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FORMULATION AND EVALUATION OF EXTENDED RELEASE PELLETS OF METOPROLOL SUCCINATE

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Abstract:

The objective of the present study was to formulate and develop extended release drug delivery system of anti-hypertensive drug Metoprolol succinate . The major indications of Metoprolol succinate is treatment and management of hypertension, angina, acute myocardial infarction, supraventricular tachycardia, congestive heart faiure, and migrane. Hypertension (HTN)is a chronic medical condition in which the blood pressure in the arteries is elevated. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg pressure . The dosage for adults is 2-3 times a day, to reduce the dosing interval to one time a day Metaprolol succinate developed as extended release capsules. Which reduces the dosing interval. Preliminary studies with different polymers such as Surelase, Ethyl cellulose N22, Kollicoat SR 30D were performed. The results of in-vitro release data showed that Kollicoat SR 30D can Extend the drug release upto 24hr. The drug content was within the range, 98.23±0.25 to 102.03±2.45%. The in-vitro metoprolol succinate release from the capsules 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. Thus the objective of extended release drug delivery system of anti-Hypertensive drug Metoprolol succinate with extended release profile was achieved.

Key Words: *Metoprolol succinate, kollicoat SR, surelase, ethyl cellulose N22,extended release.*

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INTRODUCTION:

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure is summarised by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole) and equate to a maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system[1]

In the treatment of hypertension, in most of the trials beta blockers have been used because it prevents the probability of recurrence of heart attack. Of that beta blockers, Metoprolol succinate is selected because it is extensively used $ß_1$ adrenergic antagonist in reducing the cardiovascular events and mortality in patients ,coronary heart disease. It is proven as just as effective or superior to other beta blockers and it is inexpensive than other drugs. So Metoprolol succinate is selected as a drug of choice.

Metoprolol succinate is available in the form of tablets, capsules and injections. In switching between Oral and Intravenous route(IV) dosage forms equivalent beta blocking effct is achieved in 2.5:1 ratio(oral to IV) ratio. SO oral route is the prefered route.

It is formulated as an extended release formulation because as Metoprolol succinate is a BCS-I class drug which is highly soluble and highly permeable and highly soluble. 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 1-2 hours, the drug will be eliminated within 3-4 hours. So Metoprolol succinat have to be taken 4 times daily in conventional doage forms. Based upon the relationship between the beta blocking effect and plasma drug concentration Metoprolol succinate lends itself as an extended release formulation.[1]

In comparison to tablets and capsules, Multi Unit Pellet System (MUPS) occupy a prominent role in formulations because of their greater patient compliance, process formulation and therapeutic advantages. In MUPS each of the pellet was designed to act as diffusion cell that delivers the drug at a relatively constant rate, eventually relatively independent of physiological variations within the gastrointestinal tract[2].

So due to these reasons we aimed to develop sustained release capsules of Metoprolol succinate in multiple-unit pellet system(MUPS) by extrusion spheronization method and coating pan technique. In comparison to the conventional or immediate-release dosage forms, MUPS has some unique advantages. In MUPS, pellets are often filled into hard gelatin capsules or compressed into tablets [3]. 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 [4,5,6].

Though there are many approaches to prepare pellets, such as extrusion and spheronization, fluid bed granulation [7] ,centrifugal granulation [8] ,Extrusion spheronization is one of common strategies to prepare pellets for acquiring modified release systems in pharmaceutical industry since 1970 [9], and the method consists of two basic processes of extrusion and spheronization. Pellets prepared by the method of extrusion spheronization have some advantages, such as high sphericity, compact structure, low hygroscopicity, narrow particle size distribution and smooth surface [10.11].

In this study, we attempt to apply extrusion spheronization, simply and easily industrialized preparation method to prepare uncoated pellets, followed by coating process using Surelase, Ethyl cellulose N22, Kollicoat SR 30D copolymers to achieve the sustained 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 N22 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.

