

Development and Evaluation of Elementary Osmotic Pump of Highly Water Soluble Drug: Tramadol Hydrochloride

Pramod Kumar*, Sanjay Singh and Brahmeshwar Mishra

Department of Pharmaceutics Institute of Technology Banaras Hindu University, Varanasi-221005, U.P., India

Abstract: In the present study Elementary osmotic pump (EOP) of highly water soluble drug tramadol hydrochloride (TRH) was developed and evaluated. Target release profile was selected and different variables were optimized to achieve the same. Formulation variables like levels of swellable polymer (10-21.87 %) and plasticizer (0-20% w/w of polymer), and coat thickness of semipermeable membrane (SPM) were found to affect the drug release from the developed formulations. TRH release was directly proportional to the level of plasticizer and osmotic pressure generated by osmotic agent but inversely proportional to the level of swellable polymer within the core and coat thickness of SPM. Drug release from developed formulations was independent of pH and agitation intensities of release media. Burst strength of the exhausted shells increased with increase in coat thickness but decreased with increase in level of plasticizer. The *in-vitro* results of the developed formulations were compared with performance of standard marketed formulation of TRH. The developed formulation provided more prolonged and controlled TRH release as compared to marketed formulation. The manufacturing procedure was found to be stable during six months of accelerated stability study.

Keywords: Elementary osmotic pump, tramadol hydrochloride, swellable polymer, semipermeable membrane.

1. INTRODUCTION

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. Wide spectrums of osmotic devices are in existence, out of them osmotic pumps are unique, dynamic and widely employed in clinical practice [1, 2]. Osmotic pumps offer many advantages like they (i) are easy to formulate and simple in operation, (ii) improve patient compliance by reducing dosing frequency (iii) provide good *in-vitro in-vivo* correlation [3] (iv) and their industrial adaptability vis-a-vis production scale up is easy [1, 3]. Although different types of oral osmotic systems have been reported in literature, but most important osmotic delivery system is 'Theeuwes elementary osmotic pump' (EOP) [1, 2]. Because of its simple structure and high efficiency, EOPs are the most commercially important osmotic devices and more than 240 patents have been devoted. Procardia XL[®] and Adalat CR[®] (nifedipine), Acutrium[®] (phenylpropranolamine), Minipress XL[®] (prazosin) and Volmax[®] (salbutamol) are examples of EOPs available in the market [1-3]. In this system, the osmotic core is surrounded by a semipermeable membrane drilled with a drug delivery orifice. Once this system comes in contact with the gastrointestinal fluids, the osmotically driven water enters the system through the semipermeable membrane, dissolves the soluble agents, and exits through the delivery orifice. Because these systems use osmotic pressure for the controlled delivery of the active compound(s), delivery rates are expected to be independent of gastrointestinal condition [4]. The rate of drug release from osmotic pumps is dependent on the total solubility and the osmotic pressure of the core. The poorly water-soluble

drugs do not create sufficient osmotic pressure and are delivered at low rates. To overcome this problem, other types of osmotic pumps for poorly water-soluble drug have been designed which are very complicated in design and difficult to optimize [5, 6]. In contrast, highly water-soluble drugs may create considerable osmotic pressures and may release the active drug at undesirable high rates. In some cases this problem may be solved by addition of a solubility-modulating agent to the core [7, 8]. However this approach is not satisfactory in cases where large amounts of the modulator are necessary. In addition rapid depletion of the modulator from the system will cause the device to release the drug at non-uniform rates.

Tramadol hydrochloride (TRH) a centrally acting opioid analgesic used in severe acute or chronic pains [9, 10]. It offers several therapeutic advantages over other analgesics such as good oral bioavailability, and long elimination half life (5-7 hrs). Despite the long elimination half life, TRH prescribed 3-4 times a day [11]. Frequent dosing schedule often lead to decreased patient compliance, increased incidence of side effect and tolerance development especially on long term use in conditions like arthritis, osteoarthritis, arthralgia, postoperative surgical pains etc. [12]. Thus there is strong clinical need and market potential for a delivery system that will deliver TRH in controlled manner. TRH is a freely water soluble drug (>500mg/ml) [13] hence and its release from EOP is usually high. Recently it has been reported that presence of swellable polymer within the core of EOP can modulate the drug release [14]. Inclusion of swellable polymer is expected to cause significant swelling of the core compartment which creates significant internal pressure within the core compartment. This leads to decreased imbibition of the membrane and thereby decreased release of drug from the EOP. In addition presence of PEO within the core may restrict or delay the contact of solvent molecules with

*Address correspondence to this author at the Department of Pharmaceutics Institute of Technology Banaras Hindu University, Varanasi-221005, U.P., India; Tel: 91 (0542) 2307049; Fax: 91 (0542) 2368428; E-mail: pramod_79kumar@rediffmail.com; pramod_80kumar@yahoo.co.uk

drug and osmotic agent molecules. Which results in decreased osmotic pressure generation within the device consequently decreased release of the drug from EOP [14].

Recently swellable polymers have also been used to control the release of poorly water soluble/ insoluble drugs from elementary osmotic pumps by formulating dispersion of micronized drug in the polymer matrix and compressing in the form of tablet and further coating with semipermeable membrane [15, 16].

