



Formulation of Dry Powder Suspension for Controlled Release of Tramadol Hydrochloride resinate microcapsules

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Abstract The present research was aimed to design controlled release suspension formulation of BCS class I drug Tramadol hydrochloride a centrally acting synthetic analgesic. Complexes of indion 244 ion-exchange resin and tramadol hydrochloride, a model drug, were prepared using a batch method. The prepared resinate complexes were microencapsulated by o/o solvent evaporation technique. These microcapsules were then formulated into the suspension dosage form to get the controlled release of drug for extended period. The resinate microcapsule suspensions were evaluated for the flow properties, drug content and *in vitro* drug release. Dry powder suspensions shown excellent flow properties and the *in vitro* drug release showed a significant sustained drug release up to 12 hours. The stability studies were performed as per ICH guidelines for the dry and hydrated forms of suspensions. The results obtained clearly evident that the dry powder suspensions are best suitable for the storage conditions and gives better physical and chemical stability.

Keywords Tramadol hydrochloride, ion exchange resin, controlled release, suspension.

Introduction

Tramadol hydrochloride is a centrally acting synthetic analgesic BCS class-1 drug. It is well absorbed orally, and is only 20% bound to plasma proteins [1-3]. Emerging controlled drug delivery systems has been focused on oral controlled-release dosage. In the past few decades, multiple-unit dosage forms, such as micro particles, have gained importance for the reasons when compared to non-disintegrating single-unit dosage forms. They distribute more uniformly in the gastrointestinal tract, resulting in more uniform drug absorption and reduced local irritation, and also avoid the unwanted intestinal retention of the polymeric material. In addition, micro particles based dosage forms offer the possibility of being formulated as liquid suspensions, which constitute the ideal administration form for pediatric and geriatric patients, because of their ease of administration and dosing flexibility [4-6]. Liquid dosage forms such as suspensions are advantageous but due to the difficulties associated to their development, there are few suitable liquid oral controlled-release suspensions in the commercial market. These difficulties deal principally with the diffusion and drug release into the suspending media during storage, and the interactions between vehicle and the multiparticulates, which results in undesired changes. Therefore, multiparticulates containing water-insoluble drugs can be suspended into aqueous vehicles without significant drug leaching during storage. However, water-soluble drugs would diffuse rapidly into aqueous suspending vehicles through coatings. To overcome this problem,



water-soluble drugs can be bound to ion-exchange resins, offering one of very few usable systems for achieving ready made aqueous liquid products with prolonged release. The main advantage, which the ionic complexes offer, is their ability to prevent the diffusion of drug when suspended in a non-ionic medium, because drug release will be only promoted by the presence of competing ions, such as occurs in the gastrointestinal tract upon oral administration. The release rate from the drug– resin complex can be further controlled by coating the drug–resin beads using a variety of microencapsulation or coating processes [7-9].

Reconstitutable oral systems shows adequate chemical stability of the drug during shelf life, avoids the physical stability problems related to solubility, pH, and incompatibilities with other ingredients and also reduce the weight of the final product because the aqueous vehicle is absent and consequently the transportation expenses may be reduced. The present study was mainly aimed to develop dry suspensions for reconstitution of tramadol hydrochloride resinates microcapsules using simple techniques.

Methods and Materials

Materials

Tramadol HCl was a gift sample from Sun Pharma Pvt. Ltd. India, Indion 244 procured from Ion Exchange (India) Ltd., Eudragit® RS 100; Rohm Pharma, Weiterstadt, Germany, all the other chemicals used in the present investigations were of AR grade.

Purification of ion-exchange resins

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 60 ml of 1M NaOH and 60 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.

Preparation of drug resin complexes

The tramadol hydrochloride-resin complexes were prepared by a batch processes. For the batch method, the previously purified indion 244 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). 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 hand then stored in tightly closed desiccators [10-11]. 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 10ml of a 20% (w/v) solution of the Eudragit®RS 100 in acetone with coat to core ratio(2:1) and emulsification was followed of this phase in 100 ml light liquid paraffin containing 1% Span 85(w/v). The stirrer element was set at 500 rpm till complete evaporation of acetone. Magnesium stearate (0.1% w/v) was added to overcome the problem of coalescence during solvent evaporation as droplet stabilizer. The microcapsules were separated by vacuum filtration, washed with n-hexane and air-dried for 24 h at room temperature and stored in desiccators [12].



