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Extended Release Formulation of Metoprolol Succinate Using Ion Exchange Technology

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ABSTRACT

The purpose of this research work was to prepare an extended release formulation of metoprolol succinate using Ion exchange resin. Metoprolol succinate has short half life of 3-7 hours. So it needs to be administered 3-4 times a day. Hence an extended release preparation is desired. Drug-resin complex (DRC) was obtained by loading metoprolol succinate onto a strong cation exchange resin, Indion 244 in the ratio 1.5:1 using batch method. The molecular properties of the complex were investigated by differential scanning calorimetry, X-ray powder diffraction and Infra red spectroscopy which revealed interaction of drug with resin. To achieve the desired release rate, the DRC was initially treated with an impregnating agent, polyethylene glycol (PEG) 4000 and was further treated with hydrophobic polymer ethyl cellulose. Various formulations of tablets using resinate were prepared to achieve desired drug release profile. The formulations were evaluated for hardness, friability, weight variation, *in vitro* release and assay using HPLC. Formulation (V) shows optimum results in terms of release profile, which were in accordance with the USP specifications. The *in vitro* release profile showed that complexation of drug with ion exchange resin and use of hydrophobic polymer matrix could retard the initial burst and extend the release of drug up to 24 hours.

Keywords: metoprolol succinate, Indion 244, drug-resin complex, PEG 4000, ethyl cellulose

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INTRODUCTION:

Oral sustained or extended release dosage forms have been used for improving therapeutic efficacy and patient compliance. The common methods used to achieve sustained or extended release of orally administered drugs are, reservoir diffusion system, matrix diffusion system, osmotic system, ion exchange resins, prodrugs, etc. [1] Ion exchange resins have been widely used as a drug carrier in pharmaceutical dosage forms. Complexes between ion exchange resins and drugs have been used in pharmaceutical formulations for several decades. These resins are cross-linked water insoluble polymers carrying ionizable functional groups. Majority of drugs possess an ionic site in their molecule. The charge of the resin provides a means to loosely attach such drugs to insoluble polymer and form drug-resin complex (resinate).[2] Therefore the resinate provides its unique properties such as taste masking, extended release, improving stability of drugs etc. making ion exchange resin a multifunctional excipient. Drug release from the drug–resin complex depends on the ionic environment i.e., pH and electrolyte concentration within the GIT as well as properties of the resin. Metoprolol succinate is a β_1 selective (cardioselective) adrenoceptor-blocking agent for oral administration used in hypertension, angina and heart failure. The drug has short half-life of 3-7 hours. So it needs to be administered 3-4 times a day. Hence an extended release preparation of the same would serve the purpose. [3-5]The purpose of this research work was to prepare an extended release formulation of metoprolol succinate using Ion exchange resin. DRC was obtained by loading metoprolol succinate onto a strong cation exchange resin, Indion 244. The molecular properties of the complex were investigated by differential scanning calorimetry, X-ray powder diffraction and Infra red spectroscopy. To achieve the desired release rate, the drug-resin complexes was initially treated with an impregnating agent, PEG 4000 and was further with hydrophobic polymer ethyl cellulose. Physical properties and *in vitro* drug release of tablets were also performed.

MATERIALS AND METHODS

Indion 244 was supplied by Ion exchange Ltd (Mumbai, India). Metoprolol succinate USP was obtained as gift sample from M. J. Biopharm Pvt. Ltd. (Mumbai, India). Ethyl cellulose was supplied by Research Lab Fine Chem. Industries (Mumbai, India). Talc was obtained from S. D. Fine Chemicals, (Mumbai, India). All other ingredients were of analytical grade.

Preparation of Drug Resinates

Resin pretreatment

Indion 244 was purified using the method that was previously reported. [6-7] The resin (20 g) was placed in a beaker to which 200 mL of deionized water was added. The slurry was stirred on a magnetic stirrer for 5 minutes and allowed to settle for 15 minutes. The supernatant was removed by decantation. The resin was washed twice according to the above procedure. The washed resin was collected by filtration and dried overnight in a hot air oven at 50^0 C.

