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OPTIMIZATION OF POLYMER COATING LEVEL FOR COLON TARGETED SUSTAIN RELEASE METOPROLOL SUCCINATE PELLETS USING 3^2 FACTORIAL DESIGN

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Keywords:

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ABSTRACT: The present study is an attempt to minimize the dosing frequency and to target the Metoprolol succinate to the colon. Drug loaded pellets are coated with pH independent Eudragit RS100 and further coated with pH dependent Eudragit S100 in R and D pan coater. 3^2 full factorial design is applied to study the effect of extent of Eudragit S100 coating %w/w (X1) and extent of Eudragit RS100 coating %w/w (X2) as independent variables on the dependent variables (responses) are Y1=Q5 (% released after lag time of 5h) and Y2=Q90 (90% of drug release within 12h). The formulation were further characterized by in vitro dissolution study, drug release kinetics and micromeritic properties. 3^2 factorial design reveals that coating level of both the coats play a significant role in drug release property of which coating level of Eudragit RS 100 was more significant after the tablet reaches colon. Design expert software gives D5 as optimized batch having 20% w/w Eudragit RS 100 and 30% w/w with S100 as the drug release was below 20% in SIF so that it can be efficiently colon targeted, and the release is sustained up to 12 hr which is desirable for twice daily dosing of metoprolol.

INTRODUCTION: Colon targeted Drug Delivery system (CTDDS) may be follow the concept of sustained or controlled drug delivery system, for CTDDS oral route of administration has received most attention. CTDDS should be capable of protecting the drug in route to the colon and only release and absorb drug once the system reaches the colon. [1-5] Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon.

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Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. The Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. [6, 7]

In the present study solution layering technique is used for pelletization. It involves the deposition of successive layers of drug solution on the inert starter seeds. As the solution is sprayed onto the product bed, the droplets impinge on the cores and spread evenly on the surface, provided that the drying conditions and fluid dynamics are favorable. This is followed by the drying phase which allows dissolved materials to crystallize and form solid bridges between the core and initial layer of the

drug substance as well as among the successive layers of drug substance. The process continues until the desired layers of drug and hence the target potency of the pellets is achieved. [4, 8-10]

Metoprolol succinate is an antihypertensive agent that is well absorbed in the colon than compared to stomach and intestine. Thus, this drug is considered good candidate for colonic delivery. It is used for the management of cardiovascular disorders such as hypertension and angina pectoris. It is a cardio selective β-blocker that has been categorized under class I of Biopharmaceutics Classification System (BCS) because it is highly soluble and highly permeable. After a single oral dose, peak plasma concentration occurs after about 1 to 2 h.

It is completely absorbed in intestines after oral administration and exhibits 50% bioavailability due to extensive first pass effect. The drug is eliminated within 3 to 4 h which, depending on therapeutic activity, makes it necessary to administer the formulation up to 4 times daily. These properties make metoprolol succinate a good candidate for formulating as extended release and colon targeted dosage form to decrease dosing frequency up to twice a day. [11-16]

Anil Kumar A. et al. (2012) prepared metoprolol succinate granules using Guar gum to prolong the release and target to the colon. These granules filled into the formaldehyde treated capsules and plugged with optimized HPMC plug, to maintain the 5hr lag time. Ashlesha P. et al. (2010) prepared blends of aqueous dispersion of a hydrophobic and hydrophilic polymer, namely Surelease®: hydroxypropyl methylcellulose E15 which were used as coating materials to control the drug release from coated pellets of the highly water soluble drug metoprolol succinate. Ashutosh kumar S. et al. (2010) prepared sustained release matrix tablet of metoprolol succinate by using various polymers, such as hydroxy propyl methylcellulose K4M (HPMC- K4M), hydroxy propyl methylcellulose K100M (HPMC- K100M), xanthan gum, ethyl cellulose and hydroxy propyl methylcellulose phthalate (HPMC-P).

The present study is an attempt to minimize the dosing frequency and to target Metoprolol succinate to colon by coating drug loaded pellets with two polymer coating i.e. sustained release and enteric coating.

MATERIALS AND METHODS:

Materials:

Metoprolol succinate was obtained as a generous gift sample from Lupin Research Park, Pune. Eudragit S100 and RS 100 were supplied as free gift sample from the Evonik Degussa India Pvt. Ltd., Mumbai. Non pareil seeds were purchased from. Talc, acetone, PVP K30 and Isopropyl alcohol (IPA) were purchased from Loba Chemicals (Mumbai, India).

Preparation of colon targeted extended release metoprolol succinate pellets: [17, 18]

Multiparticulate colon targeted drug delivery system of Metoprolol succinate is developed by loading drug on non pareil seeds and then these drug loaded pellets are double coated using pan coater. First coating is of sustain release polymer i.e. Eudragit RS 100 then further coated with enteric polymer Eudragit S 100.

Preparation of Drug loaded pellets:

Metoprolol succinate was incorporated on non-pareils seeds (20#24 i.e 710-850µm) by spraying drug in a solution in isopropyl alcohol containing polyvinyl pyrrolidone (PVP K30) as a binder and talc as antisticking agent by using R and D pan coater. The flow rate was maintained constant such that no agglomeration of the beads occurred during the coating process. The air flow was kept intermediate level to achieve good drying efficiency. During the layering process, the beads were intermittently dried for 10 min at room temperature. After layering, the beads were collected. The drug loaded pellets were dried at 45^0 C for 8 hours in stainless steel tray drier. Check moisture content, it should be below 1%. Then pass the pellets through sifters to remove fines.

TABLE 1: COMPOSITION FOR DRUG LOADING.

Sr. no.	Ingredients	Qty in gms
1.	Non pareil seeds 20#24	10
2.	Metoprolol succinate(15%w/v)	6
3.	PVP K30 (5%)	2
4.	Talc (10%)	0.4
5.	Non pareil seeds 20#24	10

Preparation of extended release pellets:

The composition shown in Table 2 was used for the preparation of polymer solution. The Eudragit RS100 was slowly added into 50% of the diluent mixture and stirred until the polymer was completely dissolved. The talc (anti-adherent) and triethyl citrate (plasticizer) was added in the remaining diluent mixture, stirred and poured slowly into the Eudragit solution with continuous stirring.

