Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(2): 154-162

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Design and characterization of controlled release resinates of tramadol hydrochloride

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ABSTRACT

The present research was aimed to design controlled release ion exchange resinates of BCS class I drug Tramadol hydrochloride (TH) a centrally acting synthetic analgesic. Complexes of ion-exchange resins and tramadol hydrochloride, a model drug, were prepared using different methods including a single batch and modified method with different functional groups, ion-exchange capacity, degree of crosslinking, and resin particle size. Drug loading efficiency, release profiles were investigated. Most of the functional groups of resins were loaded with tramadol hydrochloride after the completion of a double batch method and it was recommended for drug loading into the ion-exchange resin. Tramadol hydrochloride could be loaded onto resin, depending on the physicochemical properties of the resin. As the crosslinking ratio and particle size increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. In vitro drug release profiles of resinate shown the pH independent release. Also the ionic strength and valency of dissolution medium has influence on drug release. Assuming that the resin particles are uniform spheres of radius r, release mechanism was evaluated using plots of a Bt−t relationship, where B and t are the rate constant and time, respectively. The Bt−t plots displayed a straight line indicating that the diffusion of tramadol hydrochloride in the resin matrix is the rate-controlling step. Tramadol hydrochloride resinates in vitro drug release shown significant sustained release up to 6 hours.

Key words: Tramadol hydrochloride, ion exchange resins, controlled release, resinates.

INTRODUCTION

Tramadol hydrochloride is a centrally acting synthetic analgesic with active metabolites (figure 1). It is well absorbed orally, and is only 20% bound to plasma proteins. Both the parent compound and the M1 (O-desmethyltramadol) metabolite display analgesic activity; the elimination half-lives are 6.3 and 7.4 hours for the parent compound and the M1 metabolite, respectively. Steady state plasma concentrations of both tramadol and M1 metabolite are achieved within 2 days q.i.d. dosing[1-4].

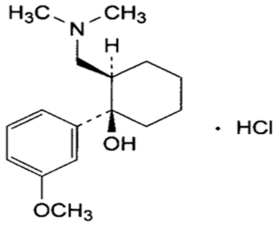


Figure 1. Structure of Tramadol Hydrochloride

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 [5-6].

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. In tablet formulations ion exchange resins have been used as disintegrants because of their swelling ability [7-13].

The objective of present study was to formulate controlled release ion exchange resinates of tramadol hydrochloride a cationic drug by using ion exchange resins. In the present study selected drug tramadol hydrochloride is basic in nature with amine functional group; hence the ion exchange resin of choice in this case for complexation would be a cation exchange resin. The ion exchange resin with strong sulphonic acid functional moiety viz Indion 224, Indion 244, Indion 254 and Indion 284 would be best expected to complex with the selected drug and thus control its rapid dissolution, a problem encountered in BCS Class I drug.

EXPERIMENTAL SECTION

Materials

Tramadol HCl was a gift sample from Sun Pharma Pvt. Ltd. India, Indion 224, Indion 244, Indion 254 and Indion 284 procured from Ion Exchange (India) Ltd., all the other chemicals used in the present investigations were of AR grade.

Characterization of resins

Resins were selected on the basis of nature of drug and requirements of formulation. In the present study selected drug tramadol hydrochloride is basic in nature with amine functional group; hence the ion exchange resin of choice in this case for complexation would be a cation exchange resin. The ion exchange resin with strong sulphonic acid functional moiety viz. Indion224, Indion244, Indion254 and Indion284 would be best expected to complex with the selected drug and thus control its rapid dissolution, a problem encountered in BCS Class I drug.

Physical properties

The organoleptic properties were observed by placing the resin sample in watch glass. Particle sizes of the resins were determined by microscopic method. Water uptake capacity was obtained by keeping 100 mg of resin in contact with 1 ml of water in a petri dish. The time required to absorb water completely was recorded.

