The Bioscan AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES
21(1) S (1) 656-662, 2026 www.thebioscan.com

Formulation and Evaluation of Sustained Release Matrix Tablets of Tramadol Hydrochloride Using Compritol 888 ATO and Precirol ATO 05 by Melt Granulation Technique

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DOI: https://doi.org/10.63001/tbs.2026.v21.i01.S.I(1).pp656-662

KEYWORDS

Tramadol Hydrochloride, Sustained release, Melt granulation, Compritol 888 ATO, Precirol ATO 05, Lipophilic matrix, Drug release kinetics.

Received on: 16-01-2026

Accepted on: 24-02-2026

Published on: 13-03-2026

Abstract

The present investigation aimed to formulate and evaluate sustained release matrix tablets of Tramadol Hydrochloride (TH) using lipophilic binders Compritol 888 ATO and Precirol ATO 05 by melt granulation technique. Preformulation studies confirmed purity of TH and λmax was found at 271 nm in both pH 1.2 and pH 6.8 phosphate buffer. Drug–polymer compatibility studies using FTIR revealed no interaction between drug and excipients. Matrix tablets were prepared in varying ratios of drug to polymer (1:1, 1:2 and 1:3) and combinations thereof. Granules exhibited excellent flow properties with angle of repose below 20° and compressibility index below 15%. Post-compression parameters such as hardness (5.2–6.5 kg/cm²), friability (<1%), drug content (95–100%) and weight variation were within pharmacopoeial limits. In-vitro dissolution studies were performed using USP type II apparatus in pH 1.2 buffer for 2 h followed by pH 6.8 phosphate buffer for 10 h. Increase in polymer concentration significantly retarded drug release. Formulations containing combination of Compritol 888 ATO and Precirol ATO 05 showed superior release retardation compared to single polymer matrices. Among all formulations, MG8 (1:2:1 ratio) exhibited maximum sustained release for more than 12 h. Drug release followed Zero-order and Higuchi kinetics with non-Fickian diffusion mechanism. The study concludes that melt granulation using lipophilic binders is an effective approach for developing sustained release formulations of highly water-soluble drugs like TH.

INTRODUCTION

Oral sustained release drug delivery systems are designed to maintain therapeutic drug concentration in plasma for extended periods of time, thereby reducing dosing frequency and improving patient compliance (Khan, 2001; Vyas and Khar, 2002). Conventional dosage forms produce fluctuations in plasma drug levels, which may result in sub-therapeutic or toxic concentrations. Sustained release formulations minimize these fluctuations and provide prolonged therapeutic action (Lachman and Liberman, 1987).

Matrix systems are among the most widely used sustained release systems due to their simplicity, cost effectiveness and ease of manufacturing (Wise, 2005). Drug release from matrix systems is governed by diffusion, erosion or swelling mechanisms (Chien, 1992). Lipophilic matrix systems are

particularly suitable for highly water-soluble drugs as they retard drug release by reducing penetration of dissolution medium and controlling diffusion (Robinson and Lee, 1987).

Tramadol Hydrochloride (TH) is a centrally acting synthetic opioid analgesic with a half-life of approximately 6–7 h. It is highly water soluble and requires frequent dosing when administered as conventional tablets. Sustained release formulation of TH can improve therapeutic efficacy and patient compliance by maintaining steady plasma concentration (Shargel and Yu, 1999).

Compritol 888 ATO (glyceryl behenate) and Precirol ATO 05 (glyceryl palmitostearate) are lipophilic excipients widely used as matrix forming agents in sustained release formulations. Their hydrophobic nature and high melting point make them suitable for melt granulation technique, which ensures uniform coating of drug particles and controlled drug release (Paradkar et al., 2001).

Therefore, the present study was undertaken to formulate and evaluate sustained release matrix tablets of TH using Compritol 888 ATO and Precirol ATO 05 by melt granulation technique and to study the effect of polymer concentration and method of preparation on drug release behavior.

MATERIALS AND METHODS

Materials

Tramadol Hydrochloride was obtained from Neon Laboratories Ltd., Mumbai. Compritol 888 ATO and Precirol ATO 05 were procured from Gattefosse, France. All other chemicals were of analytical grade.

