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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS COMPRISING COATED PELLETS

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Abstract:

The objective of the present study was for improving bioavailability and reducing the dosage frequency of Metoprolol succinate in the form of extended release pellets by pan coating technology. Preliminary studies with different polymers such as Surelase, Ethyl cellulose N50, Kollicoat SR 30D were performed. The results of in-vitro release data showed that Kollicoat SR 30D can Extend the drug release up to 24hr. Metoprolol succinate extended release tablets were prepared by MUPS Technique. The hardness of these extended release tablets was within the limit. The drug content was within the range, 98.23±0.25 to 102.03±2.45%. The in-vitro Metoprolol succinate release from the tablets was found Extended over 24 hours with korsmeyer-peppas kinetics of drug release and release pattern followed Super case- II transport. The Fourier transform Infrared spectroscopy (FT-IR) analyses indicated that there was absence of any chemical interaction between the drug and the excipients. The dissolution profiles of the developed formulation and the commercial tablet formulation, Seloken, were compared using the similarity factor (f2)and difference factor (f1). The released profile of tablet containing 7.5%KollicoatSR 30D by weight was similar to that of Seloken® providing the values of similarity factor (f2) 79.4and difference factor (f1) 4.8 of and respectively. The results of Accelerated stability studies showed that all parameters were within the expected specifications and there was no significant changes observed from initial to 3months, indicating good stability.

Keywords: *Ethyl cellulose N50, Kollicoat SR 30D, Metoprolol succinate, Surelase.*

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INTRODUCTION:

Metoprolol Succinate is a BCS-I class drug which is highly soluble and highly permeable. The drug is readily and completely absorbed throughout the whole intestinal tract but it is subject extensive first pass metabolism resulting in incomplete bioavailability (about 50%).After a single oral dose, peak plasma concentration occurs after about 1-2h, the drug will be eliminated within 3-4h.So Metoprolol succinate have to be taken 4times daily in conventional dosage forms. Based upon relationship between the beta blocking effect and plasma drug concentration. The main objective of the present study is to develop and evaluate extended-release (ER) multiple-unit pellet system (MUPS) tablets of Metoprolol succinate using Wurster process followed by compression.[1,2].

In comparison to conventional or immediate release dosage forms, MUPS has some unique advantages. In one single dose of MUPS pellets are rapidly and homogeneously distributed in the gastrointestinal tract (GIT) in spite of feeding or fasting condition, thus reduce the risk of high local concentration and side effects. Increase the contract region between drug and the GIT, furthermore, enhance drug absorption and lower the fluctuations of peak plasma. Therefore, MUPS could decrease dose frequency and increase patient compliance, improve the safety and efficacy of drug [3,4,5,].

In this study, using Wurster process by using Surelease, Ethylcellulose N50, Kollicoat SR 30D copolymers to achieve the extended release. Many factors have been studied to adjust the drug release rate by different coating formulations.

MATERIALS AND METHODS:

Metoprolol succinate was purchased from sun pharmaceutical Industries Ltd, sugar spheres (#50-#60) from Shiva shakthi Pharma, Ethylcellulose N50 from Aqualon Hercules, Kollicoat SR 30D from Colorcon, Surelease from Colorcon, Stearic acid (20% of EC) from Oleo Chemicals, PEG 6000 (10% of EC) from Clarient Chemicals, Talc from Luzenac Pharma, Isopropyl Alcohol from RA Chem Pharma Ltd.

Design and development of Metoprolol Succinate ER MUPS tablets:

Drug loaded pellets of Metoprolol Succinate were prepared by coating the drug solution on the inert core (sugar spheres) employing wurster process. Drug loaded pellets were further coated with ER coating polymers like Ethylcellulose N50 at various concentrations (7.5%, 10%, 12.5%, 15% W/W), Kollicoat SR 30D and Surelase (7.5%, 10%, 12.5% W/W) to study the impact of polymer concentrations on drug release. The optimized pellets were blended with all excipients (MCC pH102, Aerosil, Magnesium stearate, Lubritab) and compressed into tablets using rotary tablet compression machine, equipped with 9.0mm punches. Further these tablets were evaluated for various Physico-chemical properties and *In-vitro* studies. The composition of the formulation represented in Table (1-4).

Table 1: Development trial for Metoprolol Succinate Pellets

Ingredients	F1	F2	F3	F4	F5
Metoprolol Succinate	66	66	66	66	66
Sugar Spheres (#50-#60)	13	13	13	13	13
Aerosil	0.7	0.7	0.7	0.7	0.7
Sucrose	0	4	7.8	4.8	1.8
Binder solution					
Sugar	10	5	2	2	2
HPMC E5	3	1.5	0.6	0.6	0.6
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S
Coating					
Surelase	No coating	No coating	7.5	10	12.5
Stearic acid			1.5	2	2.5
PEG 60000			0.5	0.1	1.25
Talc			0.9	0.9	0.9
IPA			Nil	Nil	Nil
Purified water			Q.S	Q.S	Q.S

Table 2: Development trial for Metoprolol Succinate Pellets

Ingredients	F6	F7	F8	F9
Metoprolol Succinate	66	66	66	66
Sugar Spheres (#50-#60)	13	13	13	11.5
Aerosil	0.7	0.7	0.7	0.7
Sucrose	7.05	3.8	0.55	0
Binder solution				
Sugar	2	2	2	2
HPMC E5	0.6	0.6	0.6	0.6
Purified water	Q.S	Q.S	Q.S	Q.S
Coating				
Ethyl Cellulose N50	7.5	10	12.5	15
Stearic acid (20% 0f EC)	1.5	2.0	2.5	2.5
PEG 60000 (10% of EC)	0.75	1.0	1.25	1.25
Talc	0.9	0.9	0.9	0.9
IPA	Q.S	Q.S	Q.S	Q.S
Purified water	Q.S	Q.S	Q.S	Q.S

