Formulation and Evaluation of Sustained Release Matrix Tablets of Metoprolol Succinate

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Abstract

Metoprolol succinate is a β1-selective adrenergic receptor-blocking medication used to treat hypertension, myocardial infraction, angina pectoris, cardiac arrhythmias, heart failure and hyperthyroidism. In the current study, a sustained release formulation of metoprolol succinate was developed using a different polymer with a different concentration of Ethyl cellulose (EC), Hydroxy propyl methyl cellulose (HPMC) and combination of both Ethyl cellulose (EC) and Hydroxy propyl methyl cellulose (HPMC). This was done in an effort to decrease the frequency of dose administration to prevent nocturnal attacks and to improve patient compliance. FTIR spectroscopy was used to explore the relationship between metoprolol succinate and polymer compatibility. The precompression and post compression parameters for the powder mixtures and tablets respectively were examined. Acceptable tablet characteristics and invitro drug release were taken into consideration while formulating. The most effective formulation of the study was F9, employing the direct compression procedure using combination of both ethyl cellulose and Hydroxy propyl methyl cellulose with concentration ratio of 30:50.

Key words: *Metoprolol succinate, Sustained release, Ethyl cellulose, HPMC, Direct compression*

Introduction

Over the past 30 years, as the cost and complexity of commercializing new pharmacological entities have increased and as awareness of the therapeutic advantages of prolonged drug administration has grown, the development of oral sustained release drug delivery systems has drawn considerable attention. Designing sustained release medication delivery systems has as its goals lowering dosage, dosage frequency, and assuring consistent drug administration. Therefore, a dosage form known as sustained release is one that continuously releases medication for a predetermined period of time in a predefined pattern, either systemically or locally to a particular target organ. [1,2,3,4]

Sustained drug delivery may offer the initial dose necessary for the normal therapeutic response, followed by a steady release of medication in proportions adequate to sustain the therapeutic response, followed by a steady release of medication in proportions adequate to sustain the therapeutic response for a predetermined duration of time, often 8-12 hours. Sustained release refers to the medicine being released gradually over time. [5,6]

For use in oral sustained release formulations, hydroxy propyl methyl polymers have received extensive study. These hydrophilic polymers are preferred because of their adaptability to obtain a desired drug release profile, economic effectiveness, and broad regulatory acceptability. Because of its reliable mechanism, range of viscosity grades, non-ionic nature, constant repeatable release profiles, and broad regulatory acceptability, HPMC has traditionally been a top choice for the formulation of hydrophilic matrix systems. Ethyl cellulose also used in the formulation. It is a highly stable substance that is hygroscopic. It is frequently used for controlled release, flavour masking, and moisture barrier applications. It is inert to attack by acidic alkali even when hot and extremely concentrated. It is frequently employed in oral medication delivery systems and is non-toxic, non-irritating, and allergic free. [7,8]

Metoprolol succinate is a β1-selective adrenergic blocker that is used to treat hypertension, angina pectories, cardiac arrythmias, myocardial infraction, heart failure, and hyperthyroidism. Since the drugs half-life is only about 4-6 hours, the use of a sustained- release formulation is justified in order to prolong effect and boost patient compliance in common cardiovascular disorders, which required continuous monitoring. [9,10].

Material and methods

Materials

Metoprolol succinate obtained as a gift sample from Kausikh therapeutics Pvt Ltd. Polymer such as Hydroxy propyl methyl cellulose, ethyl cellulose and other excipients like magnesium stearate, talc were purchased from SR Scientific Pharmaceuticals. Microcrystalline cellulose was purchased from GELTECH Private Limited Pharmaceuticals.

Methodology:

Preformulation study of drug

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

The Preformulation study can be divided into two sub-classes

- Active pharmaceutical ingredient characterization.
- Drug excipient compatibility study.

- **Active pharmaceutical ingredient (API) characterization**

Organoleptic evaluation

These are preliminary characteristics of substances before going for the manufacturing process of the dosage forms. These studies are useful in identification of specific material.

Following physical properties of properties of API were studied.

a. Colour
b. Odour
c. Taste

Solubility analysis

The solubility analysis is done for the drug. The analysis is done to know the solubility characteristics of the drug and to select the best vehicle or diluent in which the drug can be dissolved or suspended to form the best pharmaceutical form.

Melting point

Melting point of the pure drug was determined by melting point apparatus. Take a little quantity of sample in the capillary tube and placed in the apparatus and switch on the button. The temperature was slowly raised and note the temperature were the sample melts.