Preformulation Studies

Preformulation parameters including description, solubility, melting point and UV spectral analysis were performed. Calibration curves were constructed in pH 1.2 and pH 6.8 phosphate buffer at 271 nm.

Compatibility Studies

FTIR spectroscopy was performed for pure drug and drug–polymer mixtures to evaluate possible interactions.

Preparation of Matrix Tablets

Matrix tablets were prepared by melt granulation technique. Lipophilic binders were melted and mixed with drug to form granules. The granules were passed through sieve and compressed into tablets. Formulations were prepared in ratios of 1:1, 1:2 and 1:3 (drug: polymer) and combinations (1:1:1, 1:2:1, 1:1:2).

Pre-compression Evaluation

Granules were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index.

Post-compression Evaluation

Tablets were evaluated for weight variation, hardness, thickness, friability and drug content.

In-vitro Drug Release Studies

Dissolution studies were performed using USP type II apparatus at 100 rpm in 900 ml of pH 1.2 buffer for 2 h followed by pH 6.8 phosphate buffer for 10 h. Samples were analyzed at 271 nm.

Drug Release Kinetics

Dissolution data were fitted to Zero-order, First-order and Higuchi models to determine release mechanism.

RESULTS & DISCUSSION

Estimation of TH by UV spectroscopy

Determination of max of TH in pH 1.2 phosphate buffer

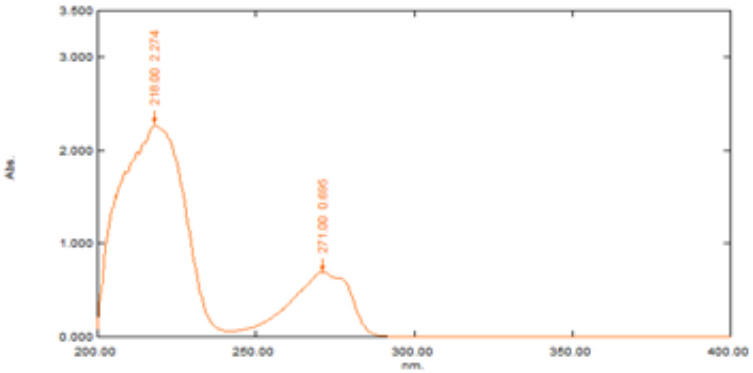


Fig 1: UV absorption spectrum of TH in pH 1.2 phosphate buffer

Determination of max of TH in pH 6.8 phosphate buffer

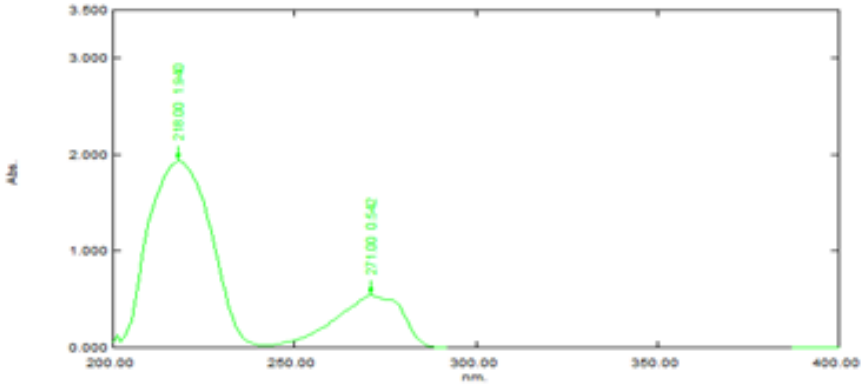
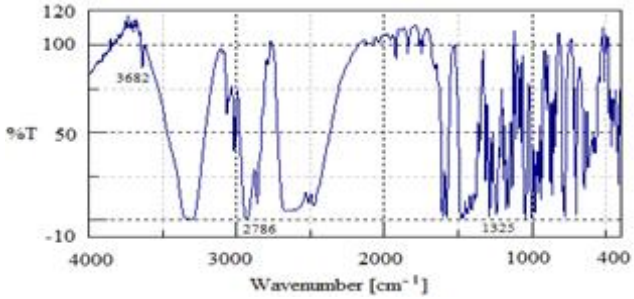
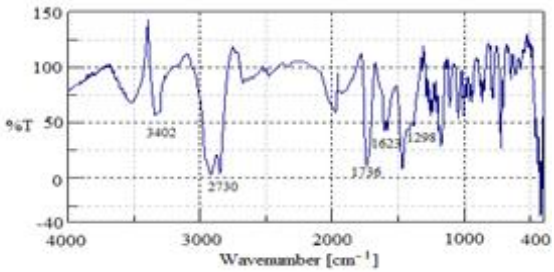