Table 3: Development trial for Metoprolol Succinate Pellets

Ingredients	F10	F11	F12
Metoprolol Succinate	66	66	66
Sugar Spheres (#50-#60)	13	13	13
Aerosil	0.7	0.7	0.7
Sucrose	7.05	3.8	0.55
Binder solution			
Sugar	2	2	2
HPMC E5	0.6	0.6	0.6
Purified water	Q.S	Q.S	Q.S
Coating			
Kollicoat SR 30D	7.5	10	12.5
Stearic acid (20% 0f EC)	1.5	2.0	2.5
PEG 60000 (10% of EC)	0.75	1.0	1.25
Talc	0.9	0.9	0.9
IPA	Nil	Nil	Nil
Purified water	Q.S	Q.S	Q.S

Table 4: Development trial for Metoprolol Succinate Tablets

S.No	Ingredients	T1(mg/tablet)	T2(mg/tablet)	T3(mg/tablet)	T4(mg/tablet)
1	Metoprolol Succinate ER coated Pellets	151.50	151.50	151.50	151.50
2	MCC pH 102	244.50	234.50	229.50	224.50
3	Aerosil	2.00	2.00	2.00	2.00
4	Lubritab	0.00	10.00	15.00	20.00
5	Magnesium Stearate	2.00	2.00	2.00	2.00

Evaluation of drug loaded Pellets:

Pre formulation study:

Pre formulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in rational development of dosage forms. Pre formulation study can divided into two substances.

Bulk density:

Bulk density was determined by pouring gently 30gm of sample (Metoprolol succinate) through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were record [6]. Bulk density was calculated as:

$$\text{Bulk density} = \frac{\text{weight of the sample}}{\text{bulk volume}}$$

Tapped density:

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 650 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.[7]

A sufficient number of taps should be employed to assure reproducibility for the material in question. The Volume was noted and the tapped density is calculated using the following formula.

$$\text{Tapped density} = \frac{\text{weight of the sample}}{\text{tapped volume}}$$

Compressibility Index and Hausner's ratio:

In recent years, the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting the powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using the bulk density and the tapped density of a powder.[7]

$$\text{Carr's index} = \frac{\text{Tapped volume} - \text{bulk volume} \times 100}{\text{tapped volume}}$$

$$\text{Hausner's ratio} = \frac{\text{bulk density}}{\text{tapped density}}$$

Angle of Repose:

The angle of repose has been used to characterize the flow properties of solids. A funnel was fixed at a height approximately 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed .Determine the angle of repose was determined by measuring the height of the cone of the powder and the radius of the heap of the pile.[7]

$$\text{Tan } \theta = \frac{h}{r}$$

Where,θ = angle of repose, h = height, r = radius.

Drug-Excipient compatability:

Drug- Excipient compatability studies has done in two ways.

a) Physical compatability

b) Chemical compatability

Physical compatability:

Physical compatability has done by keeping the pure drug(API) and along with API excipients are taken in the ratio as used in the formulation and kept at 40°C/75% RH and 25°C/60% RH for one month.

Chemical compatability:

a). D.S.C:

Differential Scanning Calorimetry (DSC) is used to check the compatability of drug with excipients.DSC measurements were done on pyris calorimeter. Approximately 3-5mg of drug were weighed accurately a into standard aluminum pan. An empty pan was used as an reference. The samples were heated from room temperature to390°C with scan rates 10°c/minute. Then the DSC curves are recorded with the help of computer scans.[8]

b). FTIR:

Identification of the pure drug and polymers was performed using infrared spectroscopy. IR spectroscopy by potassium bromide pellet method was carried out on drug, polymer, ingredients and physical mixture of drug-ingredients. About 2 mg of each sample was ground thoroughly with previously dried KBr at 120ºC for 30 min. uniformly mixed with drug and kept in sample holder and compressed under 10 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400 cm-1in a spectrophotometer and peaks obtained were recorded. Pure, completely dried KBr was used as blank and before running the sample.[9]

Assay:

Standard solution: Label claim amount of pure Metoprolol Succinate is dissolved in 100ml of water. as the drug is highly soluble in water.

Sample solution:

10 tablets are finely powdered and transfer powder equivalent to that of average weight of tablet and transferred to homogenization vessel and add 50ml of water and homogenize , finally make up the volume using water as diluents. Measure the absorbance of the test and standard using UV spectroscopy and analyze the drug content comparatively.[9]

After the evaluation of drug loaded pellets, the optimized formulation was taken and then for compressed into tablets by using direct compression method by four different trials. of all four formulations, T1-T4formulations had done by direct compression method.

Construction of calibration curve for Metoprolol succinate:

Preparation of stock solution:

Aqueous solutions of phosphate buffer of pH 6.8, were prepared as per USP25. Standard drug solution was prepared (1mg/ml) in Phosphate Buffer 6.8. The λ_{max} was determined in respective solvent and found to be 223nm.

Metoprolol (100mg) was dissolved in10ml of Phosphate Buffer6.8 and the total volume was brought to 100 ml with Phosphate Buffer 6.8 to obtain stock solution .Stock solution was further diluted to obtain 5-30 µg/ml with Phosphate Buffer6.8. standard solutions of Metoprolol succinate (10µg/ml) in Phosphate buffer 6.8 were scanned in the 200-600 nm range to determine the maximum absorbance (λ_{max}).fig no. 6 and Table no.10

Evaluation of tablets:

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.[10]

Physical appearance:

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odor, taste, surface texture and consistency of any identification marks.