TABLE 2: COMPOSITION FOR POLYMER COATING SOLUTION

Sr.no.	Ingredients	Quantity in gms
1.	Drug Layered Pellets	10
5.	Eudragit RS100	7
7.	Talc (50% w/w)	3.5
9.	Triethyl Citrate(15% w/w)	1.05
10.	Isopropyl alcohol :Acetone (1:1) qs	100

Preparation of colon targeted pellets:

Delayed release coating was applied on the extended release polymer coated pellets as we have to target formulation to the colon. The extended release coat was allowed to dry for 30 min and then over that coat, a coat of colon targeted polymer Eudragit S.

TABLE 3: COMPOSITION OF THE EUDRAGIT S100 COATING SOLUTION

Sr.no.	Ingredients	Quantity (in gms)
1.	Eudragit S100	7
2.	Talc (50% w/w	3.5
3.	Triethyl Citrate(15% w/w)	1.05
4.	Isopropyl alcohol :Acetone	100

TABLE 4: COATING PARAMETERS FOR DRUG LOADING AND POLYMER COATING OF PELLETS.

Parameters	Drug loading Specification	Extended release coating specification	Delayed release coating specification
Batch size	10gm	10gm	10gm
Spray rate	1.5gm/min	1.5gm/min	1.5gm/min
Nozzle diameter	1mm	1mm	1mm
Atomizing air pressure	1.5 bar	1.5 bar	1.5 bar
Air inlet temperature	55°C	35-40°C	45-50°C
Pan speed	30rpm	30rpm	30rpm

3^2 full factorial design: [19, 20]

To optimize the coating level of both the polymer, 3^2 full factorial design was executed. The independent variables were extent of Eudragit S100 coating %w/w (X1) and extent of Eudragit RS100 coating %w/w (X2). The dependent variables (responses) Y1=Q5 (% released after lag time of 5h) and Y2=Q90 (90% of drug release within 12h).

TABLE 5: COMPOSITION OF EXPERIMENTAL FORMULATIONS (RUNS)

Batch no.	Extent of S100 coating(%w/w)	Extent of RS100 coating(%w/w)
D1	20	15
D2	30	15
D3	40	15
D4	20	20
D5	30	20
D6	40	20
D7	20	25
D8	30	25
D9	40	25

TABLE 6: FACTORIAL DESIGN DATA

Independent variables	Coded units	Levels		
		-1	0	1
Extent of S100 coating(%w/w)	X1	20	30	40
Extent of RS100 coating(%w/w)	X2	15	20	25

Characterization of coated pellets:

The drug loaded pellets are characterized by drug loading and other formulated coated pellets were characterized using in vitro dissolution study, in vitro drug release kinetics and micromeritic properties. And characterization of optimized formulation is done by FTIR and SEM.

Fourier transformation infrared spectroscopy (FTIR):

FTIR spectra were obtained using a SHIMADZU FTIR spectrophotometer (IR Affinity 1 model, japan).The scanning range was from 4000 to 500 cm^{-1}.

Scanning electron microscopy (SEM):

The surface morphological properties of optimized formulation were investigated by scanning electron microscopy (SEM-Jeol-6360, japan). Sample was mounted on a double faced adhesive tape, sputted with platinum. Scanning electron photographs were taken at an accelerating voltage of 10kV and obtained micrographs were examined at various magnifications.

Drug content: [17]
Pellets equivalent to 50mg of drug is accurately weighed and triturated in mortar pestle. The powdered pellets were dissolved in 10ml of distilled water. Solution was filtered, suitably diluted and absorbance was measured at 220 nm using double beam UV spectrophotometer (SHIMADZU 1800, Japan). Distilled water is taken as blank. Drug content of the drug loaded pellets were calculated using calibration curve of metoprolol succinate in distilled water.

***In vitro* dissolution studies:** [18]
Place coated pellets equivalent to 50 mg of drug (based on theoretical claim) into each of three dissolution vessels were used for determining the in-vitro release of drug. The USP I Basket apparatus was used with 900 ml of Gastric fluid (pH 1.2) for 2 h. After 2 h the dissolution media was changed i.e. Intestinal Fluid (pH 6.8), this is for 3 h. Then after that, change the dissolution medium to phosphate buffer (pH 7.4) at 37^0C and 50 rpm. Samples (5 ml) were withdrawn at 1, 2, 3, 4, 5, 6, 8, 10, 11 and 12 h and were assayed spectrophotometrically at respective λmax. From the absorbance values, the percent cumulative release of metoprolol was calculated. All the experiments were performed in triplicate.

***In vitro* drug release kinetics:** [21, 22]
To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: Zero order, First order, Higuchi's model, Hixon-Crowell model and Korsmeyer-Peppas model.

Stability Studies: [23]
The stability studies were performed as per ICH guidelines at temperature of 40º C / 75% RH (Long term stability study) for 3 months. The optimized formulation was analyzed for drug content and % drug release.

RESULT AND DISSCUSSION:

Optimization of drug loading: [18, 24]
Before drug loading of nonpareil seeds, dummy batches were prepared to optimize the formulation variables as well as process variables for drug loading. Binder i.e PVP K 30 (5%) was selected to achieve proper film formation and minimize the production of fines during coating. By trial and error method following observations are made:

- At low binder concentration, the solution is so diluted that the solid particles deposited loosely on the substrate surface, resulting in low density and high porosity.

- As the binder concentration was increased to 5% the solid particles adhered tightly to the substrate surface. Thus the granule density was increased and the porosity and pore size were decreased. Owing to tight binding of the solid particles to the surface of nonpareil seeds, the pellet surface appeared to be smoother than those prepared at lower binder concentrations.

Optimization of Polymer Coating: [18, 24-26]
Dummy batches were prepared to optimize the formulation variables as well as process variables for extended release polymer coating.
Following observations are made during optimization procedure-

Process variables such as spray rate, droplet size, bed temperature, spray mode and so forth can strongly influence the drug release.

