

DEVELOPMENT OF A CHRONO MODULATED PULSINCAP DRUG DELIVERY SYSTEM OF TRAMADOL HYDROCHLORIDE FOR CIRCADIAN MANAGEMENT OF ARTHRITIC PAIN

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Abstract

This study focused on the development and evaluation of Tramadol Hydrochloride (TMH) microcapsules incorporated into a modified pulsincap system for targeted drug delivery. Eight formulations (F1–F8) were prepared using the emulsification–solvent evaporation technique, employing Eudragit RS100 and RL100 as polymers. FTIR analysis indicated the absence of significant drug–polymer interactions, while SEM images revealed the formation of spherical microcapsules with smooth surfaces. Particle size distribution played a key role in influencing the drug release behavior, with formulation F4 exhibiting the highest entrapment efficiency (96.18%). *In vitro* release studies demonstrated a controlled release pattern. Drug release followed first-order kinetics and conformed to the Higuchi diffusion model, suggesting a diffusion-controlled mechanism, while the Peppas model indicated Fickian diffusion. Further characterization using DSC and XRD confirmed that the drug retained its crystalline nature, whereas the formulation showed partial amorphization, contributing to enhanced dissolution. The modified pulsincap system, utilizing HPMC hydrogel plugs, enabled a lag time of approximately 2–3 hours before drug release. Stability studies revealed that formulation F4 remained stable over 60 days under accelerated conditions. Overall, the results demonstrate that TMH microcapsules incorporated into a pulsincap system offer promising potential for improved pain management and enhanced patient compliance.

Keywords: Tramadol hydrochloride, Microcapsules, Pulsincap system, Controlled release, *In- vitro* release studies.

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INTRODUCTION

There is growing recognition of the significance of chronotherapy in managing various disorders such as depression, anxiety, cancer, and asthma. Chronotherapy involves tailoring the timing of drug administration in accordance with the body's circadian rhythm to maximize therapeutic efficacy while minimizing adverse effects. The circadian clock enables living organisms to synchronize physiological and behavioral functions with the 24-hour light–dark cycle. External factors such as temperature and sunlight play a crucial role in regulating this internal clock, ensuring proper biological functioning.

In recent years, efforts have been directed toward the development of novel drug delivery systems (DDS) to reduce the cost and risks associated with drug development. Conventional delivery systems are primarily designed for sustained drug release to maintain therapeutic levels over an extended period. In contrast, targeted drug delivery aims to release a controlled amount of drug at specific sites, thereby enhancing therapeutic effectiveness and reducing systemic toxicity. Modern DDS technologies rely on various endogenous physicochemical triggers, including pH variations, redox gradients, and enzymatic activity, to regulate drug release. [1-4]

Advancements in “smart” drug delivery systems have further improved upon conventional DDS by mimicking physiological responses or responding to specific stimuli. These systems can be engineered using intelligent materials to achieve pulsatile drug release, ensuring that drugs are delivered at the right time, location, and dosage according to physiological needs. Such systems are referred to as Pulsatile Drug Delivery Systems (PDDS). PDDS are

specifically designed to align drug release with the body's circadian rhythms, thereby optimizing therapeutic outcomes and minimizing side effects (Fig 1). [5-9]

In PDDS, a defined lag time precedes the rapid release of a specific quantity of drug within a short duration. This delayed, burst-release mechanism makes PDDS particularly suitable for conditions requiring time-specific drug action. Typically, these systems consist of a core reservoir coated with polymeric barrier layers that prevent drug release until the coating undergoes erosion, degradation, or rupture after the lag period. Once the barrier is compromised, the drug is quickly released from the core. Pulsatile drug delivery is especially advantageous in the treatment of conditions such as peptic ulcers, arthritis, asthma, and hypertension. [10]

