Formulation Optimization of Sustained Release Resinate Microcapsules of Tramadol Hydrochloride by Using 3^2 Factorial Design

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ABSTRACT

The main aim of the present work was to develop the microcapsules of tramadol hydrochloride for the oral sustained release drug delivery. Tramadol hydrochloride a BCS class I drug a centrally acting synthetic analgesic was complexed with Indion 254 ion exchange resin. The microcapsules were prepared by encapsulating the prepared resinates by o/o solvent evaporation technique. In the investigation 3^2 full factorial design was used to investigate the joint influence of two formulation variable amount of eudragit RS 100 and plasticized PEG 400. The results of multiple linear regression analysis indicated that for obtaining a sustained release drug delivery the optimum concentrations of both the plasticizer and coating solution to be used. The factorial models were used to prepare optimized microcapsules and optimized formulations showed sustained release profiles for the extended period of more than 12 hrs. From the present investigations concluded that resinate microcapsules of highly water soluble drug can provide controlled release of drug for extended period.

Key Words: Tramadol hydrochloride, ion exchange resinate, microcapsules, sustained release

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INTRODUCTION

Tramadol hydrochloride is a centrally acting synthetic analgesic with active metabolites. It is well absorbed orally, and is only 20% bound to plasma proteins. Tramadol hydrochloride display analgesic activity with the elimination half-lives are 6 to 7 hours. Steady state plasma concentrations of tramadol are achieved within 2 days q.i.d. dosing [1-3].

Oral controlled drug delivery systems based on matrix-type tablets are generally prepared by blending a drug and carrier material followed by compression. The carrier materials can be classified into water-insoluble carriers such as polymers (e.g. ethyl cellulose, acrylate derivatives) or lipids (waxes) and water-soluble carriers (e.g.) cellulose ethers, such as hydroxyl-propyl-methyl cellulose, poly-oxy-ethylene oxide) have the advantage of complete erosion/dissolution and therefore no accumulation in the GI-tract a potentially possibility with water-insoluble polymers [4, 5]. Ion exchange resins are inert and insoluble high-molecular weight polyelectrolytes, the drug release from hydrophilic matrix tablets has been modified by the use of ion exchange resins in case of anionic or cationic drugs. Drugs adsorbed onto the ion exchange resins have been referred as adsorbents, complexes, or resinates. However simple drug-resin complexes may not satisfy the requirement of sustained release. In such cases resinates are incorporated into the matrix systems, microencapsulated or coated [6-9].

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The objective of present study was to formulate controlled release microcapsules of tramadol hydrochloride a cationic drug by using ion exchange resins. In the present study selected drug tramadol hydrochloride is basic in nature; hence the ion exchange resin of choice in this case for complexation would be a cation exchange resin. The ion exchanges resin with strong sulphonic acid functional moiety Indion 254 would be expected to complex with the drug and thus control its rapid dissolution, a problem encountered in BCS Class I drug.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was a gift sample from Sun Pharma Pvt. Ltd. India, Indion 254 procured from Ion Exchange (India) Ltd., Eudragit RS 100 was s gift sample from IPCA Pvt. Ltd. Mumbai, and all the other chemicals used in the present investigations were of AR grade.

Preparation of drug resin complexes

The resins were purified before drug loading by rinsing 10 g of wet resin with 50 ml portions of deionized water, 50 ml of 95% ethanol. Each stage of treatment lasted 1 h under magnetic stirring. The resin was then conditioned by recycling the ion exchanger twice with 50 ml of 1 M NaOH and 50 ml of 1M HCl, and washing with deionized water after each treatment. Finally, the resins were recovered by vacuum filtration, washed thoroughly with deionized water and dried to a constant weight at 50°C in hot air oven and stored in desiccators [10].

