

## Microencapsulation of Tramadol Hydrochloride and Physicochemical Evaluation of Formulations

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**Summary:** The present project involves the microencapsulation of tramadol hydrochloride with ethocel using a non-solvent addition coacervation technique. The concentration of ethocel was varied to get a prolonged release profile. Then microparticles were compressed into tablets to study the variation of drug release between the microparticles and tablets. The microparticles were off white, aggregated and irregular in morphology having good percentage entrapment efficiency and percentage production yield. Dissolution study was made using USP XXIV apparatus I and II respectively, in 900 mL double distilled water at 50 rpm maintained at 37 °C. An Initial burst effect was noted in the drug release behavior. Polyisobutylene concentration affected inversely the rate of drug release from microparticles. Dissolution media and stirring speed affected insignificantly ( $p > .05$ ) the release pattern. Tramadol hydrochloride tablets showed good stability and reproducibility. UV and FTIR spectroscopy and X-Ray diffractometry proved that tramadol hydrochloride was completely and uniformly distributed in ethocel with out any strong interaction. The mechanism of drug release was anomalous diffusion that was best fit to Higuchi's equation. It can be concluded that multi-unit, slow-release tramadol hydrochloride microparticles can be formulated efficiently with non-solvent addition coacervation technique using ethocel.

### Introduction

Tramadol hydrochloride (TH, Fig. 1A) is a centrally acting analgesic having both opioid and non-opioid effects [1]. It is administered when non steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or COX-2 inhibitors alone fail to relieve pain [2]. It is readily absorbed after oral administration. Its half life is about 6 hours [3].

Ethocel (Fig. 1B) with complete ethoxyl substitution (DS = 3) is  $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_n C_{12}H_{23}O_6$  where "n" is responsible for its wide variety of molecular weights. Ethocel, an ethyl ether of cellulose, is a long chain polymer of  $\beta$ -anhydroglucose units joined together by acetal linkages. It is used extensively as shell/coat forming polymer due to its non-toxic, biocompatible and non-biodegradable nature for the development of oral multi-unit sustained release formulation. Ethocel coated microparticles can be tabletted due to their capability to absorb pressure [4].

Patients with chronic diseases are increasing day by day who have to take many medicines simultaneously causing non-compliance to them. Drugs with short biological half lives are seriously problematic which necessitates the development of a

dosage form capable of releasing the drug gradually. Microencapsulation therefore, has been used as one of the methods to construct a formulation for delivering the drug in a controlled mode [5].

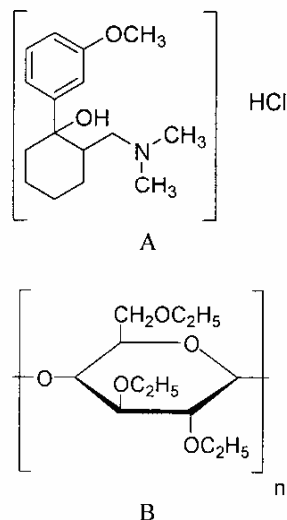


Fig. 1: Chemical structures of Tramadol hydrochloride (A) and ethocel (B).

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Microencapsulation is a process that involves the formation of the thin shell around individual drug particles with a size range between 5-5000  $\mu\text{m}$  [6].

In early projects, tramadol hydrochloride has been microencapsulated into ethyl cellulose by spray drying and into polyhydroxybutyrate by solvent evaporation [7, 8]. The objective of the present work is to encapsulate TH into ethocel by non-solvent addition-coacervation varying ethocel ratios as 1:1, 1:2 and 1:3 and other parameters. The reproducibility and stability of tableted microparticles were tested at different conditions.

## Results and Discussion

### Physicochemical Evaluation of Microparticles

SEM results showed that microparticles were off white, aggregated and irregular in shape (Fig. 2). It was found that size [9, 10], encapsulation efficiency [11, 12] and production yield of microparticles increased insignificantly ( $p > 0.5$ ) with an increase in ethocel concentration as increase in ethocel concentration produced thick coating around higher number of TH microparticles. It certifies previous results (Table-1) [13, 14]. A little increase in encapsulation efficiency and production yield and slight decrease in particle size is observed by increase in PIB contents from 6 %-12 % during microencapsulation process ( $p > .05$ ) as mentioned previously [13, 15].