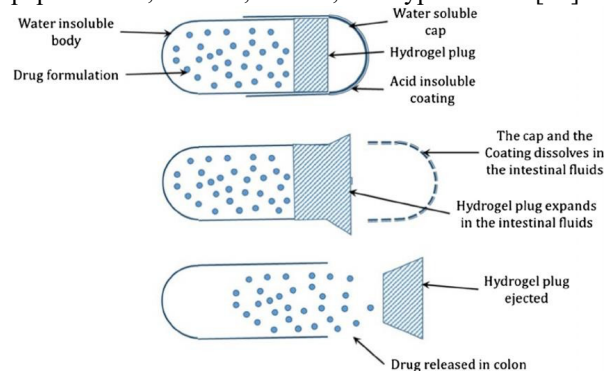


Fig 1: Mechanism of the Pulsincap colon-targeted drug delivery system [11]

Effective management of chronic arthritis requires precise and timely drug delivery. Chronotherapy, which aligns drug release with the body's natural circadian rhythms, can significantly enhance therapeutic outcomes. [12-22]. Tramadol Hydrochloride is a widely used centrally acting analgesic for alleviating arthritic pain. However, its short half-life and frequent dosing can lead to fluctuations in plasma drug levels, reducing efficacy and increasing the likelihood of adverse effects. [23-26].

To overcome these limitations, a modified pulsincap drug delivery system can be designed to mimic the body's natural pain rhythms by providing pulsatile release of the drug. The capsule-based pulsincap system utilizes a hydrogel plug to control the timing of drug release. The objective is to develop an optimized chronotherapeutic delivery system for TMH by modifying the design and composition of the pulsincap, thereby enabling targeted pain relief and improving patient compliance.[27]

MATERIALS AND METHODS

Materials: Tramadol Hydrochloride (TMH) was obtained from Zydus Life Sciences Limited, Ahmedabad. The polymers Eudragit RL-100 and RS-100 were procured from Evonik Industries, Mumbai. Acetone, span 80, light liquid paraffin, and heavy liquid paraffin were used in the study, and all other solvents and reagents employed were of analytical grade.METHODS

Preparation of microcapsules of Tramadol Hydrochloride [28]

Emulsification-solvent evaporation method.

Eudragit RL-100 and RS-100 were accurately weighed and dissolved in acetone to obtain a homogeneous polymer solution. The drug, Tramadol Hydrochloride (TMH), was then incorporated into this solution and mixed thoroughly. The resulting organic phase was slowly introduced into liquid paraffin containing 1% w/w Span 80 under continuous stirring at 1200 rpm to form a stable emulsion. The mixture was heated to about 15°C, and stirring was continued until the mixture cooled to room temperature and the acetone completely evaporated, resulting in the formation of firm, discrete microcapsules with smooth surfaces. The microcapsules were separated by decantation, washed four times with petroleum ether (40–60°C), and dried at room temperature for three hours. Finally, they were stored in desiccators over fused calcium chloride. A total of eight formulations (F1–F8) were prepared, as summarized in Table 1.

Table 1: Formulation Design of TMH Microcapsules.

Sl.No	Ingredients	Formulation Code							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Drug (mg)	100	100	100	100	100	100	100	100
2	Eudragit RL-100 (mg)	100	150	300	400	-	100	150	-
3	Eudragit RS-100 (mg)	-	150	300	100	100	100	-	100
4	Liquid paraffin light (ml)	100		50	100	-	100	100	100
5	Liquid paraffin heavy (ml)	-	100	50	-	100	-	-	-
6	Acetone (ml)	10	10	10	10	10	10	10	10

7	Span 80 (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
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Evaluation of Microcapsules [28-30]

Compatibility Studies

The development of a stable and effective solid dosage form requires the careful selection of excipients that aid in administration, ensure consistent drug release and bioavailability, and protect the drug from degradation. When novel excipients are used, compatibility studies become essential. In this study, compatibility of Tramadol Hydrochloride (TMH) with polymers such as Eudragit RS100 and RL100, along with the physical mixture, was evaluated using infrared (IR) spectroscopy. Any potential chemical interactions between the drug and excipients were assessed using the potassium bromide (KBr) pellet method.