The tramadol hydrochloride-resin complexes were prepared by a batch processes. For the batch method, the previously purified indion 254 resin particles (100 mg of dry weight resin) were dispersed in a 2 % (w/v) drug solution (50 ml) under magnetic stirring at room temperature for 2 h. After carefully decanting the clear supernatant of the above, another 50 ml of fresh drug solution was added and stirred again for 2 h at room temperature; this procedure is an alternative method called as modified batch method. 0.1ml of supernatant was collected at fixed intervals during complex formation at room temperature, diluted with water, and then the drug amount was quantified by UV spectrophotometer (Shimadzu 1600) at 271 nm. The drug–resinate beads were separated from the supernatant by filtration, washed with deionized water to remove any non-complexed drug, and then dried in an oven at 40°C for 24 h and then stored in tightly closed desiccators. Standard calibration curves were prepared before analysis to monitor the linearity from 10 to 100 µg /ml at 271 nm.

Microencapsulation of resinates

The tramadol hydrochloride-loaded resins were encapsulated with Eudragit RS 100, using the o/o solvent evaporation method. The prepared tramadol hydrochloride resinates were suspended in 10 ml of a 5- 20% (w/v) solution of the Eudragit RS 100 and 0-10% PEG 400 in acetone and emulsification was followed of this phase in 100 ml light liquid paraffin. The stirrer was set at 1000 rpm till complete evaporation of acetone. The microcapsules were separated by vacuum filtration, washed with n-hexane and air-dried for 24 h at room temperature and stored in desiccators [11].

Optimization of resinate microcapsules using a 3^2 full factorial experimental design with Indion 254

Factorial experiments 3^n (n factors each at three levels) is of historical interest and software's are usually used to analyze the outcome of factorial experiments. Tramadol HCl–resin microcapsules were prepared using a 3^2 full factorial experimental design in order to investigate the main effects as well as interaction of formulation and process variables using Design Expert® software and MS Excel. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. For this study the formulation variables were Eudragit concentration(X_1) and PEG-400(X_2). The percent drug released after 1 h (Y_1), after 6 h (Y_2) and after 12 h (Y_3) was selected as the dependent variables. Table 1, 3 illustrates the composition of the prepared microcapsules.

A statistical model incorporating interactive and polynomial terms that correlates the independent variables and response is described by equation (1);

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where b_0 is the arithmetic mean response of sixteen runs; b_1 and b_2 are the estimated coefficients for X_1 and X_2 respectively; and b_{12} is the estimated coefficients for interaction terms (X_1X_2). The model used for main effects of the variables $X_1$and X_2 represent the changing variable each at a time.

The second order interaction (X_1X_2) shows that how the value of X_1 amplifies or downplays the effect on the response of a change in X_2. The polynomial terms and is included to investigate nonlinearity [12, 13].

In vitro drug release from the microcapsules

In vitro dissolution study was carried out in triplicate for microcapsule equivalent to 100 mg of tramadol hydrochloride, by using the USP paddle apparatus (Electrolab TDT 06L). The dissolution medium was distilled water, temperature maintained at 37±0.5°C, and the paddle speed was 50 rpm. At predetermined intervals 5 ml aliquots were withdrawn and replaced with the same volume of fresh dissolution medium. The collected aliquots were filtered through whatman filter paper no.41 and amount of drug released was analyzed by UV-vis spectrophotometer at 271 nm following suitable dilutions.

In vitro drug release kinetics [14-16]

To describe the kinetics of drug release from controlled release formulation, various mathematical models have been proposed. The zero-order rate describes systems where drug release is independent of its concentration and is generally seen for poorly water soluble drug embedded in matrix.

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The first-order equation describes systems in which the release is dependent on its concentration (generally seen for water soluble drugs in porous matrix). The Higuchi model describes the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion. In order to authenticate the release model, dissolution data can be further analyzed by Peppas and Korsmeyer equation.

Zero-order kinetics

Zero-order process can be defined as the one whose rate is independent of the concentration of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of reactants. It is a constant rate processes. For zero-order process the equation becomes:

$dC/dt = - K_O C_O$

Rearranging the above equation

$dC = - K_O dt$

Integration of this equation

$C - C_O = - K_O . t$

$C = C_O - K_O . t$

Where - C_O = concentration of drug at time t = 0

C = concentration of drug yet to undergo reaction at time t

A plot of C versus t yields such a straight line having slope – K_O and y-intercept C_O.