The present study was aimed towards the development of EOP of TRH by use of swellable polymer (poly ethylene oxide). A theoretically designed zero-order delivery pattern was designed to produce plasma level within the desired range. The manufacturing procedure was standardized and the stability of the formulations evaluated during 6 months of storage at accelerated stability conditions. Finally the *in-vivo* performance of the optimized formulation was predicted.

2. MATERIALS AND METHODS

2.1. Materials

Tramadol hydrochloride (99.9% purity) was a gift sample from Win Medicare Ltd, New Delhi, India. Polyethylene oxide (M.W. 300000) was gifted from Torrent research centre, Ahmedabad, India. Following chemicals and excipients were purchased from commercial sources and used as such: cellulose acetate (39.8% acetylation), polyvinyl pyrrolidone (PVP K-30), microcrystalline cellulose (MCC pH 101), dextrose, magnesium stearate, talc, sodium chloride (all from CDH Delhi, India), acetone, methanol (HPLC grade), acetonitrile (HPLC grade), triethanolamine, fructose, mannitol (all from Qualigens Fine Chemicals, Mumbai, India) disodium hydrogen orthophosphate, orthophosphoric acid (all from S.D. Fine Chemicals, Mumbai, India). ULTRAM ER-100mg (Retail Pharmacy).

2.2. Methods

2.2.1. Preparation of Core Tablets

Before initiating formulation development, compatibility of TRH with different excipients was tested using the tech-

niques of DSC (DU-PONT, Model 9900, U.S.A) and FT-IR (SHIMADZU, Model 8400S, Tokyo, Japan). Excipients used in the final formulation were found to be compatible with TRH.

Core tablets of TRH were prepared by direct compression and batch size was kept as 100 tablets. Formula of different core formulations of TRH is listed in Table 1. TRH was mixed with polyethylene oxide (PEO) for 10 min. After passing this mixture through #30 mesh sieve, osmotic agent (mannitol), MCC and PVP were added in geometric dilution and mixing continued for additional 10 min. To this mix talc and magnesium stearate each passed through #60 mesh sieve were added and mixing continued for additional 5 min. The blend was then compressed into tablets having average weight of 300-320 mg using a single station tablet punching machine (Manesty E-2, London, U.K.) fitted with 8mm round standard concave punches. The punched tablets were of 147 ± 2 N hardness on Monsanto hardness tester. The drug content of tablets was found to be within the limit of 97.98 -102.36 %.

2.2.2. Coating and Drilling

Core tablets of TRH were coated in a conventional laboratory coating pan (Scientific instrument, New Delhi, India) fitted with three baffles placed at angle of 120° having outer diameter of 10 cm [15]. The composition of coating solutions used for coating of core tablets is given in Table 2. Various components of coating solution were added to solvent mixture in sequential manner. The component added first was allowed to dissolve before next component was added. Coating process was done on a batch of 100 tablets pan speed was maintained at 20 rpm and hot air inlet temp. was kept at 38-42°C. The manual coating procedure based on intermittent spraying and coating procedure was used with spray rate of 4-5 ml/min. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process [17]. Coating was continued until desired coat thickness (150 µm) was obtained on the core tablets. An appropriate size orifice (0.5 mm) is made on one face of all coated tablets using microdrill [18] (Kamlesh Engineers, Udaipur, India). In all cases coated tablets were dried at 50°C for 6 hrs before further evaluation.

Table 1. Formula for Different Batches of Core Formulation

Ingredients (mg/tablet)	Batch number			
	I	II	III	IV ^a
Tramadol hydrochloride	100	100	100	100
Mannitol	136	136	136	136
PEO	-	30	50	70
MCC	50	20	-	-
PVP	10	10	10	10
Talc	2	2	2	2
Magnesium stearate	2	2	2	2

PEO=polyethylene oxide, MCC=microcrystalline cellulose, PVP=polyvinylpyrrolidone

^aBatch with average weight of 320mg. Other batches average weight = 300mg

Table 2. Composition of Coating Solutions

Ingredients	Coat code		
	A	B	C
Cellulose acetate(gm)	4.00	4.00	4.00
PEG-400 (gm)	-	0.40	0.80
Methanol (ml)	10	10	10
Acetone (ml)	90	90	90

2.2.3. Evaluation of Developed Formulation

Evaluation of Powder Blend

The bulk and tap density of the powdered blend was determined using USP method I and Compressibility index and Hausner ratio were calculated.

Evaluation of Core and Coated Tablets

The core and coated tablets were evaluated for weight variation. Thickness and diameter of core and coated tablets were measured using screw gauze (Ultra Science Aid, Mumbai, India). Hardness of randomly selected tablets was tested using hardness tester (Monsanto hardness tester, Campbell Electronics Mumbai, India). Friability of core tablets was carried out on Cintex friability tester (Cintex, Mumbai, India) using 20 accurately weighed tablets.

Drug Content Uniformity

Accurately weighed 20 tablets (of all batches) were dissolved in 500 ml of distilled water [19]. The samples were sonicated for 30 min. and filtered through 0.45µm nylon membrane filter. The filtered samples, after appropriate dilution with mobile phase, were analyzed at 271 nm using HPLC [20, 21] (CECIL HPLC system, Cambridge, London).