Formation of metoprolol succinate-Indion 244 Complexes and optimization of drug-resin ratio

A glass column (2 cm diameter, 20 cm length) was plugged with cotton at the bottom. The loading of metoprolol succinate on Indion 244 was studied for 1:1, 1.5:1, 2:1 and 1:2 drug: resin ratios. Accurately weighed amount of activated Indion 244 (100 mg, 100 mg, 100 mg and 200 mg) as per the ratios was suspended respectively in deionized water to prepare slurry. The slurry was then added to column and back washed with water to eliminate air pockets and distribute the beads. The drug solution in deionized water i.e. (100 mg, 150 mg, 200 mg and 100 mg) as per the ratios were prepared respectively and added at the top of the respective columns in small portions and left to equilibrate. Elution was carried out at the required rate keeping the liquid level above the resin level to prevent the formation of air pockets. The elute was subjected to estimation of unbound drug content spectrophotometrically at 222 nm (Model UV-1601, Shimadzu, Kyoto, Japan). Once the equilibrium was obtained, the solution was completely drained and DRC bed was washed using deionized water in portions. The complex was removed from the column, filtered through vacuum and dried in oven at 40°C till constant weight.[8]

In batch process different drug-resin ratios (1:1, 1.5:1, 2:1, and 1:2) were studied. Accurately weighed amount of resin Indion 244 as per the ratio was taken in a beaker and deionized water was added. The resin was allowed to swell for 30 minutes. Accurately weighed amount of metoprolol succinate was added in the respective slurry and the contents were stirred for 3 hours. The supernatant liquid was analyzed spectrophotometrically at 222 nm for drug content. Once the equilibrium is obtained, the complex was filtered under vacuum and dried in oven at 40° C till constant weight.

Evaluation of Drug Resin Complex

Drug content

Since the ion exchange resin is insoluble in all common solvents, determination of the drug content requires complete elution from the resin. It was determined by eluting the drug in phosphate buffer pH 6.8. About 100 mg accurately weighed drug resinate was stirred in 100 mL

of pH 6.8 buffer for 8 hrs. The aliquots were pipette out and after suitable dilution the drug content was determined spectrophotometrically.[9]

Drug entrapment efficiency (DEE) was determined from the following equation,

$$EE = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \qquad [1]$$

Study of Molecular Properties of DRC

X-Ray Powder Diffraction (XRPD)

The XRPD patterns of powdered samples of drug, resin and DRC were recorded using using Philips PW 1729 X-ray diffractometer (Legroupe Interconnexion, Saint Jurie, Clubac, Canada). The samples were irradiated with monochromator Cu $K\alpha_1$ (1.54 A^0), $K\alpha_2$ (1.544 A^0) and $K\beta$ (1.39 A^0) and analyzed between 5.00-60^0 (2θ). The voltage and current used were 40 KV and 30mA respectively. [10]

Fourier Transform Infrared Spectrophotometer (FTIR)

Infrared spectra of the resin, complex and drug were obtained using Fourier-transform infrared spectroscopy (Shimadzu 8400S, Japan) using KBr pellets (scanning speed of 2mm per sec, resolution of $4cm^{-1}$ and range of 4000-$400cm^{-1}$). The 3 spectra were comparatively analyzed. [10]

Differential Scanning Calorimetry (DSC)

A Mettler Toledo differential scanning calorimeter 821 (Mettler Toledo, Greifensee, Switzerland) equipped with an intracooler and a refrigerated cooling system was used to analyze the thermal behavior of metoprolol succinate and DRC. Indium standard was used to calibrate the DSC temperature. Nitrogen was purged at 50 mL/min and 100 mL/min through cooling unit. The heating rates were 10^0C/min. All measurements were performed over 20^0 C- 160^0 C. [10]

Dose calculation

A dosage of 50 mg of metoprolol tartarate was selected based on market survey. The extended release marketed preparations of metoprolol are available in 25 mg, 50 mg, 100 mg, and 200 mg dose. Since larger dose is likely to require a significant amount of resin which could result in unacceptably large tablet, 50 mg dose was selected for formulating extended release tablets using ion exchange resin.[1-11]

Preparation of Extended Release Tablets

Direct compression method was not used to formulate extended release tablets, since the resinate was not directly compressible therefore wet granulation method was used. The DRC equivalent to 50 mg of metoprolol was treated with various concentrations of PEG 4000 (10-30% w/w of DRC). The PEG treated complex was gently passed through 16 mesh to remove any

agglomerates. The PEG treated complex was then mixed with various concentrations of ethyl cellulose and dibasic calcium phosphate (DCP), which were previously screened through 100 mesh. The mixture was wet granulated using PVP K-30 (5% w/v solution in isopropyl alcohol). The wet mass was screened through 8 mesh and the obtained granules were dried at 40^0 C for 15 minutes. The dried coarse granules were passed through 22 mesh superimposed on 44 mesh. Granules retained on 44 meshes were collected and mixed with talc. The granules were compressed into tablets on a Mini Press-10 station tablet punching machine (RIMEK, Mehsana, India), using 10 mm punch, keeping hardness constant to about 3-4 Kg/cm^2. The formulations of the preliminary trial batches U (batch U were prepared using DRC equivalent to 47.5 mg of metoprolol succinate (MS) ie equivalent to 50 mg of metoprolol tartarate(MT) , DCP as a diluents and PVPK-30 (5% W/V) as a binder) and F_1 to F_{12} are shown in Table I. Formulations U-F_6 were prepared using PVP K 30 (5% w/v) as binder and formulations F_7-F_{12} were prepared using ethyl cellulose as a release retardant as well as a tablet binder.

