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Development and *In Vitro* Evaluation of Modified Release Coated Tablets of Freely Water Soluble Drug Metoprolol Succinate

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ABSTRACT

The purpose of the present study was to design, characterize and evaluate extended release coated tablets of Metoprolol Succinate (MS) to reduce its dosing frequency. Core tablets were prepared using various matrix forming agents like HPMC, HPC, and HEC, and further subjected for coating using blend of aqueous dispersion of a hydrophobic and hydrophilic polymer, (Surelease®: HPMC E15) to control the drug release of the highly water soluble drug Metoprolol Succinate. Varying the matrix forming agent concentrations in the core tablets and percentage coating build up on core tablets showed range of drug release patterns in phosphate buffer pH 6.8. The present study dealt with the suitable grade of cellulose polymer and optimized coating composition which can modify the drug release to match up with the USP dissolution specifications and marketed product for the MS. The optimized formulation containing Metolose 90 SH 100000 and 3% coating with plasticized Surelease: hydroxypropyl methylcellulose (HPMC E15) showed extended drug release up to 24hrs and the drug release pattern was similar with the specifications. The *in-vitro* dissolution studies revealed that the release rate is inversely proportional to the concentration of matrix former in the core tablet and percent of coating thickness. The kinetic treatment illustrate that the optimized formulation HMC5 followed zero order kinetics with diffusion mediated drug release which is evidenced from n value of (0.73) Peppas equation. FT-IR and DSC studies indicated no interaction between the drug and excipients and prepared formulations showed good stability as per ICH guidelines.

Key words: Metoprolol Succinate, Extended Release, HPMC E15, Surelease, Coated Tablet

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INTRODUCTION

Metoprolol Succinate, a white crystalline powder, is freely soluble in water. It is a cardio selective β-blocker that has been classified as a class I substance according to the Biopharmaceutics Classification System, meaning that it is highly soluble and highly permeable. The drug is readily and completely absorbed throughout the intestinal tract[1]. But is subjected to extensive first pass metabolism resulting in incomplete bioavailability (about 50%). After a single oral dose, peak plasma concentration occurs after about 1 to 2 h. The drug is eliminated within 3 to 4 h which, depending on therapeutic activity, makes it necessary to administer the formulation up to 4 times daily. Based on these properties and well defined relationship between the beta blocking effect and plasma drug concentration, Metoprolol Succinate is a good candidate for developing as an extended release formulation.

Developing oral extended release systems for freely water soluble drugs having strong first pass metabolism has always posed a challenge to the pharmaceutical technologist. Most of these highly water soluble drugs, if not formulated properly, are released at a high rate and are likely to produce toxic concentrations when administered orally [2].

In the present study, development of a suitable ER tablet formulation for MS using the fast hydrating grades of HPMC, HPC and HEC polymers in the core tablet as matrix formers, and the effect of polymer viscosity and polymer level (% w/w of tablet) on the release rates of MS from these tablets were demonstrated. This study also adopted Polymeric film coating technology which often is used for achieving sustained release of an active substance from pharmaceutical formulation because a coated dosage form enables prolonged and precise release of drug with good reproducibility [3,4].

One of the most widely used hydrophobic polymers in pharmaceutical film coating is ethyl cellulose (Surelease®), due to its convenient film formability, good physiochemical properties and minimum toxicity [5]. Surelease® is an excellent polymer for modified release coating and more often used in combination with a secondary polymer such as hydroxypropyl methylcellulose (HPMC) which confers the film a more hydrophilic nature and alters its structure by virtue of pores and channels through which the drug substance can diffuse more easily to control the release properties of a drug formulation [6].

MATERIALS AND METHODS

Materials

Metoprolol Succinate, (Natco Pharma Pvt. Ltd., HYD), Benecel K200M hydroxypropyl methylcellulose (HPMC), Benecel K35M (HydroxyPropylMethylCellulose), Klucel HF Pharm (Hydroxypropyl Cellulose), Natrosol 250 Mphar (Hydroxyethylcellulose) and Metlose 90 SH 100000, Surelease® NG, E-7-1905, (Colorcon Asia Pvt. Ltd., Goa); Hydroxypropyl methylcellulose (HPMC) E15, Potassium dihydrogen phosphate, Hydrochloric acid, Sodium hydroxide, Magnesium Stearate, Talc (E. Merck Ltd., Mumbai, India)), Sodium Starch Glycolate (S.D. Fine-Chem Ltd, Ahmedabad, India.) Microcrystalline Cellulose (Avicel® PH102, Que Pharma Pvt. Ltd., Wadhwan) were used in the study. All other reagents were of analytical grade.

