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RESEARCH ARTICLE

Design and Evaluation of Sustained release matrix tablets for Tramadol Hydrochloride (TH) Melt granulation technique

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ABSTRACT
The objective of the present investigation was to design and evaluate sustained release matrix tablets for Tramadol Hydrochloride (TH) with Compritol 888 ATO and Precirol ATO 05 by melt granulation technique. Sustained drug delivery system to achieve prolonged therapeutic effect by continuous release of drug for extended period of time after single dose administration. TH is a centrally acting synthetic opioid analgesic. Twelve formulations of sustained release matrix tablets were prepared using polymer such as Compritol 888 ATO or Precirol ATO 05. The evaluation results revealed that all formulations comply with the specification of official pharmacopoeias and/or standard reference with respect to general appearance, content uniformity, hardness, friability and buoyancy. Out of all the formulations, MG8(TH:Compritol888ATO:PrecirolATO5,1:2:1) showed maximum retardation of drug release which may be attributed to high lipophilicity, high melting point(65°Cto77°C)of Compritol888ATO. Matrix tablets of TH prepared by melt granulation technique shows retardation of drug release more effectively than tablet prepared by direct compression of physical mixture.
Key words: Tramadol Hydrochloride (TH), Sustained release, Compritol 888 ATO, Precirol ATO 05, Melt granulation technique, Formulation

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CONTENTS

1. Introduction

Sustained release, sustained action, prolonged action, controlled release, extended action and timed released depot dosage forms are the terms used for identifying this drug delivery system, which achieve prolonged therapeutic effect by continuous release of drug for extended period of time after single dose administration. Sustained release defined as the any drug or dosage form modification that prolongs the therapeutic activity of the drug. The amount of drug in the body decrease slowly once the maximum level is reached. So it will take longer time to drop below the therapeutic range.

Advantages of sustained release products:

- Improved Patient compliance.
- Decreased local and systemic side effects.
- Improved efficiency in the treatment.
- Employ less total drug.
- Economy.

Melt granulation technique:

Industrial application of the extrusion process dates back to 1930's. Hot-melt extrusion is one of the most widely applied processing technologies in the plastic rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. Several research groups have evaluated this technology to achieve enhancement in dissolution rates for poorly water soluble drugs, to modify drug release and transdermal passage of the drug. Extrusion is the process of converting a raw material into a product of uniformshape and density by forcing it through a die under pressure.

Drug Profile:

Tramadol Hydrochloride (TH) is a centrally acting synthetic opioid analgesic. Binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of nor epinephrine and serotonin are considered as two possible mechanisms. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than Tramadol in producing analgesia and 200 times more potent in μ -opioid binding. The relative contribution of both Tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

2. Materials and Methods

Materials: All the materials used in the formulations, evaluations and other experiments are listed below. The chemicals used were of laboratory reagent grade. The distilled water was used in all experiments.

Table 1: List of materials used with supplier

Name of materials	Supplier/Manufacturer name
Tramadol Hydrochloride	Neon laboratories Ltd, Mumbai, India.
Compritol888 ATO	Gattefosse, France
PrecirolATO5	Gattefosse, France
Concentrated HCl	Finechemicals Ltd, Mumbai,India
Sodiumhydroxide	Finechemicals Ltd, Mumbai,India
Potassiumdihydrogenphosphate	Finechemicals Ltd, Mumbai,India
Methanol	S.D. Fine Chem. Limited, Mumbai, India
Ethanol	S.D. Fine Chem. Limited, Mumbai, India
Chloroform	S.D. Fine Chem. Limited, Mumbai, India

Table 2: List of instruments used with manufacturers

Name of instruments	Manufacturer name
Single pan electronic balance	Essae Teraoka Ltd, Mumbai.
UV visible double beam spectrophotometer	Shimadzu 1800, Japan
FTIR spectrophotometer	IRAffinity-1, Shimadzu, Japan
Digital pH meter	Digisun electronic Hyderabad.
Digital melting point apparatus	Shital scientific industries, Mumbai
Electronic water bath	Shital scientific industries, Mumbai
Sieves	Mohan industries, Mumbai
Bulk density apparatus	Biological museum, Mumbai
KBR press	Shimadzu, Japan
Pfizer hardness tester	Biological museum, Mumbai
Digital vernier caliper	Biological museum, Mumbai
Roche friability tester	Biological museum, Mumbai
USP tablet dissolution apparatus type II	Electrolab, TDT-08L

3. Results and Discussion

Pre formulation study of TH matrix tablets:

The pre formulation study of drug was carried out by conducting various physicochemical tests including description, solubility, melting point and pH determination, spectral analysis such as UV spectrum and IR spectrum for pure TH.