Table-1: Physicochemical characteristics of tramadol hydrochloride microparticles.

Formulations	TH: Ethocel ratio	PIB Conc. (%)	Entrapment (%)	Production yield (M $\pm$ S.D) %	$t_{60\%}$ (M $\pm$ S.D) (hrs)	Size (Mean Diameter) (M $\pm$ S.D) $\mu\text{m}$	Solvation rate (%)
M <sub>1</sub>	1:1	6	95.43	96.23 $\pm$ 1.56	0.86	592.55 $\pm$ 19.31	154.75
M <sub>2</sub>	1:2	6	96.25	97.20 $\pm$ 1.86	1.13	673.95 $\pm$ 27.15	164.74
M <sub>3</sub>	1:3	6	98.76	97.99 $\pm$ 1.24	1.52	722.74 $\pm$ 19.71	175.23
M <sub>4</sub>	1:2	9	97.21	97.01 $\pm$ 1.76	1.42	662.46 $\pm$ 22.64	167.64
M <sub>5</sub>	1:2	12	96.89	97.64 $\pm$ 1.21	1.69	639.56 $\pm$ 29.16	159.52

Degree of microparticle solvation is affected by solubility properties of solvent (petroleum benzin and *n*-hexane) and polymer in toluene. During microencapsulation, *n*-hexane penetrates into matrix due to its solubility in toluene and petroleum benzin. Therefore resultant microparticles are solvated at the end of process and are less prone to aggregation on drying. Moreover, residual *n*-hexane should be removed as it can affect adversely the rheological properties.

Rheological properties of all formulations are expressed in terms of bulk density, taped density,

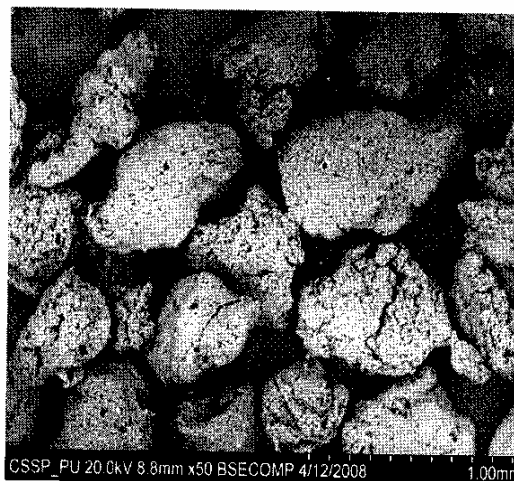


Fig. 2: Scanning electron micrographs of tramadol hydrochloride microparticles M<sub>2</sub>.

compressibility index, Hausner's ratio and angle of repose (Table-2). It was observed that bulk density decreased with the increase in drug polymer ratio. Present results are in agreement with previous observation who also reported that bulk density increased when the polymer concentration was decreased [16]. Compressibility index of all six formulations is below 15 % indicating excellent flow properties. Hausner's ratio and angle of repose were below 1.29° and 30°; respectively, for all formulated microparticles again indicating their free flow nature [17].

Table-2: Rheological properties of tramadol hydrochloride microparticles.

Formulations	Bulk density (g/ml)	Taped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose ( $\theta^\circ$ )
M <sub>1</sub>	0.21	0.23	11.0	1.16	21.87
M <sub>2</sub>	0.26	0.31	12.87	1.09	23.94
M <sub>3</sub>	0.30	0.33	10.39	1.29	27.45
M <sub>4</sub>	0.29	0.29	13.15	1.03	28.68
M <sub>5</sub>	0.24	0.26	13.62	1.17	25.13

### Physical Evaluation of Tablets

Physical parameters of the tablets *i.e.* physical appearance, tablet hardness, weight

Table-3: Physicochemical characteristics of tramadol hydrochloride tablets.