The coating temperature should be sufficiently high to achieve efficient water removal and subsequent particle coalescence. An excessively high inlet temperature can cause difficulties in processing such as electrostatic interactions and agglomeration of the beads because of excessive drying or softening and sticking of the coating.

Drug release from the coated pellets depends on the uniformity of the coating. When coating is based on weight gain, the thickness of the membrane is controlled by the surface area of the pellets on which the coating is applied.
Upon increasing the strength of coating solution, it was found that spray nozzles get blocked due to higher viscosity (because of evaporation of organic solvent inside the column). Hence the conc. of polymer coat solution was selected as 7% randomly.

To avoid the generation of electrostatic charges over nonpareil seeds in pan, small quantity of talc

was added intermittently.

As the concentration of the plasticizer is increased, porosity and the permeability also increase, whereas the lag time is decreased in dissolution studies. This is due to the increase in plasticizer concentration resulting in the formation of the porous structure in the coating layer.

Eudragit RS100 shows pH independent release and insoluble in water, they have the capacity to permeate water through swellable porous structure that they form. This property results in the release the active ingredient as a consequence of diffusion through the coating layer. As the amount of the coating layer is increased, the release time of drug is significantly increased due to the thickness of the diffusion layer. The lag time observed in coated pharmaceutical dosage forms generally depends on the coating material used in these formulations.

Eudragit S100 coated pellets release their content only after reaching to their threshold pH i.e. pH 7.2, approximating the transverse colon. Eudragit S100 contains more percentage of carboxylic groups as compare to ester group which require higher pH for hydrolysis and subsequent release of drug.

Statistical analysis of data by 3^2 full factorial design: [19, 28-30]

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost effective than the conventional methods of formulating dosage forms.

To optimize the selected formulation of preliminary experimental batch, two- factor three level (3^2) full factorial design was executed. The independent variables i.e. factors were extent of Eudragit S100 coating %w/w (X1) and extent of Eudragit RS100 coating %w/w (X2). The level of these factors is selected on the basis of initial studies and observations. All the other formulation aspects and processing variables were kept invariant throughout the study period. The dependent variables (responses) were Y1=Q5 (% released after lag time of 5h) and Y2=Q90 (90% of drug release within 12h).

The effects of independent variables upon the responses were modeled using a second order polynomial equation. The mathematical model of the effects of independent variables upon the dependent variables was performed using Design Expert® software (Design expert trial version 9.0.3.1; Stat Ease inc., Minneapolis, MN, USA) with a manual linear regression technique. A significant term ($p < 0.05$) was chosen for final equations. Finally, response surface plots resulting from equations were drawn. Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach.

The general form of the MLRA model is represented as Equation below. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). In the equation represents that by making a minor change in the setting of that factor one may obtain a significant change in the dependent variables.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X12 + b22X22$$

In above equation, Y is the dependent variable; b0 is the arithmetic average of all the quantitative outcomes of nine runs. b1, b2, b12, b11, b22 are the estimated coefficients computed from the observed experimental response values of Y. X1 and X2 are the coded levels of the independent variables. The interaction term (X1X2) shows how the response values change when two factors are simultaneously changed. The polynomial terms (X12, X22) are included to investigate nonlinearity.

Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision in the software. Level of

significance was considered at $p < 0.05$. The best-fitting mathematical model was selected based on the comparison of several statistical parameters, including the coefficient of variation (CV), the multiple correlation coefficient (R2), the adjusted multiple correlation coefficient (adjusted R2) and the predicted residual sum of squares (PRESS) provided by the software. PRESS indicates how well the model fits the data and for the chosen model it should be small relative to the other model under consideration. The 3-D response surface graphs and the 2-D contour plots were also generated by the software. These plots are very useful to see interaction effects of the factors on responses.

In order to determine the levels of factors which yield optimum dissolution responses, mathematical relationships were generated between the dependent and independent variables.

The equations of the responses are given below:

Final Equation in Terms of Coded Factors:

Q5= + 18.78 - 4.93 * A + 0.39 * B

Q90= + 11.78 + 0.17 * A + 0.67 * B

Final Equation in Terms of Actual Factors:

Q5= + 32.01556 - 0.49333 * extent of S100 coating + 0.078000 * extent of RS 100 coating

Q90 = + 8.61111 + 0.016667 * extent of S100 coating + 0.13333 * extent of RS100 coating

The above equation represents the quantitative effect of independent variables (X1 and X2) upon the responses (Y1 and Y2). Analysis of variance (ANOVA) (Table 7) indicated the assumed regression models were significant and valid for each considered responses.

TABLE 7: ANALYSIS OF VARIANCE (ANOVA) OF DEPENDENT VARIABLES

Source	Sum of squares	Degree of freedom	Mean square	F-value	p-value	Prob>F
Analysis of Variance for Y1(% of drug release after lag time of 5 hrs)						
Model	146.94	2	73.47	153.77	< 0.0001	Significant
A-extent of S100 coating	146.03	1	146.03	305.63	< 0.0001	
B-extent of RS100coating	0.91	1	0.91	1.91	0.2162	
Residual	2.87	6	0.48			
Cor Total	149.81	8				
Analysis of Variance for Y(90% of drug release within 12h)						
Model	2.83	2	1.42	11.77	0.0084	Significant
A-extent of s100 coating	0.17	1	0.17	1.38	0.2839	
B-extent of rs 100 coating	2.67	1	2.67	22.15	0.0033	
Residual	0.72	6	0.12			
Cor Total	3.56	8				

The three-dimensional (3D) response surfaces and 2D contour plot were plotted to estimate the effect of independent variables on each response shown in Figures 26 and 27. Figure 26 (a&b) shows the effect of two formulation factors on % drug release in lag time of 5 hrs and indicates that increase in coating level of Eudragit S100 decrease the % drug release in lag time of 5 hrs significantly. It was observed from the response curves and contour plots in Figure 27 (a&b) for both the responses that increasing coating level of Eudragit S100 and Eudragit RS100 retard the water uptake and thus prolongs the 90% drug release time.