Description: The sample of TH was found to be white amorphous powder, bitter taste.

Solubility: The TH was readily soluble in water, ethanol and methanol.

Melting point: The melting point was determined by open capillary method and the melting point was found to be 1800C.Thereportedmeltingpointisabout1800C to 1840C. From this result we concluded that drug sample is pure.

Estimation of TH by UV spectroscopy:

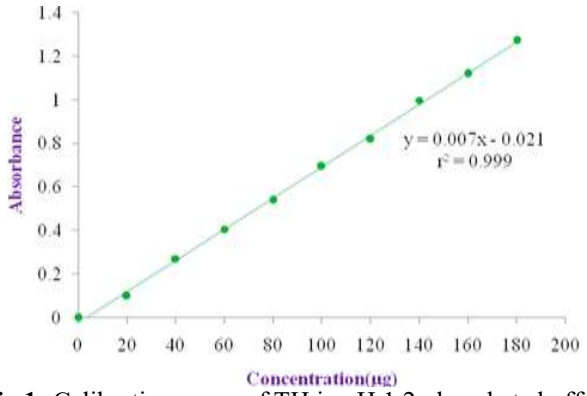

Fig 1: Calibration curve of TH in pH 1.2 phosphate buffer at 271nm

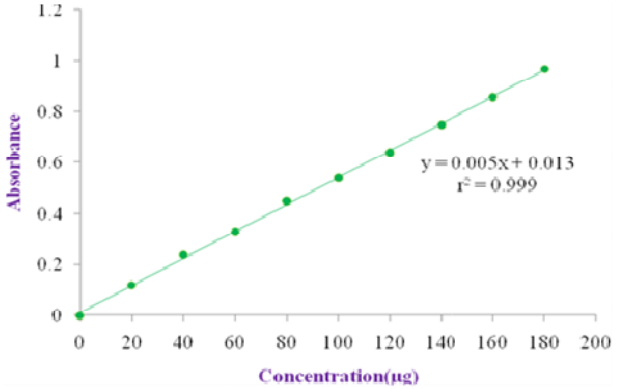

Fig 2: Calibration curve of TH in pH 6.8 phosphate buffer at 271 nm

FT-IR Studies:

From IR spectroscopic study, it was found that there was no evidence of interaction between drug and polymers.

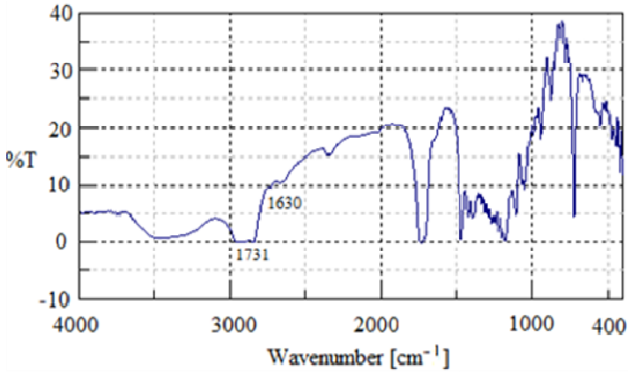

Fig 3:IR spectrum of (a) TH (b) TH: compritol 888 ATO (c) TH: Precirol ATO 5 (d) compritol 888 ATO and (e) Precirol ATO 5

Pre-compression evaluation:

Various micromeritics properties of the granules from each batch are summarized in table 6.The granules of various formulations containing drug and meltable binders were evaluated for the angle of repose, Loose Bulk Density (LBD), Tapped Bulk Density (TBD), void volume, and total porosity. These In Process Quality control (IPQC) parameters were evaluated for the flow properties and the compressibility of granules.

Post-compression evaluation of TH matrix tablets:

Tablets of each formulation type (MG1 to MG9) were evaluated for parameters such as weight variation, drug content, thickness, diameter, hardness and friability given in table 7.Tablets with acceptable physical properties were obtained in all formulations studied.

In-vitro drug release study of TH matrix tablets:

The in-vitro drug release characteristics were studied in 900 ml of pH 1.2 was used for 2 h followed by 10 h study in pH 6.8 phosphate buffer using USP type II dissolution apparatus. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermined manner.