Scanning electron microscopy (SEM)

The surface morphology of the microspheres was examined using a scanning electron microscope (JEOL JSM-840A, Japan). Samples were sputter-coated with a thin layer of gold (200 Å) and observed at an accelerating voltage of 25 kV.

Particle size

Determination of average particle size of TMH microcapsules was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of microcapsules was spread on a clean glass slide and average size of 300 microcapsules was determined in each batch.

Frequency distribution analysis

The average particle size of TMH microcapsules was determined using optical microscopy with a stage micrometer. A small quantity of microcapsules was spread on a glass slide, and the size of 300 particles from each batch was measured. Frequency distribution analysis was further performed by categorizing particle sizes into different ranges, enabling determination of the percentage of particles within specific size intervals.

Determination of percentage drug entrapment efficiency (PDE).

For drug content analysis, 25 mg of crushed microcapsules were dissolved in pH 7.4 buffer in a 100 ml volumetric flask and shaken for 12 hours. The solution was filtered, suitably diluted, and analyzed spectrophotometrically at 247 nm. Drug entrapment efficiency for each batch was calculated in terms of percentage drug entrapment as per the following formula

$$\text{PDE (\%)} = (\text{Practical Drug Loading} / \text{Theoretical Drug Loading}) \times 100$$

In-vitro dissolution studies

In-vitro dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml pH 1.2, pH 6.8 and pH 7.4 phosphate buffer, 100 rpm, 37±0.5°C). Microcapsules equivalent to 150 mg of TMH was loaded into the basket of the dissolution apparatus. 5 ml of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 247 nm against pH 7.4 blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculated data obtained was also subjected to kinetic treatment to obtain the order of release and release mechanism.

Drug release kinetics

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [$\text{Log}(Q_0 - Q)$ v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot ($\log Q$ v/s $\log t$) respectively, where Q is the cumulative percentage of drug released at time t and $(Q_0 - Q)$ is the cumulative percentage of drug remaining after time t .

Differential Scanning Calorimetry (DSC) [28]

DSC thermogram analysis for the drug TMH, Physical mixture of the TMH and blank microcapsules, TMH microcapsules was performed on 5mg sample. Samples were heated in an open aluminum pan at a rate of $10^\circ\text{C}/\text{min}$ in a 30 to 300°C temperature range under a nitrogen flow of $40\text{ml}/\text{min}$.

X-ray diffraction (XRD)

The X-ray beam diffraction of drug TMH, Physical mixture of the TMH and blank microcapsules, TMH microcapsules were recorded utilizing at PAN analytical/X Pert3 Powder of 40 kV and 20 mA . The checking speed was changed by 2 degrees each moment, and the examples were exposed to Cu-K α radiation at 2θ points going from 5° to 50° .

Preparation of cross-linked gelatin capsules [31]

Formaldehyde treatment

Cross-linked gelatin capsules were prepared using formaldehyde treatment to reduce solubility. Hard gelatin capsules (size 0) were exposed to formaldehyde vapors generated from formalin and potassium permanganate in a desiccator for 12 hours. The treated capsule bodies were then dried at 50°C and further air-dried to remove residual formaldehyde before storage.

Formulation of Pulsatile (Modified Pulsincap) Drug Delivery System

TMH treated with hard gelatin capsules of 'size 0' were chosen for the formulation. The bodies and caps were separated manually. Microcapsules equivalent to 150 mg of TMH were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the microcapsules were then plugged with HPMC hydrogel at different concentration. The joint of the capsule body and cap was sealed with a small amount of the 5% Ethyl Cellulose ethanolic solution. The sealed capsules were completely coated with 5% Cellulose Acetate Phthalate (CAP) to prevent variable gastric emptying. Coating was repeated until an 8- 12% increase in weight is obtained. % Weight gain of the capsules before and after coating was determined. The whole system thus produced is modified pulsincap.