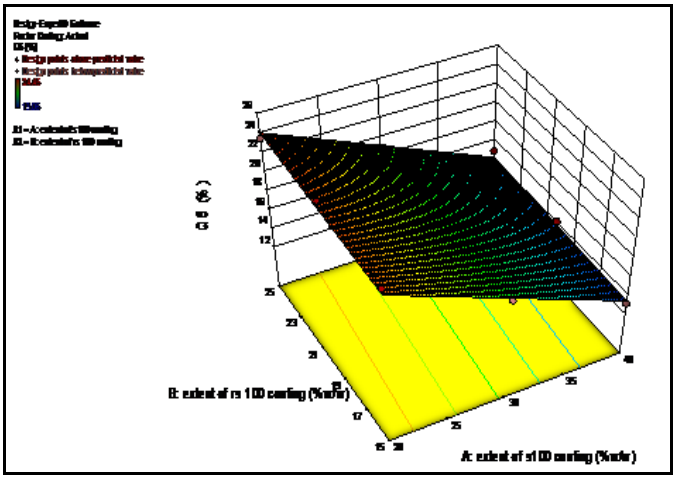

FIGURE 1 (a): Q5 3D SURFACE RESPONSE CURVE

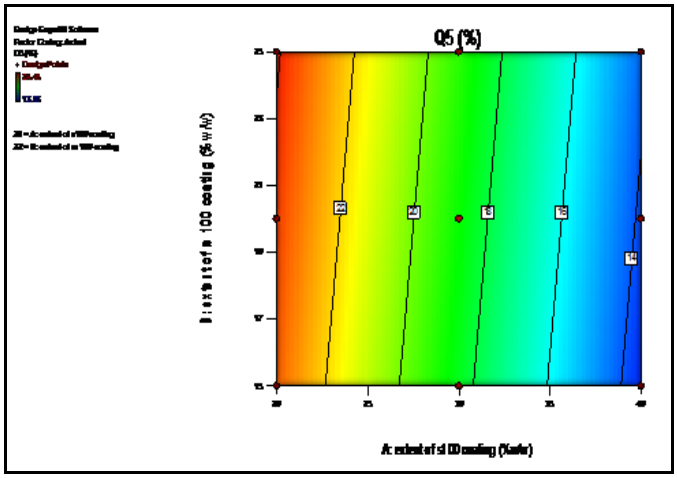

FIGURE 1 (b): Q5 2D CONTOUR PLOT

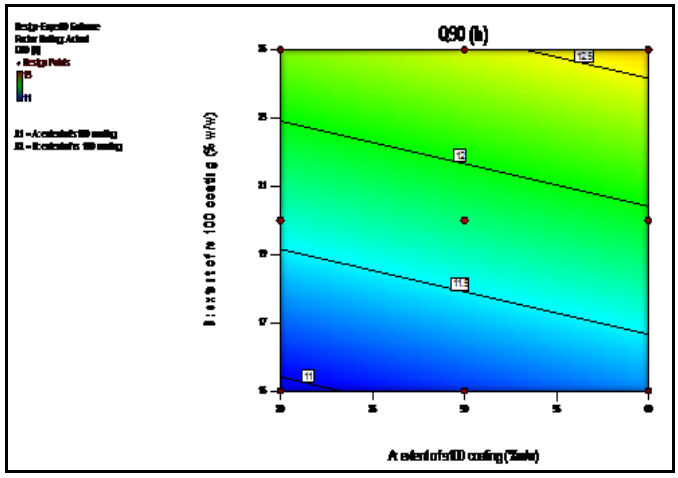

FIGURE 2 (b): Q90 2D CONTOUR PLOT

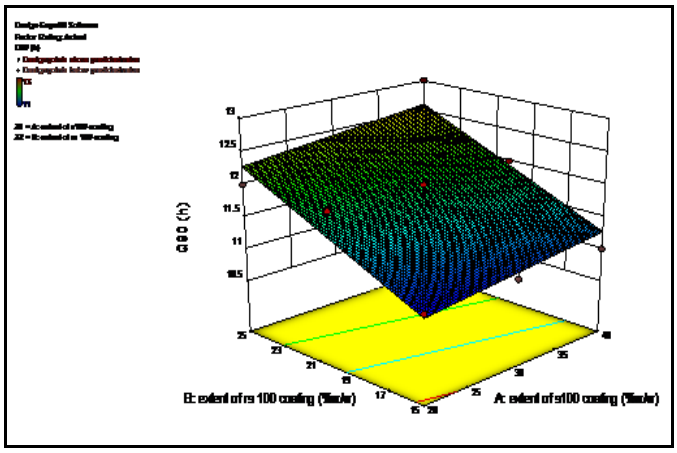

FIGURE 2 (a): Q90 3D SURFACE RESPONSE CURVE

The goal of optimization is to find a good set of conditions that will meet all the goals. The process was optimized for the dependent (responses) variables Q5 and Q90. The optimized formulation was evaluated for percentage of drug release after lag time of 5 hrs and 90% of drug release within 12 hrs.

The optimization was performed on the basis of response surface modeling by using the numerical and graphical optimization method. A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. Desirability is an objective function that ranges from zero outside of the limits to one at the goal. The numerical optimization finds a point that maximizes the desirability function. The characteristics of a goal may be altered by adjusting the weight or importance. For several responses and factors, all goals get combined into one desirability function.

TABLE 8: PROPOSED OPTIMIZED FORMULATION BY DESIGN EXPERT SOFTWARE

Constraints						
Name	**Goal**	**Lower Limit**	**Upper Limit**	**Lower Weight**	**Upper Weight**	**Impor-tance**
A:extent of S100 coating	is in range	20	40	1	1	3
B:extent of RS 100 coating	is in range	15	25	1	1	3
Q5	is in range	15	20	1	1	3
Q90	is in range	11	12	1	1	3

Solutions						
Number	**Extent of S100 coating**	**Extent of RS 100 coating**	**Q5**	**Q90**	**Desirability**	
1	31.000	20.500	18.321	11.861	1.000	Selected

Characterization and evaluation of coated pellets:

FTIR Analysis: The possible interaction between functional group of drug and excipients were studied by IR spectroscopy. From the results it was observed that all important functional groups of drug are present in the pure drug and in optimized formulation. The results revealed that there is no considerable change in IR peaks of formulations compared with pure drug spectra. This shows absence of interaction between metoprolol

succinate and various excipients in presence of various solvent used.