Table I. Tablet formulations for preliminary trials*

Ingredients (mg)	U	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
DRC ≡ 47.5 mg of MS ≡ 50 mg of MT	86.78	86.78	86.78	86.78	86.78	86.78	86.78	86.78	86.78	86.78	86.78	86.78	86.78
PEG 4000	-	8.678	8.678	8.678	8.678	21.69	21.69	26.03	26.03	26.03	26.03	26.03	26.03
Ethyl Cellulose	-	47.73	95.45	119.32	143.17	108.47	162.7	112.8	169.2	225.6	112.8	169.2	225.6
DCP	207	156.81	109.09	85.2	61.37	88.06	38.83	42.19	16.49	6.07	84.39	32.98	12.14
Lactose	-	-	-	-	-	-	-	42.19	16.49	6.07	-	-	-
PVP K30 (5% w/v)	5.8	5.4	4.4	3.9	3.5	4.1	2.8	-	-	-	-	-	-
Talc	2.8	2.8	2.9	2.98	3.08	2.8	2.9	2.5	2.3	2.3	2.1	2	1.98
Tablet weight	302	308	307	307	306.5	312	316	312.5	317	352	312	317	352

***DRC indicates drug resin complex, MS indicates Metoprolol succinate, MT indicates Metoprolol tartarate, PEG indicates polyethylene glycol, DCP indicates dibasic calcium phosphate and PVP indicates Polyvinylpyrrolidone. All ingredients are in milligrams

Evaluation of Granules

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to

flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation. [12]

$$\tan\theta = \frac{h}{r} \qquad [2]$$

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

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas. [13]

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by using Carr's compressibility index.[14]

$$\text{Carr's index } (\%) = \{(TBD - LBD) \times 100\} \ / \ TBD \qquad [3]$$

Evaluation of DRC Tablets

Thickness and Hardness

The thickness of the tablets was determined using a digital caliper (model 500-136, Mitutoyo, Japan). The hardness of tablets prepared was determined using a tablet hardness tester (model 40-2100, Vankel, Cary, NC).

Friability

Twenty tablets were weighed, and then placed in a friabilator (model PTF-1, Pharma Test, Hainburg, Germany), which was rotated for 100 revolutions at 25 rpm.[15] The tablets were weighed again and percent friability was calculated by the following formula.

$$\%\ \mathrm{F} = \frac{(\mathrm{Wo} - \mathrm{W})}{\mathrm{Wo}} \times 100 \qquad [4]$$

Where,

F = friability

Wo = initial weight of the tablets

W = final weight of the tablets.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado), and the test was performed according to the official method. [4]

Assay

An assay was performed on HPLC as per the official monograph requirement for metoprolol succinate.[4] System suitability was checked prior to sample injections.

In Vitro Dissolution Studies

The release rate of metoprolol succinate from tablets (n = 6) was determined. The dissolution test was performed using United States Pharmacopeia (USP) type II (paddle) apparatus, 900 mL of pH 6.8 buffer, at 37ºC ± 0.5ºC and 50 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at the appropriate time for 24 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted to a suitable concentration with pH 6.8 buffer. Absorbance of these solutions was measured at 222 nm using a Shimadzu UV- 1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan). Cumulative percentage drug release was calculated using PCP Disso Version 2.08 software (Poona College of Pharmacy, Pune, India).

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order, first-order,Higuchi, Hixon-Crowell, Korsmeyer and Peppas, and Weibull models to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the highest correlation coefficient was considered to be the best model.[16]

RESULTS AND DISCUSSION

Optimization of drug-resin ratio using column and batch process

The loading efficiency of drug and Indion 244 for column and batch process is shown in Table II. The loading efficiency of drug and Indion 244 (1:1, 1.5:1, 2:1, 1:2) was 77.12 %, 91.21%, 71.42% and 86.25% respectively, indicating significant complexation. The drug loading increased with the ratio 1.5:1 and 1:2 in comparisons with 1:1 and 2:1 to about 91.21 % and 86.25% respectively. But drug-resin ratio 1:2 indicates higher resin ratio which would create a problem in tablet formulation because of low compressibility of ion exchange resins. The results revealed that 1.5:1 batch had minimum resin quantity to produce maximum loading of metoprolol succinate.