Fig 2 UV absorption spectrum of TH in pH 6.8 phosphate buffer

Compatability studies

FTIR spectroscopy





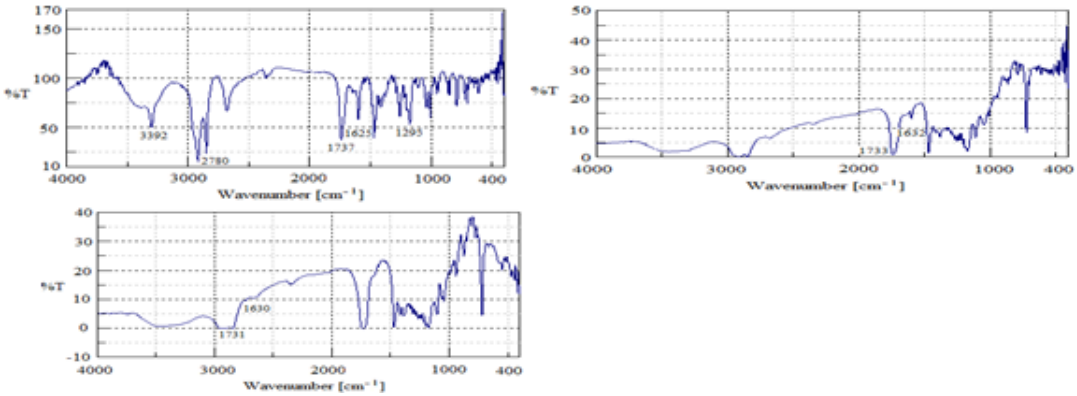


Fig 3: IR spectrum of (a) TH (b) TH: compritol 888 ATO (c) TH: Precirol ATO 5 (d) Compritol 888 ATO and (e) Precirol ATO 5

Evaluation of micromeritics properties of the granules

Formulation code	Angle of Repose (°)	Loose Bulk Density (g/cm3)	Tapped Bulk Density (g/cm3)	Void Volume (ml)	Bulkiness (ml)	Total Porosity (%)	Carr's Index (%)
MG1	18.00	0.58	0.66	0.4	1.72	11.75	12.12
MG2	19.57	0.68	0.76	0.3	1.47	10.35	10.52
MG3	16.17	0.57	0.64	0.4	1.75	11.43	10.93
MG4	19.15	0.74	0.80	0.2	1.35	7.41	7.50
MG5	17.35	0.66	0.74	0.3	1.51	10.00	10.80
MG6	16.38	0.60	0.66	0.3	1.66	9.10	9.09
MG7	19.44	0.62	0.68	0.3	1.61	9.38	8.80
MG8	18.43	0.58	0.62	0.2	1.72	5.89	6.45
MG9	16.69	0.57	0.62	0.3	1.75	8.58	8.06
DC1	18.70	0.62	0.71	0.4	1.61	11.17	12.67

Post-compression evaluation of TH matrix tablets

Formulation code	Thickness (mm)±SD	Hardness (kg/cm^2) ±SD	Friability (%)±SD	Tablet Weight (mg) ±SD	Drug Content (%)±SD
MG1	1.260±0.06	5.2±0.10	0.81±0.02	197.55±0.64	96.87±0.40
MG2	1.972±0.12	5.5±0.10	0.92±0.03	297.50±0.70	96.18±0.84
MG3	2.648±0.08	6.2±0.10	0.71±0.04	395.40±0.52	95.70±0.52
MG4	1.342±0.08	5.2±0.10	0.89±0.06	196.67±0.57	95.35±0.82
MG5	1.972±0.13	5.4±0.17	0.81±0.05	296.65±0.52	97.19±1.13
MG6	2.647±0.08	5.9±0.10	0.68±0.03	396.80±0.53	96.30±0.39
MG7	2.018±0.15	6.0±0.10	0.83±0.09	295.98±0.89	98.35±0.37
MG8	2.676±0.04	6.4±0.06	0.75±0.07	395.94±1.00	98.76±1.32
MG9	2.640±0.05	6.2±0.06	0.74±0.12	396.94±1.66	99.21±0.56
DC1	2.663±0.32	6.5±0.30	0.87±0.06	398.01±0.68	97.13±0.82