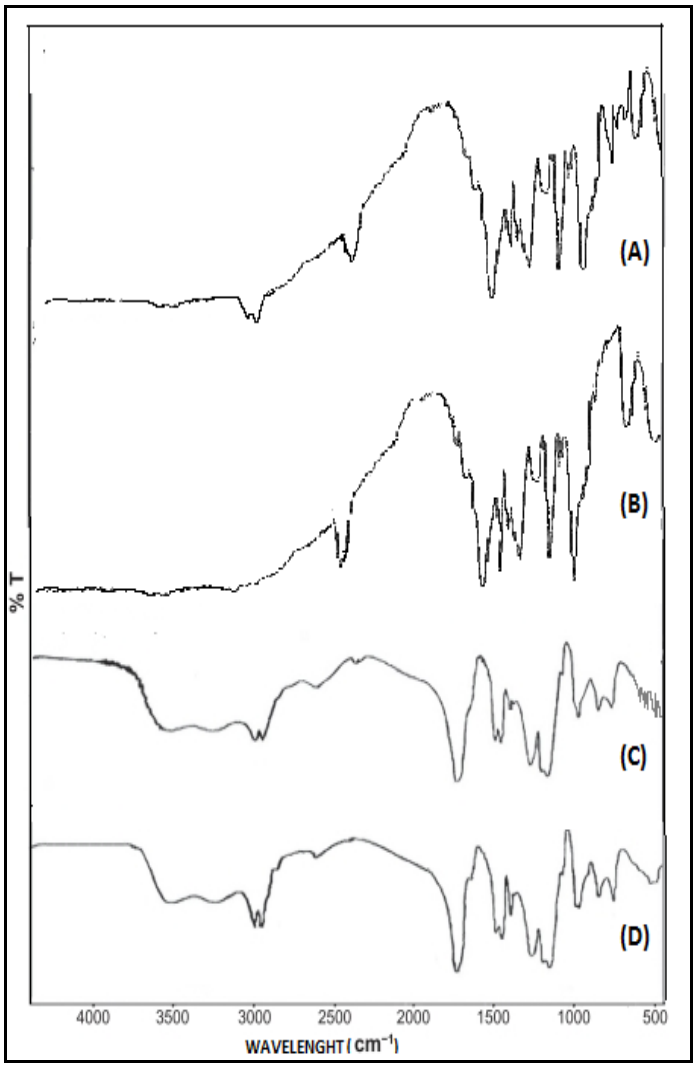

FIGURE 3: FTIR SPECTRA OF (A) D5 (OPTIMIZED FORMULATION), (B) METOPROLOL SUCCINATE, (C) EUDRAGIT RS 100 AND (D) EUDRAGIT S100

SEM photograph for evaluation of surface morphology of coated pellets:

The coated pellets were studied by scanning electron microscopy at various magnifications. The coated pellets at low magnification appeared as spherical discrete units and the surface morphology at high magnification was not homogenous or smooth, acting as entrance or exit points for the dissolution medium to dissolve the drug. Also the cross sectional images were captured to identify the drug layer and polymer layer separately. SEM photograph of Cross section of coated pellets shows three different layers over stiff drug core i.e drug layer, eudragit RS 100 layer and last one is of eudragit S100 layer.

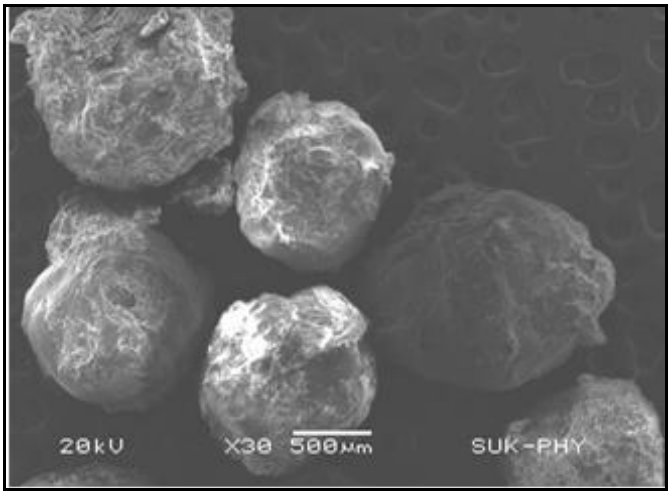

FIGURE 4: SEM PHOTOGRAPH OF COATED PELLETS (X30)

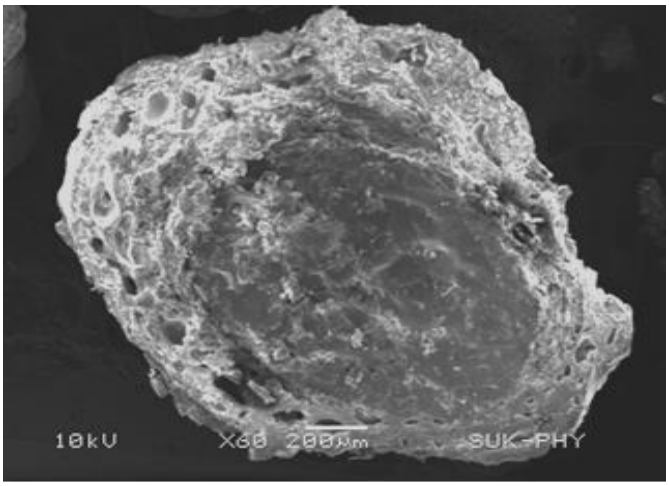

FIGURE 5: SEM PHOTOGRAPH OF COATED PELLETS (X60)

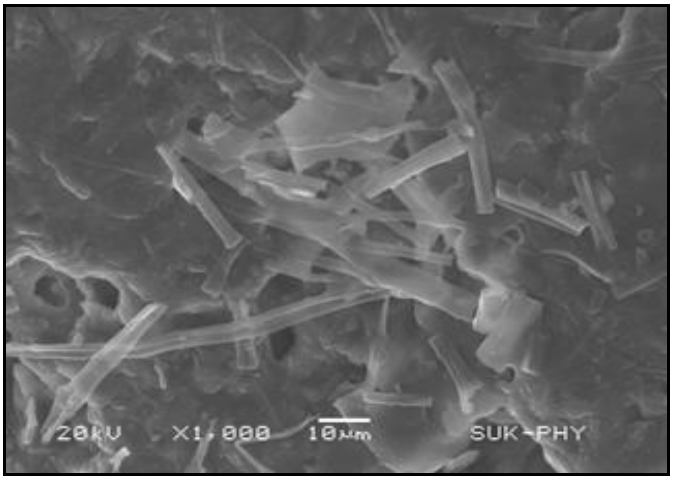

FIGURE 6: SEM PHOTOGRAPH OF CROSS SECTION OF COATED PELLETS (X1000)

Drug content:

Drug content of drug loaded pellets was found to be 98.56±2.49%.