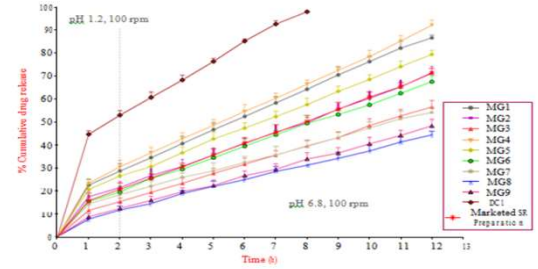

Fig 4: In-vitro drug release profile of TH matrix tablet formulation MG1 to MG9, DC1 and marketed SR preparation

In-vitro dissolution comparison of formulation MG1 to MG9 with marketed preparation: Dissolution profiles of formulation containing Compritol 888 ATO as matrix former reveals that formulation MG1, MG2, MG3 shows 86.80 ± 0.45%, 71.54 ± 1.11% and 56.59 ± 1.15% drug release at the end of 12 h respectively. In MG1 to MG3 formulations MG3 shows maximum drug release retardation because of high concentration of Compritol 888 ATO (1:3) i.e. 56.59 ± 1.15%.

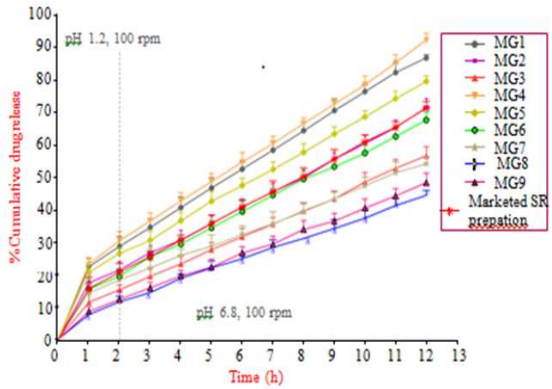

Fig 5: Comparative release profiles of formulation MG1 to MG9 with marketed preparation

In-vitro drug release study of TH matrix tablets:

The in-vitro drug release characteristics were studied in 900 ml of pH 1.2 was used for 2 h followed by 10 h study in pH 6.8 phosphate buffer using USP type II dissolution apparatus. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermined manner.

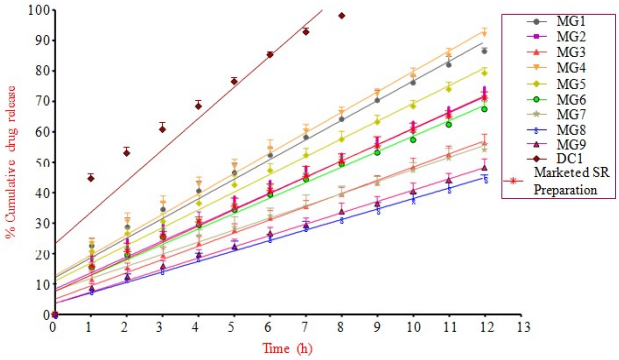

Fig 6: Zero order release kinetics profile of TH matrix tablets

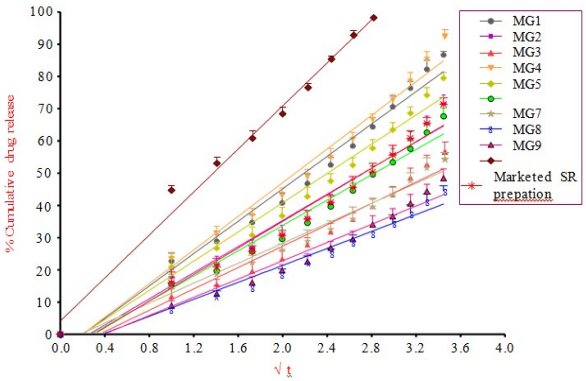

Fig 8: Higuchi release kinetics profile of TH matrix tablets

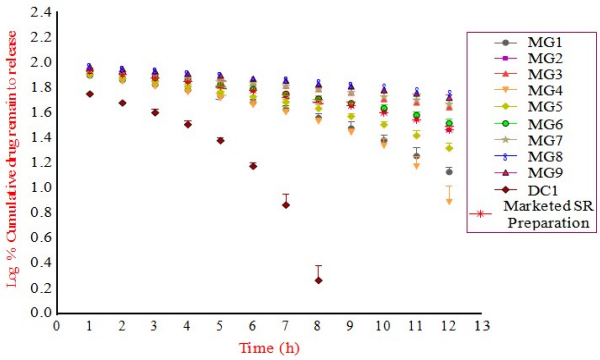

Fig 7: First order release kinetics profile of TH matrix tablets

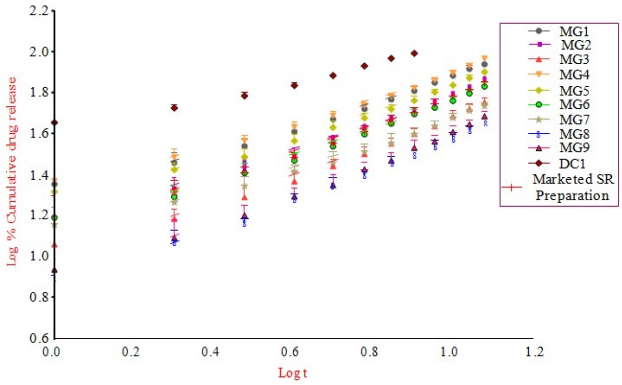

Fig 9: Peppas release kinetics profile of TH matrix tablets

Table 3: Absorbance data for the calibration curve of TH in pH 1.2 phosphate buffer at 271 nm