Standardization of metoprolol succinate by UV-Visible spectrophotometer in phosphate buffer of pH 6.8

Preparation of phosphate buffer pH 6.8

Dissolve 6.8 gm of potassium di-hydrogen phosphate in distilled water. Make up the volume up to 1000ml by distilled water and adjust the pH by using sodium hydroxide solution.

Standard calibration of metoprolol succinate in phosphate buffer of pH 6.8

The calibration curve of metoprolol succinate was obtained by dissolving the drug in pH 6.8 phosphate buffer solution. The absorbance was measured at 274nm by keeping pH 6.8 buffer solution as blank. Beers law was obeyed in the concentration range of 2-10 µg/ml in pH 6.8 phosphate buffer solution. 100 mg of metoprolol succinate was accurately weighed and taken into 100ml volumetric flask. Drug was dissolved in pH 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From stock solution I, 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From stock solution II. From the above stock solution 0.2ml, 0.4ml, 0.6ml, 0.8ml and 1.0 ml were withdrawn into 10ml volumetric flasks and diluted up to the mark with pH 6.8 phosphate buffer solution to give the concentration range of 2-10µg/ml. The absorbance was measured at 274nm. [11,12]

Drug excipient compatibility -FTIR Studies

In the preparation of sustained release tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. FTIR spectroscopy was employed to ascertain the compatibility between Metoprolol succinate and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure

Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet were prepared using KBr pellet press and spectrum was taken using FTIR. FTIR spectrum of metoprolol succinate was compared with spectrum of Metoprolol succinate and polymer. Disappearance of metoprolol succinate peaks or shifting of peak in any of the spectra was studied. [13]

Angle of repose

The angle of repose is the greatest possible angle between a powder piles surface and a horizontal plane. It is a sign of the powders flow characteristics. The funnel is fixed to a stand at a specific height (h), and the powder mixture is allowed to flow through it. [14]

The formula used to calculate it is as follows:

$$\text{Tan } \Theta = h/r.$$

where, h and r are the height and radius of the powder cone respectively.

Table 1: Standard values of angle of repose

Angle of repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
37-45	Poor
>45	Very poor

Determination of bulk density and tapped density

A precisely weighed amount of powder (W) was carefully poured into the graduated cylinder, and the volume (V0) was measured. Weigh the test sample and enter the weight into the instrument by hitting the enter key to register the weight. Fill the measuring cylinder halfway with the test sample to be tested. Keep the measuring in the cylinder holder and secure the holder assembly. After 500 taps, press the start key to start the instrument. Check that the difference between two volumes is less than 2% before proceeding to the third tapping up to 1250 taps. [15,16]

$$\text{Bulk density} = W/V0$$

$$\text{Tapped density} = W/Vf$$

Where, W, V0, and Vf are weight of the powder, initial volume of powder and final volume of tapped powder respectively.

Compressibility index

Compressibity index is an important measure that can be obtained from the bulk and tapped densities.

Table 2: Standard values of carr's index

% Compressibility index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \text{Tapped density}/\text{Bulk density}$$

Table 3: Standard values of Hausner's ratio

Hausner's ratio	property
0-1.2	Free flowing
1.2-1.6	Cohesive powder

Formulation

Different tablet formulations were prepared by direct compression. Metoprolol succinate and excipients are weighed and passed through a 30-mesh filter. The materials are combined in a polybag. Magnesium stearate and talc are filtered using a 40-mesh screen. They are combined with the ingredients listed above. Magnesium stearate was used as a lubricant. As a glider, talc was employed. Microcrystalline cellulose was utilized a diluent. After that, the powder mixture was compressed.

Table 4: Composition of metoprolol succinate tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol succinate	50	50	50	50	50	50	50	50	50
Ethyl cellulose	25	50	100	-	-	-	50	40	30
Hydroxypropyl methyl cellulose	-	-	-	25	50	100	30	40	50
Microcrystalline cellulose	121	96	46	121	96	46	66	66	66
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

Evaluation [17, 18, 19, 20,]

The prepared tablets were evaluated for the following parameters

- Appearance
- Hardness
- Uniformity of Thickness
- Weight variation
- friability
- Invitro drug release studies

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Hardness

The hardness of tablet was determined by using Monsanto hardness tester. It is expressed in kg/cm^2. The hardness should be within the range of 4-15kg/cm.

