# Formulation and *in vitro* evaluation of sustained release microspheres of Metoprolol Tartrate Loaded Eudragit-RS100

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## Abstract

*The objective of the present study was to microencapsulate the Anti-Hypertensive drug (treatment of several disease of Cardio Vascular System, especially Hypertension.) Metoprolol Tartarte to provide Sustain Release and maintain constant the plasma drug concentration and reduce the frequent administration and improve the Patient compliance, unwanted side effects and Dose dumping. Metoprolol was microencapsulated with Eudragit-RS100 using solvent evaporation techniques. The effect of different 6 Formulation variables including the drug polymer ratio. Metoprolol Microspheres was subjected to micrometritic properties including Angle of Repose, Bulk density, Carr's index, Haugner's ratio and Particle size determination. Metoprolol Microspheres was subjected to Drug Loading, invitro drug release as well as for Scanning electron microscope and kinetic drug release.*

**Key Words:** Metoprolol Tartarte, Eudragit RS100, Solvent Evaporation, Microspheres, Drug loading, Release kinetics.

## INTRODUCTION

Conventional oral drug administration does not usually provide rate-controlled release or Target specificity. In many Cases Conventional Drug Delivery provides sharp increase in concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration. In order to obtain maximum Therapeutic efficacy , it becomes necessary to deliver an agent to the target tissue in optimal amount for the required period of time, there by causing little toxicity and minimal side effects [1], Desired drug release can be provide by rate controlling membranes or by implanted Biodegradable Polymers containing dispersed medication.

Micro particulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with Specificity, to maintain the desired concentration at the site of interest without unwanted effects [2].

Microencapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance; eventually the total dose and few adverse reactions may be reduced since a steady state plasma concentration is maintained.

In administration of medication via such systems is advantageous because microspheres can be ingested or injected, can be tailored, for desired release profiles and in some cases it can provide organ Targeted release [4] [5] [6] .The meaning of microencapsulation converting liquids to solids, altering colloidal and surface properties, Providing environmental protection and controlling release characteristics by using the coating materials.

Metoprolol Tartarte is Anti-Hypertensive drug (treatment of several disease of cardiovascular system, especially by Hypertension) It also used for Long term Angina Pectoris and the treatment of Hemodynamically stable patients with definite  or suspected acute myocardial infraction to reduce cardio vascular mortality.

The aim of present work was to encapsulate Metoprolol Tartarte with Eudragit RS100 Microspheres, were prepared by solvent evaporation Techniques as sustained release, Chloroform, liquid Paraffin were used for the preparation of microspheres. The Preformulation study and the prepared microspheres were evaluated for Drug content [11], Particle size and invitro drug release [15], [19], [24], (Kinetic release) Studying.

## MATERIALS AND METHODS

### Materials
Metoprolol Tartarte was obtained as gift samples from Mano Pharma, Chennai, India. Eudragit RS100 from Micro labs, Hosur, India. Chloroform, N-Hexane from Merck Ltd, Mumbai. Heavy liquid Paraffin, Potassium dihydrogen Phosphate, Sodium hydroxide were procured from S.D. Fine chemicals, Mumbai, India.

## METHODS

*Solvent Evaporation Techniques*
Metoprolol Tartarte Microspheres were prepared by dissolving polymer Eudragit RS100 in Chloroform, Then the drug Metoprolol Tartarte was added to the polymer solution . The resulting mixture was then added drop by drop into heavy liquid paraffin while stirring continuously, stirring rate was constant at 750rpm and continued for 3hrs until chloroform evaporated completely.

The dispersed drug and polymer were transferred into fine droplets, which subsequently solidified into rigid microspheres due to solvent evaporation. The particles were collected by filtration and washed 4 to 5 times with n-Hexane and desiccated at room temperature for 24 hrs[11],

**Drug Excipient's Compatibility Studies**

Excipients are integral components of almost all pharmaceutical dosage form, thus it is mandatory to detect any possible physical or chemical interaction of the drug with the excipients, since the excipient can affect the Bio-availability and stability of drug. The drug and the excipient must be compatible with on another to produce a product that is stable, efficacy, attractive, easy to administer and safe. If the excipients are new and have not been used in formulation containing the active substance , the compatibility studies have a considerable importance , DSC and IR techniques were commonly used to investigate the compatibility between the drug and the various excipients used in the formulation.

**Sample preparation and Analysis by DSC**

The sample were prepared by Physical mixture of drug and excipients (1:1) using a clean dried glass mortar and pestle samples (5-10 mg) was accurately weighed and hermetically sealed in aluminium pans, Thermograms werwe obtained by using Shimadzu(DSC 60) instrument ,heating at a constant rate of $10^0$c /min ,over a temperature ranges of $20^0$c-$300^0$c, To maintain on inert atmosphere  nitrogen gas was purged at a rate of 20ml/min.

**Sample preparation and analysis by IR**

IR Spectra data was taken on a Shimadzu Instrument to fond out the possible interaction between selected polymer Eudragit RS100 and drug Metoprolol tartarte and also identify the compatibility between the drug and polymer.

10mg of sample and 40mg of KBR was taken in a mortar and triturated .A small amount of triturated sample was taken into a pellet marker and was compressed at 10kg/$cm^2$ using hydraulic press. The pellet was kept in a small holder and scanned from 4000 $cm^{-1}$ in Spectrophotometer.