Sl.No.	Concentration(µg/ml)	Absorbance
1.	0	0.000
2.	20	0.101
3.	40	0.271
4.	60	0.407
5.	80	0.539
6.	100	0.695
7.	120	0.819
8.	140	0.998
9.	160	1.120
10.	180	1.272

Table 4: Absorbance data for the calibration curve of TH in pH 6.8 phosphate buffer at 271 nm

Sl.No.	Concentration(µg/ml)	Absorbance
1.	0	0.000
2.	20	0.120
3.	40	0.239
4.	60	0.329
5.	80	0.451
6.	100	0.542
7.	120	0.641
8.	140	0.750
9.	160	0.858
10.	180	0.970

Table 5: Interpretation of FTIR spectrums of 1) TH 2) TH and Compritol 888ATO 3) TH and Precirol ATO 05 4) Compritol 888ATO 5) Precirol ATO 05

Sl. No.	IR spectrum	Peak area (cm-1)	Functional groups	Stretching/Deformation
1	TH	3500	N-H(3OAmine)	StretchingVibration
		1325	C-N	StretchingVibration
		2786	C-H(alkyl)	Stretch
		3652-3682	O-H(alcoholic)	Stretch
2	TH and Compritol888 ATO	3402	N-H (3OAmine)	StretchingVibration
		1298	C-N	StretchingVibration
		2730	C-H(alkyl)	Stretch
		3662	O-H(alcoholic)	Stretch
		1623	C=C(ethylene)	Stretch
		1736	C=O(carbonylgroup)	Stretch
3	THand PrecirolATO 05	3392	N-H (3OAmine)	StretchingVibration
		1295	C-N	StretchingVibration
		2780	C-H (alkyl)	Stretch
		3662	O-H(alcoholic)	Stretch
		1737	C=O(carbonylgroup)	Stretch
		1625	C=C(ethylene)	Stretch
4	Compritol888 ATO	1632	C=C(ethylene)	Stretch
		1733	C=O(carbonylgroup)	Stretch
5	PrecirolATO05	1630	C=C(ethylene)	Stretch
		1731	C=O(carbonylgroup)	Stretch

Table 6: 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

Table 7: Post-compression evaluation of TH matrix tablets

Formulation code	Thickness (mm)±SD	Hardness 2 (kg/cm)±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

SD=Standard deviation (n=3).The difference in mean of Thickness, Hardness, Friability, Tablet weight, Drug content between batch series 'MG' and batch 'DC1'wassignificant($p<0.05$).

Table 8: In-vitro drug release data of TH matrix tablet formulation MG1 to MG9, DC1 and marketed SR preparation

Time (h)	%Cumulativedrugrelease					
	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)	MarketedSR 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

Table 9: Regression coefficients fit to different drug release kinetics models for TH matrix tablets

Formulation code	Zero order (r2)±SD	First order (r2)±SD	Higuchi kinetics (r2)±SD	Peppas equation	
				(n)	(r2)±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 SRprep	0.9996±0.0001	0.9749±0.0007	0.9748±0.0008	0.6293	0.9815±0.0054

4. Conclusion

The aim of present investigation was to design and evaluate sustained release matrix tablets for TH with Compritol 888 ATO and Precirol ATO 05 by melt granulation technique. The tablets were prepared by melt granulation technique, have good hardness so that they can withstand mechanical shock and remain intact throughout gastrointestinal tract. There was no variation in content uniformity, thickness and weight. Matrix tablets of TH showed the release over a period of more than 12 h. The formulations MG7, MG8 and MG9 that is having combination of Compritol 888 ATO and Precirol ATO 05 retarded the drug release for more than 12 h.Amongst all formulation MG8 (TH : Compritol 888 ATO : Precirol ATO5, 1:2:1) showed maximum retardation of drug release which may be attributed to high lipophilicity, high melting point (65°C to 77°C) of Compritol 888 ATO. It was observed that formulations MG3 and MG6 to MG9 showed the drug release for prolonged duration than marketed preparation of TH. The best fit with the highest determination r2 was shown by both the zero order and Higuchi models. The values of n were in the range of 0.5531 to 0.7164 (n is more than 0.5) indicating non-fickian release governed by the drug diffusion.

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