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Development and In-vitro Evaluation of Oral Sustained Release Formulation of Tramadol Hydrochloride

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Abstract

Tramadol Hydrochloride (TH) is an effective centrally acting analgesic with good oral bioavailbility and relatively short elimination half-life. The usual dose of TH is 50-100mg three to four times a day, which results in decreased patient compliance and increased incidence of side effects especially on long term use, in conditions like arthritis, osteoarthritis, arthralgia etc. Thus present study was aimed to formulate and evaluate matrix tablets of TH to achieve sustained drug release with reduced frequency of drug administratiion, side effects and improved patient compliance. Matrix tablets of TH were prepared by direct compression technique, using polymers like hydroxypropyl methyl cellulose (HPMC), guar gum (GG) and xanthan gum (XG) alone and in combination in different proportions. Optional excipient, sodium carbonate and diluent lactose were also used. All the batches were evaluated for thickness, weight variation, drug content uniformity, and in-vitro drug release characteristics as per USP XXIV monograph. The drug release characteristics from matrix tablets were compared with commercial sustained release (CSR) tablet of TH. The release kinetics and mechanism of drug release by regression coefficient analysis and Peppas exponential model equation were investigated. Matrix tablets having HPMC prolonged the rate and extent of drug release maximally followed by XG and GG. Increasing percentage of sodium carbonate in core further prolonged the rate and extent of drug release. Formulations with HPMC only followed almost zero-order drug release whereas all other batches followed either Higuchi or super case II transport mechanism. Prepared matrix tablets provided more sustained drug release as compared to CRS tablets.

Keywords: Tramadol hydrochloride, Matrix tablet, Higuchi diffusion, Sustained drug release, Hydroxy propylmethylcellulose

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Introduction

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages. Sustained release dosage forms would be the most applicable one for drugs having low therapeutic indices and short elimination half-lives (George *et al.*, 1987). Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymers (Carstensen., 1987; Mokel and Lipplod., 1993; Bettini., 1997). Combination of nonionic polymer HPMC and anionic polymer Sodium CMC as the polymer matrix resulted in near zero-order release (Rani and Mishra., 2001). Matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behaviour (Mishra *et al.*, 2003). Tramadol Hydrochloride (TH) is an effective centrally acting analgesic with relatively short elimination half-life (5-6 hrs) and it is usually administered in 50-100 mg dose three to four times a day (Lee *et al.*, 1993). As a result of its short half-life and frequent administration, the development of oral sustained release formulation of this drug is highly desirable, so as to improve the therapeutic effect with minimum side effects and improved patient compliance (Tiwari *et al.*, 2003). Thus, the objective of the present study was to develop sustained release formulation of TH as matrix tablets. The drug release rates from matrix tablets were compared with commercial sustained release (CSR) tablet.

Materials and Methods

Materials

Tramadol hydrochloride (TH) was obtained as gift sample from ModimundiPharma Ltd, Modipuram, India. HPMC K4 M and Xanthan gum were obtained as gift samples from Ind-Swift Ltd. Panchkula, India. Guar gum, Lactose and Sodium carbonate were purchased from S.D. Fine Chemicals Ltd, Poicha, India. All other chemicals used were of analytical grade.

Method

Drug Analysis: TH was analysed by Ultaviolet- visible (UV) spectrophotometer (JASCO Model –7800, Tokyo, Japan) at λmax 271nm. Calibration curve was prepared in 0.1 N hydrochloric acid (pH 1.2), acetate buffer of pH 4.5, and phosphate buffer of pH 7.4 in concentration range of 1-100µg/ml. Correlation coefficients were found to be r>0.9995 in all the cases and no interference of additives used in formulation was observed.

Preparation of Matrix Tablets: The matrix tablets were prepared by direct compression technique according to formulas given in Table 1. The drug, polymer/s, diluent, sodium carbonate (Batch IX- XII) and magnesium stearate (1%) were blended uniformly in a mortor manually through geometric dilution. The homogenous blend was then compressed into tablets of 340mg weight on a single station tabletting machine (Manesty E-2 type, U.K.) using 9mm diameter standard punches. Compression force was adjusted to hardness of 6 kg/cm^2 on Monsanto hardness tester.