Sample was prepared for pure polymer, pure drug, Physical mixture of drug and polymer and drug loaded microspheres.

Determination of Drug Entrapment Efficacy, Drug Loading and Percentage yield

Microspheres (25mg) were suspended in 25ml in Chloroform and extracted with 25ml of phosphate buffer $P^H$ 7.4 and then analyzed at 276nm

$$\text{Encapsulation Efficacy (\%)} = \frac{\text{Actual Drug content}}{\text{Theoretical drug content}} \times 100$$

$$\text{Drug Loading (\%)} = \frac{\text{Weight of Drug}}{\text{Weight of Microparticle}} \times 100$$

$$\text{Yield(\%)} = \frac{\text{Weight of Microparticle}}{\text{Total Expected Weight of the drug and Polymer}} \times 100$$

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## Particle size Analysis

The Particle size of Microsphere was determined using official microscopy method[11] approximately 100 microspheres were counted for particle size using a calibrated optical microscope ( magnus mlx-Dx)

## Micrometric properties
## Angle of Repose

Angle of repose of different formulation was measured according to fixed funnel standing method

$$\theta = \tan^{-1} h/r$$

Where $\theta$ is the angle of repose, r is the radius, h is the height of the pile

## Bulk Density

Bulk density and Tapped density measured by using 10ml of graduated cyclinder , the sample powder in cyclinder was tapped mechanically for 100 times ,then tapped volume was noted down and Bulk density and Tapped density were calculated.

## Carr's Index

Compressibility index (Ci) or Carr's index value of Microparticles was computed according to the following equation

$$Carr's (\%) = \frac{(\text{Tapped density-Bulk density})}{\text{Tapped Density}} \times 100$$

## Hausner's Ratio

Haugner's ratio of microparticles was determined by comparing the tapped density to the bulk density

$$Haugner's\ Ratio = \frac{\text{Tapped density}}{\text{Bulk density}}$$

## Scanning Electron Microscopy

The Microparticles was coated uniformly with gold palladium by using Sputter coater (POLARON .SC-76430) after fixing the sample is individual stabs.
All samples were randomly examined for surface morphology of microspheres by using Scanning Electron microscope.

## *In-vitro* Release studies

*In-vitro* Release studies were carried out using USP type I apparatus at $37 \pm 0.5\ ^o$C in 900 ml of 0.1N HCL $P^H$1.2 buffer, from 0-2 hrs and in Phosphate buffer solution ($P^H$ 6.8) from 2 to 12 hrs.Microsphere equivalent to 100mg drug was placed into the baskets (tied using –muslin cloth) and rotated at100 rpm. A sample of 10ml was withdrawn at various time intervals like 1,2,3,4,5,6,7,8 & 12 and filtered analyzed by UV spectrophotomatically at 276nm using Shimadzu spectrophotometer.

## Kinetics of drug Release

The *invitro* release profile of all batches were fitted to ,first order , Koresmeyer Peppa's model to assceration the kinetic modeling of drug release, correlation co-efficient($R^2$) values were calculated for liner curves obtained by the regrestion analysis.

## First order kinetics

Log C=LogCo-Kt/2.303
C-Amount ofdrug remaind at time 't'
Co-Initial drug concentration
k-First order rate constant ($hr^{-1}$)
When data is plotted as log cumulative % drug remaining vs time yield sright line

## Korsmayer –Peppas model

To study the drug release behavior from Polymeric system

$$Mt/Ma=Kt^n$$

Mt/Ma-The fraction of drug released at time 't'
k-Constant incorporating structural and geometrical characteristic of the drug /polymer system
N-Diffusion exponent related to the mechanism of drug release
When the data plotted as log% drug released vs log time yield a straight line

## RESULTS AND DISCUSSION

The detail of quantities of drug, polymer, stabilizer and solvents used are given in table-1

**Table: 1 Composition of Metoprolol tartrate loaded Eudragit RS100 Microspheres**

| Formula Code | Drug/ Polymer ratio | Drug (mg) | Polymer (mg) | Volume of Solvent (ml) | Heavy liquid paraffin (ml) |
|---|---|---|---|---|---|
| $F_1$ | 1:1 | 500 | 500 | 25 | 300 |
| $F_2$ | 1:2 | 500 | 1000 | 25 | 300 |
| $F_3$ | 1:3 | 500 | 1500 | 25 | 300 |
| $F_4$ | 1:4 | 500 | 2000 | 30 | 500 |
| $F_5$ | 1:5 | 500 | 2500 | 30 | 500 |
| $F_6$ | 1:6 | 500 | 3000 | 30 | 500 |

**Drug-Excipient's compatibility studies**

DSC is useful in the investigation of solid –state interaction. Hence thermogram's were generated for both pure drug and polymer and drug excipient mixtures

The Dsc thermograms reveal that the physical mixture of metoprolol with Eudragit RS100 showed sharp endotherm was obtained at 123.40 for metoprolol tartrate the same melting endotherm also observed in the drug &polymer