Formulation of dry powder suspension of resinate microcapsules

The microcapsule formulation was further formulated as dry powder suspension, for the effective delivery of microcapsule in compromised, pediatric or geriatric patients. The prepared microcapsules of drug resinate were blended together with ingredients as shown in Table 1.

Table 1: Formulation of dry powder suspension of microcapsules

Ingredients	Quantity
Microcapsules	100 mg
Spray dried lactose	5%
Xanthan gum	0.4%
Sodium benzoate	0.45 %
Orange flavor	q.s.

Characterization of dry powder suspensions

Density

Bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk density was calculated using the equation;

$$\rho_b = M / V_b$$

Where, V_b is bulk volume, M is the weight of the powder

Tapped Density was determined by pouring blend and tapped into a graduated measuring cylinder for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured using the equation;

$$\rho_t = M / V_t$$

Compressibility Index

Compressibility index (I) which is calculated as follows

$$I = (\rho_t - \rho_b) / \rho_t \times 100$$

Where ρ_t = Tapped density, ρ_b = bulk density, the value below 15% indicates a powder which usually gives good flow characteristics; where above 25% indicates poor flow ability.

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. It is given by the following equation.

$$\text{Hausner ratio} = \rho_t / \rho_b$$

Where ρ_t is tapped density and ρ_b is bulk density. Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25).

Angle of repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using following formula:

$$\tan \theta = (h/r), \text{ OR}$$

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

Where, θ is Angle of repose; h = height of cone and r = radius of cone.



Evaluation of reconstituted suspensions

Dispersibility

It was measured by using a test tube method. The dry powder for reconstitution was transferred to the test tube. The test tube was filled with 20 ml distilled water; rotated at approximately 20 rpm and time required for dispersibility was recorded.

pH

The dry powder suspension was dispersed in distilled water and shaken to get consistency for a predetermined interval and pH of the resulting solution was recorded by using a digital pH meter.

Sedimentation volume

Sedimentation volume of the formulations was determined using following formula

$$V_s = H_u / H_o$$

V_s = Sedimentation volume, H_u = Ultimate settled height of suspension, H_o =Original height of the suspension before settling.

Viscosity

The viscosities of the reconstituted suspensions were determined by using Brookfield viscometer and the results were recorded.

In vitro release of microcapsule suspension

In vitro dissolution study was carried out in triplicate for microcapsule suspension 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.

In vitro drug release kinetic models

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. 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 can not be increased further by increasing the concentration of reactants. It is a constant rate processes. For zero-order process the equation becomes:

$$dC/dt = - K_0 C_0$$

Rearranging the above equation

$$dC = - K_0 dt$$

Integration of this equation

$$C - C_0 = - K_0 \cdot t$$

$$C = C_0 - K_0 \cdot t$$

Where - C_0 = 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 $-K_0$ and y-intercept C_0 .

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 proportionality 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

$$dC/dt = -K \cdot dt$$

By the integration the eq. becomes

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303 \quad \text{or} \quad \text{Log } C = \text{Log } C_0 - 0.434 Kt$$

A semi-logarithmic plot of the above equation yields a straight line with slope $= -Kt / 2.303$ and y-intercept $= \text{Log } C_0$

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.

$$\text{So } Q_t = K_H \cdot t^{1/2}$$

K_H is the Higuchi 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)

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

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 M_t / M_∞ .

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

Stability study dry powder suspensions

To understand the physical as well as chemical stability of the prepared formulation accelerated stability studies were performed for 1, 2, and 3 month duration. The formulations were subjected to accelerated temp and humidity (40°C and 75%RH) in HDPE bottles. After each month physical changes, drug assay, dissolution profile were recorded (ICH guidelines).

Organoleptic properties of the formulation

The physical properties of the samples were recorded by visual observations like colour, odour and appearance [13].