Formulations	Drug Contents (mg)	Weight Variation* (%) ( $\pm$ S.D) (n = 20)	Thickness(mm) (M $\pm$ S.D)(n = 10)	Hardness (Kg/cm <sup>2</sup> ) (M $\pm$ S.D) (n = 10)	Friability (%) (n = 10)	t <sub>60%</sub> (h)
T <sub>1</sub>	100	$\pm$ 2.1	5.46 $\pm$ 0.04	9.4 $\pm$ 0.8	0.42 $\pm$ 0.4	3.47
T <sub>2</sub>	100	$\pm$ 2.4	5.44 $\pm$ 0.05	8.9 $\pm$ 1.1	0.39 $\pm$ 0.7	6.26
T <sub>3</sub>	100	$\pm$ 2.0	5.47 $\pm$ 0.07	9.3 $\pm$ 1.4	0.28 $\pm$ 0.3	8.90
Reference	100	$\pm$ 1.9	5.40 $\pm$ 0.03	8.3 $\pm$ 0.8	0.27 $\pm$ 0.2	6.87

\*Maximum % variation from the arithmetic mean

variation, tablet thickness, friability and drug content uniformity of the tableted microcapsules were found to be satisfactory as shown in Table-3. Tablet hardness varied between  $8.8 \pm 1.2$  to  $9.4 \pm 0.8$  kg/cm<sup>2</sup> and friability was less than 0.5 % (w/w). The tablets showed low weight variation ( $< \pm 3.0$  %). The average thickness was 5.45 mm. The results fulfilled the requirements of B.P. [18].

#### In Vitro Dissolution Studies

##### Model Independent Approaches

The microparticles and tablets were also evaluated for their release profile in double distilled water and were evaluated by different mathematical kinetic models, the difference & similarity factors and one way ANOVA plus Post-Hoc Tests.

Table-1 shows that time for 60 % release of TH from M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub> was achieved in 0.86, 1.13 and 1.52 hours respectively. According to Duncan test, the t<sub>60%</sub> of all batches of TH microparticles lied in the same homogenous group (M<sub>1</sub> = M<sub>2</sub> = M<sub>3</sub>) while Tukey H.S.D. test similarized the t<sub>60%</sub> of M<sub>1</sub> and M<sub>2</sub> and differentiated them from that of M<sub>3</sub> but not significantly ( $p > .05$ ). According to difference factor ( $f_1$ ) and similarity factor ( $f_2$ ), the release profiles of following pairs of microparticle formulations are different from each other: M<sub>1</sub> VS M<sub>3</sub> and M<sub>2</sub> vs M<sub>3</sub> as their  $f_1 > 15.00$  and  $f_2 < 50.00$ . While M<sub>1</sub> VS M<sub>2</sub> has  $f_1 < 15.00$  and  $f_2 > 50.00$  that indicates the mutual similarity of the compared release profiles but to a very less extent. The results indicated that rate of drug release was slower from microparticles with low polymer amount *i.e.* microparticles having low core to wall ratio. It can, therefore, be assumed that decrease in core to wall ratio increased the wall thickness of microparticles and/or decreased the number of surface pores as evident from Fig. 3. Moreover, it is reported previously that the release of hydrophilic drugs is mainly controlled by permeation through the water filled channels within the hydrophobic polymer (Ethocel) membrane. Both of

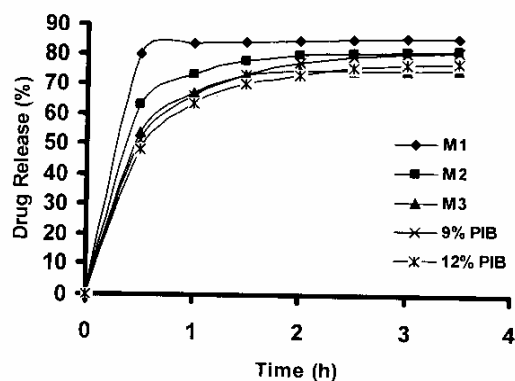


Fig. 3: The dissolution profiles of tramadol hydrochloride microparticles in distilled water showing the effect of drug polymer ratio and the concentration of PIB used in microencapsulation, on dissolution fashion. Each data point is a mean of three values.

these reasons retard the diffusion of dissolution medium through these channels that ultimately decrease the rate of drug release [13, 10, 12].