This result confirms that there is no mutual interaction between drug & polymer.
The thermograms are shown in fig-1& 2
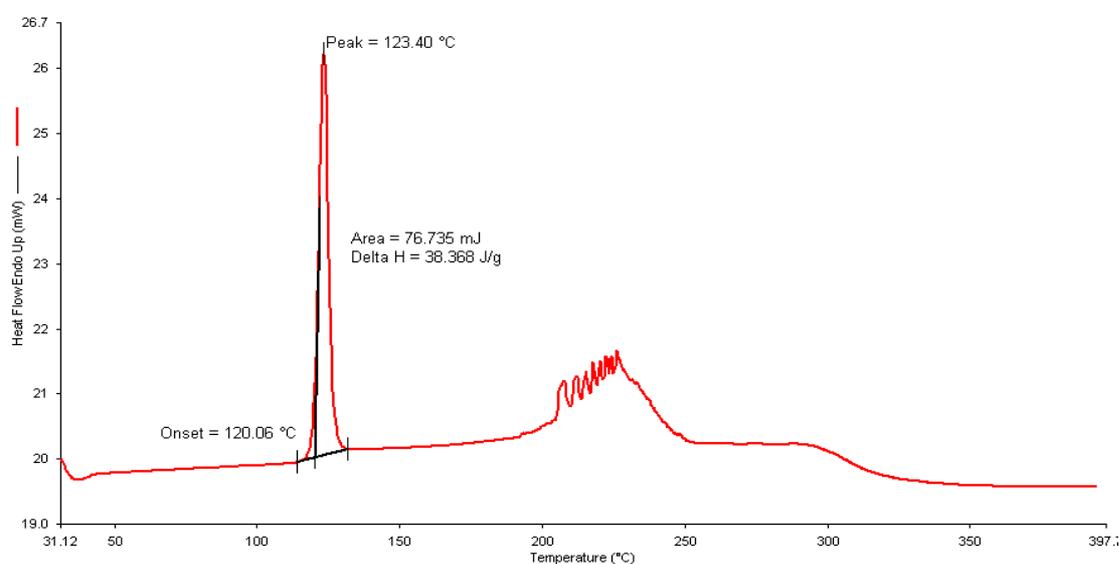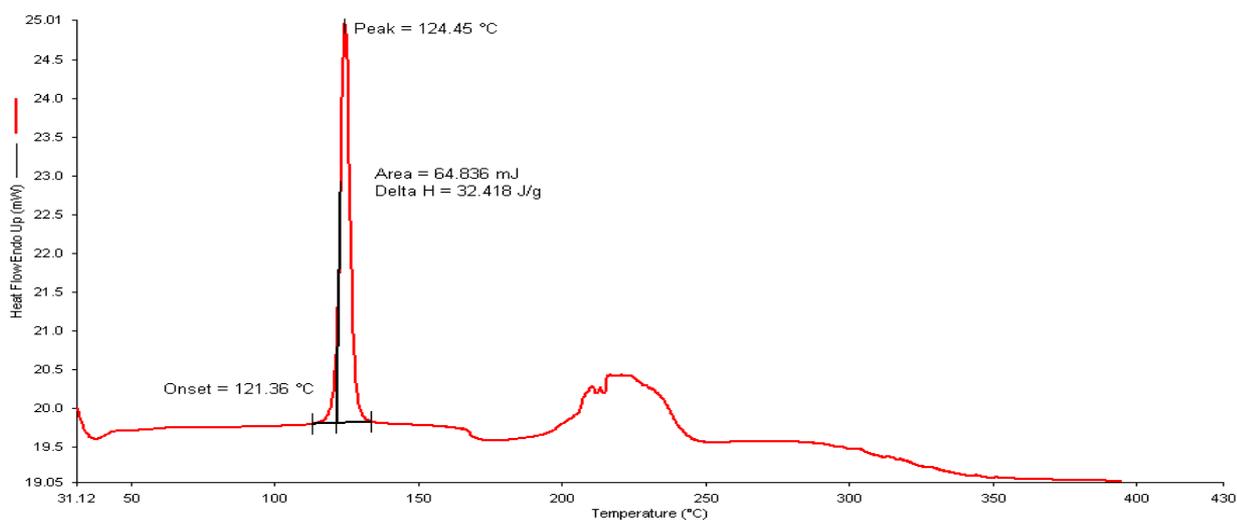
**Figure -1 DSC Of Pure Drug (Metoprolol Tartrate)**



**Figure-2 DSC Of Physical Mixture Of Metoprolol Tartrate And Eudragit Rs100**



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R   studies reveal that Metoprolol tartrate showed prominent peaks due to the presence of C-H stretching alkyl group at 2900.,2980 and C-H bending alkyl group at 1380,1480 and C≡O stretching at 1020-1120 and C-N stretching at 2200-2300 and O-H stretching at 3100-3500,The same peaks were also observed in the physical mixture of drug &polymer and drug loaded microspheres.