Drug assay

An accurately weighed 100 mg of a suspension were washed thrice with portions of 10 ml acetone then resinsates, separated by vacuum filtration and dried at 50 °C. The separated resinsates were transferred in a 500 ml flask containing distilled water on magnetic stirrer stirring briskly, elutes sampled and replaced with same amount of fresh solution. The elutes were quantified by UV spectrophotometer at 271 nm. The elution was repeated until the concentration of elute obtained an absorbance lower than 0.01. The assays were carried out to determine the stability of reconstituted suspensions after day 1, 7 and 15 days.



Thin layer chromatography method

The method for the determination of tramadol hydrochloride by thin-layer chromatography in the pharmaceutical formulations was found to be specific. The stationary phase employed was a glass plates coated with silica gel G the mobile phase containing a mixture toluene, isopropyl alcohol, and 25% ammonia water (80:19:1). Concentrated spots of the samples were applied on the coated plates. Then plates were developed in the saturated TLC chamber for NLT 20 minutes. The plates were developed until it reaches solvent front of NLT 10 cm. These plates were observed under the UV Cabinet and the Rf values were recorded (USP24).

Dissolution profiles of the suspensions were carried out to understand the drug release behavior of the prepared suspensions after the storage conditions similarly as described in the above section for the *in vitro* drug release study [11].

Results and Discussion**Preparation of drug resin complexes**

The resins 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 72.82 ± 0.24 . 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.

Preparation of coated tramadol HCl–resinate beads by microencapsulation techniques

The tramadol HCl–resinate, showing the sustained release of the drug, was selected here was Indion 244 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 two techniques - o/w method and o/o method. But the microcapsules prepared with the o/w technique were found to be sticky aggregate and non uniform on physical observations while that prepared by o/o method were uniform discrete particles with good flow properties, hence this method i.e. o/o method was adopted for further studies.

Dry powder suspension formulation of resinate microcapsules

The optimized resinate microcapsules were formulated in the suspension dosage form for ease of administration. The dry powder for reconstitution was characterized for the flow properties and results were recorded as shown in table 2.

Bulk density and tapped were determined and the compressibility index and Hausner's ratio were calculated the value of compressibility index was found to be 2.17 and Hausner's ratio 0.01 which shown the excellent flow. The angle of repose was found to be less than 25° which showed excellent flow. From the results obtained it was evident that flow properties of the dry powder suspension shown excellent flow properties. From the results obtained it was evident that flow properties of the dry powder suspension shown excellent flow properties.

Table 2: Flow properties of dry powder suspension

Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Compressibility index	Hausner's Ratio	Angle of repose($^\circ$)
0.45 ± 0.01	0.46 ± 0.01	2.17 ± 0.01	0.01 ± 0.01	12.6 ± 0.01

Mean \pm SD, n=3

Characterization of reconstituted suspensions

The dry powder for reconstitution was transferred in 50 ml distilled water and the results were recorded for the parameters of suspension as represented in table 3.



Table 3: Characterization of reconstituted suspension

pH	Dispersibility (min)	Sedimentation volume	% drug content	Viscosity (cps)
6.5 ± 0.4	8 ± 1.5	0.45 ± 0.12	97.82 ± 1.08	553 ± 2

Mean ± SD, n=3

The reconstituted suspension was characterized for the rheological behavior which showed 553 cps viscosity which is viscous flow. The pH was observed near 6.5. Dispersibility of the dry powder was also recorded and found to be about 8 minutes. The sedimentation volume was 0.45. The assay of the tramadol hydrochloride was 97.82. From these results recorded it was concluded that the reconstituted suspension had characteristic properties.

In vitro drug release through the microcapsule suspension

The dry powder suspension and reconstituted suspensions were studied for the drug release profile and the results were recorded as depicted figure 1.