Hardness test:

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. The tablet hardness of 5 kg is considered as suitable for handing the tablet.[10]

Tablet size and Thickness:

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by VernierCallipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.[10]

Friability:

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25 RPM for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%. [10]

$$\% \text{ Friability} = \frac{W1 - W2 \times 100}{W1}$$

Where, W1= weight o f tablets before test
W2 = weight of tablets after test

Weight variation of Tablets:

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits[10]. Twenty tablets were taken randomly and weighed accurately. The average weight was calculated by,

Average weight = weight of 20 tablets

20

In- vitro Dissolution study & Kinetics:

Dissolution study of formulations F3- F12 and was performed using an automated Electro lab paddle dissolution system tester coupled to an automated sample collector.[11] The study performed in 900ml of pH 6.8 phosphate buffer with USP Type-II apparatus at 50 rpm with temperature of 37 ± 0.5°C. At the predetermined sampling points (1, 4, 8, 12 and 20 hours) 5 ml of aliquot sample was withdrawn and replaced with fresh dissolution medium. Pellets release of corresponding core was determined by UV Visible Spectrophotometer at 223nm. *In vitro* drug release data was fitted into various mathematical models, zero-order, first-order, Higuchi, Korsemeyer-

peppas for determination of rate and drug release mechanism. Table no.12

Comparative dissolution profile of optimized formulation and marketed formulation:

In *vitro* dissolution profile of optimized formulation was compared with the similarity factor using marketed drug release profile (Seloken®) as a reference. Similarity factor [12,13] (f2) is a logarithmic reciprocal square root transformation to the sum of squared errors. If f2 value in between 50-100 two dissolution profiles considered to be similar.

Stability studies:

Stability studies were performed according to ICH guidelines for the optimized formulation. Optimized formulation was kept at humidity chamber maintained at25°C and 60% RH and 40°C and 65% RH for three months. The sample was analyzed for the physical changes and percent drug content at interval of 7, 15, 30, 60 and 90 days.

RESULTS AND DISCUSSION:

Pre-formulation studies:

API characterization:

These tests were performed as per the procedure and the results were illustrated in the following table no5.

Table 5: Characterization of Metoprolol Succinate (API)

S.No	PHYSICAL PROPERTIES	RESULTS
1	Physical appearance of drug	White to White colored Crystalline powder
2	Solubility	Slightly soluble in ethanol, Soluble in methanol, Highly soluble in water
3	Bulk density (gm/ml)	0.62 gm/ml
4	Tapped density (gm/ml)	0.7 gm/ml
5	Hausner's ratio	1.13
6	Compressibility index (%)	12.7%
7	Angle of repose	27°
8	Moisture content	3.4%W/W
9	Melting point	138.2°C

Drug-Excipient compatability study:

Appropriate quantities of the drug and excipients were weighed. The weighed drug and excipients were blended physically and transferred to glass vials and sealed. The sealed mixture blend were then kept at 25°C/60% RH and 40°C/75% RH for a period of 4 weeks and tested for physical and chemical compatability.

Table 6: Physical Compatibility Studies

Composition Material	Observations		Ratio (API: Excipient)	Conclusion
	Storage condition/Duration			
	40°C±2°C/75% RH ±5% RH	25°C ± 2°C /60%RH ±5% RH		
	One Month	One Month		
Metoprolol Succinate (API)	No Change	No Change	-----	Compatible
API + Sugar spheres	No Change	No Change	1:1	Compatible
API + Kollicoat SR 30D	No Change	No Change	1:1	Compatible
API + Ethylcellulose N50	No Change	No Change	1:1	Compatible
API + Sucrose	No Change	No Change	1:1	Compatible
API + HPMC E5	No Change	No Change	1:1	Compatible
API + Magnesium Stearate	No Change	No Change	1:0.25	Compatible
API + MCC PH102	No Change	No Change	1:1	Compatible
API + Aerosil	No Change	No Change	1:0.25	Compatible
API + PEG 6000	No Change	No Change	1:1	Compatible

Chemical Compatibility:

a).DSC studies: The DSC procedure is followed and DSC thermogram of API and Drug-Excipient compatability were given following figures

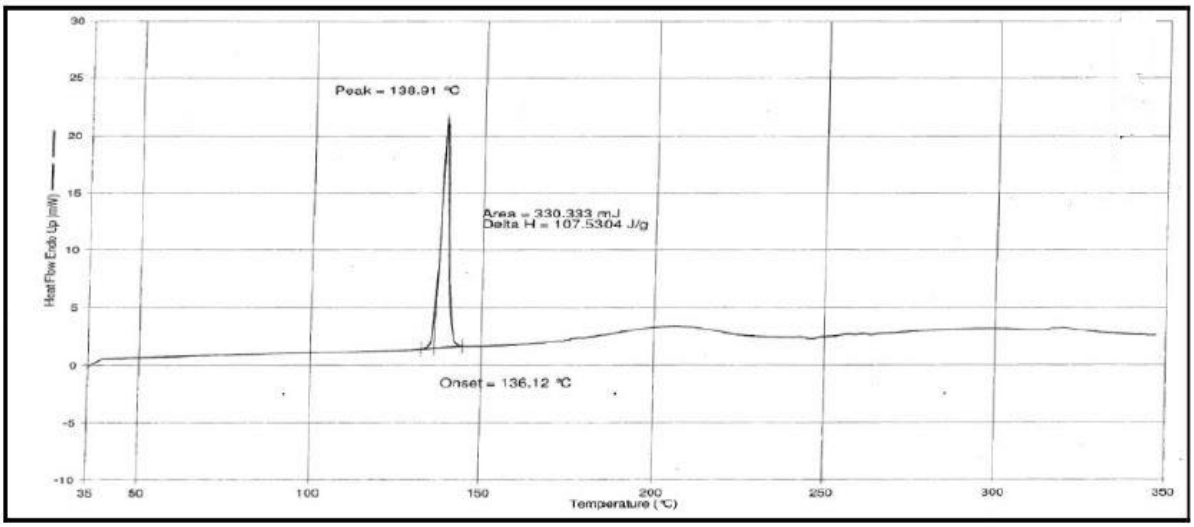

Fig 1: DSC thermogram of Metoprolol Succinate (API)