First order kinetics

The first order process is the one whose rate is directly proportional to the concentration of drug undergoing reaction, i.e. greater the concentration, faster the reaction. It is because of such a proportionally between rate of reaction and the concentration of drug that a first order process is said to follow linear kinetics. The first order process is also called mono exponential rate process. Thus a first order process is characterized by logarithmic or exponential kinetics, i.e. a constant fraction of drug undergoes reaction per unit time.

The equation becomes

$dC/dt = - K . dt$

By the integration the eq. becomes

$$\text{Log } C = \text{Log } C_O - \frac{Kt}{2.303}$$

or $\text{Log } C = \text{Log } C_O - 0.434\ Kt$

A semi-logarithmic plot of the above equation yields a straight line with slope = – Kt / 2.303 and y-intercept = Log C_O

Higuchi Model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrices. Higuchi describes drug release as a diffusion process based in the fick's law, square root time dependent.

So $Q_t = K_H . t^{1/2}$

K_H=is the Highuchi dissolution constant

Korsmeyer – Peppas Model

Korsmeyer et al (1983) developed a simple, semi-empirical model relating exponentially the drug release to the elapsed time (t)

$$\frac{M_t}{M_\infty} = k . t^n$$

Where, a constant incorporating structural and geometric characteristic of the drug dosage form. n is the release exponent, indicative of the drug release mechanism, and the function of t is.

The large value of the coefficient of determination (R^2) indicated a superiority of the dissolution profile fitting to mathematical equations.

Table 1. Full factorial 3^2 design to optimize the tramadol hydrochloride resinate microcapsules

Factors (Independent Variables)	Level used		
	-1	0	+1
X_1:Eudragit RS 100 coating solution% w/v	5	12.5	20
X_2: PEG 400 % w/v	0	5	10

Table 2. Tramadol hydrochloride loading onto ion exchange resin indion 254

% Loading of Tramadol hydrochloride			
Inactivated	1M HCl	1M NaOH	Acid +Base
54.30±1.02	55.10±0.26	56.82±0.43	58.24±1.08

Mean ±S.D., n = 3

Table 3. 3^2 full factorial design layout

Formulation code	Variable levels in coded form		Responses (Dependent Variables)		
	X_1	X_2	Y_1	Y_2	Y_3
F1	-1	1	11.95	50.15	70.48
F2	-1	-1	14.98	60.22	80.94
F3	-1	0	11.68	49.72	68.82
F4	1	1	8.02	40.25	60.51
F5	1	-1	4.31	24.42	44.82
F6	1	0	6.26	27.66	47.96
F7	0	-1	9.21	43.29	63.75
F8	0	1	9.4	49.84	68.91
F9	0	0	8.42	40.49	59.22

**Mean ±SD, n=3*

RESULT AND DISCUSSION

Preparation of drug resin complexes

The drug loading was found to be less in the inactivated resins as indicated by the % drug complexation in table 3. However the % drug complexation was found to increase in the following order of pretreatment HCl<NaOH <Acid+base as observed. From the results obtained it is evident that the activation of resin was necessary to yield the maximum drug complexation with resins. Due to the fact that the surface charge of the ion exchanger might be responsible for the drug loading on to the resins. Changing the ionic form of the IER might occasionally be required to convert resin from one form to another if it does not have the desired counter ions. Strongly acidic cation exchange resins are usually available in Na^+ form. They are usually converted into H^+ form. This may be achieved by soaking the resins into acids and alkalis respectively and subjected to washing until

elute becomes neutral. So prior to use for further investigation resins were purified and activated [11].

Microencapsulation of resinates

The tramadol HCl–resinate, showing the sustained release of the drug, was selected here was Indion 254 to be encapsulated with Eudragit® RS 100 using solvent evaporation methods to offer the desired controlled release profile to achieve extended release for 24 h. The microencapsulation process was performed using o/o method. The microcapsules prepared by o/o method were uniform discrete particles with good flow properties, hence this method was suitable for further studies.