Uniformity of thickness

The thickness of a tablet was the only dimensional variable related to the process. 10 tablets were measured for their thickness and diameter with vernier callipers. Average thickness and diameter were calculated.

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. Weight variation test was run by weighing 20 tablets. The USP allows a little variation in the weight of the tablet. The following percentage deviation in weight variation is allowed.

Table 5: Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130mg or less	10
More than 130mg or less than 324mg	7.5
324mg or more	5

Friability test

Roche friabilator is used for the measurement of friability using 20 tablets. Twenty tablets are weighed and rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\% \text{ friability} = \frac{\text{(Initial weight - final weight)}}{\text{Initial weight}} \times 100$$

Drug content uniformity

Tablets were weighed and crushed in to mortar. The powder equivalent to 10mg of drug was weighed and dissolved in 100ml methanol. From this solution 1ml of solution was diluted to 10ml with methanol. From this diluted solution 1ml solution was taken and diluted up to 10ml with methanol and assayed for drug content at 274nm.

***In-vitro* drug release studies**

Drug release study is generally determined in rotating paddle apparatus (USP type 2 paddle). Phosphate buffer of pH 6.8 is used as dissolution medium (900ml). The temperature of the bath is maintained at 37±0.5℃ and required sample (5ml) of the dissolution medium in which drug released is taken at regular intervals and the same quantity of the medium is replaced. The amount of drug released is determined at 274nm using an UV/Visible spectrophotometer. Cumulative percentage of drug release was calculated.

Results and discussion:

Preformulation studies of Metoprolol succinate pure drug

Organoleptic evaluation

Colour: white crystalline powder

Odour: characteristic

Taste: bitter

Solubility analysis

Metoprolol succinate was found to be,

- Freely soluble in water, soluble in methanol, ethanol
- Less soluble in dichloromethane and 2-propanol
- Insoluble in acetone. Ethyl acetate, diethyl ether, heptane

Melting point

The melting point of active ingredient was determined by capillary method and it was found to be 119.5℃. (Specification - 120℃) [27]

Spectrophotometric determination of metoprolol succinate

The absorption maxima for metoprolol succinate was found to be 274nm that is shown in the figure 1.

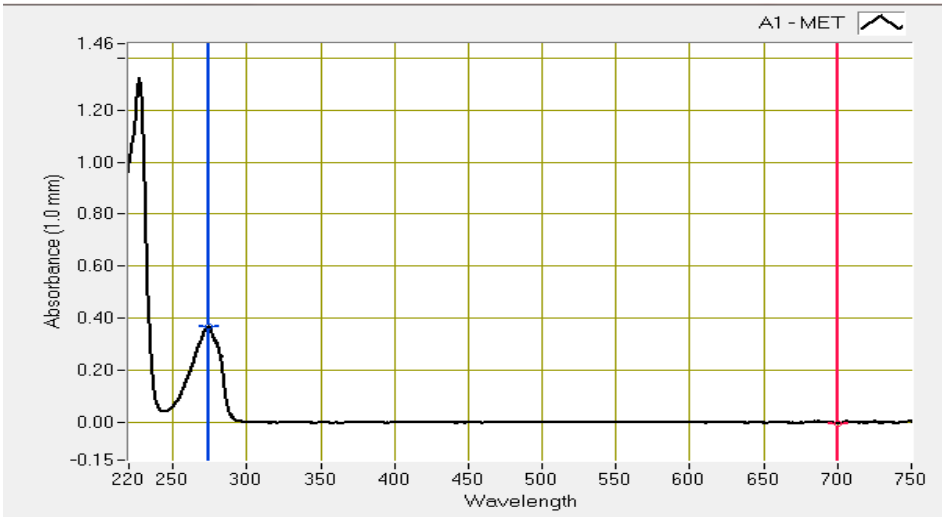

Figure 1: λmax of metoprolol succinate in pH 6.8 phosphate buffer

Table 6: calibration data for the estimation of metoprolol succinate in pH 6.8 phosphate buffer at 274nm

Concentration (µg/ml)	Absorbance
0	0.000
2	0.071
4	0.143
6	0.221
8	0.279
10	0.351

Table 3 shows the calibration data for the estimation of metoprolol succinate in pH 6.8 phosphate buffer. By using calibration data standard calibration was plotted that is shown in figure 2.