Preparation of Metoprolol Succinate Extended Release Pellets:

Formulation Steps:

Drug Loading:

Sifting and Blending:

- Sift the Metoprolol succinate with excipients Aerosi land Sucrose Powder a through #40 mesh by using Vibro shifter. Transfer the shifted material in to blender and blend the material for 15min at 12 RPM . Finally collect the blended material into High Density Poly Ethylene(HDPE) containers lined with double polyethylene bags.

Binder Solution Preperation:

- Dissolve sucrose in purified water under continuous stirring.
- Add HPMC E10 to above solution under continuous stirring and continuous stirring till to get the clear solution is formed.
- Finally filter the solution through nylon cloth or # 200 mesh.

Pelletization

- Sift the Starch pellets through (50#-#60) and collect 50# retains and #60 downs separately.
- Load the sugar spheres (50# - #60) into coating pan and start the coating pan and allow the beads to rotate.
- Adjust the compressed air pressure to 1.0 - 2.0 kg/cm^2
- Start the peristaltic pump and adjust to 10 - 40 RPM.
- Start spraying the binder solution adjusting the gun distance (15-20 c.m)
- Continue spraying until the beads become wet.
- Stop spraying and add drug mixture in small quantities to the wet beads in the coating pan until the beads are free flowing.
  Continue the spraying of syrup solution and addition of drug till the completion of the drug layering process.
- Note the parameters at every 30 minutes.

Drying:

- Load the wet drug loaded pellets into trays of tray drier and load the trays into Tray Drier.
- Set the inlet temperature around **50±5°C** to get the bed temperature between **40°C-45°**C.

  Note: i) take the pellets at every 1 hour.

  ii) Record the drying parameters every one hour

  iii) Unload the pellets after moisture content comes below 1.5% into HDPE containers lined with double polyethylene bags.

Sifting:

- Check the integrity of the sieve/screen before and after sifting. Record the observations and action taken in case of damage if any.
- Sift the dried pellets through #24and collect #24 retains and passings #24 passing through #30 and collect the retains.
- The sifted pellets (#24-#30) are collected into HDPE containers lined with double polythene bags.

Sub Coating:

Preparation of Sub coating Solutions:

Preparation of EC Coating Solution:

- Dissolve Ethyl cellulose in Isopropyl alcohol with continuous stirring till a uniform solution is obtained.
- Dissolve Polyethylene glycol in purified water.
- The above two solutions are mixed under continuous stirring till a uniform clear solution is obtained.
- Then add talc and stearic acid to the above solution.
- Pass the above solution through #200 mesh or Nylon cloth and collect the solution separately.

II. Preparation of Kollicoat SR 30D Coating Solutions:

- Dissolve Kollicoat, Polyethylene glycol in purified water.
- The above solution was mixed under continuous stirring till a uniform clear solution is obtained.
- Then add talc and stearic acid to the above solution.
- Pass the above solution through #200 mesh or Nylon cloth and collect the solution separately.

III .Preparation of SU releases Coating Solution:

- Dissolve Surelease, Polyethylene glycol in purified water.
- The above solution was mixed under continuous stirring till a uniform clear solution is obtained.
- Then add talc and stearic acid to the above solution.
- Pass the above solution through #200 mesh or Nylon cloth and collect the solution separately.

Coating:

- Load the ER coated drug pellets into Fluidised Bed Coater (FBC) the inlet cores are coated with coating solution uniformly.
- Set the inlet temperature to 45°C-50°C, maintain the bed temperature at 40°C-45°C.
- Coat the sub coated drug pellets by bottom spray wurster at peristaltic pump of 1 – 3RPM and atomizing air pressure of 0.8 – 1 Kg/cm^2 with enteric coating solution till the coating solution is completed.
- Dry the pellets in FBC for about 5 min before unloading.
- Now pass # 24 passing pellets through # 30 and collect retains and passing separately.

Sifting:

- Check the integrity of the sieves/screen before and after sifting. Record the observations and action taken in case of damage if any.
- Sift the dried pellets through #24and collect #24 retains and passings #24 passing through #30 and collect the retains.
- The sifted pellets (#24-#30) are collected into HDPE containers lined with double polythene bags.