Methods

Formulation of extended release tablets:

Preparation of core tablets

All the tablets were prepared by aqueous granulation method. In this method accurately weighed quantities of Avicel PH 101 and Hydroxypropyl methyl cellulose of different grades are taken in a mortar in a geometrical fashion and to this mixture, required quantity of drug was added and mixed with pestle. This mixture was sifted through #40 mesh to get uniform particle size and collected in a polythene bag and further mixed for about 3 minutes to ensure a homogenous mass. Purified water was used as granulating fluid to get the dough mass which was passed through #12 mesh to get wet granules. Wet granules were dried at 60^0C for 30 min, and the dried granules were passed through #16 mesh to get uniform dried granules. To this Sodium starch glycolate and arosil were added and mixed for 5 minutes. Final blend was compressed into tablets using 10 mm punches and corresponding dies on 16 station rotary compression machine (Riddhi, Ahmedabad.). The qualitative and quantitative composition of tablets was shown in Table 1.

Table 1: Composition of Metoprolol Succinate ER Core Tablets

Ingredients (mg) /Batch	HM1	HM2	HM3	HM4	HM5
Metoprolol Succinate	95	95	95	95	95
Avicel PH 101(MCC)	150	150	150	150	150
Benecel K200M(HPMC)	50	----	----	----	-----
Benecel K35M(HPMC)	---	50	---	----	----
Klucel HF Pharm(HPMC)	-----	---	50	----	----
Natrosol 250 Pharm(HEC)	-----	----	----	50	---
Metolose90SH4000 (HPMC)	-----	-----	-----	---	50
Purified Water	QS	QS	QS	QS	QS
Sodium Stearyl Glycolate	3	3	3	3	3
Aerosil(CSD)	2	2	2	2	2
Total tablet weight (mg)	**300**	**300**	**300**	**300**	**300**

Physical properties of the final blend:

Physical properties such as bulk density, tapped density, compressibility index, Hausner ratio, and the angle of repose of final blend were determined; taped density was determined by using a tapped density tester (Campbell, India). Percent compressibility and Hausner ratio were calculated using Eq 1and 2 showed in table 2

Table 2: Physical properties of powder blend

Formulation	Bulk density (g/cm^3)	Tap density (g/cm^3)	CI (%)	Hausner's Ratio	Angle of Repose (θ)
HM1	0.352	0.416	15.49	1.181	25
HM2	0.423	0.49	13.55	1.158	26
HM3	0.373	0.431	13.43	1.155	27
HM4	0.384	0.446	13.84	1.161	24
HM5	0.416	0.48	13.33	1.153	26

Compressibility Percentage

$$\text{Compressibility \%} = \frac{DF - DO}{DF} \times 100 \quad \text{---- Eq. 1}$$

(DO = bulk density and DF=tapped densities)

Hausner ratio

$$\text{Hausner found that the ratio } \frac{DF}{DO} \quad \text{---- Eq. 2}$$

Was related to interparticle friction and, as such, could be used to predict powder flow properties.

Characterization of Core tablets:

Core tablets were characterized for weight variation and thickness (n=20) using analytical balance and digital micrometer (Mitutoyo, Japan). Crushing strength (n=6) was measured with Monsanto tester, friability (n=6), with Roche type friabilator, at 25 rpm for 100 revolutions and drug content was measured by assay. All there were shown in table 4

Preparation of coated tablets:

Preparation of polymer dispersion:

Aqueous dispersion 15% w/w of Surelease® was prepared in distilled water. Similarly, a 2% solution of HPMC E15 was prepared by dispersing the powder of HPMC E15 in preheated water (80-90^{o}C) and then diluting it with cold water. Both the dispersions were mixed together and a small quantity of talc (2% w/v) was added as an anti-adherent to the coating mixture. The mixture was stirred using a magnetic stirrer prior to and throughout the coating process [7]. The core tablets were coated by the solution spraying technique. Coating parameters were set as shown in Table 3. The coating fluid was sprayed onto the core tablet with an intermittent drying

time of 5 min in a coating pan (R&D Coater, VJ Instruments, Mumbai, India). Samples were collected at 3% of coating based on w/w calculation of coating suspension.