Coating of pulsincap

5% w/w solution of CAP was prepared by using acetone: ethanol (8:2) as solvent and dibutyl phthalate as plasticizer (0.75%). Dip coating method was followed to develop the pulsincap. The capsules were alternatively dipped in 5 % CAP solution and dried. Coating was repeated until an expected weight gain of 8-12 % was obtained and the capsule resists disintegration in 0.1 N HCl for a minimum period of 2 hrs.

Evaluation of modified TMH pulsincap [32]

Thickness of cellulose acetate phthalate coating

The thickness of the cellulose acetate phthalate coating was measured using screw gauge. It was expressed in mm.

Weight variation

10 capsules were selected randomly from each batch and weighed

individually for weight variation. The test requirements are met if none of the individual weights are less than 90% or more than 110% of the average.

In- vitro release profile

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle type) with rotation speed of 100 rpm . 900 ml of the dissolution medium was used and the temperature of the medium was maintained at $37^\circ\text{C} \pm 0.5^\circ\text{C}$. The pH 1.4 buffer for 2 hours, pH 7.4 buffer for 3 hours and pH 6.8 buffer for subsequent hours were used. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed and the amount of TMH released was determined by UV absorption spectroscopy.

Stability Studies [33]

The stability study was carried out for selected formulation as per ICH guidelines. Various ICH storage conditions are available which are as $25^\circ\text{C} \pm 2^\circ\text{C}$ (60 % $\pm$ 5% RH), $30^\circ\text{C} \pm 2^\circ\text{C}$ (65 % $\pm$ 5% RH) and $40^\circ\text{C} \pm 2^\circ\text{C}$ (75 % $\pm$ 5% RH). The microcapsules of the best formulation (F4) were placed in screw capped glass container and stored at various ICH storage condition for a period of 60 days. The samples were analyzed for physical appearance and for the drug content at regular interval of 15 days.

Statistical Analysis

The data were expressed as mean $\pm$ standard error of mean (SEM). Statistical significance was analyzed by using Graph Pad (Instat) prism software version 5.

RESULTS AND DISCUSSION

Compatibility study by IR Spectroscopy

The spectra of TMH, its physical mixture with polymers, and the TMH microcapsules revealed the presence of all characteristic peaks of TMH in the combination spectrum. This confirms the compatibility between TMH and the polymers (Fig 2).

Fig 2: FTIR of (a) Blank microcapsules (b) Physical mixture of TMH and polymers

(c) Eudragit RS100 (d) Physical mixture of TMH and blank microcapsules (e) TMH

(f) Eudragit RL100

Scanning electron microscopy

The surface of the produced microcapsules was characterized using scanning electron microscopy. Spherical, smooth, and discrete particles were observed (Fig 3).

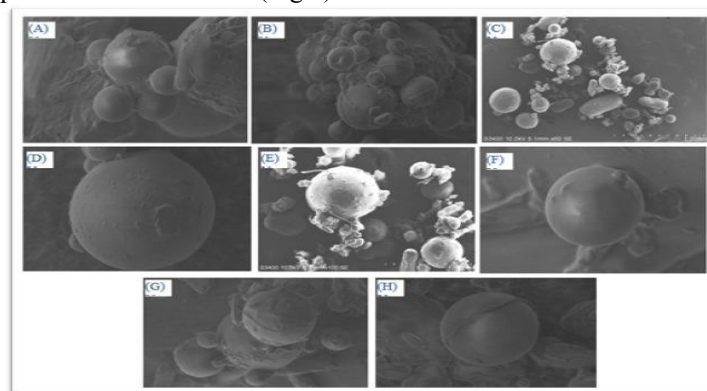


Fig 3: Photomicrographs of F1- F8 (A-H) formulations.