Table1. Formulas for preparing matrix tablets of Tramadol Hydrochloride

Batch No.	Ingredients per Tablet (in mg)						
	Drug	HPMC K4M	Xanthan Gum	Guar Gum	SC	Lactose	MS
Batch I	100	100	-	-	-	136	4
Batch II	100	150	-	-	-	86	4
Batch III	100	200	-	-	-	36	4
Batch IV	100	-	150	-	-	86	4
Batch V	100	-	-	150	-	86	4
Batch VI	100	75	75	-	-	86	4
BatchVII	100	75	-	75	-	86	4
Batch VIII	100	-	75	75	-	86	4
Batch IX	100	190	-	-	10	36	4
Batch X	100	180	-	-	20	36	4
Batch XI	100	166	-	-	34	36	4
Batch XII	100	149	-	-	51	36	4

SC: Sodium Carbonate MS: Magnesium stearate

- Indicates no ingredient

Compression parameters: All batches were evaluated for thickness, weight variation, hardness, friability and drug content uniformity as per USP XXIV monograph.

In vitro drug release studies: The studies were done on a single station USP XXIV dissolution apparatus II (Cambell Electronics, Mumbai, India). All batches of tablets were evaluated (3 runs for each batch) using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrochloric acid (pH 1.2) for first two hours, acetate buffer of pH 4.5 for next 2 hrs and then phosphate buffer of pH 7.4 for remaining 4 hours, maintained at 37 ± 0.1°C and stirred at 100 rpm. 5 ml of aliquots were withdrawn at different time intervals and an equivalent volume of medium prewarmed at 37°C was added to maintain the constant volume. Withdrawn samples were analysed spectrophotometrically at 271 nm. Actual amount of released drug was determined from the calibration curve.

Commercial sustained release (CSR) tablet: CONTRAMAL® was purchased from the market and was evaluated for thickness, weight variation, hardness, friability, drug content uniformity and *in vitro* release characteristics following the above procedure.

After analyzing the drug content in dissolution samples, corrections were made for volume replacement and the graph of cumulative percent drug release versus time was plotted. Release profiles of formulations were compared using model independent pairwise approach, which included the calculation of "difference factor" $f1$ and "similarity factor" $f2$ (Costa and Lobo, 2001). The two release profiles were considered to be similar, if $f1$ was lower than 15 (between 0-15) and $f2$ was more than 50 (between 50-100) and dissimilar when $f1$ and $f2$ were beyond the above range. Release profiles were also compared using mean dissolution time (MDT), which was calculated using following equation (Costa and Lobo, 2001)

$$\text{MDT:} \quad \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

Where j is the sample number, n is the number of dissolution sample times, t_j is the time at mid point between tj and t_{j-1}(easily calculated with the expression $(tj+t_{j-1})/2$), and ΔMj is the additional amount of drug dissolved between tj and t_{j-1}.

Statistical analysis: Experimental results were expressed as mean $\pm$ S.D. values. Student's t-test was performed to determine the level of significance. Difference was considered to be statistically significant at $p<0.05$.

Stability study: Stability studies were conducted on the promising formulation (batch-II) to assess its stability with respect to physical appearance, drug content and release characteristics. Tablets were placed in ICH certified stability chamber maintained at 40°C and 75% RH for 1and 3 months. They were withdrawn periodically (at the end of 1 and 3 months) and evaluated for drug content and release characteristics.

Reproducibility study: The reproducibility of the manufacturing procedure was confirmed by preparing three repeated batches of the promising formulation (batch-II) on three different occassions. Drug release characteristics of batches were conducted under similar conditions and were compared with previous release profiles of the same bathches.

Results and Discussion

Various physical parameters were evaluated. The variation in thickness, weight, hardness, friability and drug content values of all the prepared tablets and CSR tablet in reference to average values for each parameter were found within official limits (Table 2).

In-vitro drug release study: In-vitro release study of almost all batches showed controlled and sustained drug release profiles (Fig. 1, 2) as compared to standard marketed tablet. Further in vitro data of all the batches were evaluated to study the effect of following variables.