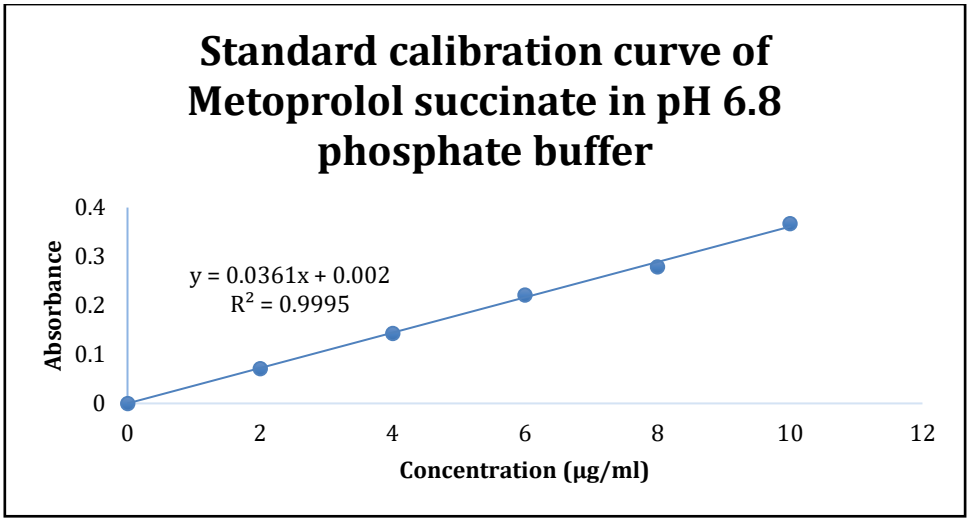

Figure 2: Standard calibration curve of metoprolol succinate in pH 6.8 phosphate buffer

The method obeyed beer lamberts law unity range of 0-10µg/ml with correlation coefficient value 0.998.