In-Vitro Drug Release Study

The developed formulations (n=3) of TRH were subjected to release studies using USP- XXIV dissolution apparatus type II (Campbell Electronics, Mumbai, India) at 50 rpm [19]. Dissolution media used was simulated intestinal fluid (SIF, pH 6.8, 900ml) maintained at 37± 0.5 °C which was found to provide sink condition (solubility of TRH was determined to be >1gm/ml) [19]. The samples (5 ml) were withdrawn at different time intervals and replaced with equivalent prewarmed (37± 0.5 °C) volume of fresh medium. The withdrawn samples, after filtration through 0.45 µm nylon membrane filters, were analyzed using an already reported modified validated HPLC method [20, 21] at 271 nm. After analyzing the drug content in the dissolution samples, correction was made for the volume replacement and the graph of cumulative percent of drug release versus time was plotted.

Further in order to study the effect of pH on drug release, release studies of the developed formulations were also carried out according to pH change method (For initial 2 hr in pH 1.2, next 2 hr in pH 4.5, another 2 hrs in pH 6.8 and finally for 2 hrs in pH 7.4).

2.2.4. HPLC Analysis

In-vitro analysis of drug samples was done on CECIL HPLC system equipped with adept series dual piston pump CE-4100 manual injector CAPPLUGS RC-11 and adept series variable wavelength UV/VIS detector CE-4201. Reverse phase HPLC method was carried out using phenomenex C-18 column (4.6×250mm, 5µm particle size) at 25° C. The optimized mobile phase composition was phosphate buffer (0.01M)-Acetonitrile- triethanolamine 75:25:0.1) at flow rate of 1 ml/min. Injected volume was 20µl and detection was performed at 271 nm using a UV/VIS detector.

2.2.5. Statistical Analysis

Experimental results were expressed as mean ± S.D. values. Release profiles of various batches were compared using model independent pair wise approach, which include the calculation of ‘difference factor’ *f1* and ‘similarity factor’ *f2*. The two release profiles were considered to be similar if *f1* value was lower than 15 (between 0 to15) and *f2* value was more than 50 (between 50 to100). Release profiles were also compared using mean dissolution time or MDT which was calculated using following equation [22].

$$MDT = \frac{\sum_{j=1}^n t_j \Delta M_j}{\sum_{j=1}^n \Delta M_j} \dots\dots\dots (1)$$

Where j is the sample number, n is the number of dissolution sample times, *t_j* is the time at mid point between *t_j* and *t_(j-1)*, and Δ*M_j* is the additional amount of drug dissolve between *t_j* and *t_(j-1)*. One way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations. Difference was considered statistically significant at p<0.05.

In this study, mean dissolution time for 50 % drug release (MDT_{50%}) was used for comparison of release profiles from different batches.

2.2.6. Swelling Index

To study the effect of swellable polymer on drug release, swelling index of developed formulations (n=3) was determined in 900 ml of SIF (pH 6.8) at 37 °C. At every hour tablets were withdrawn from dissolution fluid and weight of swollen tablets were calculated. The swelling index (S.I.) was determined from the following equation [23]:

$$SI = (W_t - W_0) / W_0 \dots\dots\dots (2)$$

where, W_t is the weight of the swollen tablet at each time interval t , W_0 is the initial weight of the tablet.

2.2.7. Burst Strength

Burst strength of the exhausted shells, after 8 hr of dissolution, was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength was determined as the force required to break/rupture the shells after dissolution studies. The texture analyzer (TAX T2i, Stable Micro systems, England) with a 5 kg load cell and 25 mm aluminum cylindrical probe was utilized for this purpose. Test speed of 0.8 mm/s was selected and the distance moved was set at 2 mm.

2.2.8. Accelerated Stability Studies

Optimized formulations of TRH were packed in strips of 0.04 mm thick aluminum foil laminated with PVC. The packed formulations were stored in ICH certified stability chambers (NSW-175, Narang Scientific work, New Delhi, India) maintained at 40 °C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for drug content, hardness, burst strength and release studies.

2.2.9. Prediction of In-Vivo Performance

Using the known pharmacokinetic properties of TRH (Table 3) and various drug release parameters (R^0 and t_{Del}), which were calculated from *in vitro* release data, steady-state plasma levels of drug were predicted by the method of superposition [22]. It was assumed that after the administration of a test dose of formulation, the drug would be released at a release rate (R^0) for a period of time (t_{Del}), shorter than the selected dosing interval (τ). Time of delivery, t_{Del} , is the time taken to deliver 90% of the total drug within a selected dosing interval ($\tau = 12$ hr). The predicted plasma levels of developed EOP were compared with those of desired level by calculating the percent-predicted error (% PD) in C_{max} and $AUC_{0-\tau}$. Bioequivalence was anticipated if the average % PD was less than 15% for C_{max} and $AUC_{0-\tau}$ [25, 26]. The % PD was calculated using the following equation:

$$\% \text{ PD} = \frac{\text{predicted value} - \text{reference value}}{\text{reference value}} \times 100 \dots\dots\dots (3)$$