Packaging and Storage:

- Collect sifted Metoprolol succinate pellets (24# - #30) in HDPE containers lined with double polyethylene bags.
- Transfer the HDPE container into Finished Goods Store below 25 º C

Formulation Trials for Pellets

Table 1: Development trials for Metoprolol Succinate pellets

Development trials for Metoprolol Succinate pellets					
Ingredients					
Drug loading	F1	F2	F3	F4	F 5
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 E10	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 6000			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 trials for Metoprolol Succinate pellets

Development trials for Metoprolol Succinate pellets				
Ingredients				
Drug loading	F 6	F 7	F 8	F 9
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 E10	0.6	0.6	0.6	0.6
Purified water	Q.S	Q.S	Q.S	Q.S
Coating				
Ethyl Cellulose N 22	7.5	10	12.5	15
Stearic acid(20% of EC)	1.5	2.0	2.5	2.5
PEG 6000(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 trials for Metoprolol Succinate pellets

Development trials for Metoprolol Succinate pellets 66%			
Ingredients			
Drug loading	F 10	F 11	F 12
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 E10	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% of EC)	1.5	2.0	2.5
PEG 6000(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

Evaluation of Pellets:

Evaluation Tests for Drug Loaded Pellets

a. Physical Description
b. Bulk Density and tapped density.
c. Angle of repose
d. Compressibility Index
e. Hausner's ratio
f. Assay
g. Dissolution studies

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 capsules content was finely powdered and transfer powder equivalent to that of average weight of capsule 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 analyse the drug content comparatively.

After the evaluation of drug loaded pellets, the optimized formulation was taken and then filled in to hard gelatin capsules.

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 no:4

Table 4: Showing the characterization of Metoprolol succinate (API)

S.NO	PHYSICAL PROPERTIES	RESULT
1.	Physical appearance of drug	A pale white to white colored Crystalline powder
2.	Solubility	Highly soluble in water, soluble in methanol, slightly soluble in ethanol
3.	Melting Point	135°C
4.	Bulk density (gm/ml)	0.61gm/ml
5.	Tapped density (gm/ml)	0.7gm/ml
6.	Compressibility index (%)	12.7%
7.	Hausner's ratio	1.14
8.	Angle of repose	27°
9.	Moisture Content	3.4 % w/w

Drug-excipient compatibility studies

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 5: For Physical compatibility:

Material	Sample status after 1 month, kept at 25°C ± 25°C /60%RH ±5% RH	Sample status after 1 month, kept at accelerated 40°C±2°C/75% RH ±5% RH
Metoprolol succinate(API)	No Change	No Change
API+ Sugar Spheres	No Change	No Change
API+ Ethyl cellulose	No Change	No Change
API+ Surerelease	No Change	No Change
API+Kollicoat	No Change	No Change
API+HPMC E5	No Change	No Change
API+Sucrose	No change	No Change
API+Mg.stearate.	No change	No change
API+MCC PH102	No Change	No Change
API+Lubritab	No Change	No Change
API+Aerosil	No Change	No Change
API+PEG 6000	No Change	No Change
Composite sample	No Change	No Change

Physical stability results:

The analysis of the drug-excipients blend and API after 30 day's storage under accelerated and real time conditions showed that the drug was stable.

Chemical compatability:

1)DSC STUDIES:

The DSC procedure is followed and DSC thermogram of API, drug-excipient compatability blend were given in the following figures.