Drug excipient compatibility studies

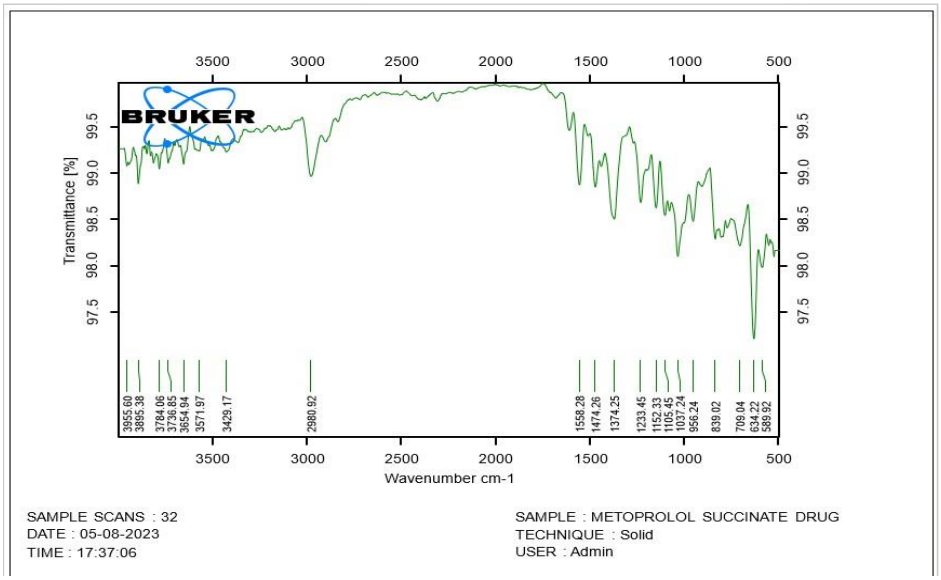

Figure 3: FTIR spectra of metoprolol succinate pure drug

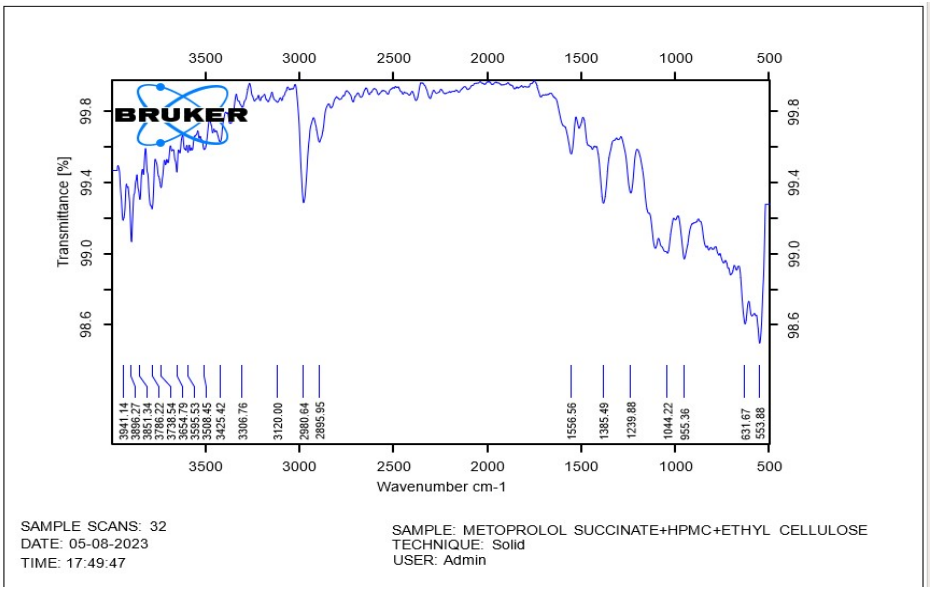

Figure 4: FTIR spectra of metoprolol succinate +Hydroxy propyl methyl cellulose +Ethyl cellulose

Table 7: Characteristic peaks of metoprolol succinate and a mixture of metoprolol succinate, ethyl cellulose and hydroxy propyl methyl cellulose.

Functional group	Actual frequency range (cm^{-1})	Observed frequency of metoprolol succinate (cm^{-1})	Observed frequency of metoprolol succinate, ethyl cellulose, hydroxy propyl methyl cellulose (cm^{-1})
C-H stretching	2990-2850	2980.92	2980.64
N-H stretching	3500-3250	3429.17	3425.42
C=C stretching	1625-1440	1558.28	1556.56
C-O stretching	1350-1260	1233.45	1239.88

Figure 3,4 & table 4 shows that the functional groups present in metoprolol succinate (drug) were also present in mixture of metoprolol succinate, Ethyl cellulose, HPMC (polymers), which indicates that there is no interaction between the drug and polymer.

Evaluation of powder blend

Angle of repose, bulk density, tapped density, compressibility index and hausner's ratio of powder blend was determined to assess the flow properties of the formulation blend. The flow properties of powder blends are given in table 5.

Table 8: Pre compression parameters

Formulation code	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%) [n=3]	Hausner's ratio [n=3]
F1	19.093±0.020	0.459±0.05	0.525±0.08	10.78±0.05	1.059±0.05
F2	23.634±0.214	0.466±0.08	0.592±0.12	11.92±0.07	1.058±0.02
F3	24.734±0.210	0.443±0.06	0.567±0.08	12.54±0.01	1.056±0.10

F4	26.652±0.013	0.434±0.08	0.558±0.02	14.53±0.02	1.055±0.03
F5	23.699±0.113	0.498±0.05	0.531±0.07	11.67±0.06	1.068±0.08
F6	24.139±0.022	0.478±0.08	0.508±0.08	12.50±0.35	1.061±0.12
F7	24.722±0.510	0.455±0.03	0.526±0.08	13.63±0.06	1.168±0.01
F8	21.520±1.030	0.476±0.02	0.556±0.02	14.28±0.30	1.170±0.40
F9	24.921±0.780	0.500±0.05	0.588±0.06	15.00±0.20	1.181±0.30

Evaluation of prepared tablets

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Hardness

The hardness of the tablet was found to be 4.01±0.03 to 5.45±0.08kg/cm^3 which was given in table 6.

Weight variation

The percentage deviation from average tablet weight of all the tablet was found to be within the specified limits.

Friability

Percentage friability of all formulations was found to be 0.3±0.02 to 0.6±0.04% was given in the table 6. This indicated good handling property of the prepared sustained release tablet.

Drug content

The percentage of drug content found in the range of 97.25 to 99.83%. the drug content of all formulations was shown in the tablet 6.