***In vitro* dissolution studies:**

In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 6.8, and 7.2 were sequentially used referred to as sequential pH change method.

When RS 100 is used alone as coating material as in batch E4 drug is completely released within 12 hrs. When coated pellets are exposed to the dissolution medium, the solvent penetrates into the free spaces between macromolecular chains of Eudragit polymer. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to polymer relaxation by the stress of the penetrated solvent. This phenomenon may be attributed to surface erosion or initial disaggregation of coated pellets prior to gel layer formation around the drug core. The active ingredients are gradually dissolved by penetration of dissolution media since release is primarily diffusion controlled.

The enteric polymeric layer is insoluble, thus this layer may act as a barrier to any early drug release in upper GIT prior to reach to the targeted site and to provide an appropriate lag phase. After reaching to its threshold pH polymer start releasing the drug at faster rate. As up to 5hr threshold pH for S100 i.e. 7.2 is not reached so drug release is less till 5 hr after that drug release increases.

To optimize colon targeted pellets 3^2 factorial design. The dissolution data of the nine formulations obtained from 3^2 factorial design clearly demonstrated that the solubility of the Eudragit S 100 and RS100 coated pellets was strongly dependent on coating levels. The release rate was slower at higher coating levels because of the increased diffusion path-length and tortuosity at higher coating levels.

Batches having 20% w/w coating levels of Eudragit S100 i.e. D1, D4 and D7 release between 23.47 to 24.45% in Simulated Intestinal Fluid (SIF) as level of coating is not sufficient to control the release in SIF. When S100 coating level is increased to 30%w/w i.e. in batches D2, D5 and D8 and when increased to 40% i.e. in batches D3, D6 and D9, the % cumulative drug release is decreased with increase in S100 coating level in SIF as threshold pH for S100 is not attained in SIF. Release profile of three coating level of Eudragit RS100 i.e. 15%, 20% and 25% shows that with increase in coating level drug release is more sustained. From the batches D1 to D9, batch D5 first coated with Eudragit RS 100 20% w/w and them further coated with S100 30% w/w were considered as promising batches as the drug release was below 20% in SIF so that it can be efficiently colon targeted, and the release is sustained up to 12 hr which is desirable for twice daily dosing of metoprolol, while other batches gave faster or slower release.

TABLE 9: DISSOLUTION STUDY OF EXPERIMENTAL FORMULATIONS (RUNS)

Time (hr)	% Cumulative Drug Release								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
1	4.23 ±0.83	3.68 ±0.92	1.25 ±0.89	4.93 ±0.98	2.11 ±1.67	1.02 ±0.78	5.24 ±1.78	2.82 ±2.07	1.02 ±1.56
2	8.87 ±1.52	6.99 ±1.67	5.41 ±2.34	9.58 ±1.87	6.27 ±2.78	6.11 ±1.89	8.01 ±2.76	6.90 ±1.65	4.47 ±3.87
3	12.67 ±1.94	9.25 ±1.23	8.94 ±3.45	12.51 ±2.89	8.41 ±1.98	9.98 ±3.78	12.28 ±1.89	10.70 ±2.56	7.53 ±1.67
4	17.95 ±2.34	12.33± 4.20	11.69 ±2.45	19.32 ±2.86	12.08 ±3.98	11.46 ±4.89	17.77 ±2.89	12.52 ±2.89	10.62 ±2.78
5	23.87 ±3.45	18.09± 1.09	13.06 ±2.34	24.45 ±1.83	17.92 ±2.67	14.23 ±3.89	23.49 ±2.98	18.95 ±4.87	14.92 ±3.76
6	40.14 ±2.34	32.56± 0.98	27.05 ±1.45	36.35 ±0.96	28.72 ±1.76	25.86 ±2.86	33.60 ±1.98	24.35 ±2.64	22.53 ±3.87
7	48.61 ±1.65	44.33± 3.37	37.16 ±1.78	45.14± 1.98	41.86 ±2.78	36.45 ±1.85	42.79 ±2.98	36.85 ±1.29	31.92 ±2.38
8	59.55 ±4.30	57.56± 3.87	48.58 ±3.98	57.03± 1.68	54.59 ±1.89	49.72 ±2.09	51.55 ±1.78	49.96 ±1.87	42.82 ±1.56

9	70.47 ±1.87	70.10± 1.98	62.76 ±2.76	65.44± 2.98	60.54 ±4.09	57.60 ±2.87	59.39 ±2.65	60.38 ±1.67	50.65 ±2.67
10	83.05 ±2.98	82.58± 2.36	80.34 ±2.76	78.89± 3.89	72.48 ±2.56	71.97 ±2.89	68.80 ±4.78	71.61 ±2.87	61.31 ±3.45
11	99.37 ±3.06	98.44± 4.09	97.81 ±1.99	87.09± 2.78	83.09 ±2.97	81.21 ±1.67	81.09 ±3.76	80.42 ±3.78	72.43 ±2.76
12				99.54± 1.76	98.68 ±2.98	92.20 ±3.94	90.62 ±2.67	89.41 ±1.86	83.27 ±3.89