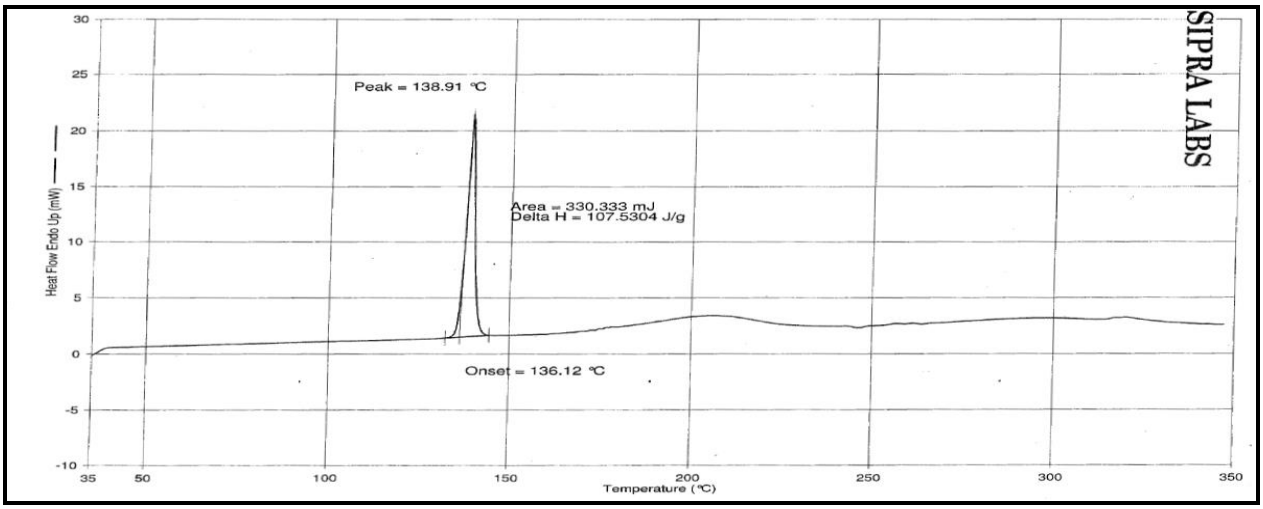

Fig 1: Thermogram of Metoprololsuccinate(API)

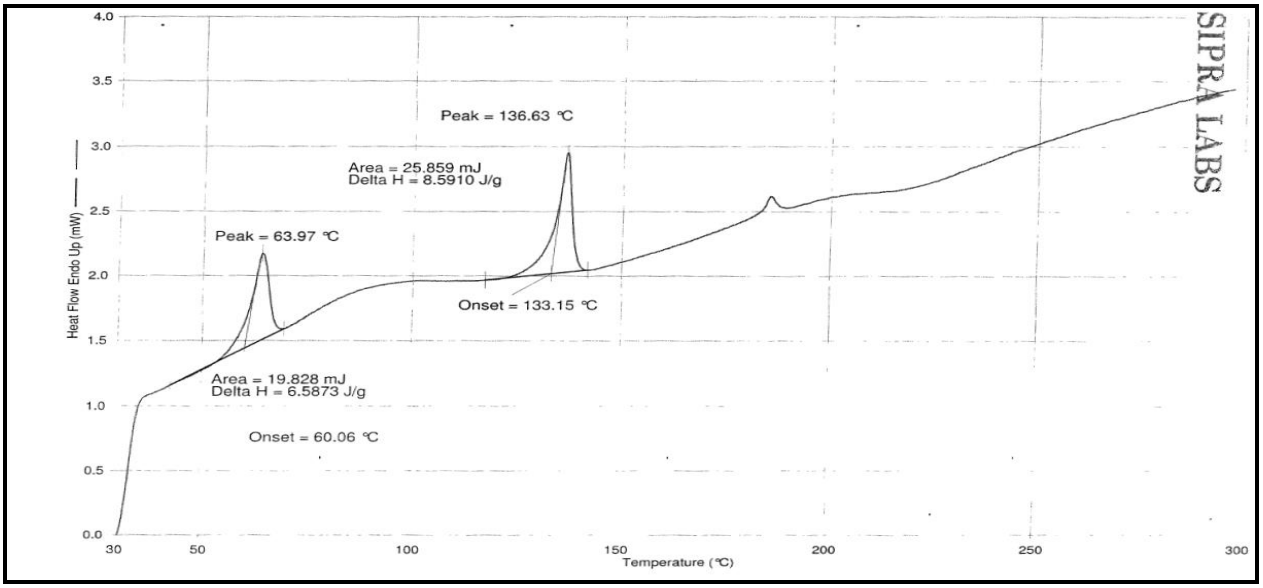

Fig 2: DSCThermogram of Metoprolol succinate (API)+Excipient

DISCUSSION:

By observing the DSC curves, it can be concluded that there was no interaction between the API and excipients.