A biphasic pattern of drug release from TH formulations was observed involving an initial rapid drug release phase (burst) was followed by the slow and prolonged phase. Thus a subsequent prolonged and continuous release of drug can be maintained after an initial high release. Diffusion of the drug bound in the surface region of microparticles was thought to be responsible for burst effect during dissolution, while slow and continuous release was due to the diffusion of drug from core region through a network of channels. Formulation with lowest ethocel concentration showed highest burst effect as evident from Figs. 3 and 4. When polymer concentration is low, the hydrated polymeric matrix would be highly porous leading to rapid diffusion of the drug from the polymeric matrix. It has also been reported previously that highly soluble drugs exhibit burst phenomenon more frequently [14, 19].

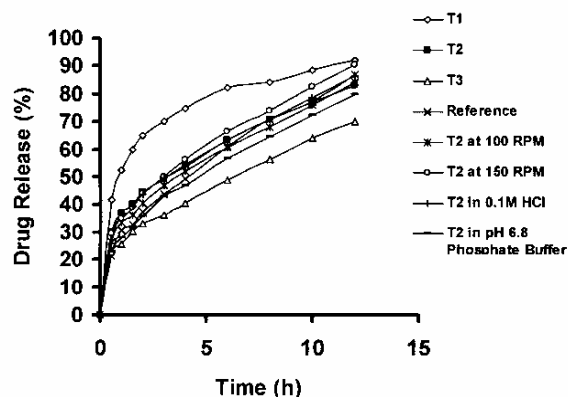


Fig. 4: The dissolution profiles of tramadol hydrochloride formulated and reference tablets showing the effect stirring speed and type of dissolution media on dissolution fashion. Each data point is a mean of three values.

#### Process Variables

PIB concentration affected microparticle dissolution profiles insignificantly ( $p > 0.05$ ,  $f_1 < 15.00$ ,  $f_2 > 50.00$ , Fig. 3) *i.e.* a slightly slow release profile was observed when PIB concentration was increased. It can be attributed to the increased formation of numerous tiny discrete coated particles [8, 15]. TH tablet release profiles did not vary when dissolution medium was changed with 0.1M HCl solution. Whereas a slight decrease in the rate of the dissolution is observed when pH 6.8 phosphate buffer was used as dissolution medium ( $p > .05$ ,  $f_1 < 15.00$  and  $f_2 > 50.00$ ). The stirring speed also affected *in vitro* dissolution rate insignificantly ( $p > .05$ ,  $f_1 < 15.00$  and  $f_2 > 50.00$ ).

#### Model Dependent Approaches

In order to find best fit kinetic model to the release profiles, dissolution data was characterized kinetically. On the basis of determination co-efficient ( $R^2$ ), all release profiles found to be best fit to Higuchi model due to the highest linearity, followed by zero order and first order, respectively. It suggests that the drug release is controlled by the diffusion of drug through the pores and not through the swollen ethocel. The value of "n" calculated by Korsmeyer-Peppas equation, attested that mechanism of TH release from all formulations was anomalous diffusion *i.e.* diffusion along with erosion. Hixson-Crowell model showed a change in surface area and diameter of the formulation with the progressive dissolution of the matrix as a function of time (Tables-4 and 5).

#### Estimation of Swelling and Erosion of Tablets

The optimum formulation undergoes swelling and erosion continuously with time (h) in dissolution apparatus as clear from Fig. 5. This phenomenon is responsible for the gradual release of drug from tablet matrix. It also confirms anomalous diffusion of TH from tableted microparticles.

#### Batch Reproducibility and Stability on Storage

No significant ( $p > .05$ ,  $f_1 = 0.29$ ,  $f_2 = 99.71$ ) difference was observed in the release pattern of different batches of TH tablets, indicating that the manufacturing process used was reliable and reproducible. Also, the release kinetics remained unaltered for up to three months of storage, and there were no changes in the tablet properties indicating that TH is stable in the tableted microparticles for the above mentioned period.

Table-4: Release rate parameters [Y-equation ( $Y = aX + b$ ), determination co-efficient ( $R^2$ ) and release exponent (n)] for release data after fitting of the whole release profiles of tramadol hydrochloride microparticles into different mathematical models.