Table 9: Post compression parameters

Formulation code	Hardness [kg/cm^2] n=3	Thickness [mm] n=3	Average weight variation [mg] n=20	Friability [%] n=10	Drug content [%]
F1	4.20±0.01	3.0±0.02	196±0.05	0.5±0.02	99.35±0.95
F2	4.01±0.03	3.2±0.04	200±0.02	0.4±0.05	98.64±0.90
F3	4.20±0.01	3.2±0.03	199±0.05	0.4±0.05	98.76±0.17
F4	4.70±0.01	3.3±0.02	196±0.04	0.5±0.02	97.25±0.95
F5	5.03±0.05	3.0±0.02	200±0.02	0.5±0.02	98.25±0.90
F6	5.45±0.08	3.4±0.01	198±0.04	0.5±0.01	98.74±0.45
F7	5.04±0.05	3.2±0.02	196±0.05	0.5±0.02	99.45±0.95
F8	5.20±0.01	3.4±0.02	197±0.04	0.6±0.40	97.28±0.85
F9	5.30±0.02	3.6±0.02	199±0.05	0.5±0.20	99.83±0.90

Invitro drug release studies

The cumulative percent drug release of metoprolol succinate sustained release tablet formulations obtained by invitro dissolution study are given in the table.

Table 10: Cumulative percent drug release of formulation F1 to F9

Cumulative % drug release									
Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	20.42	15.46	16.36	19.77	18.4	14.27	16.37	15.20	14.27
2	44.65	26.59	28.63	42.27	32.04	30.52	31.24	28.26	25.50
4	66.13	42.61	40.22	61.36	50.93	42.02	48.06	45.18	42.36
8	82.15	61.02	53.86	82.84	75.22	62.34	62.04	60.09	54.04
12	99.24	82.84	84.29	97.64	86.52	80.02	83.86	76.43	68.38
16		98.52	90.56		97.84	88.45	98.18	83.52	79.11
20			98.24			97.29		96.23	88.04
24									99.25

Table 7 shows the invitro release data & figure 5,6,7 shows the invitro release profiles of formulations F1 to F9.

In this study, effect of different concentrations of Ethyl cellulose (EC), Hydroxy propyl methyl cellulose (HPMC), and combination of both EC and HPMC polymers on the release profiles of metoprolol succinate sustained release tablets were studied.

In formulation F1, F2, F3 different concentrations of Ethyl cellulose polymer was used. The formulations show the drug release of 99.24% at 12 hours, 98.52% at 16 hours, 98.24% at 20 hours respectively. In formulation F4, F5, F6 different concentrations of HPMC was used. The formulations show the drug release of 97.64% at 12 hours, 97.84% at 16 hours, 97.29% at 20 hours. So, the polymers individually not having the capacity to extend up to 24 hours respectively.

In formulation F7, F8, F9, different concentrations of both EC and HPMC polymers in combination were used. The formulations show the drug release of 98.18% at 16 hours, 96.23% at 20 hours, 99.25% at 24 hours respectively.

Among all the formulations, formulation F9 releases the drug at a constant time interval as compared to release of drug from other formulations. Using both the polymers with the concentrations of 30:50 (EC: HPMC) have the capacity to sustain the release up to 24 hours.

So, the F9 was the optimized formulation. The most common method of modifying drug release is to include in a matrix system. From the above data, it is clear that by increasing the concentration of combination of polymers, (EC, HPMC) the release rate was sustained.

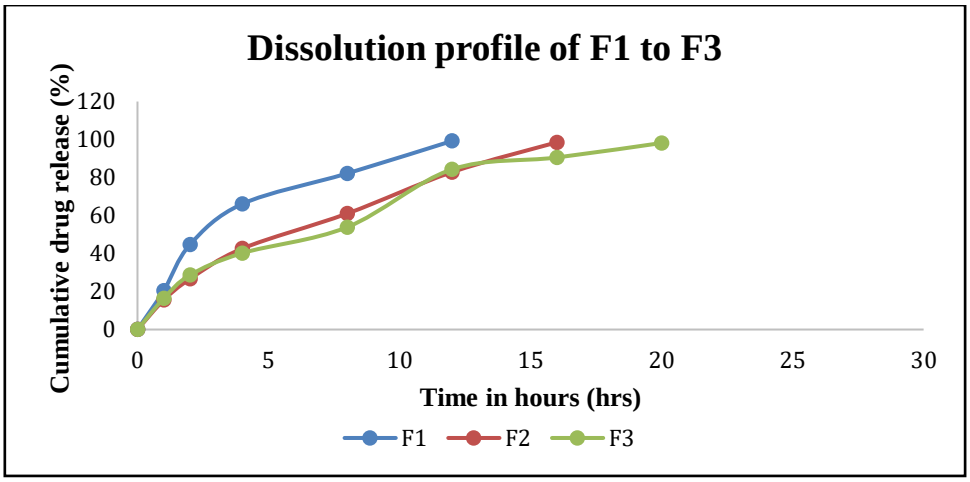

Figure 5: Invitro release profile of formulation F1 to F3 metoprolol succinate tablet