2) FT-IR Studies:

The physicochemical compatibility of the drug and excipients was obtained by FTIR studies

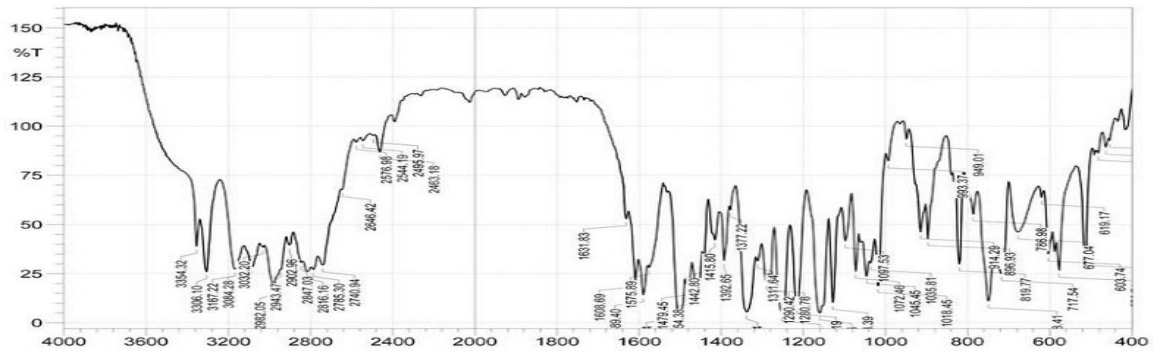

Fig 3: Spctra of pure drug of Metoprolol succinate

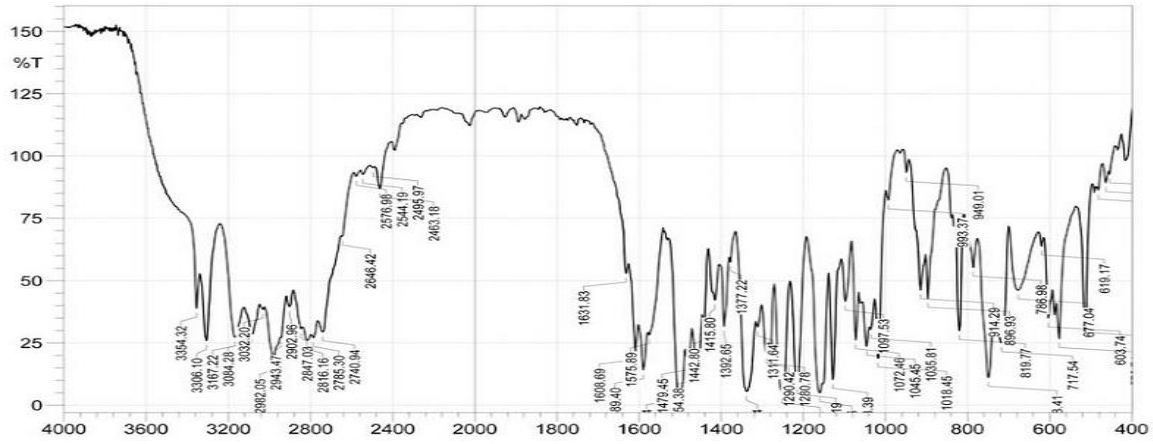

Fig 4: FTIR spctra of pure drug with Ethylcellulose N22

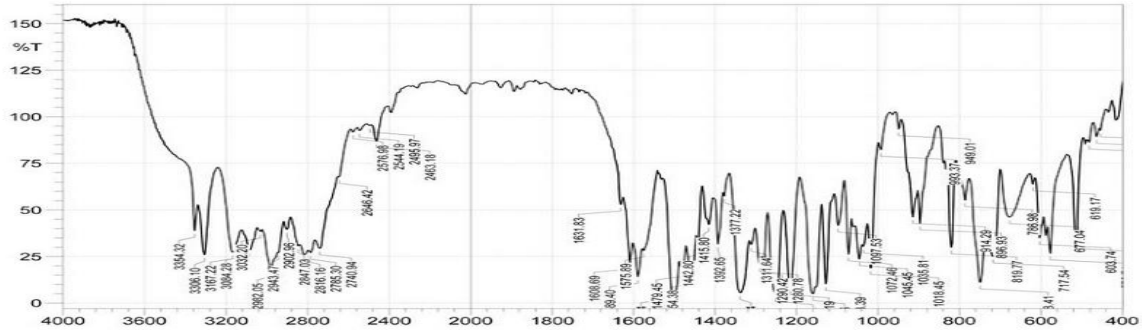

Fig 5: FTIR spectra of pure drug with Kollicoat SR 30D

Table 6: IR spectra data for pure of Metoprolol succinate

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

Table 7: IR spectra data for Metoprolol succinate with Ethyl cellulose N22

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

Table 8: IR spectra data for Metoprolol succinate with kollicoat SR30D

S.No	Functional groups	IR Absorption band of pure Metoprolol succinate+ KollikoatSR30D
1	C-N	1217
2	CH(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 (OCH_3- stretching) 3306 (C=C)confirming the purity of the drug with the standard respectively.