Particle size and frequency distribution

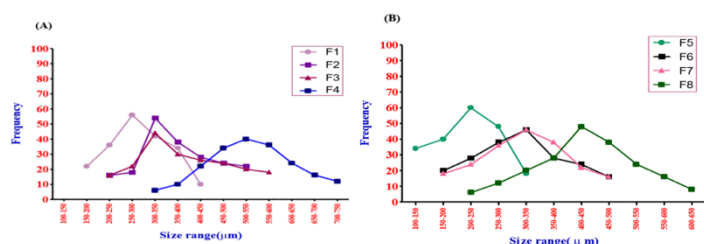


Fig 4: Frequency Distribution of TMH microcapsules

The mean particle size of the microcapsules significantly increased with increase in polymer concentration and was ranged in between 628 to 870 μ m. The reason must be, the viscosity of medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This may be resulting in the formation of larger particles. Microcapsules with normal frequency distribution were obtained (Fig 4).

Drug entrapment efficiency of TMH microcapsules

Table 2: Percentage yield, Drug content, Drug entrapment efficiency of TMH microcapsules

Formulation	% Yield	Drug Content	% Entrapment efficiency $\pm$ SD
F1	66.49	70.6	24.61 $\pm$ 0.89
F2	86.99	83.21	33.00 $\pm$ 1.19
F3	69.85	75.43	85.76 $\pm$ 1.86
F4	89.18	85.34	96.18 $\pm$ 2.21
F5	59.61	71.45	51.58 $\pm$ 1.41
F6	89.36	82.76	70.22 $\pm$ 1.61
F7	82.31	69.76	84.97 $\pm$ 2.02
F8	79.28	77.32	86.92 $\pm$ 2.71

A positive correlation between solid content and percentage yield was observed. This may be explained by the fact that though a constant amount of material is always lost in processing, this loss is proportionately less significant when the solid content is more (e.g. If the loss in processing is 10 mg then it is more significant for a 100 mg sample, but much less significant for a 500 mg sample). The percentage of entrapment efficiency range from 24.61 to 96.18 were obtained in the present study (Table 2).

Amount of microcapsules to be taken for *in vitro* release studies and further development of pulsincap was calculated based on content of drug present in each formulation.

In-vitro release and kinetics studies for TMH Microcapsules

In-vitro release studies were carried out using USP-XXIII dissolution assembly. Cumulative % drug release after 12 hrs was 74.74 $\pm$ 0.92%, 67.78 $\pm$ 0.75%, 60.16 $\pm$ 0.74%, 39.29 $\pm$ 1.58%, 81.44 $\pm$ 1.10%, 74.15 $\pm$ 1.63%, 67.74 $\pm$ 0.93% and 44.61 $\pm$ 0.97% for F1, F2, F3, F4, F5, F7 and F8 respectively. The results of in- vitro

release studies were plotted into four models of data treatment as follows

- Cumulative % drug release Vs Time (Zero order rate kinetics).
- Log cum. % drug retained Vs Time (First order rate kinetics).
- Higuchi's classical diffusion equation (Higuchi Matrix) in which cumulative % release was plotted against $\sqrt{t}$ (root time).
- Log of cum % drug released Vs log Time (Peppas exponential equation).

The release data obtained for all the eight formulations were shown in Fig 5. Plots of zero order, first order, Higuchi matrix, Peppas depicted in Fig 6. The kinetic value obtained for different formulations are indicated in Table 3