Table 2. Physical characteristics (± S.D.) of matrix tablets of Tramadol Hydrochloride

Batch No.	Weight(mg)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
Batch I	348.5±2.1	0.01	6.0±0.58	4.60±0.10	99.99
Batch II	351.3±3.14	0.09	5.5±0.78	4.55±0.10	99.45
Batch III	352.4±1.42	0.02	6.2±0.88	4.60±0.20	100.23
Batch IV	353.7±1.65	0.22	5.8±0.57	4.58±0.30	101.34
Batch V	349.5±1.55	0.19	5.6±0.76	4.48±0.10	99.37
Batch VI	355.1±1.80	0.15	5.9±0.52	4.59±0.20	99.91
BatchVII	347.2±1.50	0.07	6.0±0.55	4.60±0.13	99.93
Batch VIII	351.8±1.50	0.18	6.1±0.88	4.60±0.22	99.19
Batch IX	351.6±1.72	0.19	5.8±0.82	4.48±0.10	100.01
Batch X	348.3±1.53	0.08	5.7±0.76	4.60±0.10	100.47
Batch XI	355.1±1.80	0.11	5.6±0.41	4.59±0.20	101.22
Batch XII	347.2±1.50	0.13	5.6±0.52	4.60±0.13	99.79
CSR tablet	355.1±0.12	0.02	6.0±0.32	5.10±0.20	100.23

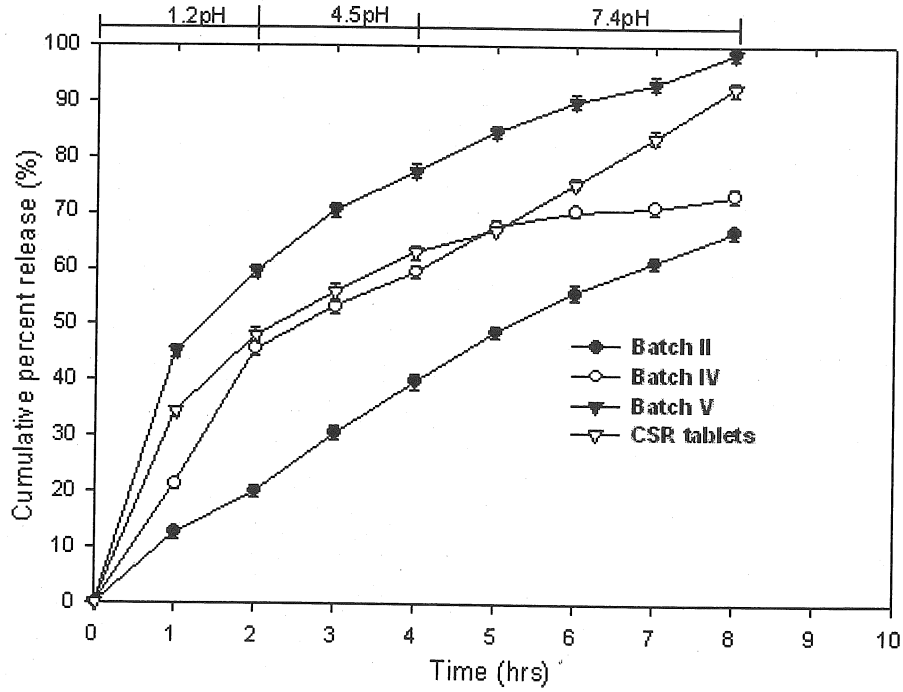

Figure 1. Effect of various polymers on TH release from the Matrix tablets in comparison to CSR tablet. Bars represent ±S.D. (n=3)