Moisture content determination of resins

One gram of accurately weighed resin was kept in oven (previously heated to 100 ^{0}C) for 24 hours; the moisture content was determined using following formula.

$$\text{Moisture Content} = \frac{\text{Weight of water in sample}}{\text{Dry weight of sample}} \times 100 \quad (1)$$

Preparation of drug resin complexes

The tramadol hydrochloride-resin complexes were prepared by a batch processes. For the batch method, the previously purified 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 (single batch). 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 (double batch). In a triple batch method, an additional batch procedure was carried out. To study how quickly equilibrium could be reached, 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 $^\circ$C for 24 hand then stored in tightly closed desiccators [13-14]. Standard calibration curves were prepared before analysis to monitor the linearity from 10 to 100 µg /ml at 271 nm. The amount of drug complexed onto resin can be determined by following equation.

$$\% \text{ Complexation} = \frac{\text{Drug(mg)}}{\text{Resin(mg)}} \times 100 \quad (2)$$

Effect of resin activation on drug complexation
Resins were pretreated to remove any impurities; resins were washed with 200 ml of deionized water and methanol (2×50 ml). The resins were activated by recycling alternatively thrice with 60 ml of 1M NaOH and 1M HCl and washing after each treatment with de-ionized water. The resins in hydrogen/acid form were washed with de-ionized water until elute was neutral and were then vacuum dried at 50 $^{\circ}$C to constant weight.

Effect of pH on drug loading
A series of solutions containing 1mg/ml tramadol hydrochloride were prepared. pH of these solutions was adjusted for 2, 4,6,7,8 and 10. Resins were transferred in each 100 ml beaker and stirred for 2 hours on magnetic stirrer. Resinates thus formed were filtered and washed by excess amount of distilled water. The drug content in the final filtrate was quantified by UV-spectrophotometer.

The equilibrium profiles of drug loading onto the ion exchange resins
Equilibrium profiles of drug loading onto the ion exchange resins were studied to see the time to reach equilibrium and loading of the tramadol hydrochloride. The particle size of the drug and degree of crosslinking is responsible for the effective surface area required for the binding of the drug. Indion 224,indion 244,indion 254and indion 284 are different particle sizes and hence the varied surface area for binding. For the single batch process the equilibrium profiles were studied for all the ion exchange resins. The modified batch loading processes like double and triple batch processes were also studied.

***In vitro* drug release from ion-exchange resinates**
In vitro dissolution study was carried out in triplicate for resinates equivalent to 100 mg of tramadol hydrochloride placed into 900 ml of Dissolution medium, by using the USP paddle apparatus (Electrolab TDT 06L). Speed of paddle rotation was fixed at 50 rpm and temperature maintained at 37 ± 0.5°C. 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.

1. Effect of pH on *in vitro* release: A claimed advantage of ion exchange delivery system is that release of drug is independent of pH of the dissolution medium. This view was investigated by preparing buffer solutions of different pH (1.2, 6.8 and distilled water).
2. Effect of ionic strength on *in vitro* release: To study effect of ionic strength on in-vitro release of drug resinate, pH 6.8 buffer with ionic strength adjusted with 0.0, 0.005, 0.10 M NaCl.
3. Effect of valency of ions in dissolution medium: to study the influence of the valency of ions in the dissolution medium adjusted to 0.1 M NaCl and0.1 M $CaCl_2$.

Modeling kinetics of drug release from resinates
A mathematical modeling was applied to know about the drug release profiles from resinates. A commonly known Boyed model was applied. The resin particles are assumed to be uniform spheres of radius r, Boyed et al., showed that where the particle diffusion was only the rate controlling process, the following expression gives the fraction of drug released F.

$$F = \frac{Q_t}{Q_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{e^{-n^2Bt}}{n^2} \quad (3)$$

Where $B = \frac{\pi^2 D^i}{r^2}$

Q_t and Q_∞ are the amounts of drug released after time t and after infinite time respectively. B is the rate constant, D^i being the effective diffusion coefficient, and n is the summation variable. For the F values higher than 0.85 the equation can be reduced to:

$$F = 1 - \frac{6}{\pi^2}e^{-Bt} \quad \text{or}$$

$$Bt = -\log_e \frac{\pi^2}{6}(1 - F)$$

$$= 2.303 \log_{10}(1 - F) - 0.498 \quad (4)$$

If the F value is lower than 0.85, the equation applied to be

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi\left(1 - \frac{\pi F}{3}\right)^{\frac{1}{2}}$$

$$= 6.283 - 3.290\ F - 6.283(1 - 1.047F)^{1/2} \quad (5)$$

At a value of F equation (4) for values from 0.86 to 1and F=0.85 equation (5) can be used give values of Bt agreement within 0.005 corresponding the variation of F at this point of less than 0.001. If the plot of Bt corresponding F values versus time is straight line, it can be assumed that drug diffusion within the resin matrix is the rate limiting step [15-16].

