AND METHODS

Metoprolol-Procured From Torrent Pharmaceuticals Ltd, Gujarat, India. Provided by SURA LABS, Dilsukhnagar and Hyderabad, Eudragit S 100-Jaxani Pharma, (Ahmedabad), India, HPMC K4 M-Merck Specialities Pvt Ltd, Mumbai, India, HPMC K15 M-Merck Specialities Pvt Ltd, Mumbai, India, PVP K30-Loba Chemicals., Mumbai, India, Mg-Stearate-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, MCC-Merck Specialities Pvt Ltd, Mumbai, India

Methodology

Analytical method development

Determination of absorption maxima

100mg of Metoprolol pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml) .From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve

100mg of Metoprolol pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg/ml of Metoprolol per ml of solution. The absorbance of the above dilutions was measured at 278 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

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 Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this

was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
21 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Propranolol Total weight of the tablet was considered as 200mg.

Procedure

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

Table 3: Formulation composition for tablets

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metoprolol	25	25	25	25	25	25	25	25	25	25	25	25
Eudragit S 100	15	30	45	60	-	-	-	-	-	-	-	-
HPMC K4 M	-	-	-	-	15	30	45	60	-	-	-	-
HPMC K15 M	-	-	-	-	-	-	-	-	15	30	45	60
PVP K30	8	8	8	8	8	8	8	8	8	8	8	8
Mg-Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4	4	4	4
MCC	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 Weight	200	200	200	200	200	200	200	200	200	200	200	200

All the quantities were in mg

RESULTS AND DISCUSSIONS

Standard Calibration curve of Metoprolol

Table 4: Concentration and absorbance obtained for calibration curve of Metoprolol in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 278 nm)
1	0	0
2	5	0.158
3	10	0.291
4	15	0.432
5	20	0.554
6	25	0.681

It was found that the estimation of Metoprolol by UV spectrophotometric method at λ_{max} 278 nm in 0.1N 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, 5-25µg/ml.

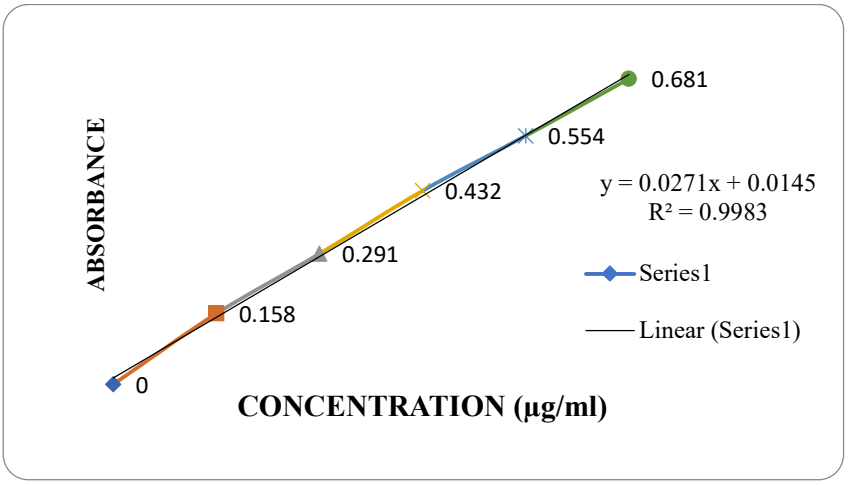


Fig 2: Standard graph of Metoprolol in 0.1 N HCl

Table 5: Concentration and absorbance obtained for calibration curve of Metoprolol in pH 6.8 Phosphate buffer.

S. No.	Concentration(µg/ml)	Absorbance* (at 280 nm)
1	0	0
2	5	0.132
3	10	0.259
4	15	0.362
5	20	0.476
6	25	0.585

It was found that the estimation of Metoprolol by UV spectrophotometric method at λ_{max} 280 nm in pH 6.8 Phosphate buffer. It 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, 5-25µg/ml.