Table II. Optimization of drug-resin ratio using column and batch process

Drug-Resin ratio	% Drug loading		% Entrapment efficiency	
	Column process	Batch process	Column process	Batch process
1 : 1	40.13 ± 0.55	38.56 ± 0.85	80.26	77.12
1.5 : 1	54.90 ± 0.69	54.73 ± 1.76	91.5	91.21
2 : 1	46.38 ± 0.77	47.62 ± 0.96	69.56	71.42
1 : 2	29.23 ± 0.68	28.75 ± 0.83	87.69	86.25

Drug Content

The drug–resin complex was prepared using batch process with drug: resin ratio 1.5:1 at room temperature using water as complexing solvent. The average drug content of DRC was found to be 54.73%.

Molecular Properties of Drug-Resin Complexes

The X-ray powder diffraction pattern of the drug, resin and the complex is shown in Figure 1. The X-ray powder diffraction pattern of drug showed number of sharp peaks due to the crystalline nature of the drug and diffraction pattern of resin showed diffused peaks due to its amorphous nature. Whereas the X-ray powder diffraction curve for DRC shows absence of drug peaks confirming that the drug is entrapped in the resin. Infrared spectra of pure drug, resin and DRC are shown in Figure 2. The IR spectrum of pure drug shows a broad peak in the range 3100-3500 (O-H and N-H *stretch*) which is absent in the IR spectra of DRC which confirms that complexation between drug and resin has taken place at the secondary amino group in the drug. Differential scanning calorimetry curves for pure drug and DRC as shown in Figure 3. The thermal behavior of pure drug shows a sharp endotherm at 136° C. whereas the thermal behavior of DRC showed absence of sharp endothermic peak that confirms complexation between drug and resin.

Dose calculation

Dose calculation is the first and the critical step in formulation development. While calculating dose it was assumed that pharmacokinetic parameters of the drug would remain constant during the course of therapy and that the drug follows open one-compartment model. The drug content of DRC is 54.73 %. Since 47.5 mg of metoprolol succinate is equivalent to 50 mg of metoprolol tartarate, 86.78 mg of DRC was used for one tablet.