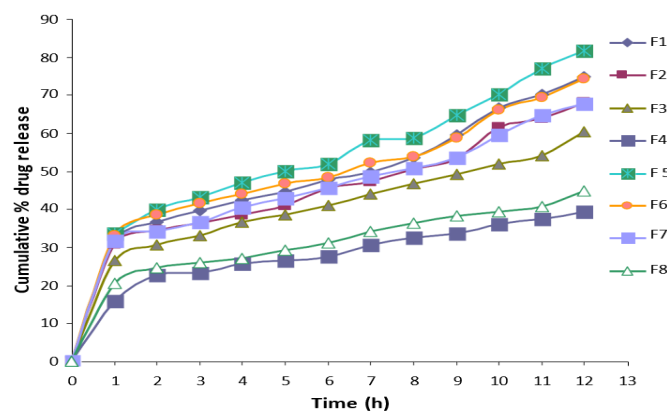


Fig 5: In-vitro drug release profile of TMH microcapsules (F1 - F8)

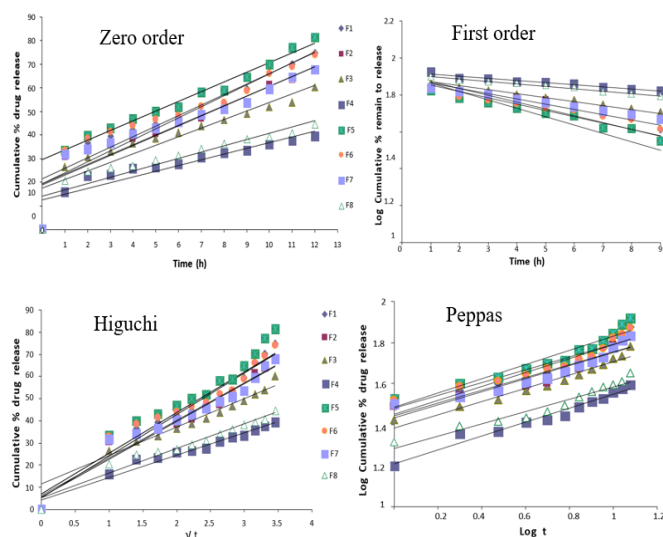


Fig 6: Release kinetics profile of TMH microcapsules from F1 - F8 Formulation.

Table 3: Regression co-efficient (r^2) values of different kinetic models and diffusion exponent (n) of Peppas model for TMH microcapsules.

Formulation code	Zero order	First order	Higuchi	Peppas	
	(r^2) $\pm$ SD	(r^2) $\pm$ SD	(r^2) $\pm$ SD	(r^2) $\pm$ SD	n
F1	0.8285 $\pm$ 0.002	0.8844 $\pm$ 0.005	0.9656 $\pm$ 0.005	0.9682 $\pm$ 0.002	0.3363
F2	0.8220 $\pm$ 0.004	0.8869 $\pm$ 0.004	0.9561 $\pm$ 0.004	0.9483 $\pm$ 0.004	0.3011
F3	0.9159 $\pm$ 0.002	0.9677 $\pm$ 0.003	0.9963 $\pm$ 0.002	0.9888 $\pm$ 0.005	0.4440
F4	0.8804 $\pm$ 0.002	0.9535 $\pm$ 0.004	0.9898 $\pm$ 0.002	0.9910 $\pm$ 0.004	0.4014
F5	0.9242 $\pm$ 0.005	0.9680 $\pm$ 0.006	0.9909 $\pm$ 0.005	0.9786 $\pm$ 0.003	0.4537
F6	0.8503 $\pm$ 0.006	0.9278 $\pm$ 0.002	0.9527 $\pm$ 0.006	0.9065 $\pm$ 0.006	0.3121
F7	0.8772 $\pm$ 0.004	0.9342 $\pm$ 0.003	0.9648 $\pm$ 0.004	0.9407 $\pm$ 0.002	0.3559
F8	0.8445 $\pm$ 0.002	0.9227 $\pm$ 0.004	0.9642 $\pm$ 0.002	0.9534 $\pm$ 0.002	0.3199

Differential Scanning Calorimetry (DSC)

DSC thermograms of TMH, physical mixture of TMH and blank microcapsules, TMH microcapsules. are shown in Fig 7.