In physical mixture of Metoprolol succinate with EthylcelluloseN22 major peaks of Metoprolol succinate were 1219(C-N) 2850(C-H Alkane) 1639(N-H Bending) 1212 (OCH_3- 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 (OCH_3- 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.

Analytical method development for estimation of metoprolol succinate:

Construction of calibration curve of Metoprolol succinate.

Table 9: Calibration data for the estimation of Metoprolol succinate.

S.no	**Concentration in mcg/ml**	**Absorbance at 223 nm**
1	0	0
2	5	0.172
3	10	0.327
4	15	0.476
5	20	0.662
6	25	0.779
7	30	0.944

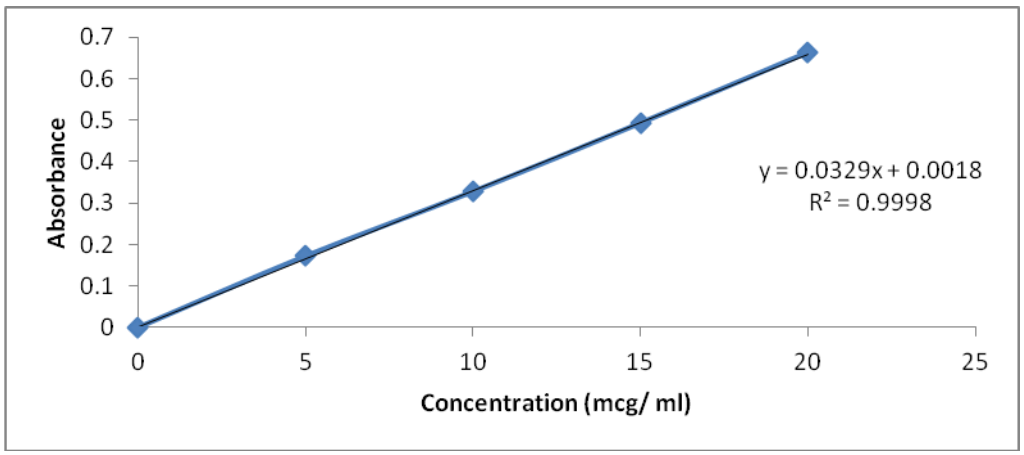

Fig 6: Standard plot for Metoprolol succinate

Evalution Parameters of Pellets:

Before filling the pellets in to capsules, pellets have to be evaluated for the following tests for all the formulations and results are as follows as given in the table no:10 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 with in the limits and that formulation will go for further formulations for the capsulation.