Table 3: Coating parameters required during coating, for selected core tablets

Conditions	Preheating	Coating	Drying
Inlet air temperature(°C)	50-65	65-60	50
Product temperature(°C)	40-45	50-55	40-45
Outlet air temperature(°C)	35-40	40-45	40-45
Spray rate (ml/min)	-	2-3	-
Atomizing air pressure(psi)	-	2.5	-
Pan speed (rpm)	25-35	25-35	15-20

FTIR and DSC Studies

Fourier transforms infrared (FTIR) analysis

FTIR spectra of the drug, formulations HMC2and HMC5 were recorded in potassium bromide disc using a PERKIN ELMER FT-IR spectrometer to ascertain compatibility.

Differential scanning calorimetry (DSC) analysis

Thermal analysis using DSC was carried out on drug, physical mixture of the drug, and formulations HMC2and HMC5. DSC 822e/TGA SDTA 851e (SWITZERLAND). Accurately weighed samples were loaded into aluminum pans and sealed. All samples were run at a heating rate of 20^{o}C/min over a temperature range 40-360^{o}C.

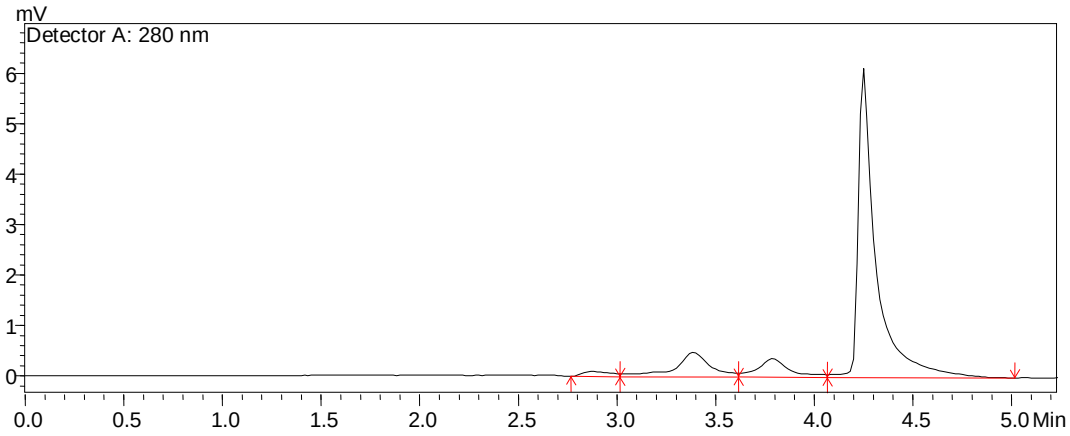

Figure 1: Representative chromatogram showing separation of MS at 4.2 minutes

Calculation of the Theoretical Release Profile of Metoprolol Succinate:

Characterization of Coated tablets:

Coated tablets were characterized for percentage weight gain and thickness variation upon coating (n=20) using analytical balance and digital micrometer (Mitutoyo, Japan). Crushing strength (n=6) was measured with Monsanto tester, and drug content in the coated tablets were analysed by HPLC (Typical Chromatogram is shown in Figure 1). Results of evaluation parameters were shown in table 5.

The total dose of Metoprolol Succinate for a once-daily ER formulation was calculated by the following equation [8]. Using available pharmacokinetic data. USP recommends the amount of drug release from an extended release dosage form in first one hour should be 20 % of the total dose; the dose of immediate release (IR) part is 20 % of 95.32 mg, i.e. 19.06 mg

Dt = Dose (1+ (0.693 X t)/ t1/2)

Where, Dt = total dose of drug; Dose = dose of the IR part; t = time (h) during which the ER is desired (23 h); and t1/2 = half-life of the drug (4 h). Dt =19.06 (1+ [0.693 X 23]/4) ≈ 95.32 Hence, the formulation should release 19.06 mg in 1 h like conventional tablets and 76.26 mg per hour up to 23 h thereafter [9].

***In vitro* dissolution**

Dissolution testing of formulations HM1-HM6 was performed using USP XXVI type I. The test was performed using 500 ml solution of pH 6.8 phosphate buffer maintained at temperature 37 ± 0.5°C stirred at a speed of 50 rpm [9]. A sample of 5 ml was taken out at an interval of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 13, 14, 20, 21, 22, 23 and 24 h and immediately replaced with 5 ml of fresh phosphate buffer pH 6.8 to maintain sink conditions in the dissolution jar. The drug content in the samples was analyzed using HPLC as per the following specifications Column: Kromasil C 18 ODS column, Mobile Phase – Buffer: Acetonitrile – 75: 25, pH of the mobile phase 3.0 (Adjusted with Orthophosporic acid), Flow Rate: 1ml/min., Injection volume- 100µl, Wavelength - 280 nm, HPLC system – Shimadzu. The prepared mobile phase was filtered through 0.45 µm micro pore filter and degassed by sonication for 8 minutes.