RESULTS AND DISCUSSION

Characterization of resins

The ion exchange resins were characterized for the appearance by visual observation and for evaluation of particle size by microscopy. The swelling time and moisture content was also determined. The particle size of resins particles of Indion 244, Indion 254 was found to be ≤0.15mm, which was confirmation with that reported in the literature. Similarly the particle size of Indion 224 and Indion 284 were also found to be within the range 0.21 to 1.2 mm as reported in the literature. Moisture content of the resin was determined and it was found to be in the range from 2- 9 % which was complying with the standards. The water uptake time of resins were found to be in the range of 42 to 70 seconds. The results were shown in Table1.

Table 1. Physical Properties of Ion Exchange Resins

Resins	Appearance	Particle Size(mm)	%Moisture content	Swelling Time (seconds)
Indion 224	Brown beads	0.205 ±2.40	2.68 ± 0.24	61 ±5
Indion 244	Light brown powder	0.121 ±4.23	5.32 ±0.48	42 ±4
Indion 254	Light cream colored powder	0.145 ±2.46	4.36 ±1.25	44 ±5
Indion 284	yellow to pale brown beads	0.560 ±1.25	8.45 ±2.4	70 ±6

Mean ±S.D., n = 3

Preparation of drug resin complexes

Effect of resin activation on drug complexation

The resinates were pretreated with 1M HCl and 1M NaOH and the percent drug loading of the drug onto resin was determined in triplicate the results found are depicted in table 2.

Table 2. Effect of resin activation on % Tramadol hydrochloride loading onto ion exchange resins

Resins	% Loading of Tramadol hydrochloride			
	Inactivated	1M HCl	1M NaOH	Acid +Base
Indion 224	50.86±0.42	51.24±0.12	51.56±0.26	51.84±0.83
Indion 244	62.64±0.63	68.30±0.22	70.52±0.48	72.82±0.24
Indion 254	54.30±1.02	55.10±0.26	56.82±0.43	58.24±1.08
Indion 284	48.12±0.24	49.10±0.42	51.22±0.29	51.34±0.62

Mean ±S.D., n = 3

The drug loading was found to be less in the inactivated resins as indicated by the % drug complexation in table 2. 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.

The equilibrium profiles of drug loading onto the ion exchange resins

The equilibrium profiles of the ion exchange resins were studied to see the time to reach equilibrium and loading of the tramadol hydrochloride. The equilibrium profiles of the drug loading on to different ion exchange resinates figure 7.7 shows that particle size of the drug and degree of crosslinking is responsible for the effective surface area required for the binding of the drug. Indion 224 and indion 284 are of larger particle size and hence the less surface area for binding. While indion 244 and indion 254 shown the rapid equilibrium profiles within the range 10-15 minutes. For the single batch process the equilibrium studied profiles shown that the equilibrium was almost reached in first 30 minutes for all the ion exchange resins. The modified batch loading processes like double and triple batch processes were also studied and from the figure 2 and 3 it is clear that next loading using double batch additional 13-19 % of drug was loaded. The triple batch process was unsuccessful for the loading of the drug because almost all the binding sites of the resin materials were saturated by drug molecules. Hence the equilibrium profiles of single batch process and double batch were utilized for further study.

When the loading of the drug onto ion exchange resins, it is desired to increase the % loading efficiency while reducing the loss of the dugs in order to minimize the size of dosage form and properties of drug delivery system. Therefore loading the drug with single batch is not enough to get highly drug loaded complexes. Based on the results double batch method could be recommended for loading drugs into the ion exchange resins. The functional group of the cation exchange resin used in this experiment is SO_3^- H^+. As complex formation progresses acidic byproducts can be produced more. If not removed from the system, these may change the pH of medium as well and compete with counter ions of drug in bulk solution, and affect equilibrium drug loading.