After interpretation through the above spectra it was confirmed that was no major
shifting of functional peaks between the spectra of drug polymer, physical mixture of drug & loaded microspheres. IR spectra are shown in fig-,3,4,

**Figure-3, Infrared Spectra Of Physical Mixture Of Metoprolol Tartrate And Eudragit RS100**
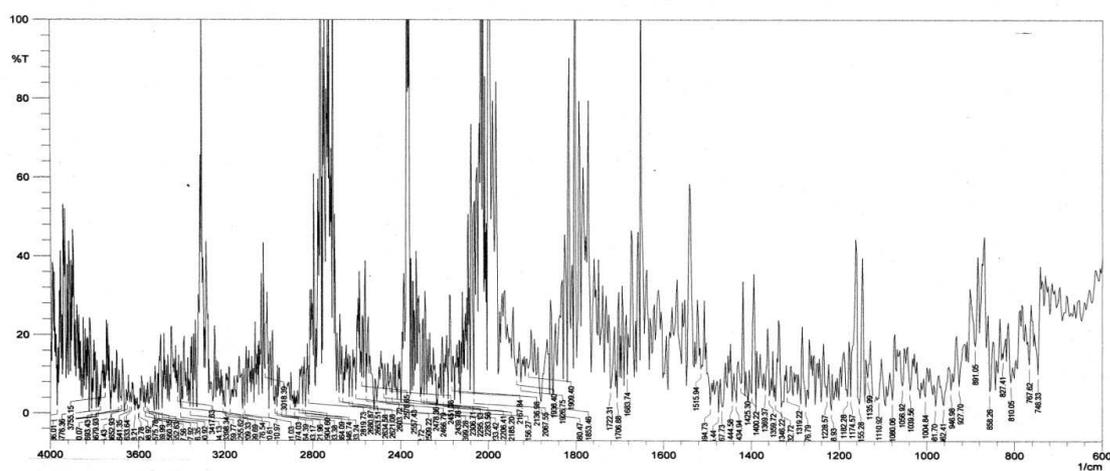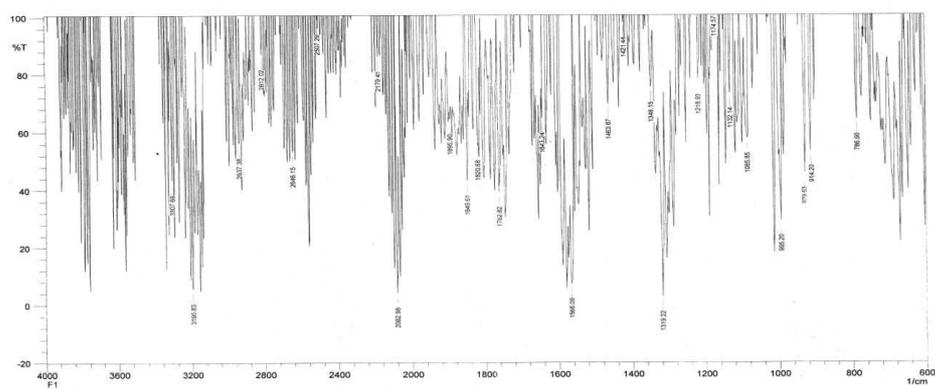


**Figure-4, Infrared Spectra Of Metoprolol Tartrate Loaded Microspheres (F$_3$)**

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## Drug Entrapment  Efficiency

The microspheres exhibited an increase in drug entrapment with an increase in the polymer ratio up to a particulate concentration ,a decrease in drug entrapment was observed after that point due to saturation capacity of the polymer , the entrapment efficiency of drug loaded batches ranges from 66.5±1.84 to 73.16±1.36 it was found that F3 (1:3) had a better drug entrapment efficiency of 73.16±1.36 ,The results were showvn in table-2.

## Drug Loading Efficiency

Loading efficiency of drug loaded batches was found to be 11.24±1.25 to 33.25±1.05, increase in the concentration of drug in the organic solvent resulated in an increase in the drug loading .the drug loading efficiency of all formulation were shown in table-2

Drug loading efficiency was better with F1(1:1) 33.25±1.05 and it was found that drug loading capacity decreased with increase in the polymer concentration. Table-2

### Table-2 Entrapment Eifficiecy,Drug Loading, Percentage Yield of Metoprolol Tartarte Microspheres

| S.No | Formulation code | Entrapment Efficiency (%) | Drug loading (%) | Percentage Yield |
|------|------------------|---------------------------|------------------|------------------|
| 1 | $F_1$ | 66.55±1.84 | 33.25±1.05 | 79.5±1.41 |
| 2 | $F_2$ | 68.28 ±2.78 | 28.46±1.45 | 81.6±1.20 |
| 3 | $F_3$ | 73.16±1.36 | 26.12±2.21 | 83.7±1.57 |
| 4 | $F_4$ | 71.33±2.09 | 18.22±1.77 | 85.6±0.54 |
| 5 | $F_5$ | 70.41±1.16 | 14.62±2.15 | 84.2±2.48 |
| 6 | $F_6$ | 69.03±1.35 | 11.24±1.25 | 83.5±1.65 |

**(± S.D. and no. of determinations = 3)**

## Percentage Yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulation may be due to microspheres lost during the washing process. Percentage yield of all formulation varies from 79.5 ±1.41 to 85.6±0.54 which are shown in table -4 and F4 shows highest percentage yield of 85.6±0.54.table-2

## Particle Size

Here, kepping drug ratio constant and varied polymer ratio as the polymer concentration increase ,viscosity  increases which influence the interaction between disperse phase and dispersion medium and affects the size distribution of particle.