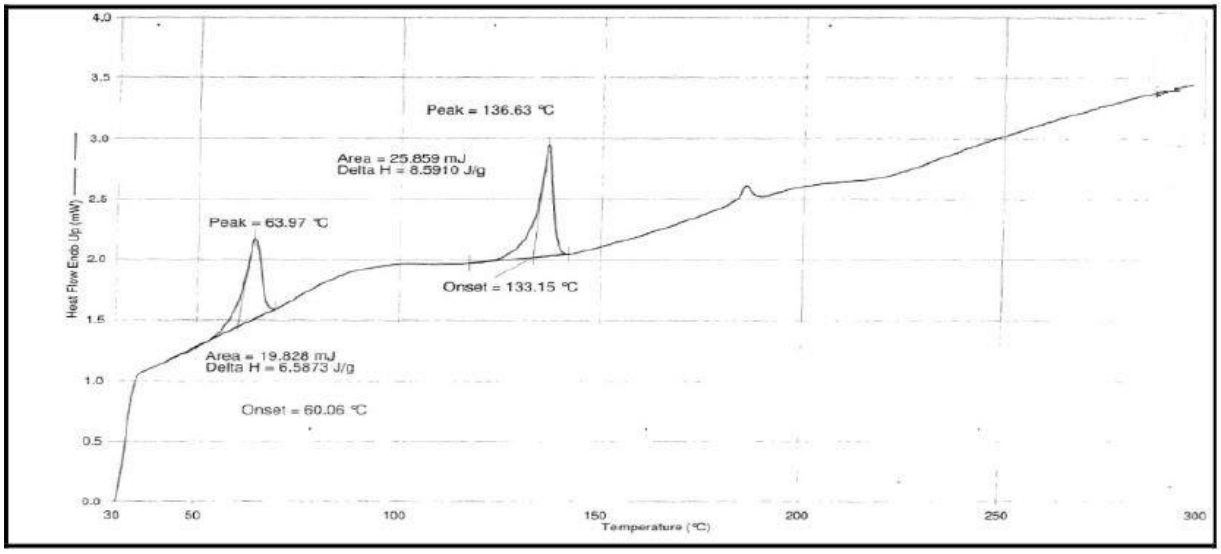

Fig 2: DSC thermogram of Metoprolol Succinate +Excipient

Discussion: By observing the Drug-Excipient compatability studies the results showed that there was no interaction between drug and its excipients, so the excipients were found to be compatible with drug.

2).FT-IR Studies: The physicochemical compatability of the drug Excipient was obtained by FT-IR studies