3. RESULTS AND DISCUSSION

3.1. Desired Release Profile

The purpose of this study was to select a release profile that could be used as a target for developed EOP of TRH. In US market, Ultram ER (BIOVAIL LABS INTL, USA) is recognized as a Reference Listed Drug [27]. The maximum steady-state plasma concentration ($C_{ss \text{ max}}$) for Ultram ER-100 mg has been reported to be in the range of 293-335ng/ml. The therapeutic range of TRH is between 100-300 ng/ml [28] therefore, the desired maximum steady-state concentration, $C_{ss \text{ max}}$ desired, was selected as 300 ng/ml. In order to provide good therapeutic effect TRH plasma level should not fall below 150 ng/ml [29]. Keeping this point in consideration desired minimum steady state concentration was kept at 200 ng/ml. Taking different pharmacokinetic parameters of TRH into consideration (Table 3) a zero-order based delivery strategy was designed to produce the desired plasma levels of TRH [24]. Series of simulations (using Sigma plot-10) were performed and it was found that a delivery rate of 8.11 mg/h for a period of 8.28 hr was found to meet the above requirements. The simulated plasma concentration–time profile using this approach and the corresponding *in vitro* drug release profile are shown in Fig. (1) (a and b respectively). Since, this delivery pattern was expected to maintain plasma levels of TRH within desired range and also close to that produced by Ultram ER (Biovail Labs Int, USA), it was selected as target release profile.

3.2. Formulation Aspect of Core Tablet

3.2.1. Effect of Levels of Swellable Polymer

In initial trial, core tablets of TRH (batch-I) were coated with coating composition B (formulation code batch-IB). Results of release studies showed that more than 84% of drug was delivered within 5 hr. This may be due to high solubility of TRH.

Osmotic pumps per se are suitable for delivery of drugs having intermediate water solubility [3, 4]. It has been reported that in case of high water soluble drugs, meaningful release rates may not be obtained using elementary osmotic pump (EOP) or controlled-porosity osmotic pump (CPOP) [1, 3]. This is because the kinetics of osmotic drug release is directly related to solubility of drug within the core. Assum-

Table 3. Various Pharmacokinetic Parameters of Tramadol Hydrochloride

Pharmacokinetic parameters	Value	Reference (s)
Bioavailability (f)	74 %	[9, 10]
Elimination half life ($t_{1/2}$)	6.3 h	[9, 10, 11]
Terminal disposition rate constant (K_{el})	0.11 h ⁻¹	[9]
Apparent volume of distribution (Vd)	2.7 l/kg	[9, 10]
Maximum effective conc. (C_{max})	0.3 µg/ml	[26]
Minimum effective conc. (C_{min})	0.1 µg/ml	[26]
Clearance total (Cl_T)	8.5 ml/min/kg	[9, 10, 11]

ing a tablet core of pure drug, the fraction of drug released with zero-order kinetics is given by;

$$F(z) = 1 - \frac{S}{\rho} \dots\dots\dots (4)$$

where F(z) is the fraction released by zero-order kinetic s, S the drug’s solubility (g/ml), and ρ is the density (g/ml) of the core tablet. Drugs with a solubility of ≤ 0.05 g/ml would be released with ≥ 95% zero-order kinetics according to Eq. (4). However, the zero-order release rate would be slow according to Eq. (5) due to small osmotic pressure gradient

$$\frac{dm}{dt} = \frac{A}{h} \sigma L_p (\Delta\pi - p) C \dots\dots\dots (5)$$

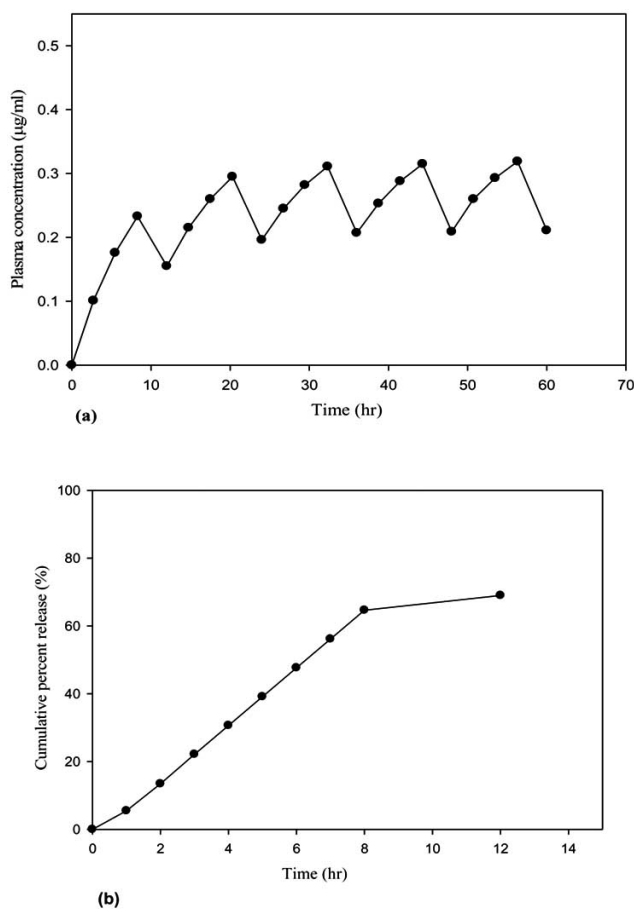


Fig. (1). (a) Predicted steady state plasma levels of TRH using theoretical zero-order delivery approach. and (b) corresponding in-vitro profile.