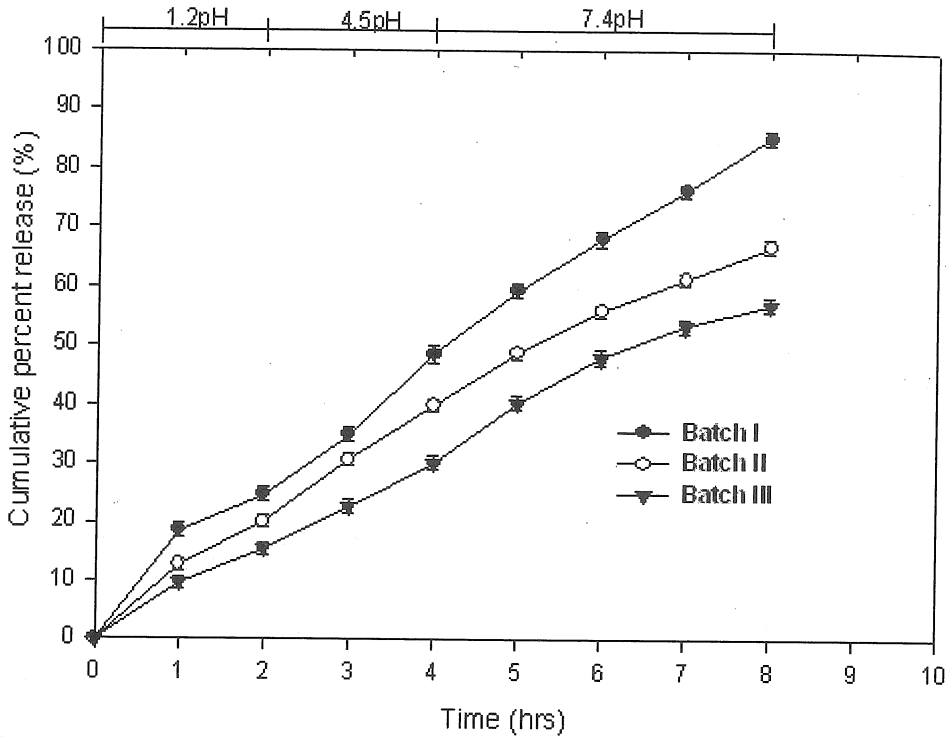

Figure 2. Effect of different amounts of HPMC on TH release from matrix tablets. Bars represent ±S.D. (n=3)

Effect of different polymers: Three different polymers hydroxypropyl methylcellulose (HPMC), xanthan gum (XG) and guar gum (GG) have been used to prepare the matrix tablets. To study the effect of different polymers on TH release, in-vitro drug release profiles of batches II, IV and V having HPMC, XG, and GG, respectively (each in drug, polymer ratio of 1:1.5) are compared in Fig 1. Results indicated that HPMC based (Batch II) tablet provided significantly ($p<0.05$) more sustained TH release followed by XG (Batch IV) and GG (Batch V) based tablets. Drug release from Batch II was more linear. This might be due to higher viscosity and high molecular weight of HPMC K4 M in addition to its slower rate of erosion and higher swelling than XG and GG (Lucy *et al.*, 1992). GG and XG based tablets exhibited burst drug release in the acidic medium (Khullar *et al.*, 1998) for first two hours followed by slower drug release profiles. However, XG based tablets exhibited more sustained drug release than GG based tablets. Performance of marketed tablet in terms of rate and extent of drug release was faster than Batch-II, almost equal to Batch-IV and slower than Batch-V.

Effect of amount of polymer: To study the effect of different amounts of polymer (HPMC) on drug release, release profiles of Batches I, II, III having HPMC to drug ratio 1:1, 1.5:1 and 2:1 respectively were compared in Fig 2. Results suggested that release of TH significantly ($p<0.05$) decreased with increase in polymer concentration. All batches exhibited linear drug release profiles without any burst effect.

Effect of combination of polymers: Effect of combination of polymers on drug release were studied by preparing matrix tablets (Batches VI-VIII) using combination of any two polymers in drug-polymer ratio 1:1.5 and polymer- polymer ratio 1:1. Release profiles of Batches VI, VII and VIII having combination of HP: XG, HP: GG and GG:XG, respectively, were compared in Fig. 3.