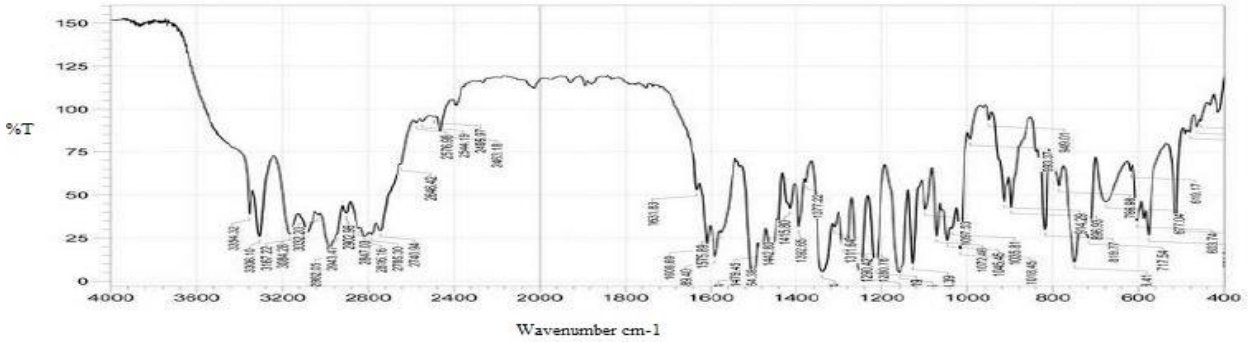

Fig 3: FT-IR Spectra pure drug of Metoprolol Succinate

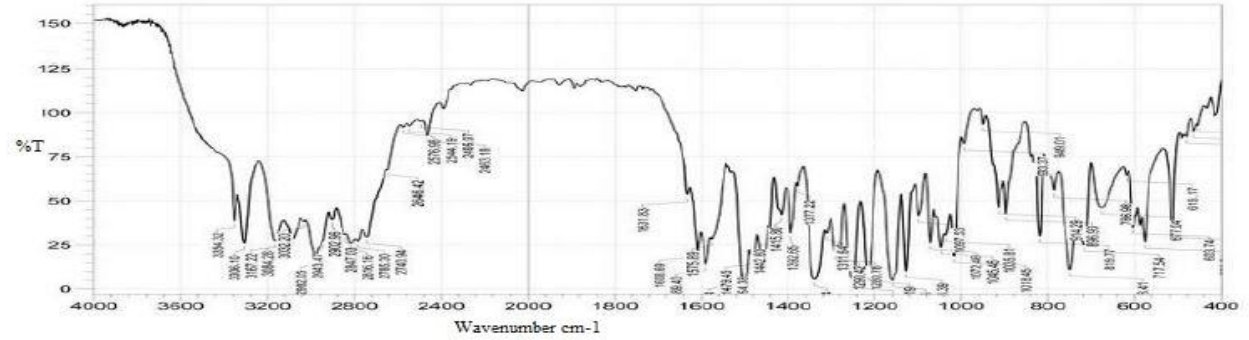

Fig 4: FT-IR Spectra pure drug with Ethylcellulose N50

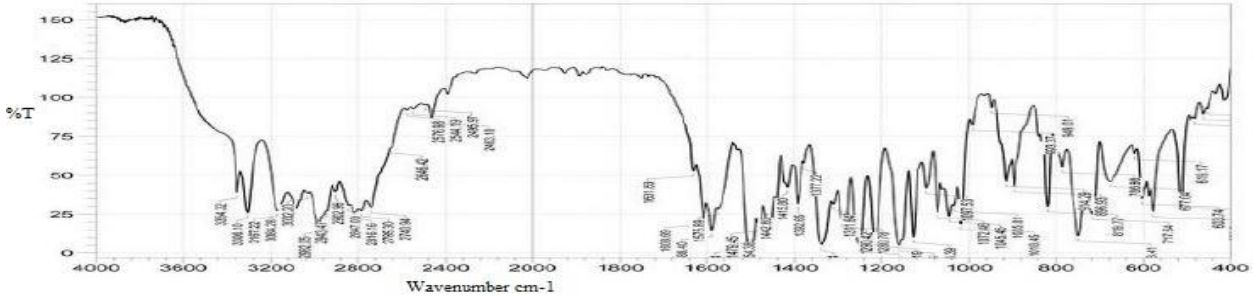

Fig 5: FT-IR Spectra pure drug with Kollicoat SR 30

Table 7: FT-IR Spectra data for pure drug of Metoprolol Succinate

S.No	Functional groups	IR Absorption band of pure Metoprolol succinate
1	C-N	1215
2	C-H(Alkane)	2847
3	N-H(Bending)	1630
4	OCH_3	1159
5	C=C	3306

Table 8: FT-IR Spectra data for pure drug with Ethylcellulose N50

S.No	Functional groups	IR Absorption band of pure Metoprolol succinate+ Ethylcellulose N50
1	C-N	1219
2	C-H(Alkane)	2850
3	N-H(Bending)	1639
4	OCH_3	1212
5	C=C	3312

Table 9: FT-IR spectra data for pure drug with Kollicoat SR30D

S.No	Functional groups	IR Absorption band of pure Metoprolol succinate+ KollikoatSR30D
1	C-N	1217
2	C-H(Alkane)	2855
3	N-H(Bending)	1649
4	OCH_3	1219
5	C=C	3318

DISCUSSION:

IR Spectral analysis Metoprolol succinate (drug) showed the peaks at wave numbers of 1215(C-N) 2847 (C-H Alkane) 1630 (N-H Bending) 1159 (OCH3- stretching) 3306 (C=C)confirming the purity of the drug with the standard respectively.

In physical mixture of Metoprolol succinate with EthylcelluloseN50 major peaks of Metoprolol succinate were 1219(C-N) 2850(C-H Alkane) 1639(N-H Bending) 1212 (OCH3- stretching)3312(C=C) wave numbers. However the additional peaks were observed in physical mixtures which could be due to the presence of excipients and it can be said that there was no chemical interaction between the drug and excipients from the spectra.

In physical mixture of Metoprolol succinate with Kollicoat SR30D major peaks of Metoprolol succinate were 1217(C-N) 2850(C-H Alkane) 1646(N-H Bending)1219 (OCH3- stretching) 3318(C=C) wave numbers. However the additional peaks were observed in physical mixtures which could be due to the presence of excipients and it can be said that there was no chemical interaction between the drug and excipients from the spectra.

Construction of calibration curve of Metoprolol succinate:

Table 10: Calibration data for the estimation of Metoprolol succinate

S.No	Concentration ((µg /ml)	Absorbance at 223nm
1	0	0
2	5	0.162
3	10	0.317
4	15	0.476
5	20	0.632
6	25	0.789
7	30	0.961

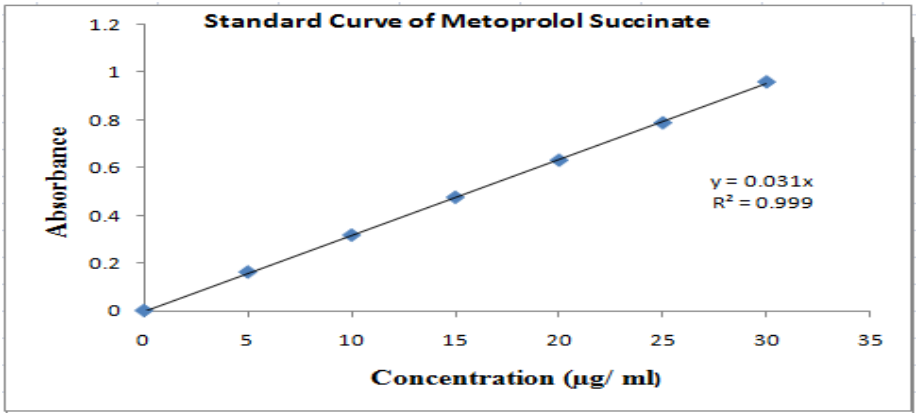

Fig 6: Standard plot for Metoprolol Succinate

Evaluation Parameters of Pellets:

Before the compression of tablets pellets have to be evaluated for the following tests for all the formulations and results are as follows as given in the table no.11 the formulation F1,F2 are not evaluated for physicochemical parameters because the pellets are not good enough because they are formed like lumps due to high concentration of binder. The pellets which has the specifications within the limits and that formulation will go for further formulations for the compression of tablets.