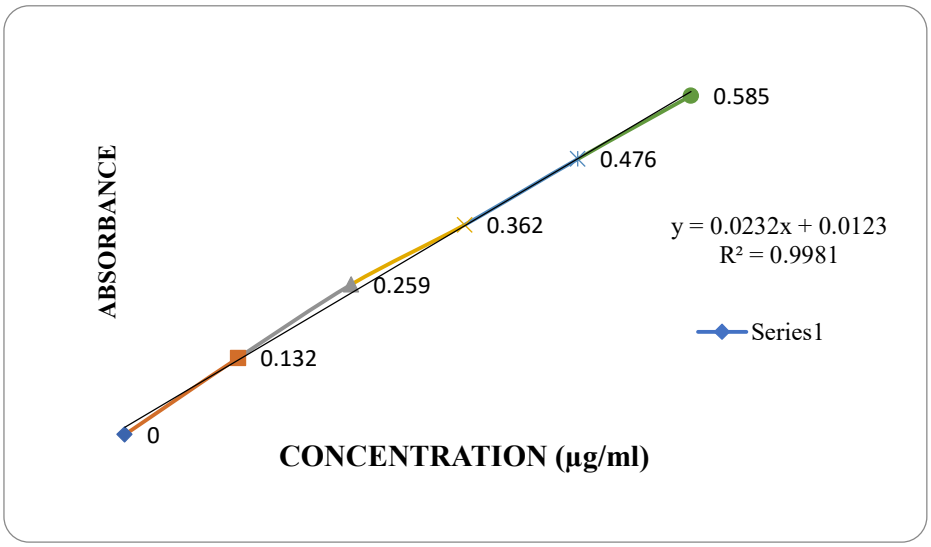


Fig 3: Standard graph of Metoprolol in pH 6.8 Phosphate buffer

Evaluation Parameters for sustained release tablets of Metoprolol

Pre-compression parameters

The data's were shown in Table 6. The values for angle of repose were found in the range of 22.8±0.06-25.2±0.13. Bulk densities and tapped densities of various formulations were found to be in the range of 0.301±0.09 to 0.319±0.15 (gm/cc) and 0.310±0.05 to 0.390±0.11 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 10.8±0.06 % to 15.1±0.09%. The Hausner ration fall in range of 1.11±0.05 to 1.19±0.07. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 6: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
F_1	0.307±0.07	0.310±0.05	14.7±0.06	1.17±0.05	23.7±0.11
F_2	0.304±0.09	0.341±0.09	11.4±0.05	1.14±0.07	23.4±0.08
F_3	0.301±0.09	0.371±0.11	15.1±0.09	1.11±0.05	24.1±0.16
F_4	0.312±0.12	0.321±0.08	10.8±0.06	1.18±0.09	24.8±0.12
F_5	0.305±0.14	0.350±0.09	12.5±0.13	1.15±0.06	24.5±0.09
F_6	0.308±0.08	0.381±0.08	13.2±0.08	1.12±0.09	25.2±0.11
F_7	0.313±0.09	0.331±0.13	11.3±0.11	1.19±0.07	24.9±0.12
F_8	0.306±0.12	0.363±0.09	11.6±0.05	1.16±0.05	23.6±0.09
F_9	0.319±0.15	0.390±0.11	13.9±0.05	1.13±0.07	24.3±0.13
F_{10}	0.308±0.17	0.354±0.16	13.2±0.05	1.12±0.07	25.2±0.13
F_{11}	0.315±0.13	0.322±0.04	11.4±0.07	1.14±0.08	23.4±0.07
F_{12}	0.309±0.11	0.377±0.07	13.8±0.10	1.18±0.11	22.8±0.06

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 7. The average weight of the tablet is approximately in range of 196.78 to 200.1 mg, so the permissible limit is ±5% (200 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 7. The results showed that the hardness of the tablets is in range of 4.1 to 4.9 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 7. The result showed that thickness of the tablet is raging from 3.15 to 3.95 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7. The average friability of all the formulations lies in the range of 0.17 to 0.72 % 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 95.28 -99.41%.