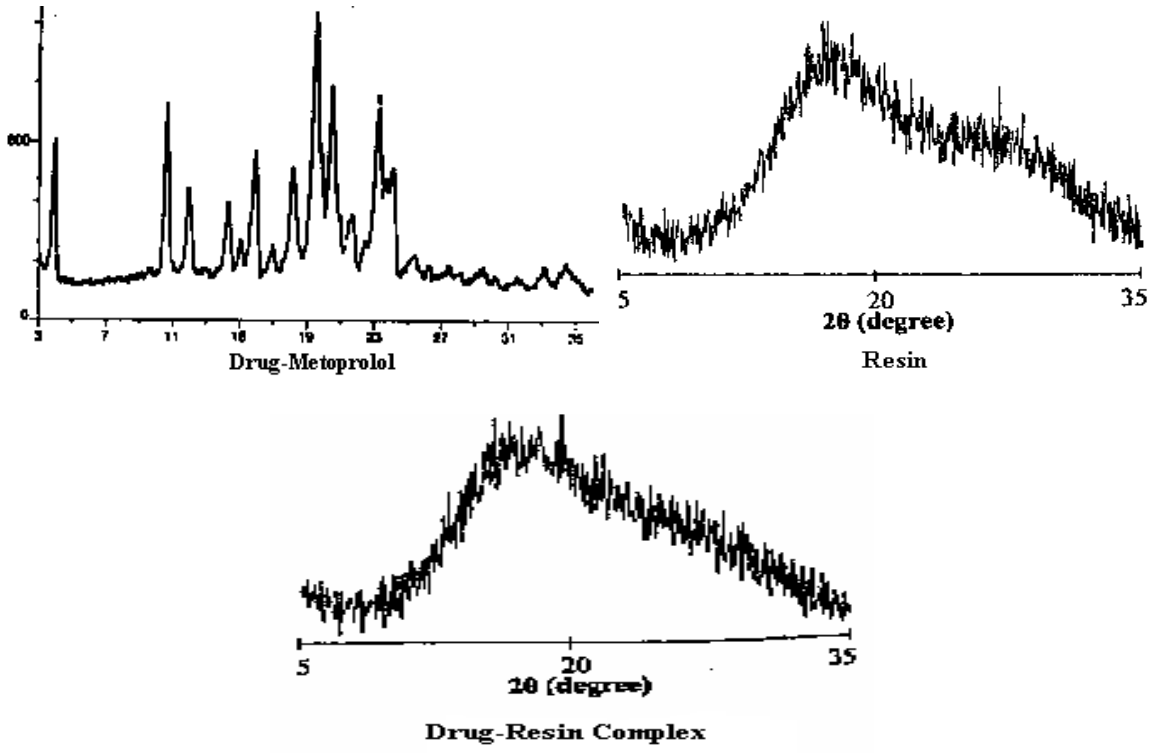

Figure 1. X-ray powder diffraction curves of drug (a), resin (b) and drug-resin complex (c)

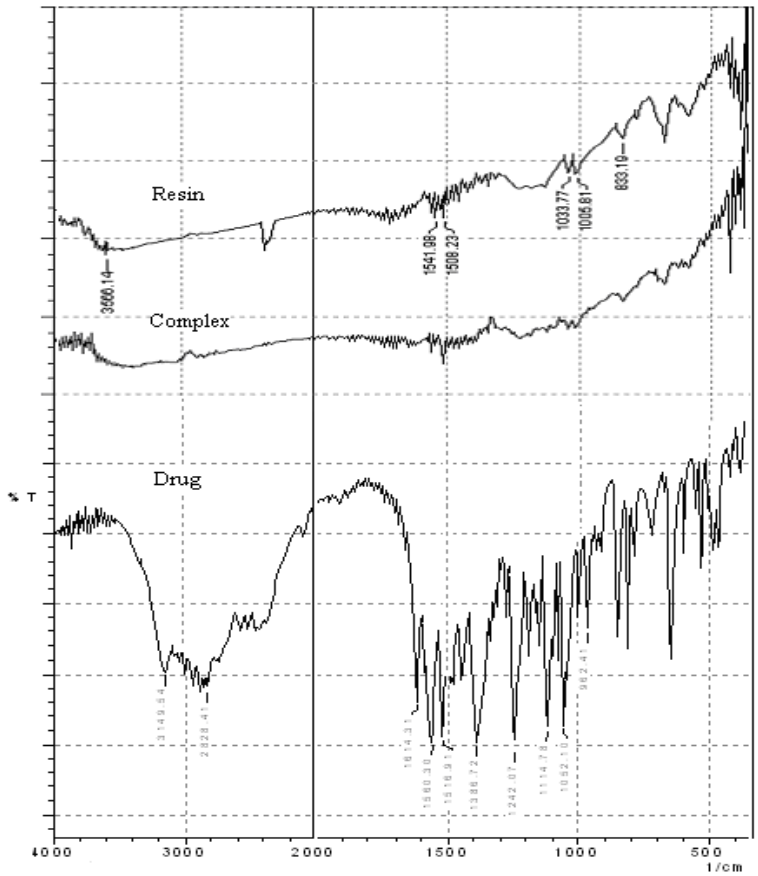

Figure 2. IR spectrum of resin, complex and drug

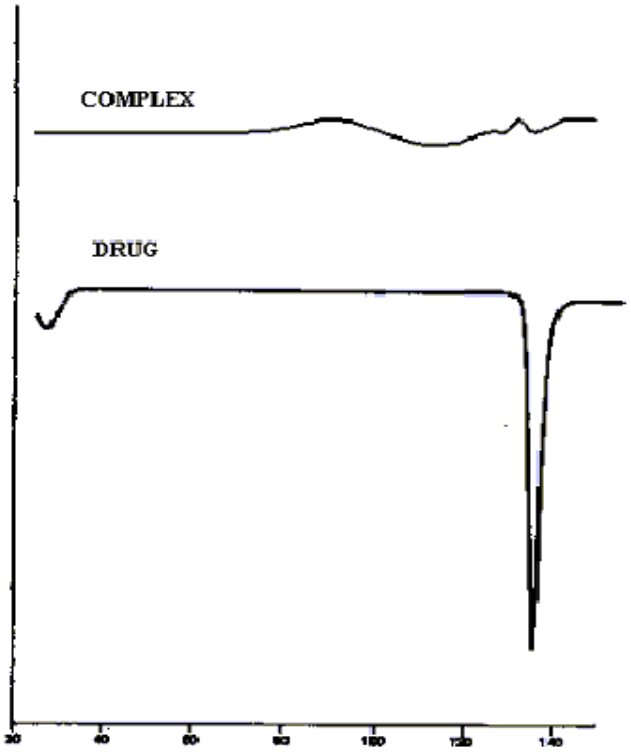

Figure 3. Differential scanning calorimetry curves of complex and drug

Evaluation of Granules

The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, total porosity, and drug content which are shown in Table III. All these results indicate that the granules possessed satisfactory flow properties and compressibility.