Table 11: Evaluation parameters of pellets

FORMULATION	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Angle of Repose (°)	29.2	25.6	29.0	31.7	27.74	27.7	27.4	24.32	29.77	30.2
Bulk Density (gm/ml)	0.703	0.627	0.621	0.614	0.614	0.655	0.694	0.697	0.66	0.621
Tapped Density (gm/ml)	0.792	0.777	0.727	0.712	0.712	0.742	0.775	0.702	0.703	0.727
Compressibility Index (%)	11.1	19.2	14.6	13.7	13.06	11.7	11.5	10.1	6.11	19.2
Hausner's Ratio	1.15	1.23	1.17	1.15	1.15	1.13	1.13	1.11	1.16	1.17
Loss on Drying (%)	1.02	1.25	1.30	1.43	1.24	1.34	1.49	1.32	1.20	1.45
Assay (%)	97.78	99.45	101.4	98.86	97.7	99.6	104.6	99.95	98.65	102.3

DISCUSSION:

The parameters of all formulations were found to be satisfactory. But of all formulations, F10 formulation was having good flow properties and loss on drying is within limits as per specifications and assay of the formulation was 99.79% .So, F10 formulation was selected as the optimized formulation

Table 12: Invitro dissolution study of pellets

S.NO	Formulations	Mean percentage of Drug dissolved (in pH 6.8 phosphate buffer)					
		0 hrs	1 hrs	4 hrs	8 hrs	12 hrs	20 Hrs
1	Innovator	0	8.5	25.2	47.9	65.8	88.5
2	F3	0	19.6	45.4	64.6	80.1	90.6
3	F4	0	6.4	22.7	42.1	62.5	84.2
4	F5	0	3.9	19.1	42.5	60.5	81.9
5	F6	0	33.5	45.6	68.9	83.5	95.6
6.	F7	0	26.1	45.2	67.1	84.9	93.1
7	F8	0	18.8	44.8	65.3	81.1	90.6
8	F9	0	15.6	39.6	58.6	75.2	88.6
9	F10	0	7.1	23.6	50.6	68.9	92.1
10	F11	0	3.9	19.1	42.5	60.5	83.9
11	F12	0	0.6	16.5	33.5	55.2	67.8

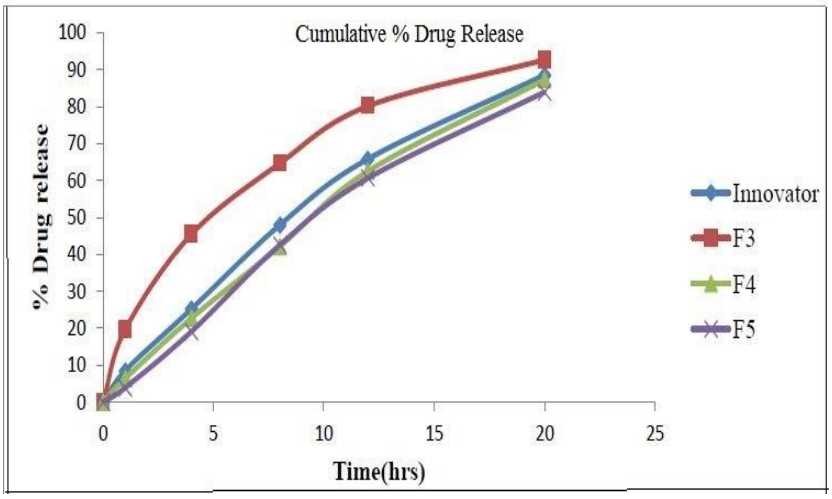

Fig 7: In vitro dissolution studies of the formulations F3, F4, F5 and innovator in pH 6.8Phosphate buffer

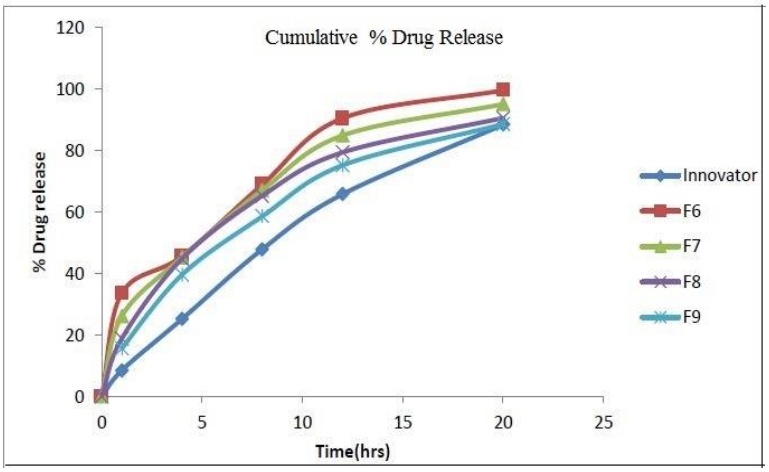

Fig 8: In vitro dissolution studies of the formulations F6, F7, F8,F9 and innovator in pH 6.8Phosphate buffer

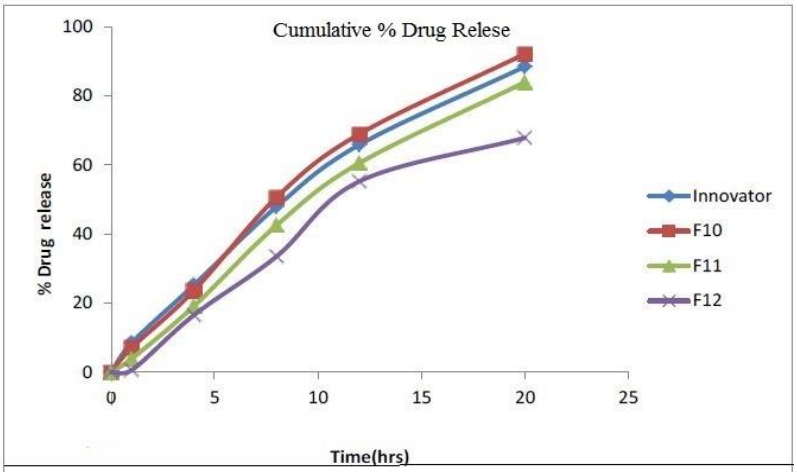

Fig 9: In vitro dissolution studies of the formulations F10, F11, F8,F12 and innovator in pH 6.8Phosphate buffer