Models	Formulations	M <sub>1</sub>	M <sub>2</sub>	M <sub>3</sub>	M <sub>4</sub>	M <sub>5</sub>
Zero Order	Y-equation	15.03x + 47.07	16.241x + 38.564	15.65x + 34.185	17.98x + 32.107	17.278x + 30.322
	R <sup>2</sup>	.384	.513	.546	.639	.645
First Order	Y-equation	0.7509x + 2.5612	0.7702x + 2.4447	0.768x + 2.3725	0.7999x + 2.3407	0.7945x + 2.3069
	R <sup>2</sup>	.345	.378	.390	.416	.420
Higuchi	Y-equation	5.0925x + 26.382	5.1808x + 19.18	4.9241x + 16.135	42.146x + 13.366	40.395x + 12.438
	R <sup>2</sup>	.666	.790	.818	.885	.889
Hixson-Crowell	Y-equation	-0.4061x + 3.4993	-0.4322x + 3.8242	-0.3873x + 3.95	0.8121x + 2.2215	0.8025x + 2.1792
	R <sup>2</sup>	.435	.613	.626	.448	.451
Korsmeyer-peppas	Y-equation	0.697x + 3.5552	0.7708x + 3.4387	0.7922x + 3.3529	0.8564x + 3.3473	0.8568x + 3.3039
	R <sup>2</sup>	.086	.110	.121	.139	.142
	n	.70	.77	.79	.86	.86

Table-5: Release rate parameters [Y-equation ( $Y = aX + b$ ), determination co-efficient ( $R^2$ ) and release exponent ( $n$ )] for release data after fitting of the whole release profiles of tramadol hydrochloride from its tablets into different mathematical models.

Models	Formulations	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	Reference
Zero Order	Y-equation	5.1338x + 42.175	5.2952x + 26.849	4.6454x + 18.648	5.6992x + 18.46
	R <sup>2</sup>	.627	.826	.887	0.923
First Order	Y-equation	0.1584x + 3.1597	0.1733x + 2.8401	0.1773x + 2.582	0.1909x + 2.6022
	R <sup>2</sup>	.248	.329	.383	0.414
Higuchi	Y-equation	2.9257x + 23.408	2.7963x + 10.609	2.3851x + 5.3577	2.8812x + 2.7876
	R <sup>2</sup>	.865	.968	.983	0.991
Hixson-Crowell	Y-equation	-0.1729x + 3.8694	-0.1434x + 4.2211	-0.107x + 4.3589	0.2038x + 2.3455
	R <sup>2</sup>	.935	.991	.998	0.497
Korsmeyer-peppas	Y-equation	0.6116x + 3.209	0.6587x + 2.9049	0.6691x + 2.653	0.7238x + 2.6755
	R <sup>2</sup>	.247	.317	.364	0.397
	n	.61	.66	.67	.72

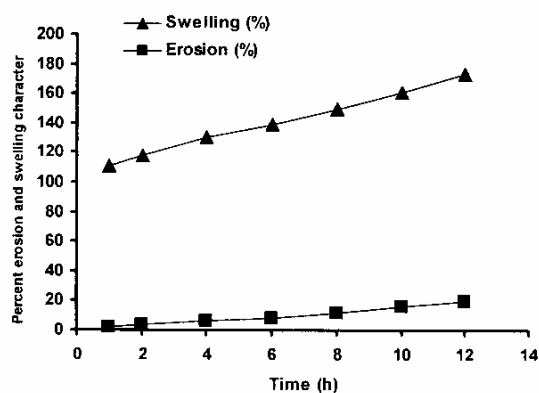


Fig. 5: Percent erosion and swelling character of optimum formulation T<sub>2</sub>. Each data point is a mean of three values.