Factorial design

Tramadol hydrochloride–resin microcapsules were prepared using a 3^2 full factorial experimental design in order to investigate the main effects as well as interaction of formulation and process variables using Design Expert® software and MS Excel. The effect of variables and respective responses are presented in table 3. The model analyzed for the significant role of each variable and interaction terms on the response by regression data analysis. The model was found significant for the investigation of main effects of variables and interaction. The model was analyses on the basis of p value. The coefficient obtained after multiple linear regression analysis were retained for predicting the optima only if their p value was less than 0.05 ($p>0.05$). The ANOVA for testing the models at responses drug released after 1hr, 6 hrs and 12 hrs are presented in the table 4. The statistical models further utilized to formulate the optimized microcapsules.

The result obtained clearly indicates that the increased concentration of polymer Eudragit RS 100 had a profound influence in the extent of coating (Figure 1-3). Further helps in retarding the drug release showing the sustained release profiles.

After 1 hour the drug release

The formulations F1 to F9 were analyzed by regression the results as indicated in table 4.

The coefficients estimates shows the main effect of the formulation variables the significant terms in the selected models were X_1, X_2, X_1X_2 depending on the p value less than 0.05. All the other terms were non significant. The Model F-value of 40.68 implies the model is significant. There is only a 0.06% chance that an F-value this large could occur due to noise. The "Pred R-Squared" of 0.7991 is in reasonable agreement with the "Adj R-Squared" of 0.9370; i.e. the difference is less than 0.2. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Here the ratio of 18.809 indicates an adequate signal. This model can be used to navigate the design space.

Drug releases after 6 hours

The significant terms were X_1, X_1X_2, X_2^2 depending on the p value less than 0.05 and were retained in the reduced model. The Model F-value of 58.60 implies the model is significant. There is only a 0.08% chance that an F-value this large could occur due to noise. The "Pred R-Squared" of 0.8935 is in reasonable agreement with the "Adj R-Squared" of 0.9664; i.e. the difference is less than 0.2. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Here the ratio of 22.894 indicates an adequate signal. This model can be used to navigate the design space.