Table III. Properties of the granules*

Formulation No.	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	% Compressibility
U	0.45±0.04	0.5±0.06	28.48°	10
F_1	0.45±0.02	0.51±0.07	27.54°	11.76
F_2	0.44±0.012	0.5±0.06	29.41°	12
F_3	0.46±0.07	0.53±0.005	29.47°	13.2
F_4	0.45±0.002	0.51±0.001	27.34°	13.4
F_5	0.45 ± 0.03	0.52 ± 0.03	29.57°	13.46
F_6	0.44± 0.09	0.512 ± 0.06	27.33°	14.06
F_7	0.45±0.04	0.52±0.01	29.56°	13.46
F_8	0.45±0.06	0.51±0.004	27.38°	11.76
F_9	0.44±0.08	0.5±0.06	28.45°	12
F_{10}	0.47 ± 0.015	0.53 ± 0.1	27.26°	11.3
F_{11}	0.46 ± 0.05	0.5 ± 0.09	29.36°	8
F_{12}	0.45 ± 0.08	0.51 ± 0.05	31.66°	11.76

***** All values are expressed as mean ± SE, n = 5

Evaluation of DRC tablets

The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter, uniformity of weight, drug content, hardness, friability, and *in vitro* dissolution, results of which are shown in Table IV. All the tablet formulations showed acceptable physicochemical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability.

Table IV. Evaluation of tablets

Formulation	Diameter* (mm)	Thickness* (mm)	Hardness‡ (kg/cm^2)	Friability† (%)	Uniformity of weight† (mg)	Drug content* (%)
U	10 ± 1	2 ±1	3.5 ± 0.5	0.353 ±0.05	302 ± 2	98.64 ±2.0
F_1	10 ± 1	2 ±1	3.5 ± 0.5	0.342 ±0.05	308 ± 4	97.29 ± 3.0
F_2	10 ± 1	2 ±1	3.5 ± 0.5	0.369 ±0.05	307 ± 3	96.68 ± 2.5
F_3	10 ± 1	2 ±1	3.5 ± 0.5	0.313 ±0.05	307 ± 2	98.47 ± 2.0
F_4	10 ± 1	2 ±1	3.5 ± 0.5	0.328 ± .05	306.5 ± 3	96.72 ± 3.0
F_5	10 ± 1	2 ±1	3.5 ± 0.5	0.305 ± 0.05	312 ± 2	98.52 ± 2.0
F_6	10 ± 1	2 ±1	3.5 ± 0.5	0.329 ± 0.05	316 ± 4	96.89 ± 2.5
F_7	10 ± 1	2 ±1	3.5 ± 0.5	0.385 ± .05	312.5 ± 4	98.75 ± 3.5
F_8	10 ± 1	2 ±1	3.5 ± 0.5	0.324 ± .05	317 ± 3	98.57 ± 2.0
F_9	11 ± 1	2.5 ±1	3.7 ± 0.5	0.335 ± .05	352 ± 4	98.82 ± 2.5
F_{10}	10 ± 1	2 ±1	3.5 ± 0.5	0.365 ± 0.07	312 ± 2	98.23 ± 3.0
F_{11}	10 ± 1	2 ±1	3.5 ± 0.5	0.311 ± 0.05	317 ± 3	98.06 ± 2.0
F_{12}	11 ± 1	2.5 ±1	4.0 ±0.5	0.329 ± 0.07	352 ± 4	96.22 ± 2.5

*** All values are expressed as mean ± SE, n = 5. † All values are expressed as mean ± SE, n = 20. ‡ All values are expressed as mean ± SE, n =6**