Table 10: 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

Results:

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 11: *In vitro* 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	24 Hrs
1	F3	0	19.6	45.4	64.6	80.1	90.6
2	F4	0	6.4	22.7	42.1	62.5	84.2
3	F5	0	3.9	19.1	42.5	60.5	81.9
4	F6	0	33.5	45.6	68.9	83.5	95.6
5	F7	0	26.1	45.2	67.1	84.9	93.1
6	F8	0	18.8	44.8	65.3	81.1	90.6
7	F9	0	15.6	39.6	58.6	75.2	88.6
8	F10	0	7.1	23.6	50.6	68.9	92.1
9	F11	0	3.9	19.1	42.5	60.5	83.9
10	F12	0	0.6	16.5	33.5	55.2	67.8

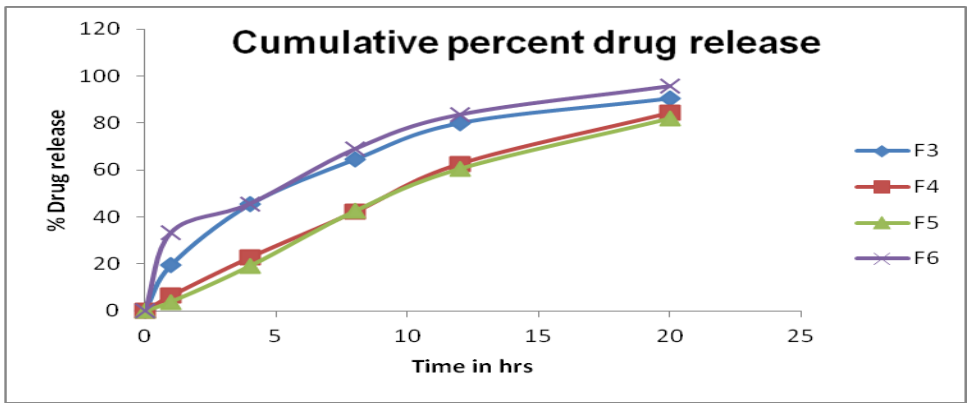

Fig 7: Cumulative percent drug release curves of F3 to F6 formulations

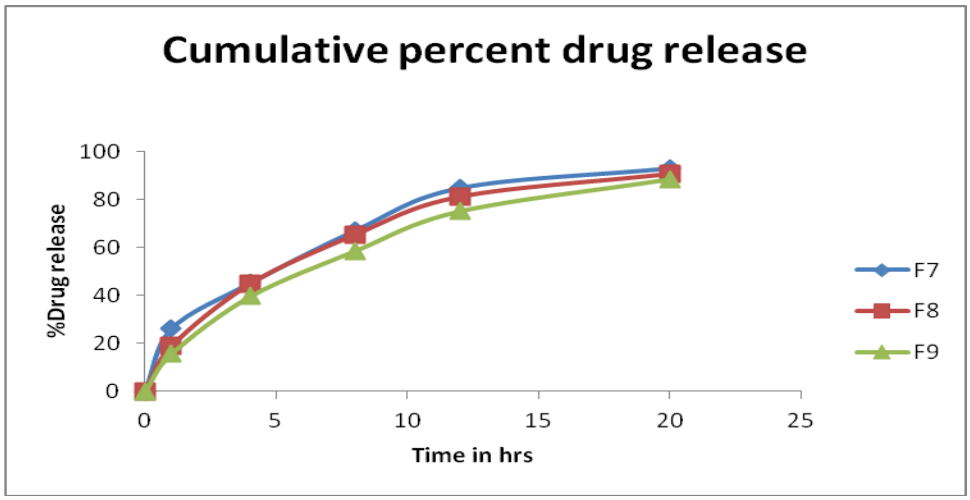

Fig 8: Cumulative percent drug release curves of F7 to F9 formulations

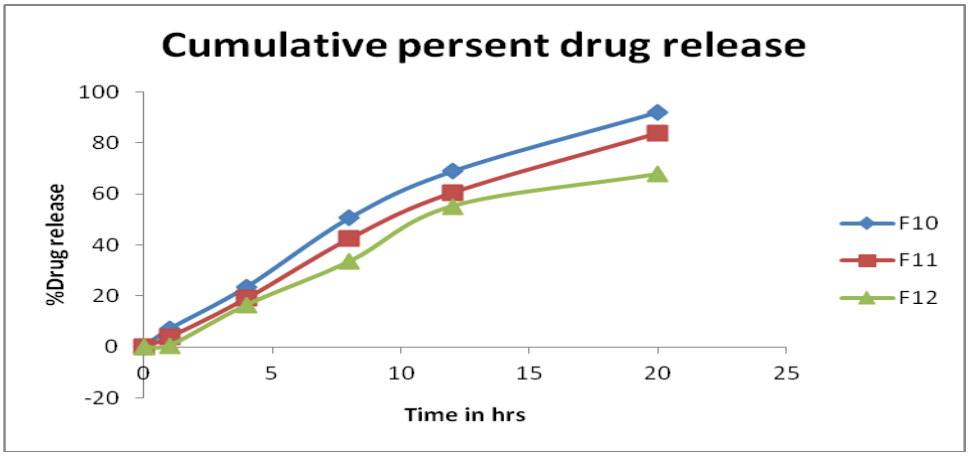

Fig 9: Cumulative percent drug release curves of F10 to F12 formulations

Inference:

In formulation 3, 4, 5 Invitro %drug release from pellets formed using Surelease 7.5% concentration, 10% concentration,12.5% concentration showed 90.6, 84.2%,81.9% drug release at the end of 24 hrs respectively.

In 7.5% concentrationof Surelease fast drug release may observed because of low concentration of coating solution.

In case of 10% concentration Surelease of coating solution sustained release characterstics may observed. Flow properties also good. Dissolution profile is also good. The next formulation was carried out by increasing the concentration of coating solution.

In case of 12.5% concentration Surelease coating, slow dissolution characterstics are observed because of increased concentration of coating thickness drug release is not proper.

In formulations 6,7,8,9 pellets are coated with Ethyl cellulose N 22. In these formulations, invitro %drug release from pellets formed using EC N 22 7.5% concentration, 10% ,12.5% and 15% concentration showed 95.6%, 93.1%, 90.6%, 88.6% drug release at the end of 24hrs respectively