If there was increase in the amount of polymer concentration, there was increase in relative viscosity so as resulted in an increase in mean particle size. The ranges form 116±16.99 to 391±37.41µm, The mean particle size of all the formulation was shown in table-3

## SEM Studies

The scanning electron micrograph of microspheres of formulation F3 is shown in fig5. It can be seen that microspheres are almost spherical & discrete

**Table-3,Particle Size Of Metoprolol Tartrate Microspheres**

| S.No | Formulation Code | Particle size |
|------|------------------|---------------|
| 1 | $F_1$ | 116±16.99 |
| 2 | $F_2$ | 160±21.60 |
| 3 | $F_3$ | 215±25.49 |
| 4 | $F_4$ | 277±30.73 |
| 5 | $F_5$ | 335±32.99 |
| 6 | $F_6$ | 391±37.41 |

(± S.D. and no. of determinations = 3)

**Figure 5 : SEM Of Formulation F3**
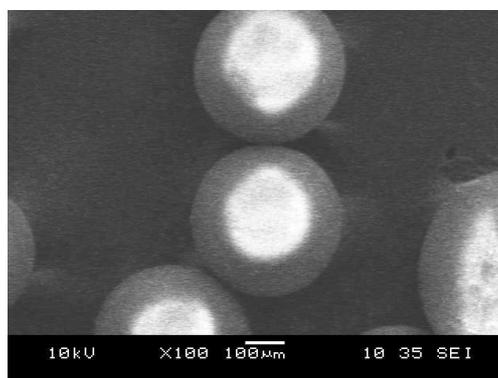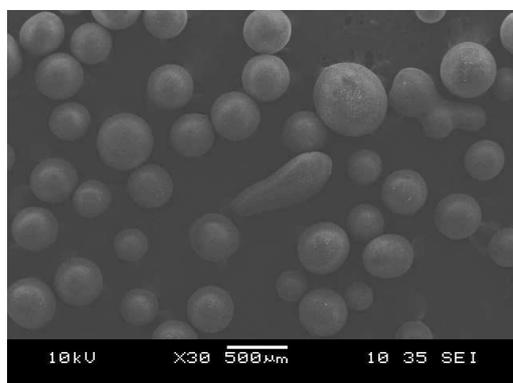


**Micromeritics properties of Metoprolol tartrate Microspheres**

**Angle of Repose**
Angle of repose value of all the formulation were in the range of 19.54±0.742 to 33.25±0.771 which shows free flow nature of the prepared microsphere table-4.

**Bulk density & tapped density**
It has been stated that , bulk density values less than 1.2gm/cm³ indicate good flow and values greater than 1.5gm/cm³ indicate poor flow characteristic. It is seen from table-4 that the bulk density values are less than 1.2gm/cm³ indicating good flow characteristic of the microsphere. Table-4

**Carr's Index (ci)**
The carr's index of the all the formulation was less than 20 i.e from 10.6±0.778 to 19.86±0.982, which indicate good flow properties and good compressibility. Table-4.

**Hausner's ratio**
Hausner's ratio was ranging from 1.11±0.029 to 1.25±0.040 i.e all the preparation showed that they had good flow properties the improvement in flow  properties suggests that the microspheres can be easily handled during processing the result shown table-4

**Table -4, Micromeritic Properties Of Metoprolol Tartrate Microspheres**

| S.No | Form. code | Angle of Repose | Bulk Density | Tapped Density | Carr's Index | Hausner's Ratio |
|------|------------|-----------------|--------------|----------------|--------------|-----------------|
| 1 | $F_1$ | 19.54±0.742 | 0.421±0.005 | 0.471±0.008 | 10.6±0.778 | 1.11±0.029 |
| 2 | $F_2$ | 20.64±0.472 | 0.435±0.004 | 0.499±0.006 | 12.82±0.732 | 1.14±0.021 |
| 3 | $F_3$ | 24.25±0.464 | 0.460±0.008 | 0.540±0.011 | 14.81±0.828 | 1.17±0.054 |
| 4 | $F_4$ | 27.12±0.679 | 0.491±0.009 | 0.588±0.007 | 16.49±0.962 | 1.19±0.049 |
| 5 | $F_5$ | 30.45±0.641 | 0.539±0.014 | 0.650±0.006 | 17.07±0.873 | 1.20±0.08 |
| 6 | $F_6$ | 33.25±0.771 | 0.588±0.010 | 0.735±0.010 | 19.86±0.982 | 1.25±0.040 |