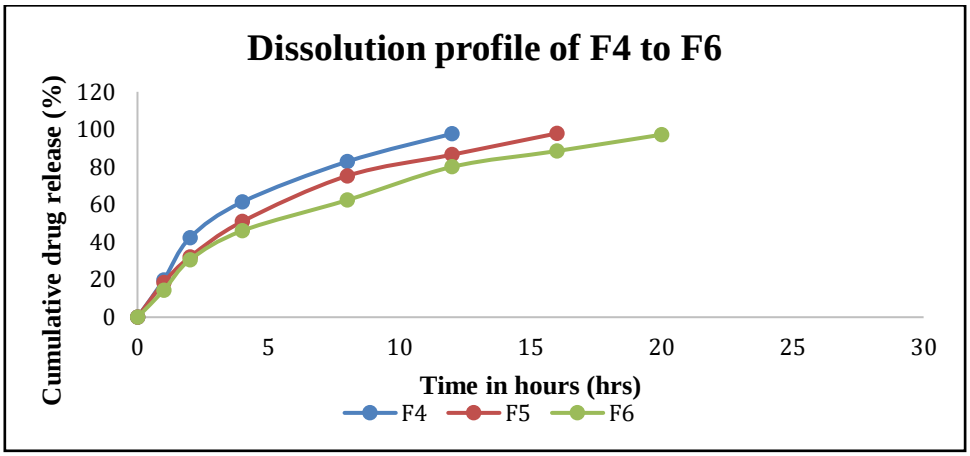

Figure 6: Invitro release profile of formulation F4 to F6 metoprolol succinate tablet

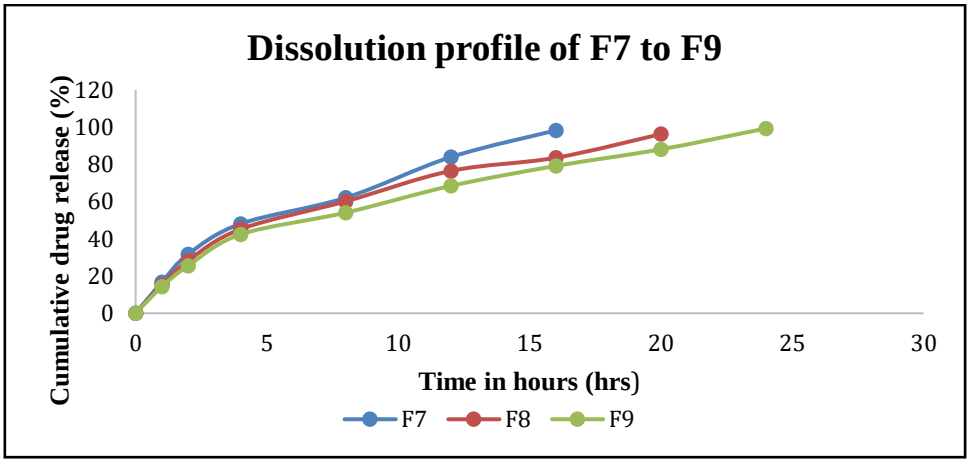

Figure 7: Invitro release profile of formulation F7 to F9 metoprolol succinate tablet

Conclusion

Metoprolol succinate sustained release matrix tablet were prepared by direct compression method using different concentrations of polymers like Ethyl cellulose (EC), Hydroxy propyl

methyl cellulose (HPMC) and combination of both Ethyl cellulose (EC) and Hydroxy propyl methyl cellulose (HPMC). The nature of the polymer influences the physical and drug release characteristics of matrix tablet. The FTIR studies revealed that there is no interaction between drug and polymer. All the flow properties of all formulations were within the specified limits. Weight variation of all formulations were within the specified limits and the results of friability indicated good handling property. According to invitro release studies, the release rate was sustained with increase in concentration of combination of polymers (ethyl cellulose & HPMC). The results of the study clearly demonstrated that combination of both polymers ethyl cellulose & HPMC matrix tablet formulation F9 is an effective and promising drug delivery system for once daily administration of metoprolol succinate.

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