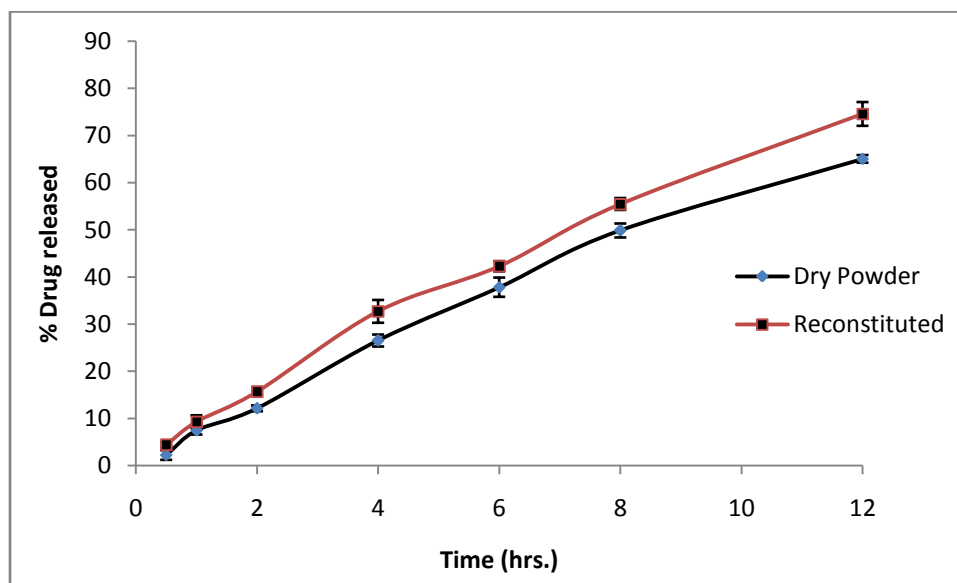


Figure 1: *In vitro drug releases through the dry powder and reconstituted microcapsulesuspension*

The drug release profile from the reconstituted suspension shown increase in drug release as compared to the dry powder suspension this might be due to the hydration of the microcapsular suspensions. The hydration of microcapsules lead to the leaching of the plasticizer and then the diffusion flux of the drug is observed.

Drug Release kinetic models

Table 4: Release Kinetic models

Model	Dry suspension		Reconstituted suspension	
	Slope	R ²	Slope	R ²
Zero order	5.554	0.9867	6.138	0.9894
First order	-0.038	0.9975	-0.048	0.9889
Higuchi	23.159	0.988	25.564	0.9885
Korsmeyer-Peppas	1.027	0.9829	0.886	0.9966

The release profiles were fitted to the mathematical model and the table shows the kinetic behavior of drug release. The large value of the coefficient of determination (R²) indicated a superiority of the dissolution profile fitting to



mathematical equations (as shown in Table 5.). The results obtained for the release kinetic studies it was clear that the formulations The dry powder suspensions shows the first order release kinetics ($R^2=0.990$). While the hydrated suspension showed fickian diffusion as its $R^2=0.99$. The release of the drug is expected to be with the diffusion from the microcapsules. The observed results are complying with the expected release profile of the drug from the microcapsular suspensions in the hydrated form.

Stability study dry powder suspensions

To understand the physical as well as chemical stability of the prepared formulation accelerated stability studies were performed for 1, 2, and 3 month duration. The results obtained for the stability studies as presented in table 5 shows that dry powder suspensions remain unchanged for the period of 3 months. Further the chemical stability of the table suspension formulation was determined by the % drug content and the R_f values indicates that there was 2-3% change when compared with the initial state. The stability study for the dry powder suspensions better stability over a prolonged period of 90 days and the results are in the acceptable limit.

Table 5: Stability study data of dry powder suspensions formulation

Stability parameter	Initial	After1 Month	After2 Month	After 3 Month
Colour	Light cream colored powder	No change	No change	No change
Nature	Free flowing powder	No change	No change	No change
Odour	Orange flavor	No change	No change	No change
% Drug content	97.82 ± 0.28	96.34 ± 0.46	95.89 ± 0.72	95.77 ± 0.35
R_f	0.62 ± 0.12	0.61 ± 0.18	0.62 ± 0.25	0.60 ± 0.05

Mean ±SD, n=3

In vitro drug release studies dry powder suspensions the results obtained for the *in vitro* drug release study data presented in table 5. Shows that there were similar profiles were obtained for all the storage conditions i.e. after 1, 2 and 3 months duration. The drug release after 12 hrs was found to be 65± 3% which is in the acceptable limits. Figure 2 shows that very negligible change in the release profiles of the drug. From the stability data obtained after 1, 2 and 3 months concluded that all the dry powder suspensions remained stable.