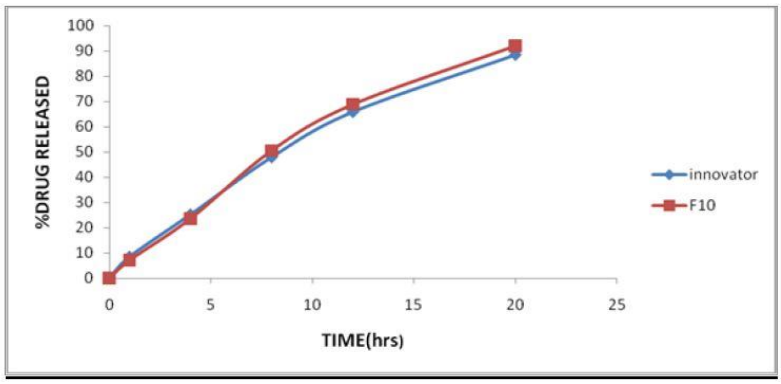

Fig 10: optimized formulation(F10) comparison with Innovator

Evaluation of tablets:

Table 13: Evaluation parameters of tablets

F.Code	Hardness (Kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug Content (%)
T1	3.169	5.17	397.6	0.13	98.5
T2	3.925	5.35	401.2	0.15	98.7
T3	4.537	5.80	399.9	0.14	100.1
T4	5.047	5.44	404.5	0.12	99.5

Among all formulations, T1, T2 formulations were not meeting the specifications Because in this formulations using of low concentration Lubritab. T4 formulation were meeting the specification limits so, further scale up batch is performed for T4 formulation.

Dissolution studies of tablets:

Table 14: In vitro dissolution studies of the tablets (MUPS) in pH6.8 phosphate buffer.

S.No	Formulation	Mean percentage of Drug dissolved in (pH 6.8 phosphate buffer)					
		0 hrs	1 hrs	4 hrs	8 hrs	12 hrs	20 hrs
1	Innovator	0	8.5	25.2	47.9	65.8	88.4
2	T1	0	9.7	30.5	55.5	72.9	96.7
3	T2	0	11.3	29.7	56.7	69.7	97.8
4	T3	0	6.9	23.6	52.6	68.9	90.05
5	T4	0	7.1	22.5	50.1	67.9	91.5

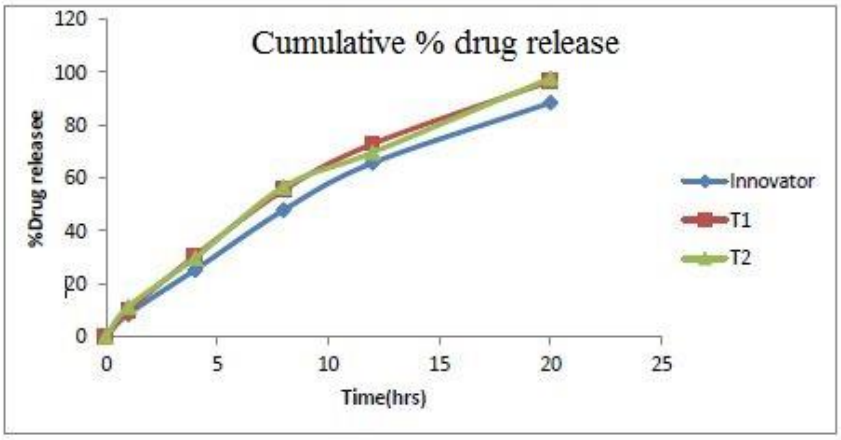

Fig 11: Invitro dissolution studies of the formulations T1, T2 and innovator in pH 6.8 Phosphate Buffer

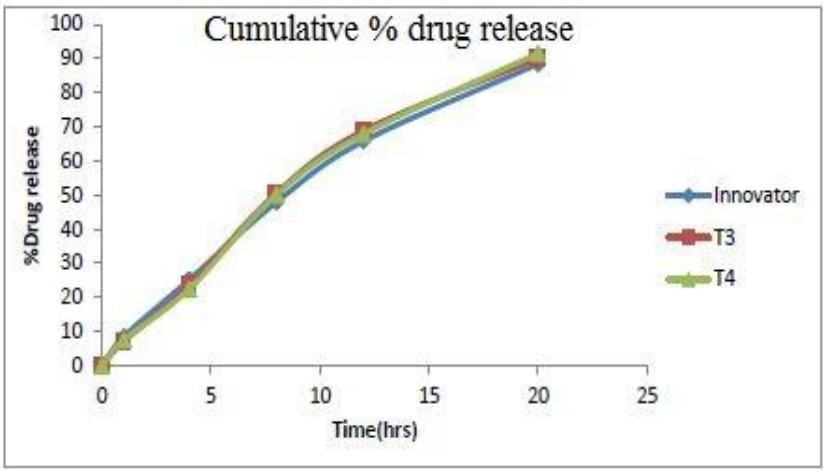

Fig 12: Invitro dissolution studies of the formulations T3, T4, and innovator in pH 6.8 Phosphate Buffer

Kinetic analysis of dissolution data:

The optimized formulation (T4) had their release kinetics in order to know their mechanism of release. The kinetic data is illustrated in the table no

Table 15: Kinetic analysis of dissolution data

Time (hr)	√T	Log T	Cumulative % Drug Release	Log Cumulative % Drug Release	Log Cumulative % Drug Remaining
0	0	0	0	0	0
1	1	0.	6.9	0.8388	1.968
4	2.000	0.602	22.5	1.3521	1.889
8	2.828	0.903	50.1	1.6998	1.689
12	3.464	1.0792	67.9	1.8318	0.506
20	4.472	1.301	91.5	1.9614	0.929