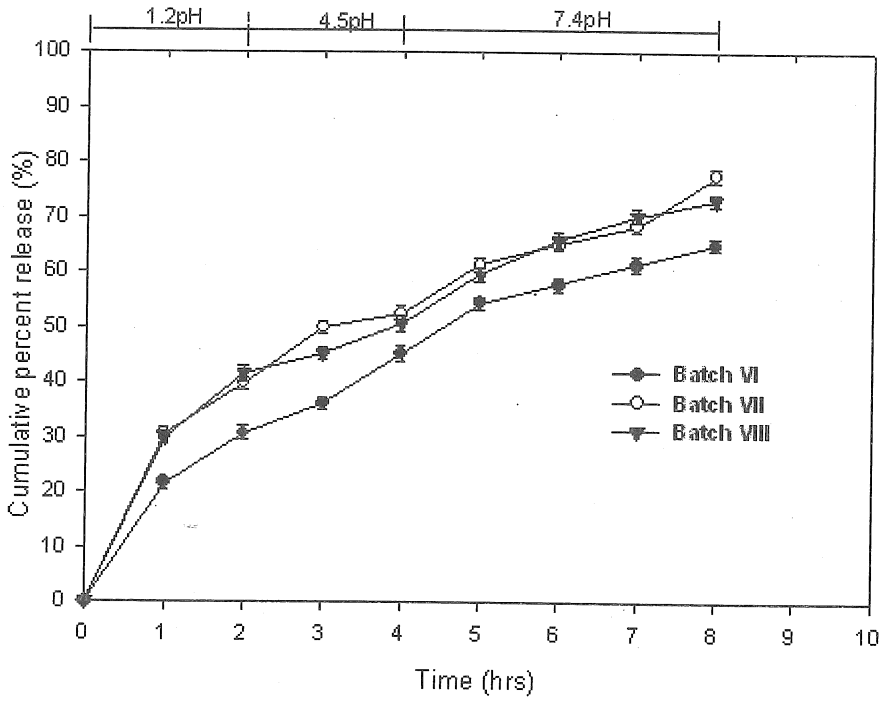

Figure 3. Effect of combination of any two polymers on TH release from matrix tablets. Bars represent ±S.D. (n=3)

Results indicated that batch VI (HPMC: XG) significantly ($p<0.05$) sustained the drug release (65% in 8 hrs) followed by batch VIII (GG: XG, 73.18%) and batch-VII (HPMC: GG, 77.65%). This effect was due to high molecular weight and viscosity of individual polymers in Batch VI as compared to other batches containing HPMC:GG and XG:GG polymers (Bhardwaj., 2001). Further when the release profiles (Fig. 3) of batches VI to VIII

containing combination polymers were compared with profiles (Fig.1) of batches II,IV and V containing individual polymers, it was observed that combination of polymers either further sustained the drug release or exhibited similar rate and extent of drug release in some cases, as provided by single individual polymer.

Effect of sodium carbonate (SC): The effects of different amounts (3%, 6%, 10% and 15% w/w of total weight of tablet) of sodium carbonate on drug release profiles from HPMC based matrix tablets were compared with profile of batch II (without SC) in Fig 4.

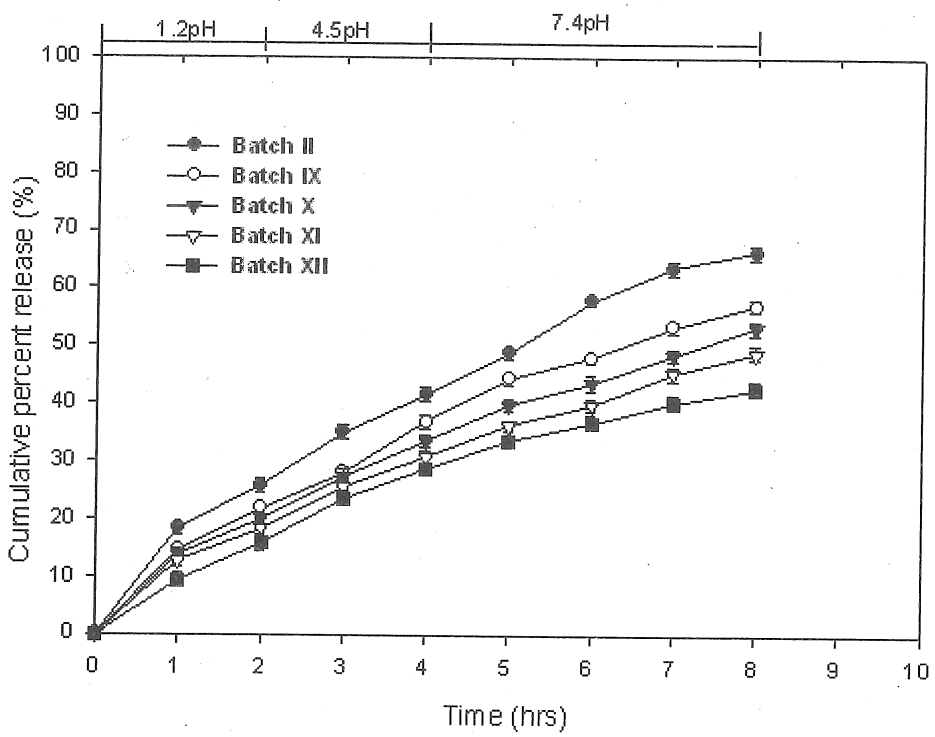

Fig. 4. Effect of different amounts of sodium carbonate on TH release from HPMC based matrix tablets. Bars represent ±S.D. (n=3)