#### UV and FTIR Spectroscopy and X-Ray Diffractometry

The UV spectra of the pure drug solution and the solution prepared for the determination of drug entrapment efficiency of the drug loaded microparticles were of the same kind. The  $\lambda_{max}$  of TH, in pure and encapsulated form, was observed at 271 nm. Common characteristic and prominent peaks of TH, in pure and encapsulated form, were observed in FTIR spectrum (Fig. 6) that denied any strong TH-ethocel interaction when TH was encapsulated into ethocel coats. X-Ray patterns of pure TH and TH loaded microparticles showed that intensity of pure TH was sharp but when TH was incorporated in microparticles, sharpness of its peaks slightly decreased indicating insignificant change in crystalline structure of TH (Fig. 7).

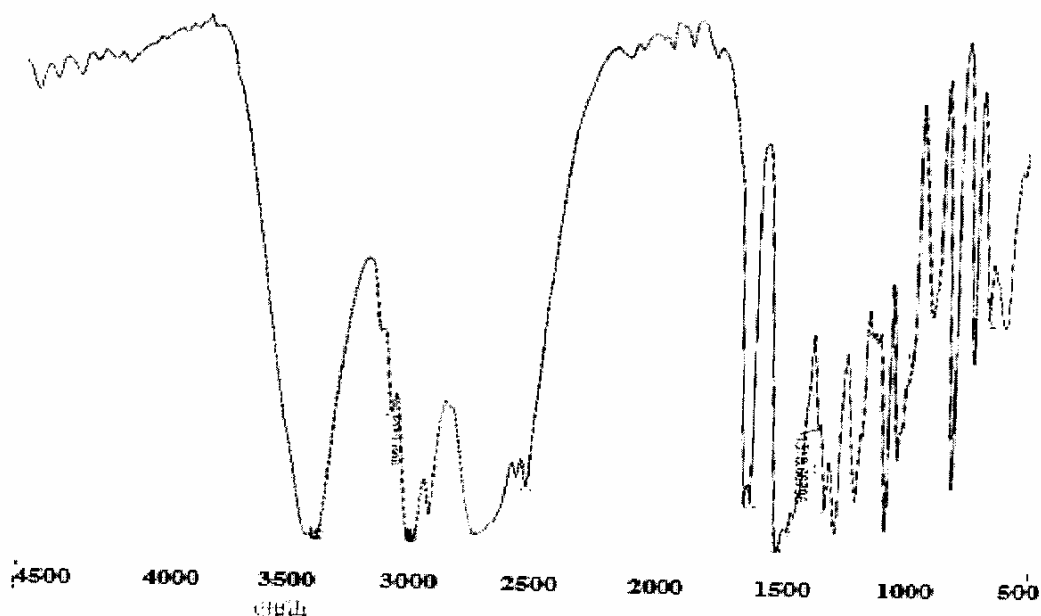


Fig. 6: FTIR spectra of tramadol hydrochloride formulation M<sub>2</sub>.

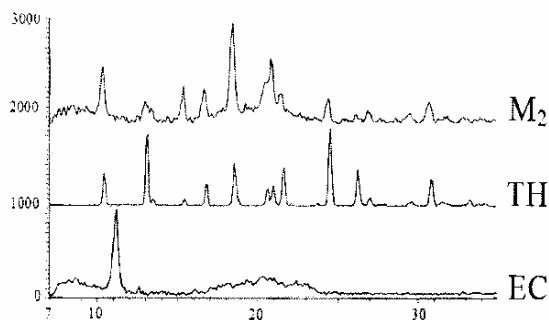


Fig. 7: XRD spectra of TH, EC and M<sub>2</sub>.

## Experimental

### Materials

Tramadol hydrochloride (Sami Pharmaceuticals), Ethocel 22 cp (Sigma, USA), Toluene (Merck, Germany), Polyisobutylene (PIB, Acros Organics, USA), Petroleum ether (40-60 °C, BDH, England), Methanol (Merck, Germany), Distilled water (Instrumental laboratory, IUB, Pakistan). All other chemicals were purchased through commercial sources.

### Preparation and Physicochemical Evaluation of Microparticles

Polyisobutylene (6 %, w/w) was dissolved in toluene (20 mL per gram ethocel) using a closed beaker with magnetic stirrer (Velp, Europe) at 500 rpm for 6 h. Ethocel (1 g, 2 g or 3 g) was added to this mixture followed by dispersion of TH in it. After stirring the system for 15 min, petroleum ether (non-solvent) was added slowly to induce phase separation. The system was cooled to 5 °C with ice for the solidification of microparticles. Petroleum ether (800 ml) was added continuously in short steps followed by filtration each time. The stirring was continued throughout the procedure. Finally, microparticles were refiltered, washed with n-hexane and dried in air for 2 hours followed by drying in oven (Mettler, Germany) at 50 °C for 4 h [13].