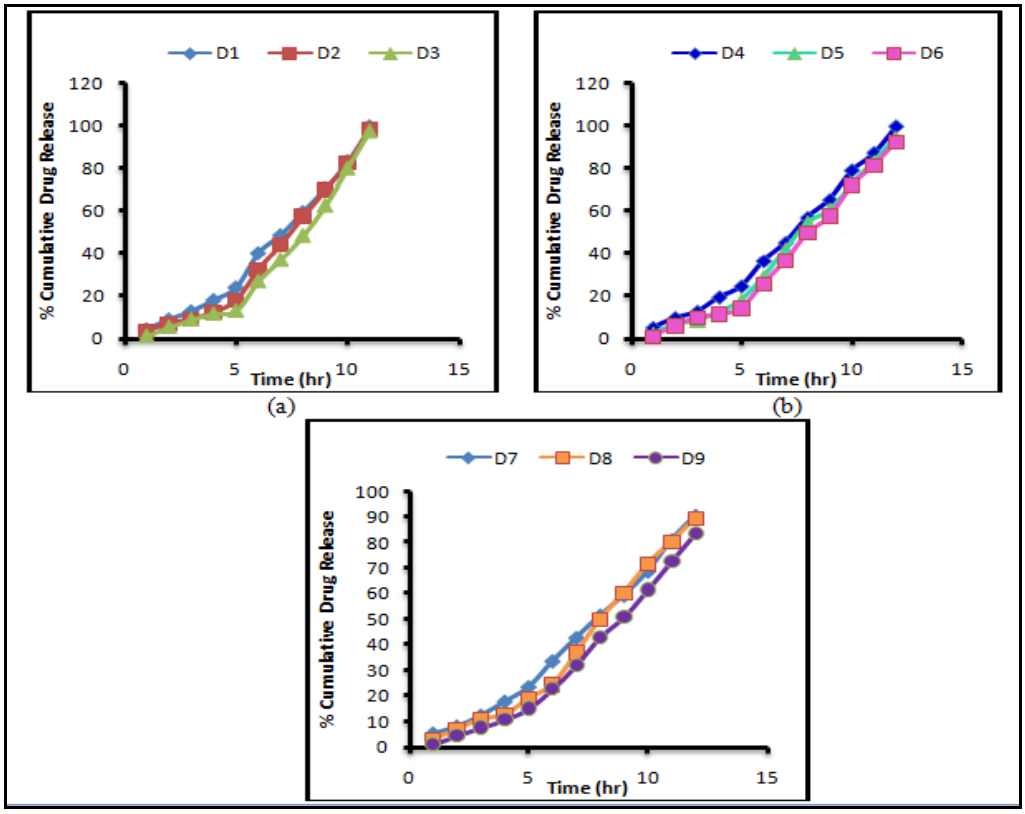

FIG.7: DISSOLUTION PROFILE OF COLON TARGETED PELLETS BATCHES OBTAINED FROM 3^2 FACTORIAL DESIGN. (a) BATCHES HAVING 20%w/w S100, (b) BATCHES HAVING 30%w/w S100 AND (c) BATCHES HAVING 40%w/w S100

***In vitro* drug release kinetics:** [22, 29]

The data was processed for regression analysis and interpretation of data was based on the value of resulting correlation coefficients. D7 follows zero order kinetics have higher regression coefficient (r^2). D1, D2, D3, D4, D5, D6, D8, and D9 follows Korsmeyer–Peppas model.

TABLE 10: KINETIC MODELS SHOWING DRUG RELEASE PATTERN OF VARIOUS FORMULATIONS

Formulations	Zero-order(r^2)	First-order (r^2)	Higuchi (r^2)	Hixen-Crowel (r^2)	Korsmeyer-Peppas	
					r^2	N
D1	0.969	0.660	0.899	0.819	0.980	0.763
D2	0.943	0.647	0.857	0.795	0.948	0.713
D3	0.919	0.616	0.826	0.756	0.978	0.576
D4	0.963	0.636	0.890	0.825	0.981	0.830
D5	0.978	0.602	0.913	0.814	0.980	0.639
D6	0.956	0.589	0.878	0.535	0.979	0.564
D7	0.980	0.838	0.916	0.906	0.976	0.831
D8	0.960	0.846	0.884	0.899	0.978	0.715
D9	0.959	0.849	0.880	0.897	0.994	0.573

To confirm the diffusion mechanism, the data were fitted into Korsmeyer- Peppas equation. The values of n for pellets indicates that different mechanisms of release were observed for drug according to the polymer content. The formulations showed good linearity (r2 = 0.807 to 0.994) with slope (n) between 0.5- 0.831, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion (Non –fickian transport). This was attributed to changes in drug release mechanism from erosion to diffusion. This mechanism assumes the polymer to be a continuous phase in which the plasticizer and other additives are dispersed homogeneously. The polymer film has molecular sized openings between the cross-linked polymer chains. Most likely, the drug molecules diffuse through these openings in a process known as hindered molecular diffusion. The openings must be wetted for drug molecules to diffuse; a process which is effected by the plasticizer and other additives.