Drug release kinetics:

The description of dissolution profiles has been attempted using different release models. The data was evaluated according to the following equations [8].

Zero order: $M_t = M_o + K_o t$

First order: $\ln M_t = \ln M_o + K_1 t$

Higuchi model: $M_t = K_H \sqrt{t}$

Korsmeyer –Peppas model: $M_t/M_o = K_k t^n$

Where M_t is the amount of drug dissolved in time t, M_o the initial amount of drug, K_1 is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and *n* is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient r was used as an indicator of the best fitting, for each of the models considered and shown in table 10

The magnitude of the exponent *n* indicates the release mechanism as Fickian diffusion, as case II transport, or as anomalous transport. In the present study the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of *n* between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous non-Fickian transport. Values of *n* greater than 0.89 indicates a super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport.

Statistics

To compare the means of all release data and to assess statistical significance between them, either 1-way analysis of variance (ANOVA) or an unpaired 2-tailed t test was performed at the 5% significance level, using Graph Pad Software Version 3.05.

RESULTS AND DISCUSSION:

Since constant plasma concentration of MS is required, it makes it a good candidate for making it as an extended-release dosage form. In order to develop an optimized extended-release MS dosage form, HPMC, HPC and HEC were used as matrix formers in the core formulation. Initial trials were made using various concentrations of drug: polymer with all three polymers. Among all the fabricated formulations, five batches (HM1, HM2, HM3, HM4 and HM5) of core tablet formulations were optimized based on the in vitro dissolution studies and these optimized core tablets were further subjected for the polymeric coating with widely used hydrophobic polymers like ethyl cellulose (Surelease®), and in combination with a secondary polymer such as hydroxypropyl methylcellulose (HPMC).

The final blend of optimized batch showed good flowability (angle of repose 26^0) and compressibility 13%, Hausner ratio 1.1.

The physical parameters like weight variation, hardness, thickness, drug content of the prepared core and coated tablets were within the Pharmacopoeial limits. The results of the test were tabulated with the standard deviation and shown in table 4 & 5.

Table 4: Evaluation of core tablets

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability	Drug Content (%)
HM1	301.8 ± 2.52	7 ± 0.26	4.94 ± 0.017	0.18 ± 0.04	98.14±1.23
HM2	302.6 ± 3.23	7.3 ± 0.32	4.82 ± 0.014	0.16 ±0.08	99.98±1.98
HM3	300.9 ± 2.51	7 ± 0.31	4.78 ± 0.016	0.21 ±0.06	99.36±1.34
HM4	301.5 ± 3.02	7.32 ± 0.33	4.82 ± 0.013	0.19 ±0.05	99.12±1.30
HM5	300.7 ± 2.45	7.73 ± 0.42	5.23 ± 0.018	0.22 ±0.02	100.96±1.33

Table 5: Evaluation of coated tablets

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability	Drug Content (%)
HMC1	316.9 ± 1.19	8.24 ±0.33	5.26 ± 0.016	0.14 ± 0.03	99.63±1.99
HMC2	317.1 ± 1.28	8.66 ±0.25	4.99 ± 0.019	0.13 ±0.09	98.79±1.20
HMC3	318.2 ± 1.17	8.56 ±0.34	4.95 ± 0.017	0.16 ±0.06	97.82±1.54
HMC4	317.4 ± 1.56	8.68 ±0.43	5.13 ± 0.018	0.14 ±0.05	99.12±1.44
HMC5	316.6 ± 1.48	8.44 ±0.28	5.91 ± 0.014	0.19 ±0.03	98.64±1.09