Eq. (5) describes drug release from osmotic pumps, where dm/dt is the drug delivery rate; A and h are the membrane area and thickness respectively; C is the concentration (or the solubility, when excess of drug is present in the core) of drug in the dispensed fluid, $\Delta\pi$ is the osmotic pressure difference across the film, σL_p is the hydraulic permeability of the membrane and p is the hydrostatic pressure within the core compartment [4].

According to Eq. (5) highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However it is possible to modulate the solubility of drugs within the core, and thus extend this technology for delivery of drugs which otherwise may be poor candidates for osmotic delivery.

TRH is a basic drug with very high water solubility, the pKa value of TRH is 9.41 hence solubility is also pH independent [9-11]. In order to get the desired release from the developed systems, swellable polymer PEO was added in core formulation to modulate the solubility of TRH within the core. Inclusion of PEO is expected to control the release of TRH from the EOP [14]. Three batches were prepared in which concentration of PEO was varied, batch-II, III, IV coated with coating composition B coded as batch II B, III B, IV B containing 10 %, 16.66 %, and 21.87 % w/w of PEO respectively. *In-vitro* release profiles of three batches (II B, III B, and IV B) in comparison to batch IB (containing 0% PEO) were compared in Fig (2). It is clearly evident that the concentration of PEO has indirect effect on drug release. With increase in concentration of PEO within the core there was decrease drug release and increase in swelling index of the formulations due to higher internal pressure generated by PEO. Table 4 shows the swelling data (maximum swelling achieved), MDT_{50%} of all the formulations. The difference in MDT_{50%} between I B, II B, III B, IV B was found to be statistically significant (P<0.05). One way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations.

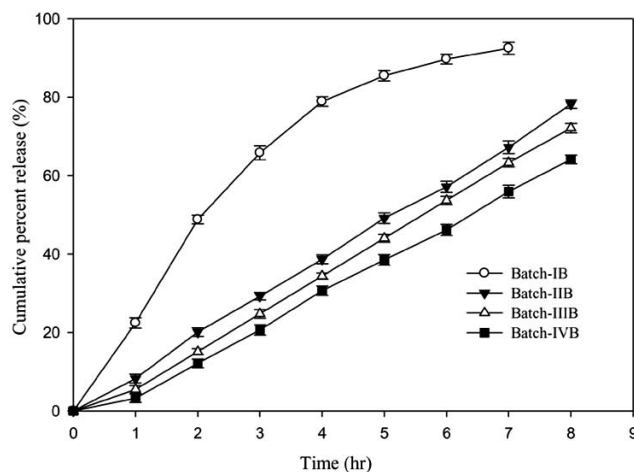


Fig. (2). Profiles showing the effect of PEO on TRH release from the formulation. Bras represent + S.D. (n=3).

3.3. Evaluation of Membrane Variables

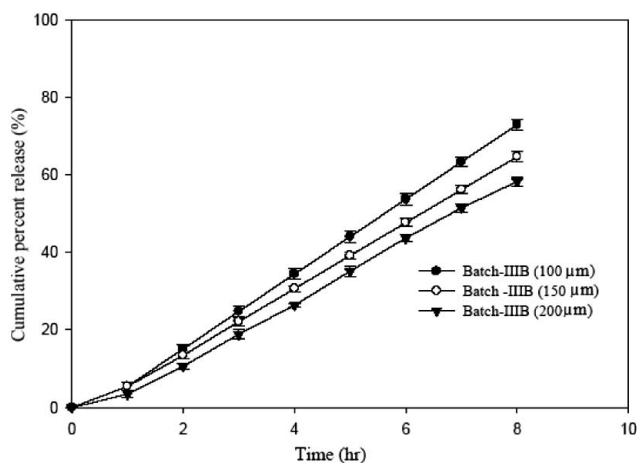
3.3.1. Effect of Coat Thickness

To study the effect of coat thickness of SPM on drug release, core formulation of batch III were coated with coating composition B so as to give different coat thickness (100 µm, 150 µm, 200 µm). Release profiles of TRH from these formulations are shown in Fig. (3). Drug release was decreased with increase in coat thickness of SPM. The increase of SPM thickness resulted in an increased resistance of SPM

Table 4. Swelling Index Data (Maximum Swelling Achieved) of Core Formulation and their Effect on Mean Dissolution Time (MDT_{50%})