***In- vitro* drug release studies**

Time (h)	% Cumulative drug release					
	MG1(±SD)	MG2(±SD)	MG3(±SD)	MG4(±SD)	MG5(±SD)	MG6(±SD)
1	22.50±1.00	17.40±1.00	11.45±1.00	23.25±0.80	20.69±1.22	15.44±1.22
2	28.66±1.25	21.42±1.04	15.26±0.65	30.46±1.19	26.49±0.78	19.49±0.99
3	34.53±0.98	26.70±0.97	19.40±1.07	36.62±0.97	30.56±1.08	25.48±1.10
4	40.63±1.30	30.65±1.23	23.28±1.01	42.74±1.04	36.59±1.07	29.39±0.86
5	46.69±1.26	35.74±0.96	27.61±0.89	48.66±1.02	42.63±1.19	34.42±0.83
6	52.49±0.94	40.72±1.04	31.64±1.06	54.66±1.20	47.41±0.93	39.46±1.25
7	58.39±1.12	45.60±0.99	35.54±0.81	60.39±0.90	52.41±0.95	44.50±0.92
8	64.37±1.15	49.73±1.01	39.57±0.91	66.56±0.74	57.68±1.11	49.50±1.02
9	70.61±1.35	55.66±0.78	43.28±1.01	72.62±0.73	63.44±0.91	53.31±0.85
10	76.42±0.87	60.41±0.98	48.54±1.21	78.54±1.13	68.61±0.81	57.51±1.07
11	82.30±1.16	65.37±0.93	52.71±1.13	85.35±1.01	74.24±0.96	62.57±0.98
12	86.80±0.45	71.54±1.11	56.59±1.15	92.34±0.89	79.58±0.71	67.66±1.02

Time (h)	% Cumulative drug release				
	MG7(±SD)	MG8(±SD)	MG9(±SD)	DC1(±SD)	Marketed SR Preparation (±SD)
1	14.30±1.12	7.67±0.16	8.62±0.61	44.66±0.60	15.67±1.38
2	18.32±1.01	11.60±0.68	12.30±1.03	53.02±0.80	20.67±1.11
3	22.03±0.90	14.44±0.33	15.84±0.72	60.79±0.93	25.60±0.69
4	25.95±0.77	18.88±0.49	19.62±0.69	68.40±0.82	30.50±0.65
5	28.68±1.42	21.96±0.89	22.29±0.99	76.51±0.54	35.64±1.11
6	32.41±1.06	24.87±0.61	26.64±0.80	85.33±0.40	40.87±0.88
7	35.66±1.51	28.43±0.90	29.35±0.99	92.78±0.57	45.47±1.36
8	39.45±1.13	31.18±0.31	33.89±1.12	98.18±0.20	50.32±1.07
9	43.29±0.89	34.20±1.08	36.46±0.98		55.59±1.22
10	47.46±1.05	37.37±1.09	40.50±1.13		60.90±0.90
11	51.47±1.32	41.30±0.87	44.22±0.91		65.47±0.72
12	54.25±0.88	44.43±0.63	48.36±1.17		71.37±0.83