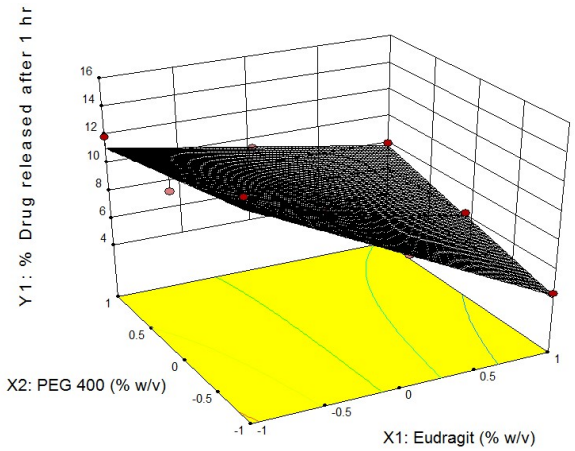

Figure 1. Response surface plots of X_1 and X_2 for responses Y_1

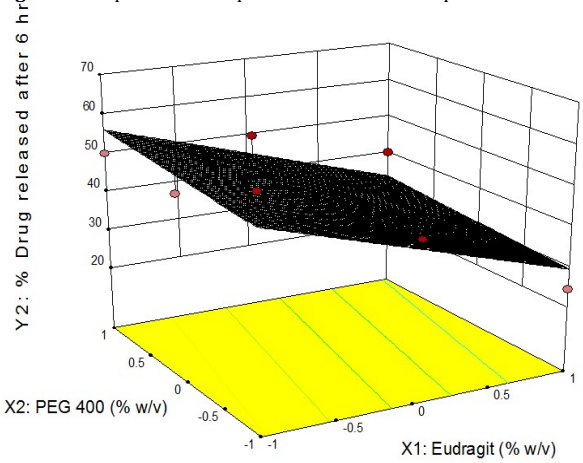

Figure 2. Response surface plots of X_1 and X_2 for responses Y_2

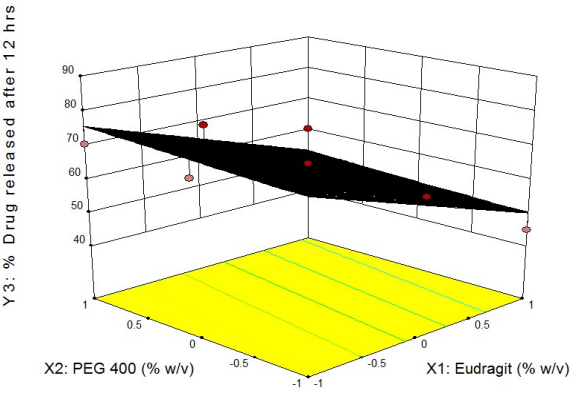

Figure 3. Response surface plots of X_1 and X_2 for responses Y_3

Table 4. ANOVA for testing the models

% Drug released after 1 hour	Df	SS	MS	F	R^2	Significance F
Regression						
FM	5	80.304	16.060	40.614	0.985	0.0058
RM	3	78.157	26.078	40.68	0.961	0.000
Error						
FM	3	1.186	0.395			
RM	5	3.334	0.555			
% Drug released after 6 hrs						
Regression						
FM	5	1028.825	205.764	119.94	0.995	0.0012
RM	4	1016.62	254.16	58.60	0.983	0.0007
Error						
FM	3	5.146	1.715522			
RM	4	42.604	8.520877			
% Drug released after 12 hours						
Regression						
FM	5	1019.56	203.912	135.46	0.995	0.001
RM	4	1013.75	253.44	98.14	0.989	0.00026
Error						
FM	3	4.516	1.505			
RM	4	10.33	2.58			

**Df indicates: degrees of freedom, SS: sum of squares; MS: mean of squares; F: Fischer's ratio, R^2: regression coefficient, FM: full model and RM: reduced model*

Table 5. The coefficients and estimates of full model

Coefficient	Coefficient Estimate		
	Y_1	Y_2	Y_3
b_0	8.44	40.94	59.80
b_1	-3.34	-11.29	-11.16
b_2	0.14	2.05	1.73
b_1b_2	1.69	6.47	6.54
b_1^2	0.52	-2.47	-1.71
b_2^2	0.86	5.41	6.23

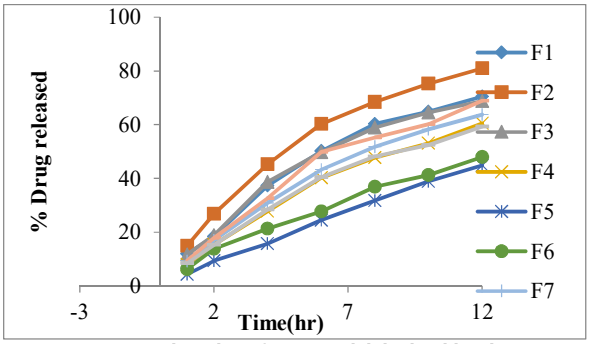

Figure 4. Zero order plots for tramadol hydrochloride resinate microcapsules F1 to F9

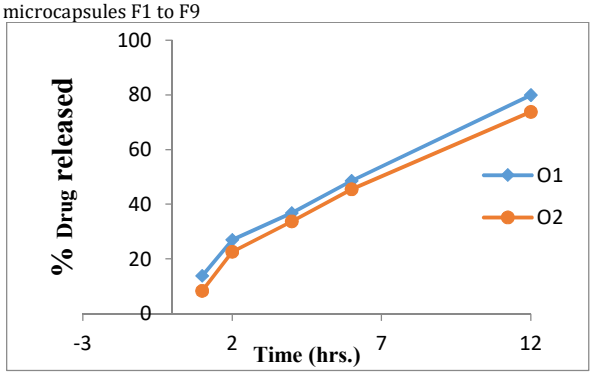

Figure 5. Drug release profiles of optimized formulations

Drug releases after 12 hours

The significant terms were X_1, X_1X_2, X_2^2 depending on the p value less than 0.05 and were retained in the reduced model. The Model F-value of 98.14 implies the model is significant. There is only a 0.03% chance that an F-value this large could occur due to noise. The "Pred R-Squared"" of 0.9311 is in reasonable agreement with the "Adj R-Squared" of 0.9798;"i.e. the difference is less than 0.2."Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Here the ratio of 29.547 indicates an adequate signal. This model can be used to navigate the design space.