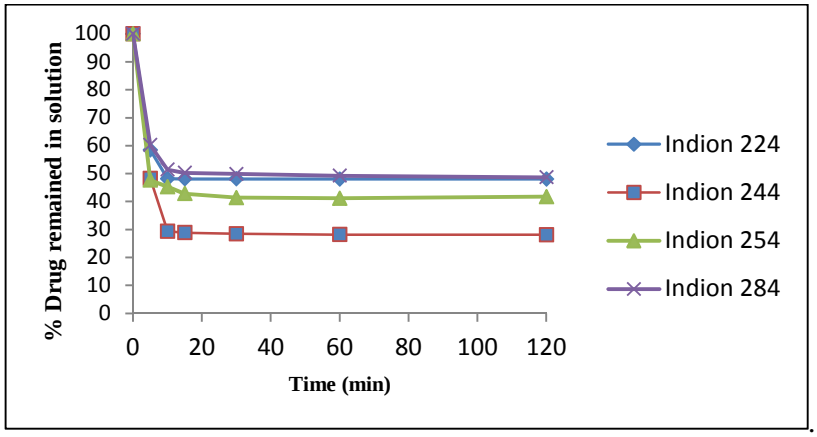


Figure 2. Equilibrium profiles for the drug loading onto ion exchange resins by single batch process

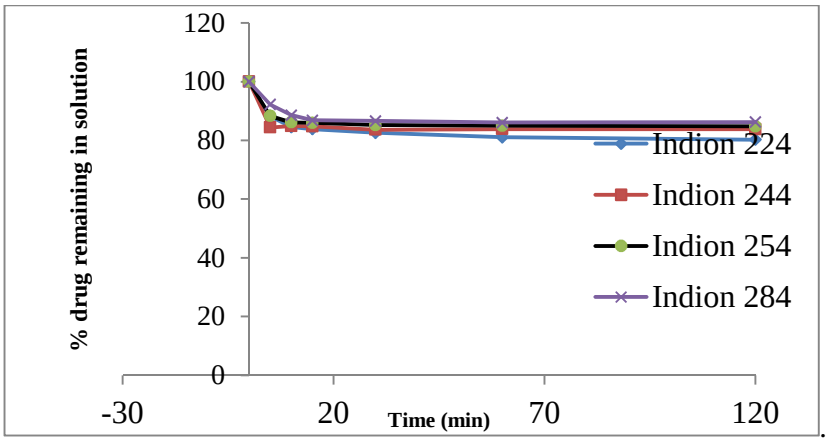


Figure 3. Equilibrium profiles for the drug loading onto ion exchange resins by double batch process

Effect of pH on drug loading

The loading of tramadol hydrochloride was studied at various pH medium to understand the effect of pH on drug loading onto the different resins and the results obtained are presented in table 3.

Table 3. Effect of pH on drug loading onto resins

pH	Indion 224	Indion 244	Indion 254	Indion 284
2	51.84±0.22	72.82±1.02	58.24±0.44	50.48±0.16
4	51.25±0.68	71.22±0.34	58.04±0.63	50.27±0.47
5	50.88±0.29	70.92±0.28	58.29±0.38	49.81±0.52
6	51.28±0.54	71.08±0.26	57.98±0.29	50.09±0.18
7	51.24±0.28	71.12±0.51	58.08±0.25	49.98±0.53
8	48.04±0.37	69.35±0.37	56.28±0.84	46.09±0.38
10	46.32±0.19	68.83±0.12	55.21±0.39	44.94±0.62

Mean ±S.D., n = 3

As per pH partition hypothesis since pKa of tramadol hydrochloride is 9.41, it is completely ionized at all pH values (1-8). All Indion the resins which possess sulphonic (strong acid) moiety cation exchangers will also be ionized irrespective of pH changes. From the figure- 4 negligible effect of pH was observed. It was thus concluded that pH has no effect on drug loading at the lower pH values but at the higher pH there was presence of less H^+ exchangeable ions in the loading media which resulted into increased complexation of the drug. From these studies it was concluded that pH of loading medium did not influenced the tramadol hydrochloride complexation with the

ion exchange resins. Moreover, when the complex formation approached completion the pH returned to the initial pH of the eluent due to the limited amount of H^+ ions available for the exchange.