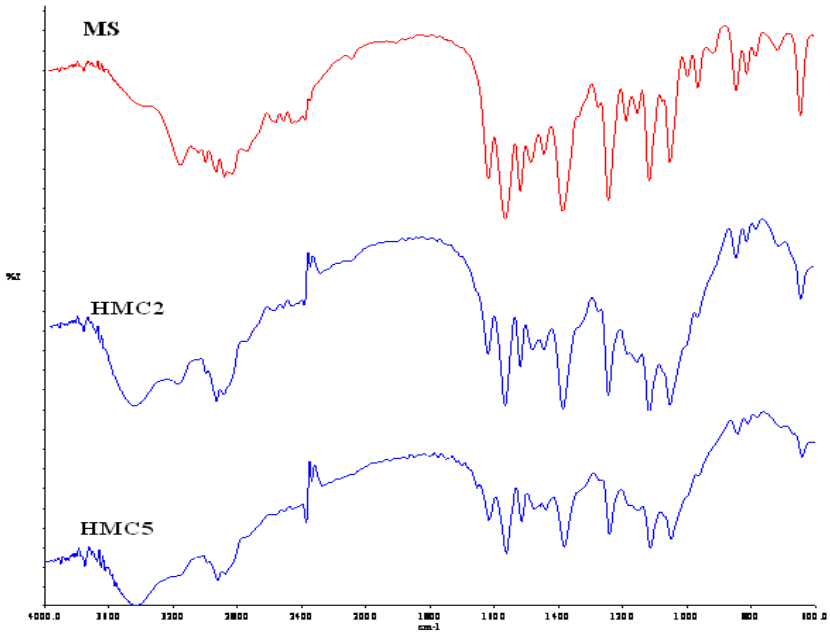

Figure 2: FTIR spectra of MS: Metoprolol Succinate, HMC2 and HMC5 Coated tablet.

Differential scanning colorimetry

FTIR studies

To know the compatibility between drug and polymers used in the development of sustained release matrix tablets, IR spectroscopy was carried out for the formulations HMC2 and HMC5.

The IR spectra of the formulations showed the same absorption bands same as the physical mixtures and the pure drug indicating the absence of interaction between Metoprolol succinate, coated tablets (Figure 2). It presumably suggests that the drug molecule is present in an unchanged state in the sustained release matrix tablet.

The DSC thermogram of the pure drug and the physical mixture of drug and polymer (kept at 40ºC and 75%RH) showed an endothermic peak of melting of drug at about 145.07ºC, indicating that there was no incompatibility between drug and polymer (Figure 3).

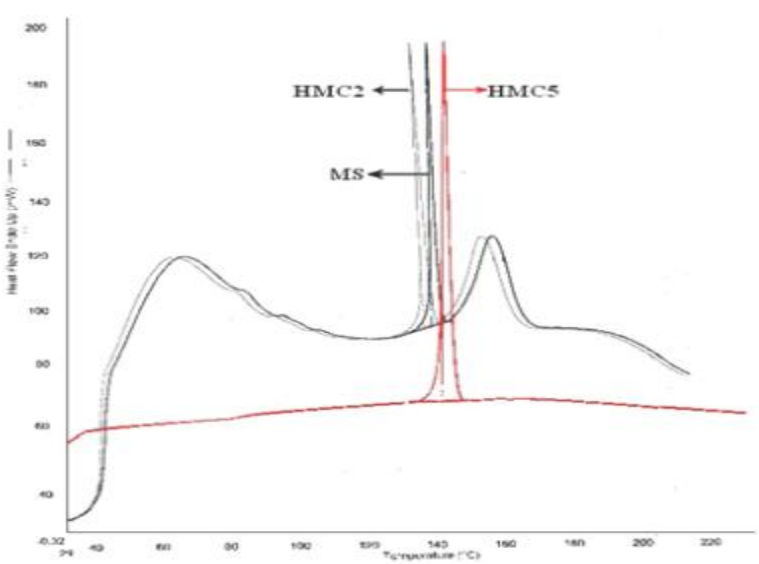

Figure 3: DSC thermograms of MS: Metoprolol Succinate, HMC2 and HMC5 Coated tablet.

In order to delay the drug release, corresponding to the extended-release component of the matrix system, HPMC, HPC and HEC were used as matrix agents to control release of the drug from the core tablets. In matricial systems, the characteristics of the matrix forming agent play an important role in the release mechanism(s) of the drug. Different grades of commercially available hydrophilic and hydrophobic polymers HPMC, HPC and HEC differ in their relative proportion of the hydroxy propyl and ethyl substitutions. In each grade for a fixed polymer level the viscosity of the particular polymer selected governs the performance of the matrix by affecting the diffusional and mechanical characteristics of the gel. All of these formulations were composed of MS and selected polymers were prepared by wet granulation method. The viscosity of 2% solutions of chosen polymers Klucel 1500 to 3000 cps, Natrosol 250 Mpham 4500 t0 6500, Benecel K35 35000 cps, Benecel K200M 150,000 cps, Metlose 90 SH SR 100000. Formulation with lower viscosity grades (Benecel K200M, Klucel HF pharm and Natrosol 250 Mphar) showed faster release of MS and drug release ranged from 43% to 86% in 1 hr and the

higher viscosity grades (Benecel K35M and Metlose 90SH 100000) showed slower release of MS ranging from 24% to 31% in 1hrs.