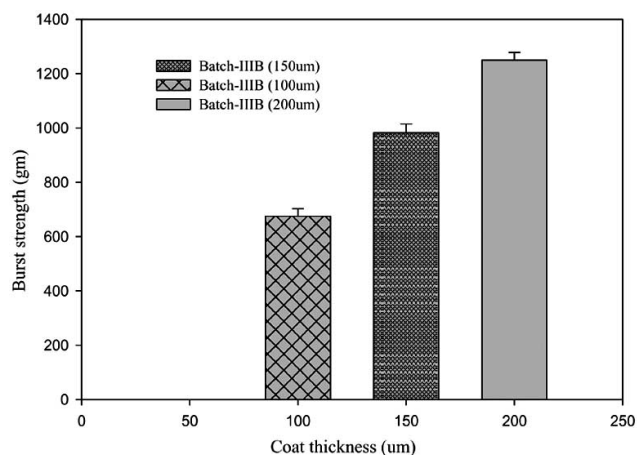
Batch No.	Core composition	Swelling index (%)	MDT _{50%} (hrs)
I	0%w/w PEO+mannitol	2.98	1.441
II	10%w/w PEO+mannitol	14.77	2.585
III	16.6%w/w PEO+ mannitol	17.98	3.190
IV	21.87% w/w PEO+mannitol	21.06	3.563

to water imbibition, causing a rate of decreased water imbibition consequently causing a decrease in rate of liquefaction/ dissolution of drug in core, and ultimately resulted in decline in TRH release. MDT_{50%} value between different batches (2.56, 3.19, 4.12 hr for formulation with coat thickness of 100 μm , 150 μm , 200 μm respectively) were found to be statistically significant ($P < 0.05$). No bursting of the systems was observed during the dissolution run in any of the formulations. In addition, exhausted tablets (after 8hr of dissolution studies) were evaluated for burst strength to assure that the tablets maintain their integrity in GIT and do not lead to dose dumping [30, 31]. Fig. (4) shows the dependence of burst strength of the exhausted shells on coat thickness. The strength of mechanical destructive forces in the GIT of humans and dogs has been reported to be 1.9 N (approximately 190 g) and 3.2 N (approximately 320 g), respectively [32, 33]. It has been reported that osmotic pumps having the burst strength in the range of 500–600 g were intact in the GIT of dogs while those having burst strength of around 200 g were compromised [30]. In all cases, the value is much higher than the mechanical destructive forces in GIT, thus assuring that the formulations can be expected to remain intact in GIT without any incidence of dose dumping.

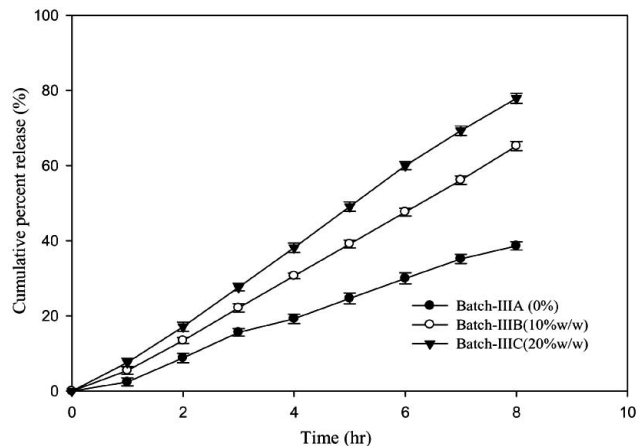
**Fig. (3).** Profile showing the effect of coat thickness on TRH release from EOP. Bars represent +S.D. (n=3).

3.3.2. Effect of Level of Plasticizer

To study the effect of level of plasticizer (PEG-400), core formulation of batch-III were coated with coating formulation A and C containing 0% and 20% w/w (of cellulose ace-

**Fig. (4).** Bar diagram showing the dependence of burst strength thickness of membrane. Bars represent + S.D. (n=3).

tate) of PEG-400 respectively coded as batch III A and batch III C. Release profiles of these batches in comparison with batch-III B (containing 10% w/w PEG-400) are shown in Fig. (5). It is clearly evident that level of plasticizer (PEG-400) has direct effect on the drug release. As the level of PEG-400 increases the membrane become more porous due to solubilization of water soluble PEG-400 in dissolution media resulting in higher drug release [34]. Another parameter affected by the level of plasticizer was burst strength of the exhausted shells. With the increase in level of PEG-400,

**Fig. (5).** Profiles showing the effect of plasticizer (PEG-400) level release from developed EOP. Bars represent + S.D. (n=3).

the membrane became more porous after exposure to water, leading to a decrease in its strength. Effect of level of PEG-400 on burst strength is shown in Fig. (6).

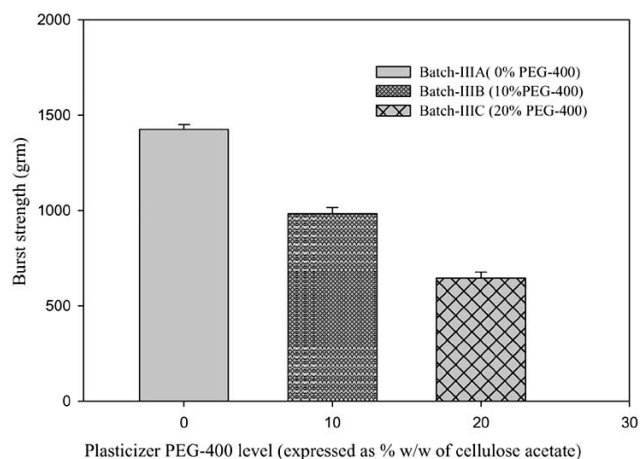


Fig. (6). Bar diagram showing the dependence of burst strength on plasticizer PEG-400 level (at 150 μ m coat thickness) Bars represent + S.D. (n=3).