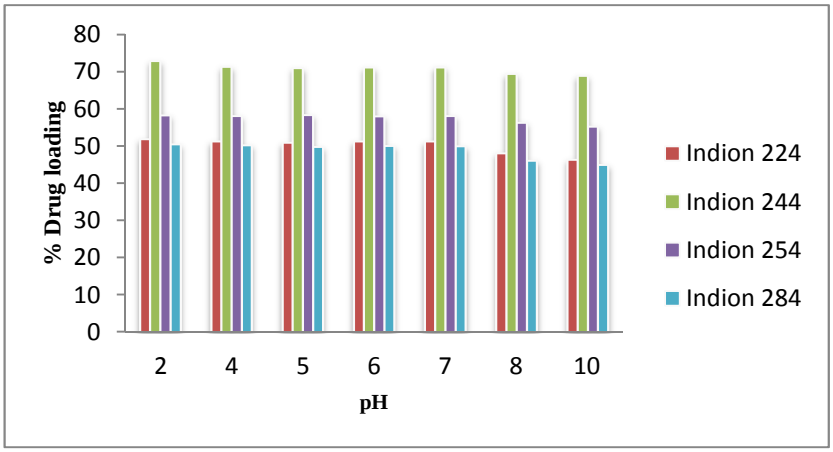


Figure 4. Effect of pH on drug loading onto reins

In vitro **drug release profiles of resinates**

Effect of pH media on drug release from the resinates

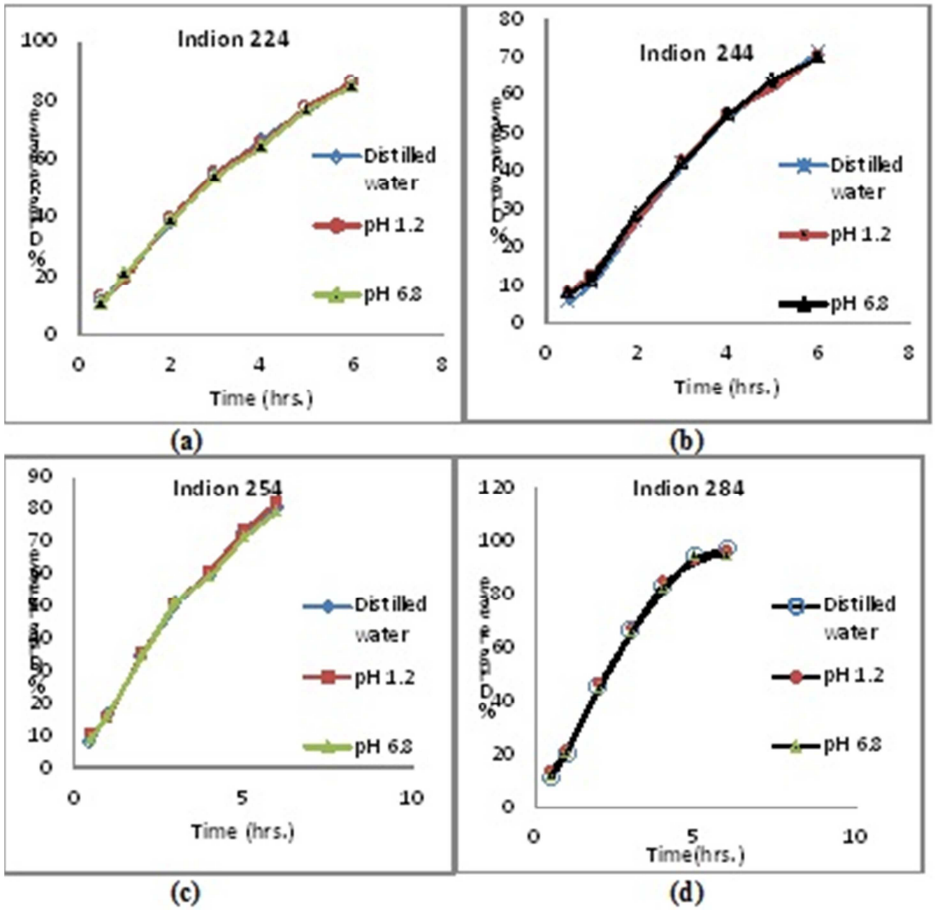


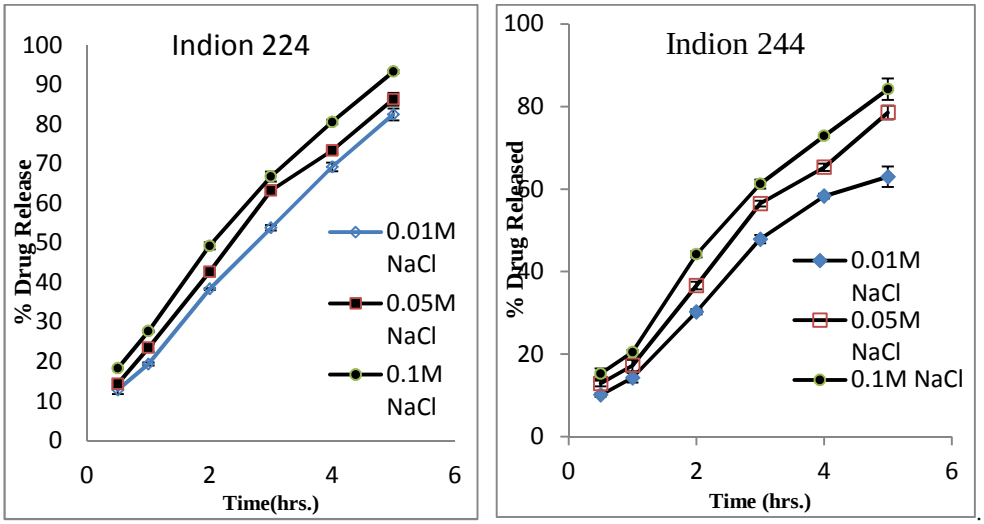
Figure 5. Effect of pH of dissolution media on the release of tramadol hydrochloride from the prepared resinates

To study the effect of pH media on the drug release from the resinates, the release studies were performed in the media of different pH, viz. distilled water, 0.1N HCl and pH 6.8 buffer. The release profiles Figure 5 shows that there was negligible effect of pH on the drug release. The drug release mechanism clearly depends on the degree of the ionization of the resin particles in the dissolution media. The results revealed that the drug release takes place principally due to replacement of drug ions by the H^+ ions in the dissolution medium. The release profiles in different dissolution medium clearly indicated that the amount of drug released was not influenced by the pH of the

medium. This may be due to the similar ionization of resin in the dissolution media selected in the study. Hence it was decided to carry out all the further dissolution study in distilled water.

Effect of ionic strength of dissolution medium on drug release

The effect of the ionic strength of the dissolution medium was studied by adjusting the ionic strength of the dissolution medium by 0.01 M, 0.05M and 0.1 M NaCl.



(a) (b)

Figure 6. Effect of ionic strength of dissolution medium on % drug release from the (a) drug-Indion224 resinate and (b) drug-Indion244 resinate

The amount of drug released from tramadol-resin complexes as a function of ionic strength of dissolution medium was investigated. To study the effect of the ionic strength of dissolution medium on % drug released. From figure 6.(a & b) it was clearly evident that the ionic strength of dissolution media has marked influence on the release of the drug from resinates particles. It may be due to the fact that as the electrolyte concentration increased in the medium it decreased Donnan potential and thereafter the decrease in the affinity of the drug with resin. Therefore the drug release mechanism was accelerated.

Effect of valency of ions in dissolution medium

To understand the influence of valency of ions in the dissolution medium 0.1 M NaCl (Na^+)and 0.1M $CaCl_2$(Ca^{2+}) were used to study the release mechanism of drug from two model resinate i.e. tramaodol hydrochloride - Indion 254 and Indion 284.