In Vitro Dissolution Studies

In batch U, the DRC tablets were prepared using DCP as diluents and PVP K-30 as a binder. The tablet did not remain intact and about 70 % of the drug was released in 1 hour and it took about 8 hours for 100% of drug to get release. This shows that alone DRC could not retard the release of drug for a significant period of time. Therefore to achieve adequate or desirable control on release rate, the drug was further treated with various combinations of polymers, PEG 4000 and ethyl cellulose. Hence Batch F_1 was prepared using DRC, PEG 4000 (10% w/w of DRC) and ethyl cellulose in DRC: polymer ratio 1: 0.5. The tablets failed to remain intact. Dissolution study showed that about 51% of drug was released in 1 hour and about 100% of drug was released with 12 hours. Batches F_2, F_3 and F_4 were prepared keeping the PEG 4000 concentration same as that for F_1 but the ratio of ethyl cellulose was increased to 1:1, 1: 1.25 and 1: 1.5 respectively. The tablets remained intact for about 2-3 hours. Dissolution studies of F_2 an F_3 showed that about 100% of drug was released in around 12 hours and for F_4 it was around 20

hours. Batches F_5 and F_6 were prepared using PEG 4000 (25% w/w of DRC) and ethyl cellulose in the ratio 1:1 and 1:1.5 respectively. The tablets remained intact for about 5 hours. A dissolution study of F_5 showed that about 97% of drug was released within 20 hours. Whereas dissolution studies of F_6 showed about 26% release of drug within 1 hour and it took 24 hours for 100% of drug to get released. But these formulations failed to meet the USP specifications for metoprolol succinate extended release tablets. Thus batches F_7, F_8 and F_9 were formulated using PEG 4000 (30% w/w), DCP and lactose as diluents and ethyl cellulose in the ratios 1:1, 1:1.5 and 1:2 respectively. The tablets failed to remain intact and got disintegrated within 1 hour. PVP K-30 was not used as a binder in these formulations, as large proportions of ethyl cellulose itself acts as a retardant as well as a binder. Dissolution studies of F_7 and F_8 showed about 100% drug release in 8 hours whereas for F_9 it was around 12 hours. Batch F_{10} was prepared using PEG 4000 (30% w/w) and ethyl cellulose in the ratio 1:1 (DRC: polymer). The tablets remained intact and drug release was in accordance with the USP specification. Batches F_{11} and F_{12} showed greater retardation of drug release because of the high concentration of polymer. The dissolution profile of various batches of metoprolol succinate is shown in Figure 4.A & B

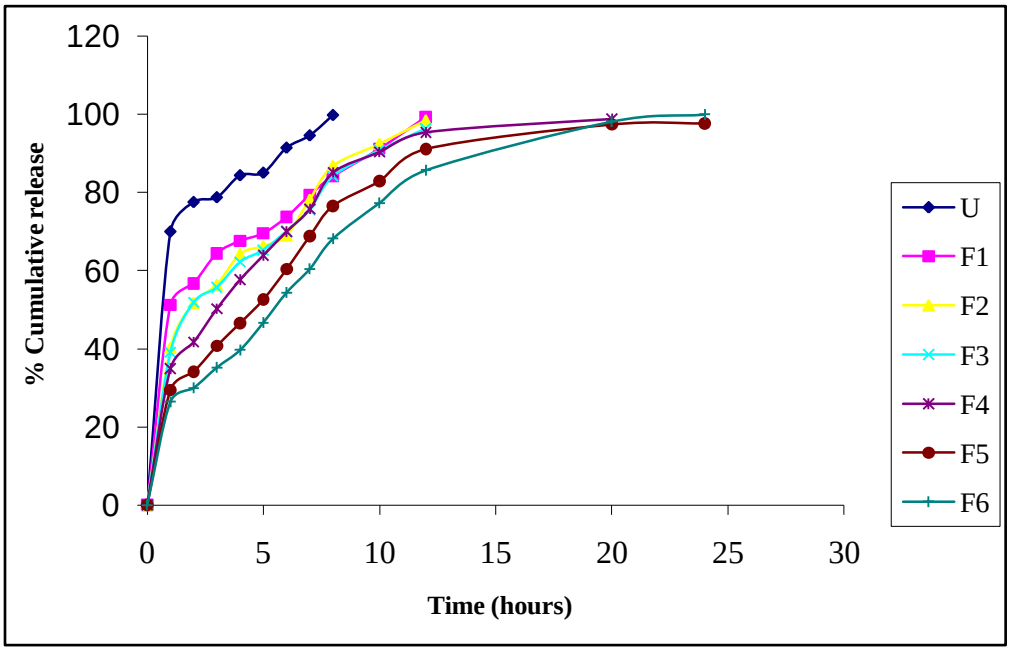

Figure 4.A Release profile of metoprolol succinate from tablet formulations for trial