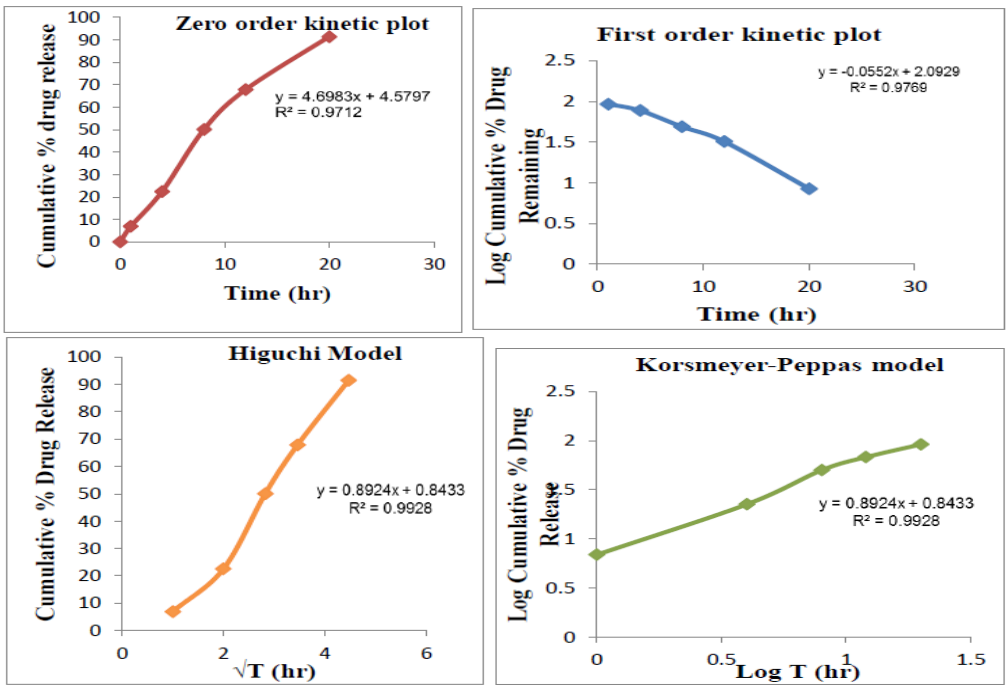

Fig 13: Kinetic plots for Optimized formulation (T4)

DISCUSSION:

The release rate kinetic data for the T4 as shown in Figure.10, drug release data was best explained by Korsemeyer equation, as the plots showed the highest linearity (r2 = 0.992). Based on n value the drug release follows super case-II transport (Anomalous diffusion) by erosion and diffusion mechanism.

Comparative dissolution profile of optimized formulation and marketed formulation:

Similarity factor of optimized formulation (T4) and marketed formulation was79.4. f2 is greater than 50. Then two formulations are identical.

Stability studies:

Samples were withdrawn and retested for drug content after intervals of 7, 15, 30, 60 and 90 indicating that no significant reduction in the content of active drug was observed over a period of 3 months; the percent drug contained is found within a specified limit of USP. Therefore, there was no evidence of degradation of drug quantity.

CONCLUSION:

Metoprolol Succinate is a β selective adrenergic neurotransmitters such as catecholamine's for binding at beta (1)-adrenergic receptors in the heart. Beta (1) -receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.Metoprololsuccinate pellets were prepared by using coating pan method with different polymers like Ethyl cellulose N50,Surelease, Kollicoat SR 30D. out of 12 pellet formulations, F10 (Kollicoat) was found to be the best formulation. By using this F10 formulation pellets, totally four tablet formulations (MUPS) have been prepared and out of this, T4 was found to be most promising formulation. Stability studies indicated that there is no much variation in stability parameters. In future in vivo studies have to be carried out.

REFERENCES:

1. Sakthikumar, N.N.Rajendran, R.Natarajan, Formulation of extended release tablet of Metoprolol Succinatefor the treatment of hypertension. IJPR.2011;vol(4):1532-1543.
2. Rama Rao Nadendla, Design and in-vitro evaluation of sustained release pellets of Metoprolol Succinate. Journal of Pharmacy Research., 2011,4(4),1157-1160
3. Marvola M, Nykanen P, Rautio S, et al. Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery system. Eur J Pharm Sci 1999;7;25e267
4. Clarke GM, Newton JM, Short M. Comparative gastrointestinal transit of pellet system of varying density. Int J Pharm 1995;114:1e11.
5. Hu Ld, Liu Y, Tang X, et al. Prepartion and In-Vitro/In-vivo evaluation of sustained-Release Metformin hydrochloride pellets. Eur J Pharm

Biopharm 2006;64;185e192
6. Liu Y, Sun Yh, Sun J, et al. Prepartion and In-Vitro/In-vivo evalution of sostained release venlafaxine hydrochloride pellets.Int J Pharm 2012;426;21e28.
7. John W, Anderson B, Kendall Mj. Pharmacokinetic consideration of Formulation of extended rlease Metoprolol Succinate in the treatment of heart failure. Journal of cardiovascular pharmacolog. 2003;41:151-157.
8. Mariyam Akter, SujanBanik,Mohammed Salim Hossain., 2012.Invitro evaluation of oral extended release drug delivery system for Metoprolol Succinate using Kollidon SR. Journal of applied pharmaceutical science.02(05),188-192.
9. Moreshwar N., Kulkarni ., 2009. Development and validation o spectrophotometric method for determination of Metoprolol succinate, International Journal of ChemTech Research. Vol.1,No.4, pp 1273-1277.
10. T. Sakthikumar., 2011. Formulation &in vitro release characterization of Metoprolol succinate Extended release Tablets. International journal of pharmaceutical science and nanotechonology. Vol (4),1532-1543.
11. Aqil M, Sultana Y, Ali A. Matrix type transdermal drug delivery systems of metoprolol tartrate: In vitro characterization. Acta Pharm 2003;53:119-25.
12. Gohel MC, Panchal MK. Novel use of similarity factors f 2 and S d for the development of diltiazem HCl modifiedrelease tablets using a 3^2 factorial design. Drug Dev Ind Pharm.2002; 28:77-87.
13. Banakar UV. Pharmaceutical dissolution testing. New York: Marcel Dekker; 1992.