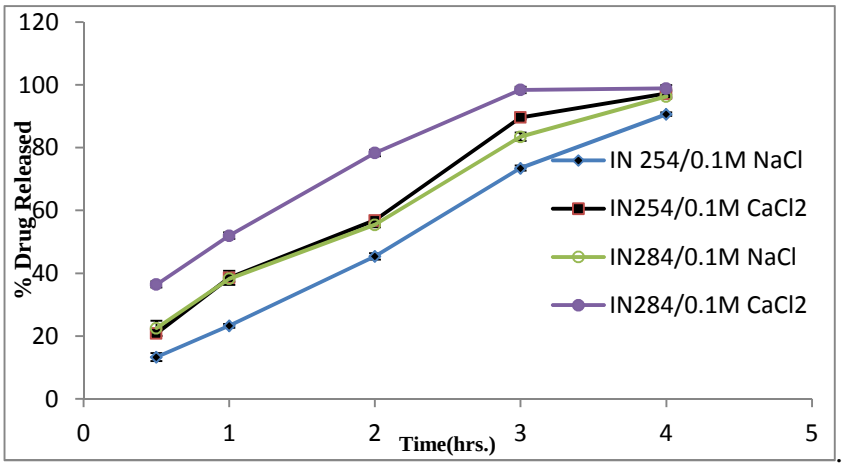


Figure 7. Effect of valency of ions in dissolution medium on %drug released from prepared resonates

Figure -7 shows that the % drug release profiles obtained for the study of influence of valency of ions in the release medium from prepared tramadol hydrochloride resinates. Rapid release of drug from resinate was observed in the dissolution medium containing divalent ion i.e. Ca^+ as compared to dissolution medium containing mono-valent ions

i.e. Na^+. The release data in these two different medium shows that there is a marked influence of valency of ions on the drug release from drug- resinate.

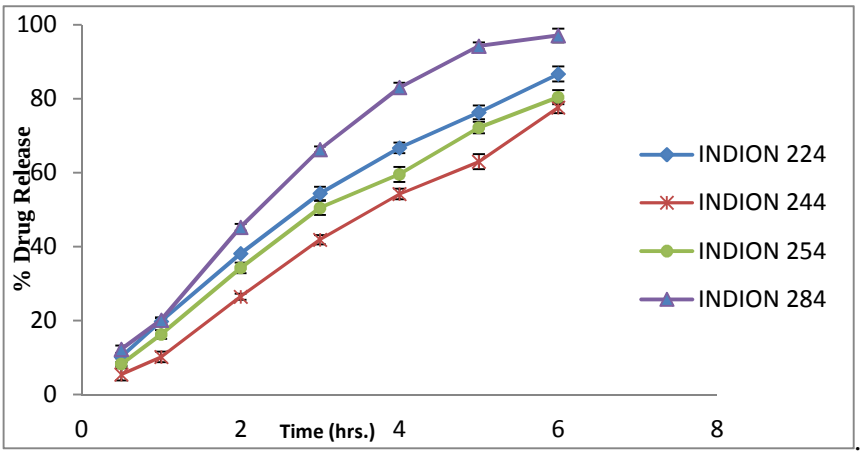


Figure 8. In-vitro drug release profiles of tramadol hydrochloride loaded resinates

The release profiles of different ion exchange resins used were studied and the release profiles were compared to see the effect of properties of different IER (ion exchange resin) material such as particle size, moisture content and degree of cross linking of IER. From the results of in vitro release profiles (and Figure 8) it was concluded that the particle size and degree of cross linking of the IER seem to have significant role on drug release.

Fine particles have more surface area then coarse particles as internal volume for ions to diffuse, so less time can be required to establish equilibrium. Similarly desorption of bound drug from the complex will be faster in fine particles moreover when an ion exchange resin is highly cross linked the diffusion of various ions can be impeded and this will increase the time required to reach equilibrium and reduce the amount of drug loaded. The particle size of the Indion 224 and Indion 284 which is within the range of 0.2- 1.2 mm is larger as compared to Indion 244 and 254 having particle size $\leq$ 150 µ. This may be the reason that higher drug release was obtained in the resinates of Indion 224 and Indion 284 as compared to resinate of Indion 244 and 254. This phenomenon may be further explained on the basis of surface area of the IER. Smaller particles bear the larger surface area and this may be reason that the release profiles of Indion 224 and 284 shows rapid release while others shows time dependent controlled release. However higher cross linked resins display the more sustained release effect then lower cross linked resins, as can be noticed from the release profile figures.

Modeling drug release kinetics through resinates

The resin particles are assumed to be uniform spheres of radius r, Boyed et al., showed that where the particle diffusion was only the rate controlling process, the following expression gives the fraction of drug released F.