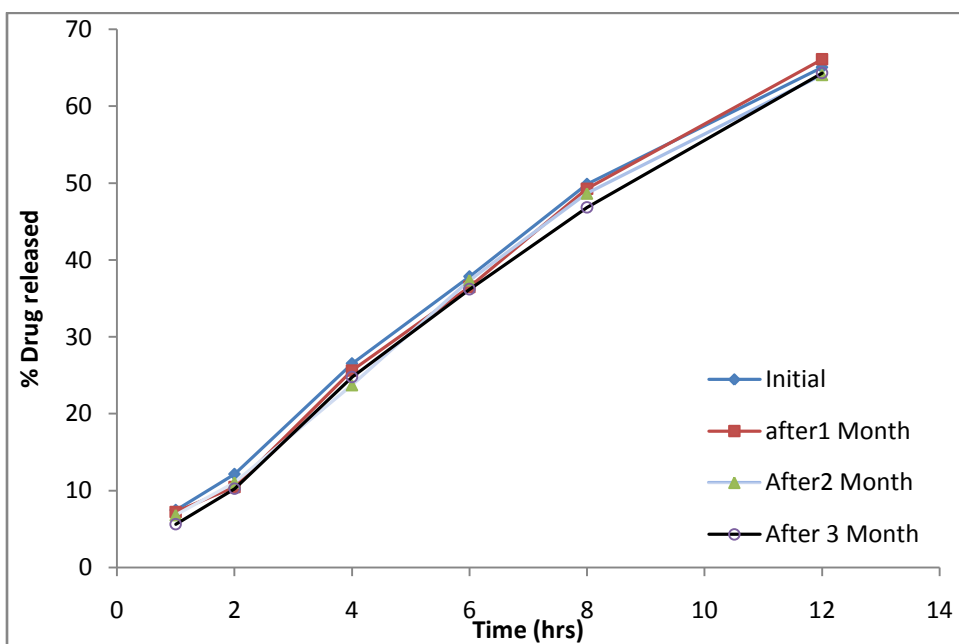


Figure 2: Drug release profiles of dry powder suspensions for stability studies



Therefore, the release profiles of microcapsule suspensions shows at storage temperatures and times were equivalent to that of the dried microcapsules, leading to the conclusion that there was no influence of the storage time and temperature over the release profile of the tramadol hydrochloride–resin microcapsule suspensions.

The dry powder suspensions were reconstituted in distilled water and the stability studies were conducted for 15 day as presented in table 6. The reconstituted suspensions were characterized for the change in pH, re-dispersibility and % drug content. The estimates of this study in table 5. Shows that pH of the suspensions was changed to about 1-2%. All the formulations for the period of 15 days were re-dispersible with the 6-10 strokes. But the % drug content was reduced to about 5% which indicated degradation of the drug up to some extent. This may be due to the leaching of the drug from the microcapsules by replacement of trace cationic ion in the suspending medium

Table 6: Stability of dry powder suspensions after reconstitution

Stability parameter	1 st day	7 th day	15 th day
pH	6.5±0.4	6.6±0.5	6.7±0.2
Re-dispersibility No. of strokes	8 ± 2	6 ± 2	10 ± 5
% Drug content	97.82 ±0.57	96.05 ± 0.71	94.27 ±0.12