Table 7: post compression parameter

FD	Average weight(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	199.61	4.7	3.15	0.17	97.74
F_2	198.52	4.4	3.44	0.64	99.41
F_3	199.28	4.1	3.79	0.51	96.15
F_4	199.48	4.8	3.27	0.38	98.82
F_5	200.10	4.5	3.59	0.45	97.52
F_6	198.62	4.2	3.87	0.22	95.28
F_7	196.78	4.9	3.38	0.62	97.96
F_8	199.35	4.6	3.67	0.49	98.69
F_9	198.19	4.3	3.95	0.56	99.38
F_{10}	199.35	4.2	3.19	0.43	97.24
F_{11}	197.62	4.4	3.54	0.72	99.42
F_{12}	199.84	4.8	3.85	0.44	98.87

***In-Vitro* Dissolution studies**

In-Vitro dissolution studies were carried out by using 900ml 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 buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min, 1 hour, 2, 3,4,5,6,7,8,9, 10, 11 and 12 hours respectively. The results were displayed in table 8.

Table 8: *In -vitro* dissolution data

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	27.52	22.60	23.32	43.53	17.75	13.61	13.62	8.25	31.30	8.16	11.08	21.91
2	34.11	35.82	46.67	46.39	24.98	24.18	16.17	11.71	54.01	14.36	14.31	24.56
3	41.75	41.91	51.23	51.48	31.57	27.27	21.34	24.59	57.10	22.84	23.64	37.15
4	52.24	44.76	54.47	64.32	42.92	32.69	34.23	27.31	62.53	35.33	26.72	39.28
5	55.96	53.95	57.62	67.67	55.11	45.41	42.60	32.29	65.16	43.94	31.09	42.87
6	68.21	66.72	59.83	70.52	58.35	58.61	45.57	35.40	73.29	51.41	42.15	55.19
7	86.79	75.95	60.76	72.28	63.42	63.83	53.82	48.01	86.44	54.66	55.16	58.69
8	99.63	85.10	62.91	75.32	66.57	66.71	61.71	53.32	92.57	62.07	57.85	63.38
9		91.86	68.54	83.94	72.20	72.82	65.22	56.75		75.14	69.41	66.79
10		94.25	69.43	85.71	75.39	75.29	79.99	62.21		83.37	74.03	73.33
11			73.27	88.15	81.48	80.32	81.18	65.98		96.05	75.81	76.94
12			78.56	89.40	87.21	93.53	98.29	74.25		97.92	83.32	79.68

From the tabular column 8.5 it was evident that the formulations prepared with Eudragit S 100 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. Eudragit S 100 in the concentration of 60 mg showed good % drug release i.e., 89.40 in 12 hours. Where as in case of formulations prepared with HPMC K4 M as retarding polymer, the formulations with 30 mg concentration of polymer showed complete drug release in 12 hours only, whereas the concentration of polymer increases the retarding nature also increased. The Formulation Containing HPMC K4 M in 45 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.29 %. Where as in case of formulations prepared with HPMC K15 M as retarding polymer, the formulations with 10 mg concentration of polymer showed complete drug release in 12 hours only, The Formulation Containing HPMC K15 M in 30 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 97.92 %. From the above results it was evident that the formulation F7 is best formulation with desired drug release pattern extended up to 12 hours.

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 mode.

Table 9: Release kinetics data for optimised formulation

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
13.62	1	1.000	1.134	0.000	1.936	13.620	0.0734	-0.866	86.38	4.642	4.420	0.221
16.17	2	1.414	1.209	0.301	1.923	8.085	0.0618	-0.791	83.83	4.642	4.377	0.265
21.34	3	1.732	1.329	0.477	1.896	7.113	0.0469	-0.671	78.66	4.642	4.285	0.357
34.23	4	2.000	1.534	0.602	1.818	8.558	0.0292	-0.466	65.77	4.642	4.037	0.605
42.6	5	2.236	1.629	0.699	1.759	8.520	0.0235	-0.371	57.4	4.642	3.857	0.784
45.57	6	2.449	1.659	0.778	1.736	7.595	0.0219	-0.341	54.43	4.642	3.790	0.852
53.82	7	2.646	1.731	0.845	1.664	7.689	0.0186	-0.269	46.18	4.642	3.588	1.054
61.71	8	2.828	1.790	0.903	1.583	7.714	0.0162	-0.210	38.29	4.642	3.371	1.271
65.22	9	3.000	1.814	0.954	1.541	7.247	0.0153	-0.186	34.78	4.642	3.264	1.377
79.99	10	3.162	1.903	1.000	1.301	7.999	0.0125	-0.097	20.01	4.642	2.715	1.927
81.18	11	3.317	1.909	1.041	1.275	7.380	0.0123	-0.091	18.82	4.642	2.660	1.982
98.29	12	3.464	1.993	1.079	0.233	8.191	0.0102	-0.007	1.71	4.642	1.196	3.446

From the above graphs it was evident that the formulation F7 was followed Zero order release mechanism.