### Physicochemical Evaluation of Microparticles

The mean size and morphology of microparticles were determined by light and scanning electron microscope (SEM) respectively [13]. At the

end of each microencapsulation process, microcapsules were weighed immediately ( $M_1$ ) and after drying to a constant weight ( $M_2$ ) [20].

$$\text{Microcapsule solvation (\%)} = (M_1/M_2) \times 100$$

Bulk density was determined by following formula [17];

$$\text{Bulk Density} = \text{Sample weight} / \text{Sample volume}$$

Tap density was measured by employing the conventional tapping method using 10 mL measuring cylinder and the number of tapings was reduced to 100 as it was sufficient to bring about a plateau condition. Taped density, compressibility index (Ci) and Hausner's ratio (index of flowability of microcapsules) was calculated by following formulas [16];

$$\text{Tapped density} = \frac{\text{Weight of microcapsules}}{\text{Volume of microcapsules after 100 tapings}}$$

$$Ci = \left\{ \frac{\text{Initial volume} - \text{Final volume}}{\text{Initial volume}} \right\} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Volume before taping}}{\text{Volume after taping}}$$

Angle of repose was measured by passing microcapsules through a funnel on the horizontal surface. The height (h) of the heap formed was measured and radius (r) of cone base was also determined. The angle of repose was calculated by following formula [16];

$$\tan \theta = h / r$$

In order to assay TH, an accurately weighed quantity of microparticles from each batch was dissolved in small amount of methanol (about 5 ml) to dissolve ethocel coat. To it, 15 mL of distilled water was added and the solution was heated to evaporate methanol. Then final volume was made to 25 mL with distilled water, filtered to remove insoluble ethocel and diluted to make volume upto 900 mL with distilled water. This solution was then analyzed spectrophotometrically at 271 nm, against its standard solution exposed to the same conditions. Three determinations of the microparticle TH contents from the same batch were made [11]. TH (%) loading and encapsulation efficiency were calculated using the following equations:

$$\text{Drug loading (\%)} = \frac{\text{Amount of drug in microparticles}}{\text{Amount of microparticles}} \times 100$$

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100$$

The percentage production yield of the produced microparticles was calculated for each batch by dividing the weight of microparticles (M) by the total expected weight of TH and ethocel (M<sub>T</sub>):

$$\text{Production yield (\%)} = \frac{M}{M_T} \times 100$$

Each determination was performed in triplicate [9, 21].

#### Preparation and Physicochemical Evaluation of Tablets

Each batch of microcapsules was mixed with 1 % Talc, 0.5 % Magnesium stearate and lactose (used as filler). Each mixture was compressed separately into tablets by direct compression on a single punch tablet machine. The microparticles containing 100 mg TH were present in each tablet of TH. Three batches of tablets were prepared for each formulation of TH. Weight variation, hardness, friability and thickness of the tablets were measured using different instruments [18].

In case of tablets, 20 tablets were taken from each batch of tableted microparticles to determine their drug contents. These tablets were weighed and finely ground separately. An adequate amount of this powder was accurately weighed and repeated the same procedure as mentioned earlier in the assay of microparticles.

#### In vitro Dissolution Studies

The USP XXIV apparatus I and II (six replicates, pharma test, Germany) methods were used for *in vitro* dissolution studies of microparticles and tablets respectively, in 900 mL double distilled water at 50 rpm. An accurately weighed quantity of microparticles or tablets containing 100 mg TH was placed in dissolution medium maintained at 37 ± 1 °C. 5 mL of the sample was sucked and filtered through milli pore filters (Pharma test, Hainberg,

Germany) at 0, 30, 60, 90, 120, 150 and 180 minutes for microparticles and 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h for tablets with an automatic sample collector (Pharma Test, Germany). The dissolution media was replaced by 5 mL of fresh distilled water to maintain a constant volume in the dissolution flask. TH samples were analyzed directly at 271 nm using a UV-Visible spectrophotometer (Shimadzu 1601, Japan) [22].