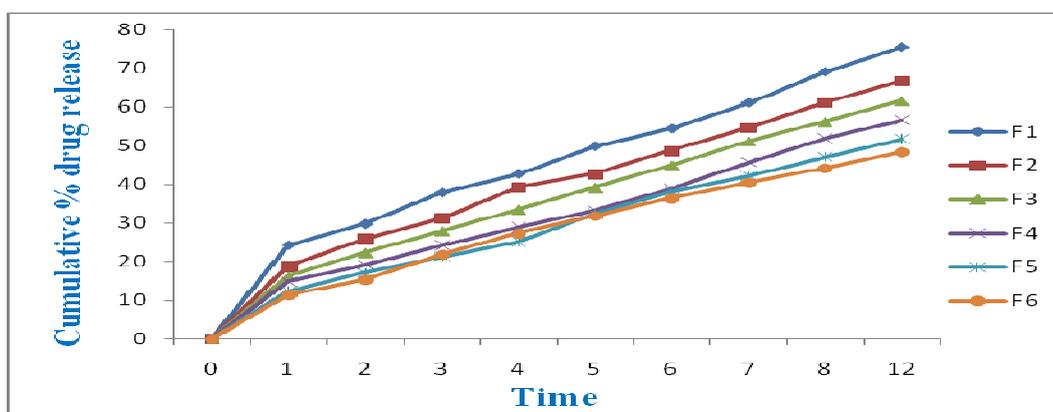*Invitro* **Release Studies**
Cumulative percentage release of Metoprolol Tartrate loaded microspheres carried out in 0.1N HCL 1.2  $P^H$ buffer for 2 hours and then 6.8 $P^H$ phosphate buffer up to 12hours.

The release rate was decrease by increasing the polymer concentration and particle size.

The rapid release was obtained in formulation F1 due to low concentration of polymer  and size of the particle results in higher contact of dissolution medium due to increased surface area,drug release from all the formulation was slow and sustained over 12 hours,by the end of 12hours, F1, F2 ,F3 ,F4 ,F5 ,F6 released 75.33±0.604, 66.73±0.857, 61.61±0.695, 56.68±0.735, 51.78±0.816, 48.36±0.899 % of loaded drug respectively. The polymer /drug ratio 1:3(F3) showed better sustained release pattern and drug entrapment and found to be most suitable among all the other formulation. Table5& Figure 6

**Table-5,** *Invitro* **Dissolution Profile of Metoprolol Tartrate Microspheres (F₃)**

| S.No | Time (Hrs) | Absorbance (nm) | Concentration µg/ml | Percentage Release (%) | Mean Cumulative Percentage (%) release |
|------|------------|-----------------|---------------------|------------------------|----------------------------------------|
| 1 | 1 | 0.122 | 1.794 | 16.147 | 16.18±0.817 |
| 2 | 2 | 0.168 | 2.470 | 22.23 | 22.27±0.601 |
| 3 | 3 | 0.211 | 3.102 | 27.92 | 27.94±0.750 |
| 4 | 4 | 0.252 | 3.705 | 33.33 | 33.57±0.828 |
| 5 | 5 | 0.296 | 4.351 | 39.17 | 39.21±0.701 |
| 6 | 6 | 0.339 | 4.985 | 44.86 | 44.92±0.652 |
| 7 | 7 | 0.386 | 5.676 | 51.08 | 51.19±0.756 |
| 8 | 8 | 0.425 | 6.251 | 56.25 | 56.28±0.701 |
| 9 | 12 | 0.465 | 6.838 | 61.54 | 61.61±0.695 |

**Figure-6, InvitroReleaseOfMetoprololTartarteFromF1To F6**



***Invitro* release kinetics**

The invitro release data were applied to various kinetics models to predict the drug release mechanism and kinetics.

When log percentage of drug remaining to be released Vs time was plotted, in accordance with first order equation, straight lines were obtained with correlation coefficient 'R2' value of 0.943 to 0.975 table- indicated that drug release followed first order kinetics.Table6& figure7 Log cumulative percentage release Vs by log time curves shows high linearity figure 8- for korsmeyer – Peppa's model and shows better correlation coefficient R2 value of 0.974 to 0.988. the slope 'n' value for all the formulation were in the range of 0.502 to 0.644 indicate that the mechanism of drug release was Non –Fickian type diffusion the result were shown in table-7 & Figure 8

**Table-6 First Order kinetics**

| Time | Log Cumulative % of drug remaining to be released | | | | | |
|------|-------|-------|-------|-------|-------|-------|
|      | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ |
| 1 | 1.87 | 1.90 | 1.92 | 1.93 | 1.94 | 1.95 |
| 2 | 1.84 | 1.86 | 1.89 | 1.90 | 1.91 | 1.92 |
| 3 | 1.79 | 1.83 | 1.85 | 1.87 | 1.89 | 1.89 |
| 4 | 1.75 | 1.78 | 1.82 | 1.85 | 1.87 | 1.86 |
| 5 | 1.70 | 1.75 | 1.78 | 1.82 | 1.83 | 1.83 |
| 6 | 1.65 | 1.70 | 1.74 | 1.78 | 1.79 | 1.80 |
| 7 | 1.59 | 1.65 | 1.68 | 1.73 | 1.76 | 1.77 |
| 8 | 1.49 | 1.58 | 1.64 | 1.68 | 1.72 | 1.74 |
| 12 | 1.32 | 1.52 | 1.58 | 1.63 | 1.68 | 1.71 |
| $R^2$ value | **0.975** | **0.968** | **0.962** | **0.958** | **0.951** | **0.943** |