Fig 7: DSC Thermogram of (a) TMH Microcapsules (b) TMH, (c) Physical Mixture of TMH and blank microcapsules

The DSC trace of drug showed a sharp endothermic peak at 183.72°C, its melting point. The physical mixture of TMH and blank microcapsules showed the endothermic peak at 182.81°C as the drug, indicating that there was no interaction between the TMH and the polymer in the solid state and the drug still present in its crystalline state in the physical mixture of Tramadol hydrochloride and blank microcapsules. The absence of endothermic peak of the TMH at 183.72°C in the DSC of the TMH loaded microcapsules suggests that the drug existed in an amorphous or disordered crystalline phase as a molecular dispersion in the drug loaded microcapsules.

X-Ray Diffraction

In order to confirm the physical state of the TMH in the microcapsules, powder X-ray diffraction studies of the TMH alone, physical mixture of TMH and blank microcapsules, TMH loaded microcapsules was carried out. TMH is still present in its crystalline state in the physical mixture of TMH and blank microcapsules, where as it is completely amorphous or disordered crystalline phase as a molecular dispersion in the TMH loaded microcapsules. This may be due to the conditions used to prepare the microcapsules lead to cause complete drug amorphization (Fig 8).

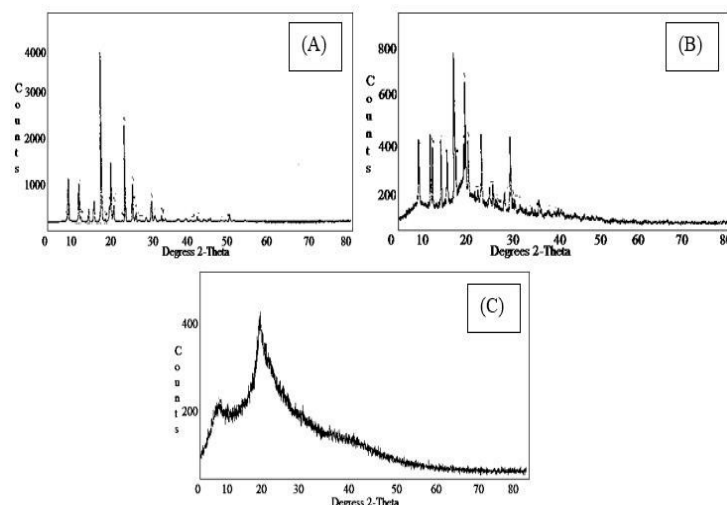


Fig 8 XRD: (A) Tramadol Hydrochloride, (B) Physical mixture of TMH and blank microcapsules, (C) TMH microcapsules

EVALUATION OF MODIFIED TMH PULSINCAP

Weight variation

The filled capsules pass the weight variation test as their weights are within the specified limits. Thickness of Cellulose Acetate Phthalate (Table 4).

Table 4 Coating thickness

FORMULATION	Thickness of coating (mm)
F2	0.067
F4	0.056
F6	0.059

In-vitro release studies for pulsatile capsule device

The *in-vitro* dissolution profiles of the pulsatile device over a 24 hours study demonstrated excellent sustained release efficacy. Among the eight formulations tested, F2, F4, and F6 showed the best results in Fig 9. Comparative *in-vitro* release profiles, represented as cumulative % release versus time, were plotted for formulations F2, F4, and F6, which contained hydrogel plugs of HPMC at varying concentrations of 20 mg, 30 mg and 40 mg, respectively.