In this investigation it is concluded that as the levels of coating polymer increased there is increase in the retardation of drug flux while the plasticizer influences the drug release due to its hydrophilicity and further formation of porous film on dissolution. It was observed that the PEG does not have any considerable effect on release of drug in the first hour. The PEG 400 is hydrophilic in nature and due to this reason there was increase in the drug release after 6 and 12 hrs. Table 5 shows the coefficients in the equations for the prediction of response. Further the coefficients are used for the desired responses and two optimized formulations were prepared.

The *in vitro* drug release profiles figure 4 shows that the higher concentration of eudragit polymer decreased % drug release was observed as in F5 i.e. that is less than 45 % drug was released while the F2 showed the rapid drug release in 12 hrs. Most of the formulations shown the controlled release of drug which is suitable for formulating a controlled release drug delivery of a drug for constant release extended up to 24 hours.

In the table 6 higher the values of the R^2 indicates the best fit of model. The in vitro drug release data was fitted to different mathematical models and it is found that the F5 was following zero order, F2, F4, F6 and F7 showed higuchi model all the remaining formulations showed the Korsmeyer- Peppas kinetics. A model-independent technique was used to compare the dissolution profiles of the optimized microcapsules.

The model, based on similarity factor f_2, described using the following equation [17].

$$f_2 = 50\ \mathrm{Log}\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\times 100\right\}$$

Where R_t and T_t are the reference and test product results at time point t, respectively, and "n" is the number of sampling points.

The $f_2$value within the range 50 to 100 suggests that the release profiles are similar. Here the f_2 for the optimized formulation was found to be 61.44 which imply that drug release profiles for optimized microcapsules were similar. The zero order kinetics for the optimized formulations was found to be 0.986 and 0.974 respectively.

Table 6. Kinetic models

Formulation code	Zero order		First order		Higuchi model		Korsmeyer-Peppas	
	K_o	R^2	K_1	R^2	K_H	R^2	n	R^2
F1	5.452	0.949	0.036	0.975	25.102	0.989	0.750	0.986
F2	5.926	0.942	0.056	0.967	27.04	0.991	0.684	0.986
F3	5.286	0.940	0.037	0.976	24.442	0.987	0.744	0.983
F4	4.736	0.973	0.024	0.978	21.692	0.997	0.816	0.993
F5	3.702	0.997	0.023	0.982	16.59	0.984	0.939	0.997
F6	3.660	0.986	0.022	0.983	15.56	0.992	0.867	0.988
F7	4.898	0.968	0.034	0.964	22.87	0.997	0.790	0.993
F8	5.344	0.952	0.038	0.968	24.56	0.988	0.808	0.986
F9	4.616	0.964	0.029	0.986	23.26	0.982	0.797	0.992

Table 7. Formulation of optimized microcapsules

Sr. No.	Variables		Predicted Response			Observed Response		
	X_1:Eudragit	X_2:PEG 400	Y_1	Y_2	Y3	Y_1	Y_2	Y_3
O_1	6.500	1.00	10.00	45.00	74.38	13.89±1.29	48.62±2.61	79.96±3.22
O_2	9.50	9.00	10.00	46.8	71.254	8.41±2.32	45.53±0.93	73.82±2.14

**Mean ±SD, n=3*

CONCLUSION

Tramadol hydrochloride is highly water soluble drug of BCS class I due to its solubility it is rapidly absorbed in the conventional dosage forms. But it is also required to get consistent levels after administration. The present investigation was primarily aimed to control the release of tramadol hydrochloride to get the extended drug release. The use of ion exchange resins shows the drug release independent of the pH of media due to the pKa of tramadol hydrochloride as it get ionized at all the pH. Drug resin complexes do not have much retardation of the drug. But by means of incorporating resinates in to polymeric coatings better sustained release drug delivery can be achieved. The present investigation shows the in vitro drug release profiles but further investigations are required to know clinically relevant plasma profiles of the drug and then after commercialization of the proposed work.

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