FTIR

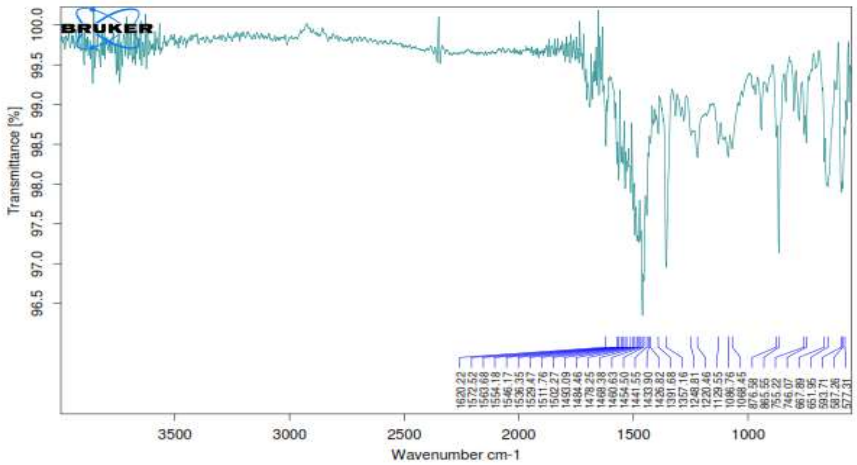


Fig 4: FT-TR Spectrum of Metoprolol pure drug

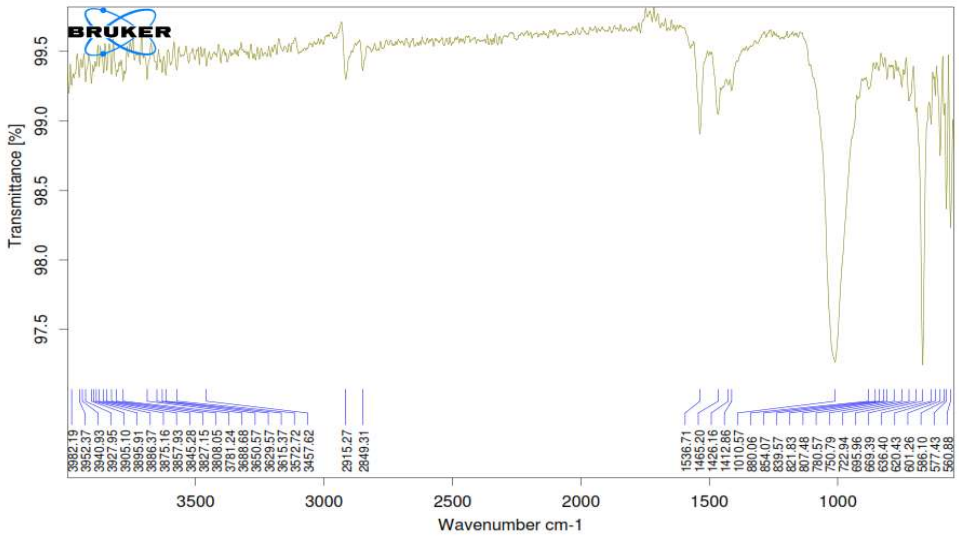


Fig 5: FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION

Controlled release tablets Metoprolol was formulated by direct compression method using the semi synthetic polymers Eudragit S 100, HPMC K4 M and HPMC K15 M. Infrared spectra of the drug along with polymers reveal that there is no significant interaction between drug and polymers. Preformulation studies were done initially and the results were found within the limits. The evaluation tests results are found to be within Pharmacopeial specifications. From *in-vitro* dissolution study it was concluded that the formulation F7 containing HPMC K4 M in the ratio 1:3 was taken optimized formulation of Controlled release tablet for 12 hours release as it fulfills all the requirement of Controlled release tablets. Kinetic studies were observed as Zero order release mechanism.

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