It was observed that, even after decreasing the amount of polymer in the tablet with consequential increase in SC concentration, the rate and extent of drug release was significantly ($p<0.05$) decreased.It is evident from the fact that batch XII containing maximum percentage (15%) of SC delivered only 38% of drug in 8 hrs followed by batch XI (43%), batch X (53%), IX (56%) and batch II (which does not contain SC, 66%). This may be attributed to competing effect of SC against polymer for available water molecule, thus retarding the immediate hydration of the polymer. SC molecules could also compete with

TH for water molecule causing slower solubilization of TH, thus avoiding not only the immediate burst effect but also could cause further sustaining drug release.

Release Kinetics: In order to investigate the drug release kinetics, data were fitted to models (Sankar *et al.*, 2001) representing zero-order, first-order and Higuchi's square root of time. The data were analysed by the regression coefficient method and regression coefficient value (r^2–value) of all batches were shown in Table 3. On analysing regression coefficient values of all batches, it was found that Batches IV, V, VI, VII and VIII, and CSR tablet followed Higuchi model, whereas Batches IX, X, XI, and XII followed first order kinetics.

Table 3. Release kinetics of Tramadol Hydrochloride from Matrix and CSR tablets.

Batch No.	**Regression Coefficient (R)**		
	Zero-order	**First order**	**Higuchi**
Batch I	**0.9940**	0.9789	0.9774
Batch II	**0.9948**	0.9885	0.9922
Batch III	**0.9912**	0.9897	0.9779
Batch IV	0.8202	0.9053	**0.9100**
Batch V	0.9514	0.9968	**0.9976**
Batch VI	0.9706	0.9851	**0.9871**
BatchVII	0.9617	0.9899	**0.9927**
Batch VIII	0.9054	0.9917	**0.9927**
Batch IX	0.9701	**0.9886**	0.9776
Batch X	0.9717	**0.9898**	0.9815
Batch XI	0.9727	**0.9894**	0.9809
Batch XII	0.9608	**0.9915**	0.9773
CSR tablet	0.9507	0.8667	**0.9966**

However, Batches I, II, III exhibited almost zero-order kinetics. Furthermore, to understand the drug release mechanism, the data were fitted to Peppas exponential equation $M_t/M_\infty = Kt^n$, where M_t/M_∞ was the fractional drug release into the dissolution medium, K was a constant which incorporates the properties of the macromolecular polymeric system and drug and n was the diffusional exponent, which characterized the drug transport mechanism (Agarwal and Mishra., 1999).

Where n ≤ 0.5 indicates quasi-Fickian diffusion mechanism, n > 0.5 an anomalous non-Fickian diffusion and the special case of n = 1 that has gained importance due to its potential application in the development of swelling controlled drug delivery systems with zero-order kinetics indicates pseudo-case-II transport mechanism. In the present study it was observed (Table 4) that except batches V-VII and CSR tablet (n value <0.5) all other prepared tablets followed non-Fickian diffusion mechanism (n value >0.5), which indicated drug release to occur through diffusion and relaxation.

Table 4. Drug release Mechanism from different matrix tablets (using Peppas exponential model equation)

Batch No.	**K**	**n**	**r^2**
Batch I	10.65	0.7788	0.9940
Batch II	8.22	0.8319	0.9948
Batch III	7.11	0.9061	0.9961
Batch IV	9.03	0.5547	0.9100
Batch V	12.33	0.3759	0.9976
Batch VI	7.62	0.4936	0.9908
BatchVII	9.70	0.4591	0.9927
Batch VIII	9.39	0.4834	0.9929
Batch IX	6.98	0.6853	0.9886
Batch X	6.85	0.6665	0.9898
Batch XI	6.22	0.6661	0.98943
Batch XII	5.54	0.7446	0.9915
CSR tablet	11.5	0.4539	0.9958

Stability Study: Prepared formulations were paked in strip of 0.04mm thick aluminium foil laminated with PVP and stored in ICH certified stability chamber maintained at 40 ^{O}C and 75% RH for 3 months. The tablets were periodically

withdrawn (1, 3 Month) and evaluated for drug content, and release profiles. The formulations were found to be stable in terms of drug content and dissolution stability (Table 5).