**Figure-7,First Order Kinetics**
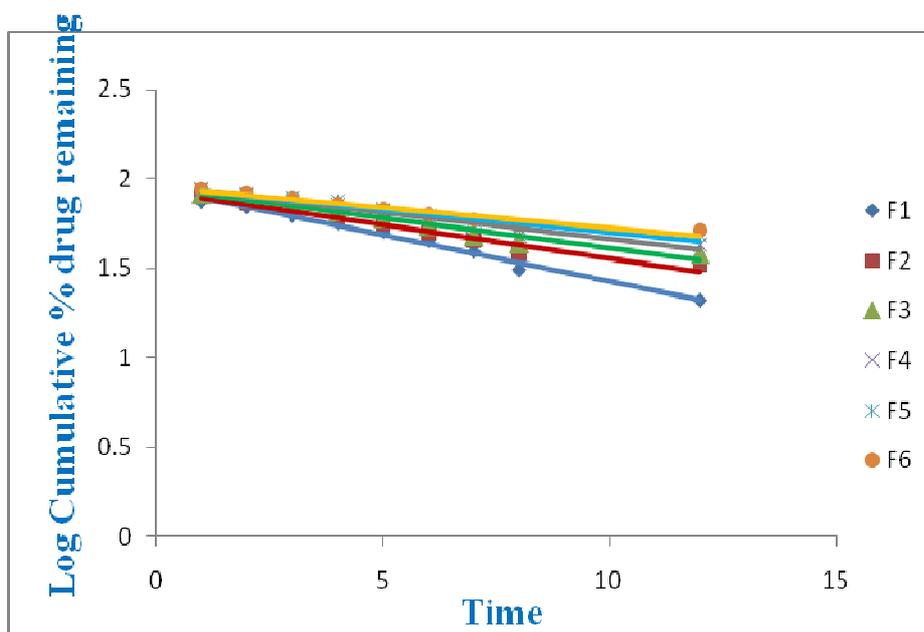
## Table -7 Korsmeyer-Peppas Model

| Log time | Log Cumulative % of drug released | | | | | |
|---|---|---|---|---|---|---|
| | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ |
| 0 | 1.38 | 1.27 | 1.20 | 1.17 | 1.09 | 1.05 |
| 0.301 | 1.47 | 1.41 | 1.34 | 1.28 | 1.23 | 1.18 |
| 0.477 | 1.57 | 1.49 | 1.44 | 1.38 | 1.32 | 1.33 |
| 0.60206 | 1.63 | 1.59 | 1.52 | 1.46 | 1.40 | 1.43 |
| 0.69897 | 1.69 | 1.63 | 1.59 | 1.52 | 1.51 | 1.50 |
| 0.778151 | 1.73 | 1.68 | 1.65 | 1.59 | 1.58 | 1.56 |
| 0.845098 | 1.78 | 1.73 | 1.70 | 1.66 | 1.65 | 1.60 |
| 0.90309 | 1.83 | 1.78 | 1.75 | 1.71 | 1.67 | 1.64 |
| 1.079 | 1.87 | 1.82 | 1.78 | 1.75 | 1.71 | 1.68 |
| $R^2$ value | **0.980** | **0.988** | **0.986** | **0.974** | **0.976** | **0.981** |
| n value | **0.502** | **0.547** | **0.583** | **0.590** | **0.633** | **0.644** |

## Figure-8, koresmeyer-peppas model

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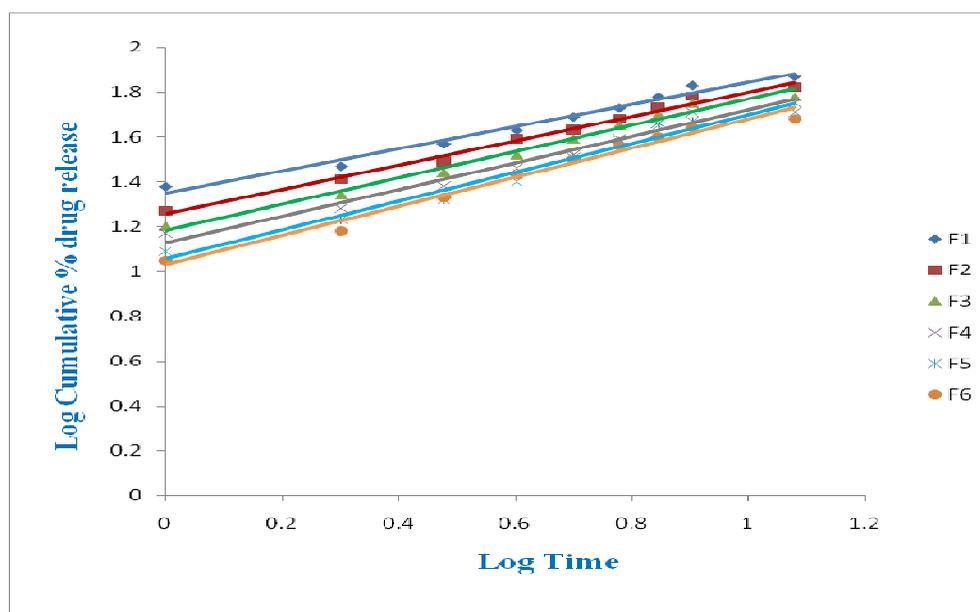
## CONCLUSION

Metoprolol Tartrate Microsphere were prepared successfully by using the solvent evaporation method, polymer – drug ratio influence the particle size as well as drug release pattern of Microsphere.