Mean ±SD, n=3

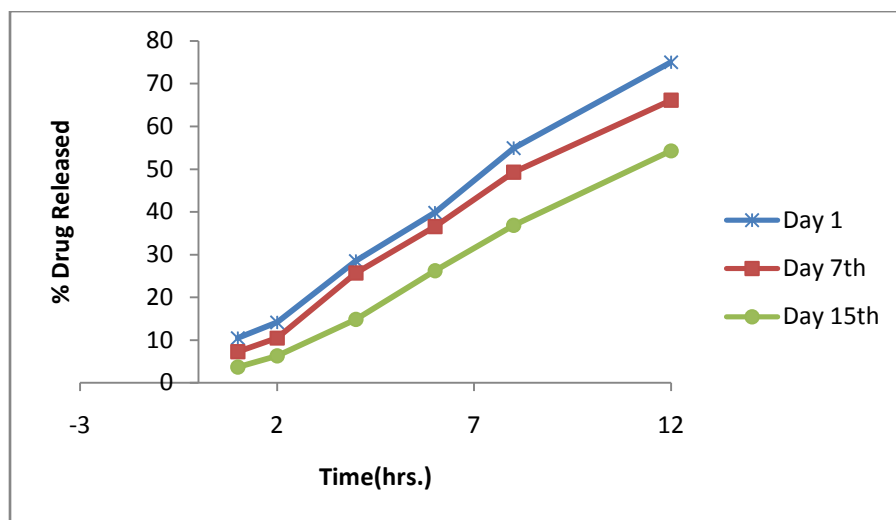


Figure 3: Drug release profiles of dry powder suspensions for stability studies

The figure 3 shows that the release of the drug at the day first showed the release of the drug from the microcapsules was decreased with the time of storage of the reconstituted suspensions as there may be the degradation of the drug in the solution i.e. reconstitution medium. The decrease in release might be due to the fact that the hydration of coating leads to the more stagnant boundary formation and increased thickness of the coating layer due to hydration. The results obtained for the stability studies of the suspensions in hydrated suspension forms clearly indicates that the drug release profiles and the content of the drug is influenced in the liquid state. Due to this reason the suspension to be prepared in the dry powder for reconstitution forms.

Conclusion

The present investigation concludes that tramadol hydrochloride can be suitably loaded on to the ion exchange resins by simple batch process. Further the drug loaded resinates can be encapsulated into the polymeric coatings for the sustained release of the drug from the microcapsules. The ease of the drug delivery can be modified by formulating the microcapsules in the suspension dosage forms. The dry powder suspensions give better stability as



compared to the liquid reconstituted suspensions. The future prospective a commercialization of this work should be augmented with the clinical investigations.

References

1. Gibson TP. Pharmacokinetics, efficacy, and safety of analgesia with a focus on tramadol HCl. *The American journal of medicine*, 1996, 101: S47-S53.
2. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clinical pharmacokinetics*, 2004, 43(13): 879-923.
3. Bodalia B, McDonald, CJ, Smith KJ, O'Brien C, Cousens L. A comparison of the pharmacokinetics, clinical efficacy, and tolerability of once-daily tramadol tablets with normal release tramadol capsules. *Journal of pain and symptom management*, 2003, 25(2): 142-149.
4. Lee VHL Lee. Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design. 2nd ed. Marcel Dekker, Inc. New York: 1987, pp 16-25.
5. Ho WH, Lee VHL. Sustained Drug Delivery Fundamentals and Applications: Design and fabrication of oral controlled release drug delivery system. 2nd ed. Marcel Dekker Inc, New York, 1987, pp 373-420.
6. Sagraves R. Pediatric dosing and dosage forms. In: Encyclopedia of Pharmaceutical Technology, vol. 11. Marcel Dekker, New York, 1994, pp. 329-367.
7. Cuna M, Jato JV, Torres D. Controlled-release liquid suspensions based on ion-exchange particles entrapped within acrylic microcapsules. *International Journal of Pharmaceutics*, 2000, 199(2), 151-158.
8. Raghunathan, Y. U.S. Patent No. 4,221,778. Washington, DC: U.S. Patent and Trademark Office, 1980.
9. Sprockel OL, Price JC. Evaluation of sustained release aqueous suspensions containing microencapsulated drug-resin complexes. *Drug Development and Industrial Pharmacy*, 1989, 15(8): 1275-1287.
10. Jeong SH, Park K. Drug loading and release properties of ion-exchange resin complexes as a drug delivery matrix. *International Journal of Pharmaceutics*, 2008, 361: 26-32.
11. Junyaprasert VB, Manwiwattanakul G. Release profile comparison and stability of diltiazem-resin microcapsules in sustained release suspensions. *Int J Pharm*, 2008, 352(1-2): 81-91.
12. Haznedar S, Dortunc B. Preparation and *in vitro* evaluation of Eudragit microspheres containing acetazolamide. *International journal of pharmaceutics*, 2004, 269(1): 131-140.
13. Guideline, I. H. T. Stability testing of new drug substances and products. Recommended for Adoption at Step, 2003, 4.