Table 5. Evaluation of formulation (Batch II) after 3 month of storage at 40°C and 75% RH

Parameter	Initial	One month	Three month
Drug content (%)	99.99	99.89	98.62
Hardness(kg/cm^2)	6.0±0.58	5.8±0.48	5.6±0.98
f 1	-	8.23	8.05
f2	-	69.55	68.69
$MDT_{65\%}$ (hrs)	3.470	3.465	3.478

MDT: Mean dissolution time

Reproducibility Study: Three repeat batches of promising Batch-II were prepared and release studies were conducted under the same conditions. It was observed that each set produced similar rate and extent of drug release, without any significant difference at any of the sampling times (Fig. 5), demonstrating that the manufacturing procedure was reliable and reproducible.

The f1 and f2 values were found to be 8.95 and 72.68 for Batch IIa and IIb, 9 and 70.84 for Batches IIa and IIc, and 6.84 and 76.52 for batches IIb and IIc, respectively indicating no significant difference in release data for the same batch II prepared on three different occasions.

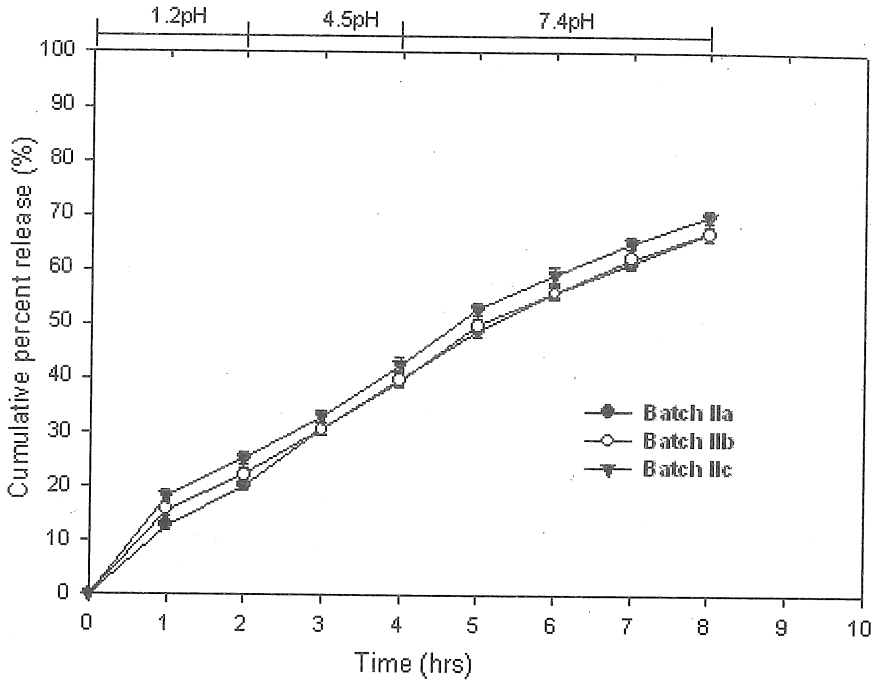

Figure 5. Reproducibility of manufacturing procedure- TH release from three repeat batches of Batch II. Bars represent ±S.D. (n=3) (a,b,c represent same batch prepared on three different occasions)

Conclusion

Results indicated that viscosity of polymer, amount of polymer and presence of SC in formulation significantly affect the TH release from Matrix tablet. Thus, it was concluded that the potential sustained release matrix tablets of TH could be prepared using optimized amount of polymer(s) (HPMC alone or in combinations with other swellable polymers like XG and guar gum) and electrolyte like sodium carbonate. Prepared matrix tablets of TH have shown more sustained release as compared to CSR tablet of TH.

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