#### Process Variables

PIB concentration was varied as 6 %, 9 % and 12 % during microencapsulation to study its effect on release profile of TH microparticles. Dissolution media (Distilled water, 0.1M HCl and pH 6.8 Buffer) and stirring speed (50, 100 and 150 rpm) were also varied to study their effect on dissolution behavior.

#### UV and FTIR Spectroscopy and X-Ray Diffractometry

UV spectra of the following solutions were recorded in the range of 200-400 nm using UV-Visible spectrophotometer (Shimadzu 1601, Japan): (i) Pure TH solution in distilled water, (ii) Pure ethocel solution and (iii) The solution prepared for the determination of drug entrapment efficiency of drug loaded microparticles [23]. TH, ethocel and microparticles were also evaluated using FTIR spectrophotometer (Shimadzu, Japan) in the range of 400-4000 cm<sup>-1</sup>. X-Ray powder diffractometry of TH and its microparticles was carried out to study the effect of microencapsulation process on crystallinity of drug [21].

#### Model Analysis and Statistics

##### Model Dependent Approaches

Following five different model-dependent approaches were applied to study dissolution kinetics of all formulations *i.e.* Zero Order [24]:  $M_t = M_0 + K_0t$  (Eq. 1), First Order [24]:  $\ln M_t = \ln M_0 + K_1t$  (Eq. 2), Higuchi [25]:  $M_t = M_0 + K_H t^{1/2}$  (Eq. 3), Hixson-Crowell [26]:  $M_0^3 - M_t^3 = K_{HC}t$  (Eq. 4) and Korsmeyer-Peppas [27]:  $M_t/M_0 = K_k t^n$  (5).

$M_t$  is the cumulative amount of drug released at any specified time point and  $M_0$  is the initial amount of drug in the formulation.  $K_0$ ,  $K_1$ ,  $K_H$ ,  $K_{HC}$  and  $K_k$  are rate constants for zero order, first

order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models respectively. In equation (5),  $M_t/M_a$  is the percentage of the TH release at time  $t$  and  $n$  is the release exponent that characterizes different release mechanisms. The  $n$ -value is calculated from the slope of Korsmeyer-Peppas plot.

#### Model Independent Approaches

One way ANOVA plus Post-Hoc analysis (Duncan and Tukey H.S.D.) for significance at  $P < .05$  was conducted for whole release profiles using SPSS version 12.0 [28]. Pair wise procedures include the difference factor ( $f_1$ ) [Eq. (6)] and the similarity factor ( $f_2$ ) [Eq. (7)]. According to the FDA guidelines, values of  $f_1$  between zero and 15 and of  $f_2$  between 50 and 100 ensure sameness or equivalence of the two dissolution profiles. In both equations,  $R_t$  and  $T_t$  represent the dissolution data values at  $P$  time points of the reference and test, respectively [29].

$$f_1 = \left\{ \left[ \sum_{i=1}^P |R_t - T_t| \right] / \left[ \sum_{i=1}^P R_t \right] \right\} \quad (6)$$

$$f_2 = 50 \log \left\{ \left[ 1 + (1/P) \sum_{i=1}^P (R_t - T_t)^2 \right]^{1/2} \times 100 \right\} \quad (7)$$

#### Batch Reproducibility and Stability on Storage

Three batches of tablets  $T_1$ ,  $T_2$  and  $T_3$  were prepared and evaluated physicochemically. A specific number of tablets from each batch were stored in air tight amber glass bottles at 25 °C and 40 °C and tested physicochemically for three months following above described procedure.

#### Conclusion

Non-solvent addition coacervation technique is an appropriate method to prepare tramadol hydrochloride-ethocel microparticles and the variation observed in entrapment efficiency, production yield, mean particle size and the drug release behavior among the formulations are the result of the drug polymer ratio employed. This study may suggest the potential application of ethocel microparticles as a suitable multi-unit sustained release drug delivery system after every 12 hours.

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