3.4. Influence of Release Media

To study the effect of pH and to assure a reliable *in-vivo* performance release study of the batch-III B was conducted according to pH change method and compared with release profile in SIF. There was insignificant effect ($p > 0.05$) of different pH of release medium on TRH release from developed EOP when compared to *in-vitro* data of Batch-III B in simulated intestinal fluid (pH 6.8) only. The f_1 and f_2 values of batch-III B were found to be 2.65 and 91.85 respectively taking the release profile in SIF as the reference

Drug release from osmotic pumps to a large extent is independent of agitation intensity of the release media. To study effect of this parameter the release studies of batch-III B were carried out in USP-XXIV dissolution apparatus type II at varying rotational speed (50, 100, and 150 rev./min). There was insignificant effect of rotational speed ($p > 0.05$) on TRH release from developed formulations when all the three release profiles were compared. The f_1 and f_2 values were found to be 4.22 and 85.09 between 50 and 100 rev./min, 3.71 and 85.78 between 100 and 150 rev./min, and 7.77 and 73.33 between 50 and 150 rev./min, respectively. Hence it can be expected that the release from the developed formulations will be independent of the hydrodynamic conditions of the absorption site

3.5. Evaluation of Optimal Formulation

To evaluate the performance of developed formulations release profiles of promising formulations (batch II B, III B, and IV B) were compared with theoretically desired release profile of TRH (prepared by superposition method in section 3.1) and with marketed sustained release formulation Ultram ER-100 mg in Fig. (7). It is clearly evident that developed formulations provided more controlled and prolonged drug release as compared to marketed sustained release (Ultram ER-100 mg) formulation of TRH. Drug release from batch III B (Batch-III coated with coating composition B coat thickness of 150 μ m and orifice diameter of 500 μ m) was found closest to desired release profile. The f_1 and f_2 values of batch-III B were found to 4.22 and 91.87 respectively

taking desired release profile as reference. Hence this formulation was selected as the optimized formulation and evaluated further.

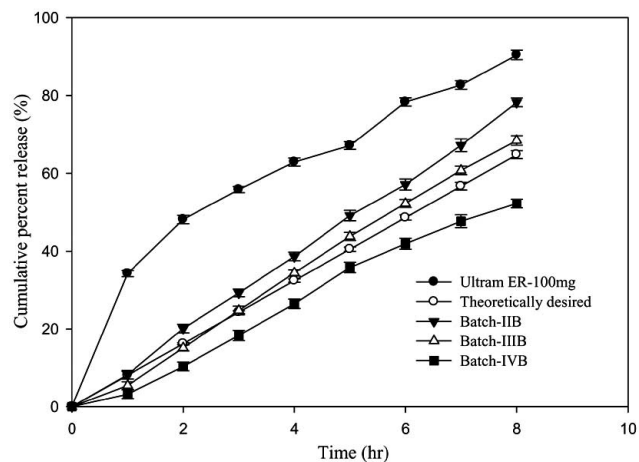


Fig. (7). Release profile of promising formulations in comparison to formulations and theoretically desired release profile. Bars represent + S.D.(n=3).

The optimized formulation was evaluated for various pharmacopoeial and non-pharmacopoeial tests, results of which are listed in Table 5. The powder blend was free flowing as demonstrated by the values of compressibility index (less than 15) and Hausner ratio (less than 1.25). Other parameters for the uncoated and coated tablets were also within limits. Exhausted shells after dissolution were visually observed for any imperfection or cracks in the coating. There were no visible cracks in the coating and it was found to be intact in all the batches after 8 hr of dissolution studies.

3.6. Kinetics and Mechanism of Drug Release

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), Akaike information criterion (AIC) and best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model. Drug release from optimized formulations (batch-III B) fitted well into zero-order kinetics (Table 6) confirming that the release from formulation is close to desired release.

3.7. Accelerated Stability Study

The stored formulations of batch-III B were found to be stable in terms of drug content and dissolution stability (Table 7). In all the cases, the burst strength was higher than the reported values of mechanical destructive forces in the GIT ensuring the formulations to be intact in GIT without any incidence of dose dumping even after storage.

3.8. In-Vivo Prediction

Method of superposition was used to predict steady state plasma levels of TRH after administration of a test dose (100 mg) of optimized formulation (Batch-III B). Since osmotic pumps are reported to exhibit a significant *in vitro/in vivo*

Table 5. Properties of the Powdered Blend, Core Tablets, and Final Coated Tablets of the Optimized Formulation (Batch-IIIB)

Parameters	Mean value± S.D.
Bulk density ^a (mg/cm ³)	415
Tap density ^a (mg/cm ³)	464
Compressibility index ^a (%)	8.69
Hausner ratio ^a	1.08
Tablet weight (mg, n=10) Core tablet Coated tablet	300± 5.21 318± 4.62
Thickness (mm, n=10) Core tablet Coated Tablet	4.12±0.02 4.48±0.02
Diameter (mm, n=10) Core tablet Coated tablet	8.11±0.11 8.32±0.02
Hardness (N) Core tablet Coated tablet	147 ± 4 245 ± 4
Friability ^b (%)	0.096
Content uniformity ^c (% , n=5)	102.46±2.24

^a properties of powder blend; ^b property of the core tablet; ^c property of final coated tablet

Table 6. Fitting Drug Release Data of the Optimized Formulation (Batch-IIIB) According to Various Mathematical Models

Model	Parameters used					
	R ²	Intercept (%)	Slope (%/hr)	k	SSR	AIC
Zero-order	0.9992	-2.9071	9.423	8.1411	25.8	15.36
First-order	0.8779	1.9157	0.332	0.3326	216.12	32.36
Higuchi model	0.9807	-36.8103	37.359	37.3597	128.42	26.18

R², goodness of fit; r, correlation coefficient; SSR, sum of squares of residuals; AIC, Akaike information criteria; and k, release rate constant for respective models (k₀ in mg/h, k₁ in h⁻¹, and k_H in %/h^{1/2} for zero-order, first order, and Higuchi rate equations respectively).