The *in vitro* release studies of MS core tablet formulations HM1, HM2, HM3, HM4 and HM5 were carried out, and effect of Hydroxy propyl methyl cellulose, (HPMC), Hydroxypropyl cellulose (HPC) and Hydroxy ethyl cellulose (HEC) in different levels on the drug release from core tablets were studied (Table 7). Formulation HM1, containing Hydroxypropylmethyl cellulose (Benecel K200M) showed faster drug release i.e. 66.5% in first hour and more than 85 % of the drug was released in 4hrs, where as formulations HM2 containing Hydroxypropylmethylcellulose (Benecel K35M) showed 24.3±1.50, 55.3 ± 1.65, 79±1.71 and 98.8 ±1.12 of drug release in 1, 4, 8, and 20th hrs with extended release characteristics, which nearly match with the USP dissolution specification of MS (Table 7& Figure 4). Formulation HM3 containing Hydroxypropyl cellulose (Klucel HF Pharm) as a matrix former did not show any extended release characteristics and released more than 86.9 ± 0.55% of the drug in first hour from the core tablets. Drug release from the formulation HM4 containing Hydroxyethylcellulose (Natrosol 250 Pharm) core tablets fails to show extended drug release characteristics and drug release was found to be 40.4± 1.12% in first hour and more than 75 % in 4hrs. Formulation HM5 containing Hydroxypropyl methylcellulose (Metlose 90 SH 100000) as release modifier showed 31.3± 1.05, 70.4 ± 1.3, 89.9± 1.1 and 101.5± 1.25 % of the MS in 1, 4, 8, and 20th hrs and also drug release pattern was within USP limits (Table 6).

Table 6: USP Limits of Metoprolol Succinate [11].

Time in (hr)	USP Specifications	Innovator Specification (Seloken® XL 100mg)	HMC5
1st hour	NMT 25 %	11.50 ± 2.34	10.70± 2.56
2nd hour		18.11 ± 3.32	17.01 ± 2.44
3rd hour		23.22 ± 2.76	22.87 ± 2.54
4th hour	Between 20 % to 40 %	27.40 ± 2.79	29.0 ± 3.02
6th hour		38.39 ± 2.76	39.90 ± 2.74
8th hour	Between 40 % to 60 %	48.60 ± 2.56	46.30 ± 2.84
10nd hour		58.10± 2.67	59.43 ± 2.98
12th hour		64.98 ± 2.65	63.44 ± 2.57
16th hour		70.20 ± 2.55	71.24 ± 2.87
18th hour		86.65 ± 2.44	85.45 ± 2.98
20th hour	NLT 80 %	98.50 ± 2.43	99.30 ± 2.67

Table 7: Cumulative % release of Core tablets

Cumulative% drug release (mean ± SD) (n=3)					
Time(hrs)	**HM1**	**HM2**	**HM3**	**HM4**	**HM5**
1	66.5 ± 1.60	24.3 ± 1.50	86.9 ± 0.55	43.4 ± 1.12	31.3 ± 1.05
4	85.7 ± 1.83	55.3 ± 1.65	95.5 ± 1.34	76.4 ± 0.9	70.4 ± 1.30
8	93.6 ± 0.96	79 ± 1.17	98.7 ± 0.91	96.6 ± 1.64	89.4 ± 1.13
20	99.7 ± 1.15	98.8 ± 1.12	99.6 ± 1.20	101.3 ± 1.60	101.5 ± 1.25

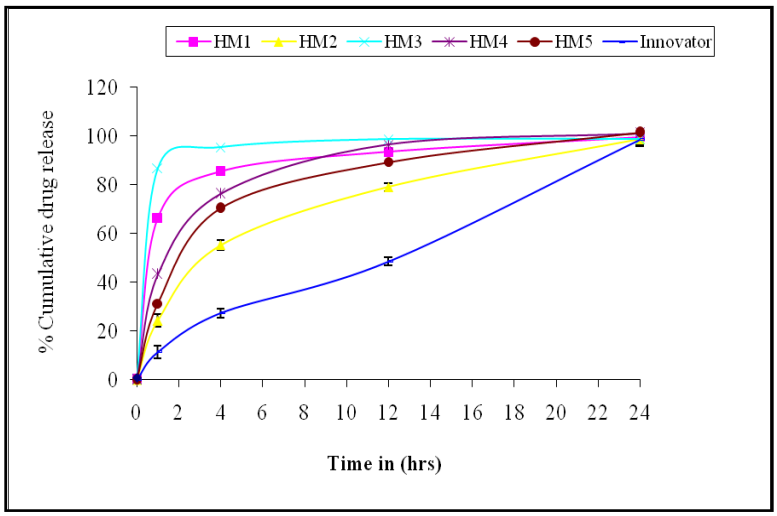

Figure 4: *In vitro* release profile Metoprolol Succinate ER matrix tablets in pH 6.8 phosphate buffer using various grades of cellulose polymers.