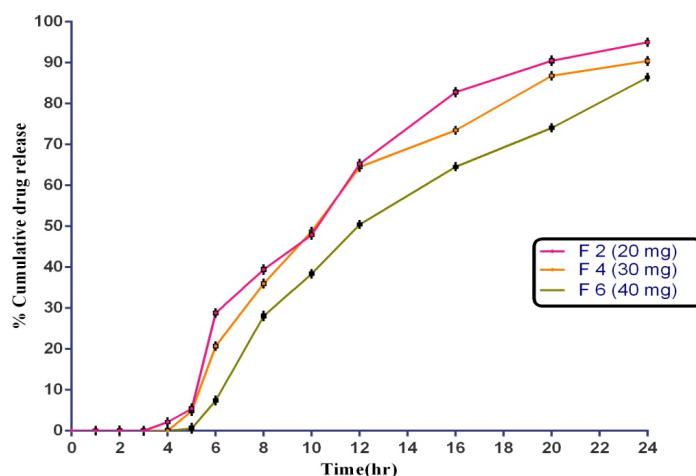


Fig 9 Comparative *In vitro* release profile of TMH pulsatile device

STABILITY STUDIES

The results of the stability studies, which were conducted for 60 days, are given in the Table 5 and Fig 10 explains the stability studies of F4 formulation at varied temperature

Table 5: Stability Studies data of F4 Formulation

NO. of Days	25 ⁰ C ± 2 ⁰ C/60% RH ±5% RH		30 ⁰ C ± 2 ⁰ C/65% RH ±5% RH		40 ⁰ C ± 2 ⁰ C/75% ± 5% RH	
	Physical Appearance	% Drug Entrapment	Physical Appearance	% Drug Entrapment	Physical Appearance	% Drug Entrapment
0	No Change	100	No Change	100	No Change	100
15	No Change	98.78	No Change	98.64	No Change	98.52
30	No Change	98.15	No Change	97.21	No Change	98.68
45	No Change	98.71	No Change	97.30	No Change	97.90
60	No Change	98.04	No Change	96.97	No Change	96.96

% Drug Entrapment

Fig 10: Stability Studies of F4 formulation (60 days)

CONCLUSION:

The formulation and characterization of TMH microcapsules and the modified pulsincap drug delivery system was successfully carried out, yielding promising results for controlled and pulsatile drug release. IR spectroscopy confirmed the compatibility between TMH and the polymers Eudragit RS100 and RL100, with no significant chemical interactions, ensuring the drug's stability and therapeutic efficacy within the formulation. Scanning electron microscopy revealed that microcapsules from formulations exhibited smooth, spherical surfaces. Particle size distribution indicated variability in particle sizes, with smaller particles typically exhibiting faster drug release profiles. The drug entrapment efficiency was highest in formulation F4 (96.18), correlating with better-controlled release and consistent in-vitro performance.

In-vitro release studies demonstrated that formulations provided controlled release of Tramadol hydrochloride, with F4 showing the most favorable release profile. The release kinetics followed first-order, with the highest correlation observed in the Higuchi diffusion model, indicating that the drug release was predominantly diffusion-controlled. The Peppas model confirmed the Fickian diffusion release mechanism. Thermal and structural characterization via DSC and XRD showed that TMH remained in a stable crystalline form in the microcapsules, while the formulation exhibited amorphous characteristics, potentially enhancing dissolution rate and bioavailability.

The modified pulsincap system demonstrated effective pulsatile drug release, with HPMC hydrogel plugs providing delayed release. Formulations F4, F5, F6, and F7 exhibited the best pulsatile release profiles, with drug release occurring after a lag time of 2–3 hours, which is ideal for targeting specific gastrointestinal conditions. The

coating thickness was carefully controlled, ensuring that the system withstood the gastric environment before releasing the drug in the small intestine. Stability studies confirmed that the F4 formulation remained stable under accelerated storage conditions for 60 days, with minimal changes in physical appearance and drug content, indicating that it maintains its integrity and therapeutic effectiveness over time.

Overall, the study demonstrated that TMH microcapsules and the modified pulsincap drug delivery system provide a controlled and pulsatile release of the drug, enhancing therapeutic outcomes and patient compliance. The formulations were stable and effective, making them promising candidates for clinical use in pain management with improved pharmacokinetics and extended-release capabilities.

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