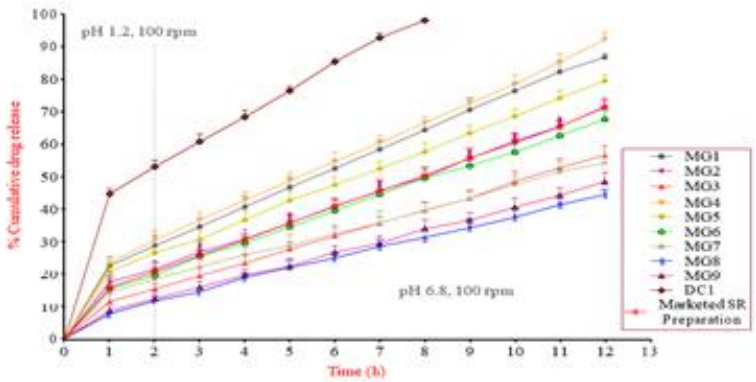


Fig 4: *In-vitro* drug release profile of TH matrix tablet formulation MG1 to MG9, DC1 and marketed SR preparation

Different drug release kinetics models for TH matrix tablets

Table 5: Regression coefficients fits to different drug release kinetics models for TH matrix tablets

Formulation code	Zero order (r^2) ± SD	First order (r^2) ± SD	Higuchi kinetics (r^2) ± SD	Peppas equation	
				(n)	(r^2) ± SD
MG1	0.9980±0.0012	0.9496±0.0057	0.9780±0.0033	0.5679	0.9775±0.0064
MG2	0.9967 ±0.0022	0.9663±0.0064	0.9658±0.0081	0.5903	0.9680±0.0115
MG3	0.9985±0.0007	0.9840±0.0034	0.9715±0.0022	0.6670	0.9804±0.0081
MG4	0.9990±0.0004	0.8970±0.0051	0.9763±0.0040	0.5639	0.9801±0.0046
MG5	0.9994±0.0003	0.9637±0.0006	0.9752±0.0018	0.5616	0.9747±0.0046
MG6	0.9991±0.0001	0.9843±0.0018	0.9790±0.0014	0.6203	0.9818±0.0038
MG7	0.9983±0.0012	0.9886±0.0013	0.9737±0.0026	0.5531	0.9761±0.0070
MG8	0.9981±0.0010	0.9950±0.0020	0.9812±0.0020	0.7164	0.9936±0.0002
MG9	0.9986±0.0004	0.9899±0.0023	0.9728±0.0036	0.7075	0.9879±0.0031
DC1	0.9974±0.0003	0.8535±0.0089	0.9840±0.0070	0.5868	0.9701±0.0085
Marketed SR prep	0.9996±0.0001	0.9749±0.0007	0.9748±0.0008	0.6293	0.9815±0.0054

SD=Standard deviation (n=3) The difference in mean of Zero order, First order, Higuchi kinetics, Peppas Equation between batch series 'MG', batch 'DC1' and marketed SR preparation was significant ($p < 0.05$).

DISCUSSION

Preformulation studies confirmed purity and suitability of TH for sustained release formulation. FTIR spectra indicated absence of chemical interaction between drug and polymers.

Granules exhibited excellent flow properties and compressibility. Post-compression evaluation confirmed mechanical integrity of tablets. Increase in lipophilic binder concentration resulted in increased hardness due to enhanced interparticulate bonding.

In-vitro dissolution studies demonstrated that drug release decreased with increasing polymer concentration. Hydrophobic matrices restricted penetration of dissolution medium and slowed drug diffusion. Combination of Compritol 888 ATO and Precirol ATO 05 showed synergistic effect in retarding drug release.

Formulation MG8 (1:2:1) provided optimum sustained release beyond 12 h and showed comparable or better performance than marketed sustained release preparation.

Release kinetics indicated Zero-order and Higuchi model predominance with non-Fickian diffusion mechanism.

CONCLUSION

Sustained release matrix tablets of Tramadol Hydrochloride were successfully formulated using Compritol 888 ATO and Precirol ATO 05 by melt granulation technique.

Increase in lipophilic binder concentration significantly retarded drug release. Combination of both polymers was more effective than single polymer systems. Formulation MG8 was identified as optimized

formulation providing sustained release for more than 12 h.

Melt granulation technique proved superior to direct compression method in achieving controlled drug release. Thus, lipophilic matrix systems are suitable for sustained release formulation of highly water-soluble drugs like TH.

ACKNOWLEDGMENT

The authors thank the Dr K V Subba Reddy Institute of Pharmacy, Kurnool, A.P, India, for technical assistance and support.

CONFLICT OF INTERESTS

The authors declare no conflict-of-interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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