Table 8: Cumulative drug release of formulations HMC1 to HMC5

Time	Cumulative% drug release (mean ± SD) (n=3)		
(hrs)	**HMC2**	**HMC5**	**Innovator (Seloken® XL 100mg)**
1	5.3 ± 0.888	10.7 ± 0.953	11.5
4	20.1 ± 1.4	29 ±1.113	27.4
8	44 ± 1.682	46.3 ±1.530	48.6
20	85.6 ± 1.135	99.3 ±1.058	98.5

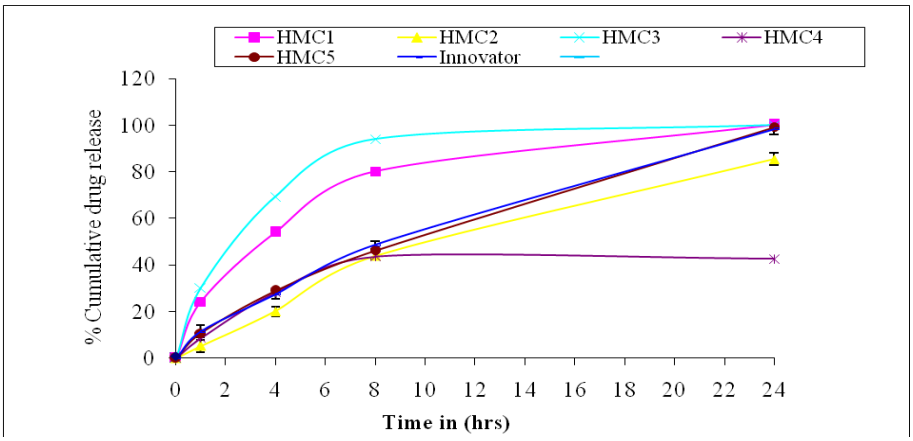

Figure 5: *In vitro* release profile Metoprolol Succinate ER matrix coated tablets and innovator (Seloken® XL) in pH 6.8 phosphate buffer

In vitro dissolution study results of the core tablets revealed that among all the formulations tested HM2 and HM5 showed extended drug release up to 20 hrs and release pattern was similar with that of the USP dissolution specification of MS. Hence these two formulations were further subjected for polymeric coating to match up exactly with the desired in vitro drug release specifications of USP and also to get similar dissolution profiles in comparison with the marketed product.

Polymeric coating was subjected on core tablets using aqueous dispersions of hydrophobic polymer ethyl cellulose (Surelease®), and in combination with a secondary polymer such as Hydroxypropyl methylcellulose (HPMC E 15) by conventional coating technique with optimized processing parameters. (Table -3). The coating solution was sprayed on the core tablets and the process was continued up to 5% w/w gain was obtained on core tablets, and coated tablets were tested for *in vitro* drug release studies. Drug dissolution study results of coated tablets HMC2 and HMC5 showed extended drug release up to 24 hrs with identical release profiles in comparison to USP specification and as well as marketed product(Table 8 & Figure 5). When the optimized formulations tested for the similarity (f_2) factor with marketed product (Seloken® XL 100mg) was found to be 53.05 and 88.25 for HMC2 and HMC5 respectively.

Basing on the similarity factor values, formulation containing(HMC5) Metlose 90SH 100000 as release modifier and 5% coating build up with blend of aqueous dispersions of ethyl cellulose (Surelease®) and Hydroxypropyl methylcellulose (HPMC E 15) showed maximum similarity when compared with HMC2.

Optimized formulations were kept for stability studies as per ICH guide lines at 25±2^0 C / 60±5% RH, 40±2^0 C/75±5% RH[10]. When the stability results of best formulae after 180 days were compared with their initial results it was found that there was no significant difference in the drug content between control and the test formulations (Table 9).