The yield & Entrapment efficiency of drug loade was good for all the batches but was highest better drug entrapment efficiency of F3 (1:3) 73.16±1.36 , as the polymer concentration increase ,the particle size increases the results of carr's index and angle of repose values indicated that all the formulation showed good flow properties.

*Invitro* drug release from all the formulation was found to be slow and sustained over the period of 12 hours, among other formulation F3 showed better sustained release pattern and the cumulative percentage release at the end of 12 hours was found to be 61.61 ±0.695 .

*Invitro* release data followed korsmeyer –peppa's model with first order release kinetics . The mechanism of drug release was found to be Non-Fickian type .

Hence it can be concluded that Metoprolol Tartrate loaded Eudragit RS100  Microsphere may be useful to achieve sustained drug release profile suitable for oral administration and may help to reduce the dose of drug , dosing frequency side effects & to improve patient comp

## REFERENCES

[1] Jayakrishnan A, Latha MS. Biodegradable polymeric microspheres as drug  carriers. In:Jain NK,Editor. Controlled and Novel drug delivery. New Delhi: CBS publishers. **1997** pp. 236-255

[2] Vyas SP,Khar RK.Protiens and peptide delivery consideration.In:Vyas SP, Khar RK,Editor .Controlled drug delivery concepts and advance . I$^{st}$ed. New Delhi:CBS publisher and Distributor. **2002**; pp.549

[3] Fu,X,Ping Q,Gao Y. *J  Microencap* **2005**;22(7), 705-714.

[4] S.P. Vyas and R.K.Khur., Eds, Targeted and controlled drug delivery, First edition, CBS publishers, New Delhi, **2002**, pp. 331-386.

[5] N.K.Jain, Controlled and Novel drug delivery, 4$^{th}$ Edition, pp.236-239.

[6] Alagusundaram M., Madhusudana chetty, *International journal of pharmaceutics* **2009**, 1(3), 526-534.

[7] Goodman & Gillman's 'The pharmaceutical basis of therapeutics' eleventh edition (**2005**), edited by Laurance L. Brunton, John S. Lazo, Keith L. Parker,  673-679.

[8] R.S.Satoskar,     S.D.Bandarkar, S.S.Ainapure, 'Pharmacology and pharmacotherapeutics' Fourteenth edition, pp. 351-354.

[9] The Merck Index, An encyclopedia of chemicals and drugs and biological, 12$^{th}$ edition **2006** & co., Inc, NJ, USA. 1050.

[10] Wade A, Weller, P.J, Hand book of excipients, 2$^{nd}$ edition,   pp. 332-336.

[11] S.K. Basu, R.Adhiyaman, *Tropical Journal of Pharmaceutical Research*, Sep **2008**, 7(3), 1033-1041.

[12] S Tamizharasi,JC Rathi, V Rathi, *Indian Journal of Pharmaceutical Sciences* **2008**, 70(3), , 333-337.

[13] Sunit Kumar Sahoo , Abdul Arif Mallick , BB Barik and Prakash Ch Senapati, *Trop. J. of Pharm.Research,* June **2005**, 4(1),  369-375

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[14] BC Behera, SK Sahoo, S Dhal, BB Barik, BK Gupta, *Trop. J. of. Pharm. Research*, March **2008**, 7(1), 879-885.

[15] Mohan raj Palanisamy, Jasmina Khanam, N Arun Kumar and C Rani, *Res. J. Pharm and Tech,* Apr-June **2009**, 2(2), 349-352.

[16] M.Nappinnai, V.S.Kishore, *Indian Journal of Pharmaceutical Sciences* **2007**, 69(4),511-514.

[17] Parul Trivedi, AML Verma, N Garud, *Asian journal of Pharmaceutics* **2008**, 2(2), 110-115.

[18] S Tamizharasi, R Jagdish Chandra, R Vaishali, *Journal of Young Pharmacist* **2009**, 1(2), 121-124.

[19] K.Kannan, P.K.Karar, R.Manavalan, *Journal of Pharm.Sci & Res* **2009**, 1(1), 36-39.

[20] Sandile M. Khamanga, Natalie Parfitt, Tsitsi Nyamuzhiwa, The evaluation of Eudragit microcapsules manufactured by solvent evaporation using USP apparatus 1, Dissolution Technologies, May **2009**.

[21] B. K. Kimy, S. J. Hwang, J. B. Park and H. J. Park, *Journal of microencapsulation* **2002**, 19, 811-822.

[22] T.Higuchi, *journ. of pharm.sciences*, 52(12),1145-1149.

[23] RW Korsmeyer, R Gurny, p Buri, *International j. of Pharmaceutics*,**1983**,15(1), 25-35

[24] Specification and test methods for Eudragit RS100, www.pharmapolymers.com.

[25] Yogesh S. Gattani, Durga Charan, A.Bhagwat, and Akhil P.Maske, *Asian Journal of Pharmaceutics* **2008**, 2(4), 228-231.

[26] K PR Chowdary, NK Rao, K Malathi, *Indian journal of Pharmaceutical Sciences* **2004**, 66(4), 412-416.

[27] P. S. Rajinikanth, C. Sankar, B. Mishra, *Drug Delivery*, Jan **2003**, 10(1), 21 – 28.

[28] M.D.Dhanaraju,R.Manikumar, *Der Pharmacia Lettre*, **2009**, 1, 2, 279-286