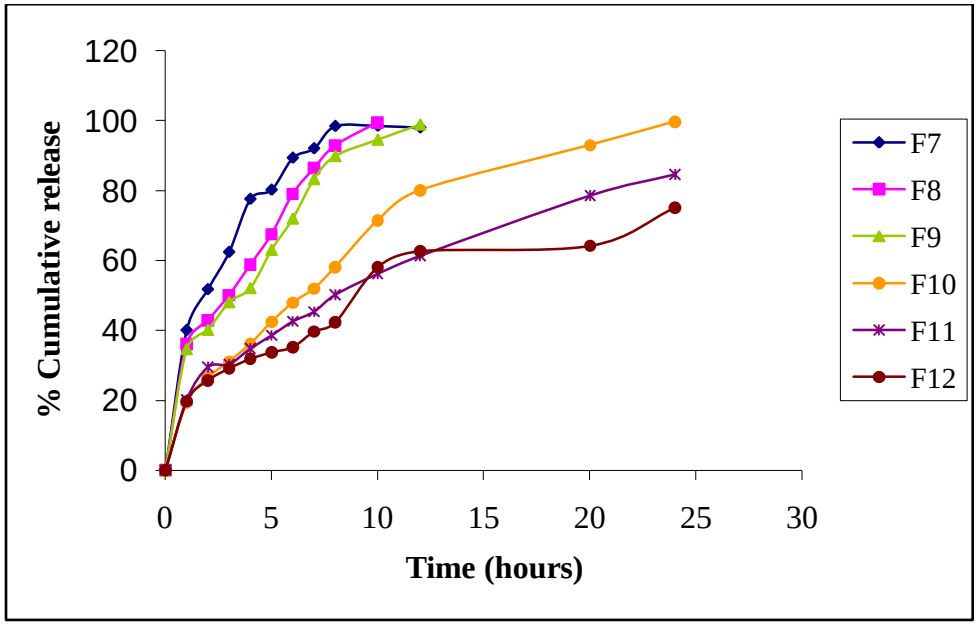

Figure 4.B Release profile of metoprolol succinate from tablet formulations for trial

Table V. Dissolution kinetics and model fitting data of extended release tablets

Formulations	Models	R	n	K
F_5	Zero order	—	—	—
	First order	0.9277	—	—
	Matrix	0.9562	—	—
	Peppas	0.9671	0.4157	27.1310
	Hixon-Crowell	0.8358	—	—
F_6	Zero order	—	—	—
	First order	0.9861	0.4622	22.7675
	Matrix	0.9837	—	—
	Peppas	0.9799	—	—
	Hixon-Crowell	0.9384	—	—
F_{10}	Zero order	—	—	—
	First order	0.9895	—	—
	Matrix	0.9898	0.4933	19.6595
	Peppas	0.9893	—	—
	Hixon-Crowell	0.9597	—	—
F_{11}	Zero order	—	—	—
	First order	0.9568	—	—
	Matrix	0.9948	0.4280	19.4401
	Peppas	0.9937	—	—
	Hixon-Crowell	0.9009	—	—
F_{12}	Zero order	—	—	—
	First order	0.8731	—	—
	Matrix	0.9728	—	—
	Peppas	0.9737	0.4107	18.1802
	Hixon-Crowell	0.8093	—	—

Kinetic modeling of drug release

The formulations that retard the drug release upto 24 hrs were taken for kinetic studies. The results of kinetic studies and model fitting are given in Table. V. The release of Metoprolol extended release formulation F_{10} is controlled by Matrix diffusion i.e., Higuchi square root kinetics.

$$Q = k\, t^{1/2}$$

Where, Q is the amount of drug released at time t and k is the diffusion rate constant.

CONCLUSION

Complexes between ion exchange resins and drugs are a promising approach to extend the release of drug that possesses an ionic site in their molecule. Ion exchange technology was used to formulate extended release preparation of metoprolol succinate by complexing with a strong cation exchange resin Indion 244. The complexation process was optimized for process conditions such as sorption technique, drug-resin ratio. A batch process with drug-resin ratio 1.5:1 gave an optimum drug binding with INDION 244 at room temperature using water as the complexing solvent. It shows highest entrapment efficiency of 91.2%. In vitro dissolution study showed that alone drug-resin complex could not retard the release of drug at desired rate. Therefore using Pennkinetic technology, the formulations were prepared in which the DRC was initially treated with an impregnating agent, PEG 4000 followed by a hydrophobic (Ethyl cellulose) polymer matrix. A series of tablet batches coded (F_1-F_{12}) were prepared using different combination and ratio of various excipients in order to optimize the drug release rate. The dissolution study of formulation **F_{10}** containing PEG 4000 (30%) and drug to ethyl cellulose ratio (1:1) shows excellent release profile, which complies with the USP specifications for extended release tablets of Metoprolol succinate. From the model fitting data it was observed that formulation F_{10} follows Higuchi model.

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