Table 9: *In vitro* drug release profile of Stability batches

Formulation Code	Initial	30^{0}C/60%RH	40^{0}C/75%RH
		180 days	180 days
HMC2	99.63	99.24	98.64
HMC5	99.15	99.13	98.91

CONCLUSION

Extended release tablets of Metoprolol Succinate were successfully prepared with polymers like HPMC, HPC and HEC. From the pre-formulation studies for drug excipient compatibility, it was observed that the selected excipients used in this study were not involved in any physical changes of the drug. The formulated batches were evaluated for physicochemical parameters and

dissolution profiles. The physical parameters like hardness, weight variation, and friability of majority of formulations complied with the pharmacopoeial specifications. The drug content was in the range of 98-101%.From the *in vitro* dissolution analysis the following conclusions are drawn. Formulation batches with HPMC (Metlose 90SH 4000) showed better release than the formulation batches with other polymers. It was observed that by increasing coating percentage of the concentration of polymer a retarding effect on the drug release was seen from the polymer matrix. Coating of the formulation with hydrophobic polymers like Ethyl cellulose in the form of aqueous dispersion (Surelease) showed a retarding effect on the drug release from the polymer matrix. Increase in viscosity of the same polymer caused decrease in the release of the drug from the polymer matrix. Formulation batch HMC5 was observed to have the similar dissolution profile as that of the marketed product when compared to other formulations (Figure 6). It showed a similarity factor f_2 equal to 83.75. The polymer used is HPMC (Metolose 90SH 4000). From the dissolution profile modeling it was found that the optimized formulation followed Higuchi model and almost followed Zero order kinetics. It followed Korsemeyer- Peppas model. (n>0.5) showing non- Fickian or anomalous diffusion behavior. Most of the formulations followed Korsemeyer- Peppas and Higuchi model, which indicates that the drug mechanism was diffusion. Controlled and followed fickian transport (Table 10). When the stability results of best formulae after 180 days were compared with their initial results it was found that there was no significant difference in the drug content between control and the formulations stored at 30^0C, 40^0C.

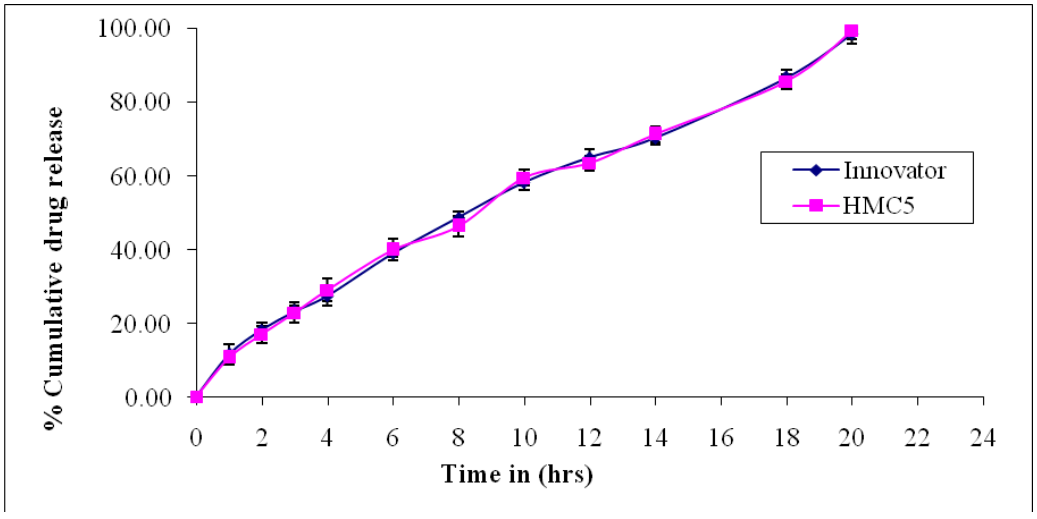

Figure 6: *In vitro* drug release profile of formulation HMC5 and marketed product (Seloken® XL 100mg)

Table 10: Mathematical Modeling, Drug Release Kinetics of core and coated Tablets.

Formulation	R^2				Peppas(n)
	Zero order	First order	Higuchi	Peppas	
HM1	0.833	0.690	0.946	0.972	0.486
HM2	0.826	0.678	0.943	0.968	0.479
HM3	0.573	0.562	0.752	0.913	0.047
HM4	0.639	0.571	0.808	0.918	0.295
HM5	0.7313	0.585	0.859	0.925	0.402
HMC1	0.697	0.651	0.854	0.957	0.137
HMC2	0.985	0.784	0.988	0.994	0.944
HMC3	0.648	0.554	0.815	0.909	0.415
HMC4	0.565	0.490	0.743	0.868	0.563
HMC5	0.996	0.856	0.979	0.998	0.737

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