Table 7. Evaluation of Batch-IIIB Formulation for 3 Months Storage at 40°C and 75% RH

Parameter	Initial	1 month	2 month	3 month
Drug content (%)	102.60± 1.44	99.68±1.87	98.14±1.67	104.60±1.61
Hardness (N)	155 ± 5	196 ± 5	180 ± 4	199 ± 5
Burst strength (g)	845.88±1.62	912±1.82	823±1.42	945±1.92
<i>f1</i>	-	2.32	4.52	5.12
<i>f2</i>	-	92.62	84.62	82.24
MDT _{50%} (hr)	3.004	3.271	3.151	3.208

Table 8. Predicted *In-Vivo* Performance of the Developed EOP of TRH

Product	Predicted $C_{ss\ max}$ (ng/ml)	% PD	Predicted $AUC_{0-\tau}$ (ng hr/ml)	% PD
Desired ^a	319.14	-	665	-
Batch-IIIB ^b	320.31	+0.36	673	+1.20

% PD= Percent predicted error

^a Predicted from desired zero-order delivery profile (dose=100mg, R^0 = 8.119 mg/h, and t_{del} = 8.313 h).

^b Predicted from drug release study (dose=100mg, R^0 = 8.141 mg/h, and t_{del} = 8.413 h).

correlation, predicted data of steady-state plasma levels from drug release studies can be used for comparison with the desired plasma levels. The desired steady-state plasma levels of TRH were predicted from a theoretically designed zero-order delivery system. Prediction of steady-state levels of TRH after administration of a test dose of optimized formulation showed that plasma levels are between 200 ng/ml to 335 ng/ml. Fig. (8) shows predicted steady-state plasma levels after administration of a test dose of Batch-III B formulation in comparison to the desired steady state plasma levels. It is clearly evident from the figure that the predicted steady-state plasma levels are very close to the desired levels. The predicted $C_{ss\ max}$ and $AUC_{0-\tau}$ after administration of optimized formulations of TRH, in comparison with the desired ones is listed in Table 8. The % PD of the steady-state parameters of optimized formulations was calculated taking the data of desired profile as the reference. The absolute % PD was found to be less than 15%, ensuring that the optimized formulations will produce plasma levels close to the desired ones [25, 26]. Thus, it can be concluded that the developed optimized formulation (batch-III B) will produce plasma levels well within the therapeutic range. Since osmotic pumps are reported to exhibit a good *in vitro/in vivo* correlation, based on *in vivo* performance prediction, the developed formulations can be expected to perform similar *in vivo*.

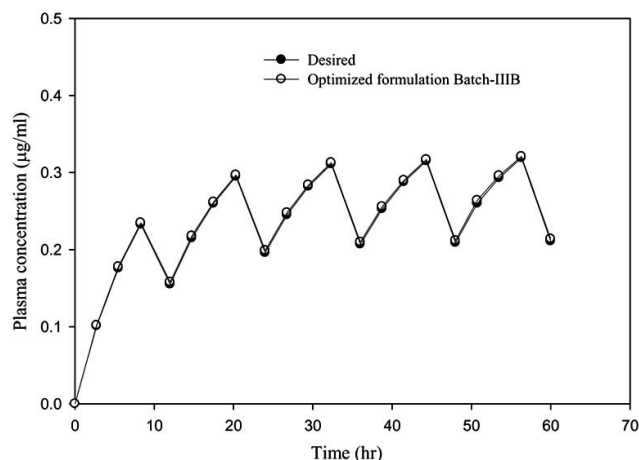


Fig. (8). Predicted steady-state plasma levels of TRH after administration of a test dose of optimized formulation (Batch-IIIB) in comparison with the desired profile.

CONCLUSION

In the present study, EOP of highly water soluble drug TRH was developed and evaluated. Target release profile

was selected and different formulation variables were optimized to achieve the same. Drug release from the developed formulations was independent of pH and agitation intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the absorption site. TRH release from developed EOP was directly related to the level of plasticizer but inversely proportional to the level of swellable polymer and coat thickness of SPM. Drug release data from TRH formulations fitted well into zero-order kinetics. From drug release studies, steady-state plasma levels were predicted using the method of superposition. The predicted steady-state plasma levels were within the desired range (200-300 ng/ml) to show the safe therapeutic effect. Since osmotic pumps are reported to exhibit a good *in vitro/in vivo* correlation, based on *in vivo* performance prediction, the developed formulations can be expected to perform similar *in vivo*. Developed formulations were found to be stable during six months of storage at accelerated stability condition.

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