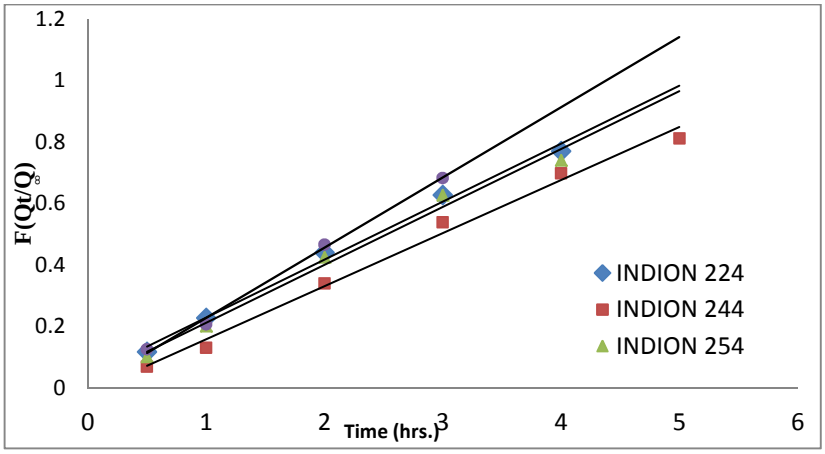


Figure 9. Kinetic drug release profiles for fraction of drug released F

All the F values below 8.5 are showing (Figure 9) the linearity so the drug release from drug- resinate assumed to be by diffusion as a rate limiting step. Further the F values more than 0.85 are reduced for the Bt estimates and the further studied for the release behavior of resinates [15-16].

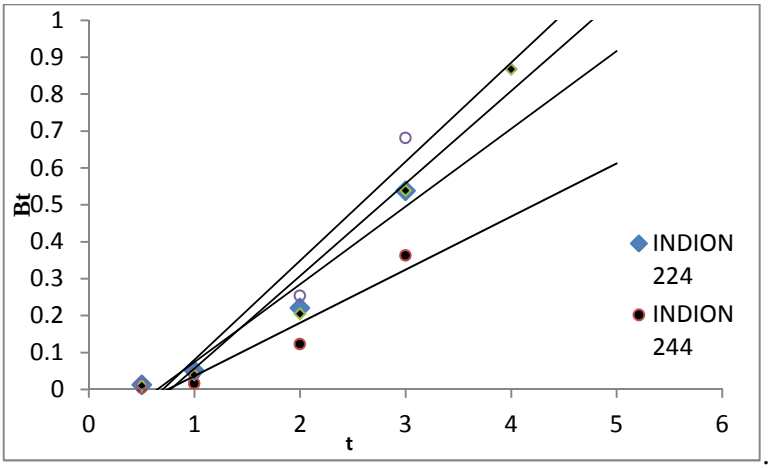


Figure 10. Bt – t plots particle diffusion from the prepared drug resinate

Table 4. Drug Release kinetics data for the Bt-t plots

Drug –resin complex	Equation of linearity	R^2
INDION 224	y = 0.2107x - 0.1366	0.9513
INDION 244	y = 0.1438x - 0.1072	0.9782
INDION 254	y = 0.2506x - 0.1941	0.9613
INDION 284	y = 0.2683x - 0.1881	0.9424

From the Figure-10 and table 4 the corresponding $R^{2;}$ the plot of Bt corresponding to F values versus time is straight line, it can be assumed that drug diffusion within the resin matrix is the rate limiting step for release of drug during the initial 3-5 hrs of release. The increasing concentration of drug in the release medium and formation of the stagnant boundary around the resin particle might lead to another kinetic-release behavior.

CONCLUSION

Tramadol hydrochloride resinates were prepared successfully using Indion 224, 244, 254 and 284 and evaluated. The physical properties of resinates were found to be optimal for manufacturing process. The release profiles of all formulations when applied to Boyed model kinetics shows the diffusion mechanism as a rate limiting step. *In vitro* drug release profiles of resinate shown the pH independent release. Also the ionic strength and valency of dissolution medium has influence on drug release. Resinates (complexes) retarded the release of tramadol and further sustain the release profiles can be obtained by incorporation of resinates in polymer matrices. The present investigation controlled release resinates, further to insure safety and improvement of efficacy of drug through maintenance of consistent drug level as well as patient compliance by reducing the frequency of administration.

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