In above formulations the rate of drug release is very high which relieve damage to a coating with a loss of the extended release property because of weak mechanical properties of EC. Due to low values of punches strength elongation less than 5%

In formulation 10,11,12 pellets are coated with Kollicoat SR 30D.Invitro %drug release from pellets formed using Kollicoat SR 30D 7.5% concentration, 10% concentration and 12.5% showed 92.1%, 83.9, 67.8 %drug release at the end of 24hrs respectively.

The drug release from Kollicoat SR 30D coated pellets found no difference between the drug release profile of the compressible and un compressed pellets.

In formulation 10, 7.5 % concentration of Kollicoat SR 30 D, Compression parameters are satisfactory and high extended release characterstics was also observed.

In formulation 11&12 10% and 12.5% concentration of kollicoat SR 30D drug release is not proper because of the coating thickness is high.

Results:

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 with in limits as per specifications and assay of the formulation was 99.79% .So, F10 formulation was selected as the optimized formulation

Kinetic analysis of dissolution data:

Table 12: kinetic data of optimized (F10) Formulation

Zero order	First order	Higuchi	Korsemeyer-Peppas	
r^2	r^2	r^2	r^2	N
0.982	0.946	0.946	0.997	0.892

CONCLUSION:

Metoprolol Succinate is a β selective adrenergic neurotransmitters such as catecholamines 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.Metoprolol succinate pellets were prepared by using extrusion-speronization method with different polymers like ECN22, Surelease, Kollicoat. In formulation 1 and formulation 2 No coating has been done physical observation of pellets are failed, because of high concentration of the binder solution, pellets formed like lumps. So for F1 and F2 formulations dissolution studies were not conducted. Out of 12 pellet formulations F10 (Kollicoat) was found to be the best formulation. In future in vivo studies have to be carried out.

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