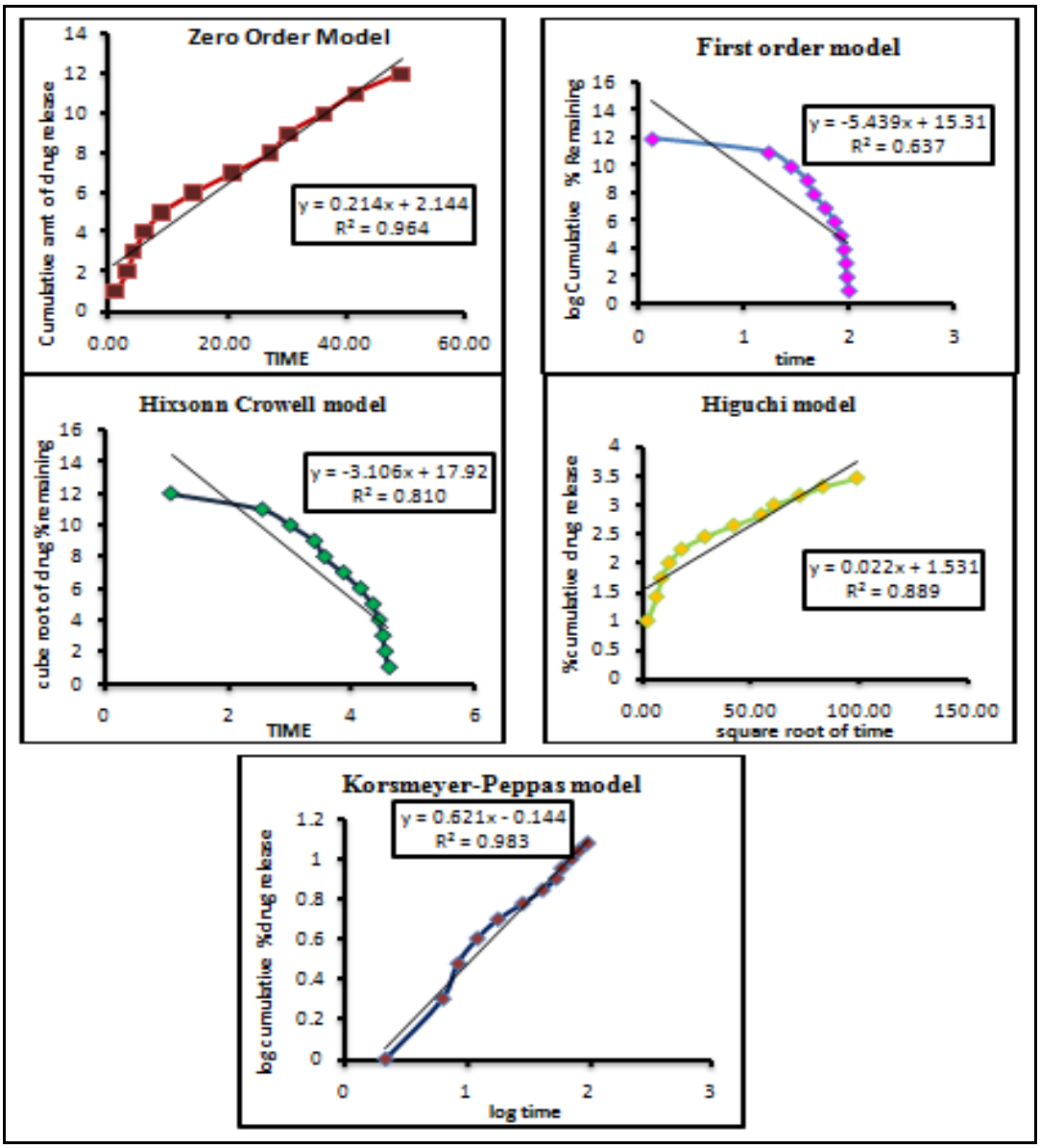

FIGURE 8: KINETIC MODELS OF OPTIMIZED FORMULATION I.E. D5.

Stability studies: [23] In view of the potential utility of optimized formulation for targeting of Metoprolol succinate to colon, stability studies were carried out at 40°C / 75% RH for 3 months to assess their long term stability. There is no appreciable change in drug content and dissolution profile of optimized formulation after storage at 40°C / 75% RH for 3 months. Drug content of optimized D5 batches before stability study was found to be 97.23±0.98 % and after stability study was found to be 95.78±1.23%.

TABLE 11: DISSOLUTION STUDY OF D5 BATCH BEFORE AND AFTER STABILITY STUDY.

Dissolution fluid	Time (hr)	% Cumulative Drug Release	
		D5 Before stability study	D5 After stability study
0.1 N HCl pH 1.2(Gastric fluid)	1	2.11±1.67	1.76±0.197
	2	6.27±2.78	5.14±1.62
Phosphate buffer pH 6.8 (Intestinal fluid)	3	8.41±1.98	7.89±2.67
	4	12.08±3.98	14.34±1.89
	5	17.92±2.67	16.57±3.39
Phosphate buffer pH 7.4 (Colonic fluid)	6	28.72±1.76	30.35±2.56
	7	41.86±2.78	38.76±3.89
	8	54.59±1.89	53.25±4.94
	9	60.54±4.09	60.02±5.22
	10	72.48±2.56	70.94±2.61
	11	83.09±2.97	81.39±2.98
	12	98.68±2.98	96.94±4.34

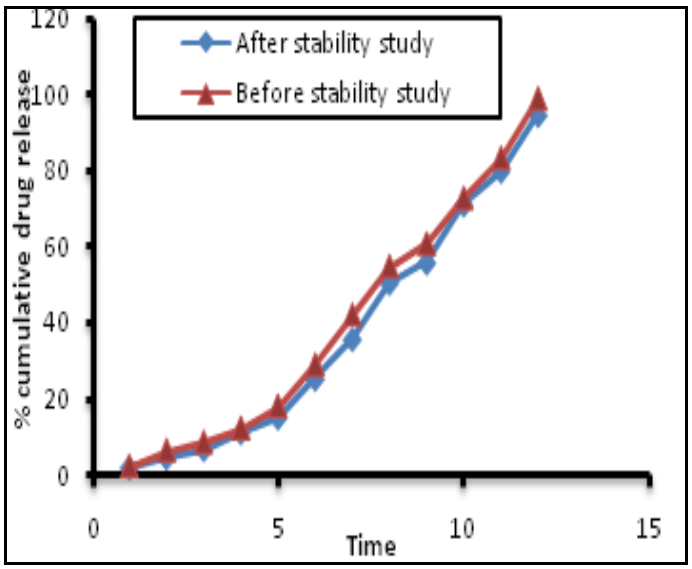

FIGURE 9: DISSOLUTION PROFILE OF D5 BATCH BEFORE AND AFTER STABILITY STUDY.

CONCLUSION: The *in vitro* drug release studies indicate that batch D5 (optimized formulation) coated with Eudragit RS 100 20% w/w and further coated 30%w/w S100 were considered as promising batches as the drug release was below 20% in SIF and the release is sustained up to 12 hr which is desirable for twice daily dosing of metoprolol. From overall study it can be concluded that at particular coating level of Eudragit S100 and RS100, formulation shows better performance. The reason behind this is as the amount of the coating layer is increased, the release time of drug is significantly increased due to the thickness of the diffusion layer.

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