ORIGINAL ARTICLE

Development of Osmotically Controlled Oral Drug Delivery Systems of Tramadol Hydrochloride: Effect of Formulation Variables on *In Vitro* Release Kinetics

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Abstract

Aim: Numerous technologies have been used to control the systemic delivery of a pharmacologically active ingredient in a predetermined, predictable, and reproducible manner. One of the most interesting approaches is osmotically controlled oral drug delivery systems. By optimizing formulation and processing parameters, it is possible to develop osmotic systems to deliver drugs of diverse nature at a predetermined rate with high *in vitro-in vivo* correlation. The aim of the current study was to formulate elementary osmotic pump (EOP) device of freely water-soluble tramadol hydrochloride, a non-steroidal anti-inflammatory agent. **Materials and Methods:** Formulations were prepared by wet granulation method, coated with cellulose acetate (CA)/ethyl cellulose solution containing varying amounts of dibutylphthalate as a plasticizer. Drug release was studied using USP Type II apparatus. The effect of different formulation variables on drug release, namely, type and concentration of osmogen and plasticizer, size of the delivery orifice, nature of the rate controlling membrane, and membrane weight gain was studied. **Results:** The formulation containing mannitol in the drug:osmogen ratio of 1:0.5 and lactose in the ratio 1:0.25, and 1:0.5 (drug:osmogen) showed more than 80% of drug release in 6 h with zero-order release pattern. The 4% CA solution in acetone with dibutylphthalate (15% w/w of polymer), with orifice diameter 480 µm, 565 µm, and 8% increase in weight on coating, were found to control the drug release. Drug release from the developed formulations was found to be independent of pH and agitation intensity. The manufacturing procedure was reproducible, and formulations were stable upto 3 months as per ICH guidelines. **Conclusion:** EOPs and process parameters of tramadol hydrochloride were developed based on osmotic technology.

Key words: Burst strength, *in vitro* release, osmogen, osmotic pumps, semipermeable membrane, tramadol hydrochloride

INTRODUCTION

Controlled release (CR) dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate. A number of design options of per oral CR dosage forms are available to control or modulate the drug release from a dosage form which falls in the category of matrix, reservoir, or osmotic systems. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/coated by a rate controlling membrane. However, factors such as pH, presence of food, and other physiological factors may affect drug release from these systems. Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Oral osmotically CR delivery system provides a uniform concentration/amount of drug at the site of absorption, and thus after absorption, it allows maintenance of plasma concentration within the therapeutic range, which minimizes side effects and

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also reduces the frequency of administration. Drug release from these systems is independent of pH and other physiological parameters to a large extent, and it is possible to modulate the release characteristics by optimizing the properties of drug and system.[1-3] Osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new or existing drugs.[4-6] At the same time, they can also be utilized to deliver drugs at a controlled and predetermined rate.

Tramadol hydrochloride, a non-steroidal anti-inflammatory drug, is used in the treatment of osteoarthritis when non-steroidal anti-inflammatory drugs such as acetaminophen or cyclooxygenase-2 inhibitors alone produce inadequate pain relief. Tramadol hydrochloride is freely soluble in water. After oral administration, tramadol is rapidly and almost completely absorbed throughout gastrointestinal tract (GIT) with a half-life of 5-6 h.[7] Long-term treatment with sustained-release tramadol once daily is generally safe in patients with osteoarthritis or refractory low back pain and has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance.

The present study was aimed toward the development of sustained-release formulations of tramadol hydrochloride based on osmotic technology. Different formulation variables were studied and optimized to achieve the desired drug release profile. The manufacturing procedure was standardized and the stability of the formulations evaluated after 3 months of storage at accelerated stability conditions.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was gift sample from Euro chemicals. Mannitol, lactose, dicalcium phosphate, magnesium stearate, talc, hydrochloric acid, and sodium hydroxide were purchased from S.D. Fine Chemicals, Mumbai. Polyvinyl pyrrolidone (PVP) K-30 was purchased from Himedia Laboratories Ltd., Mumbai. Cellulose acetate (CA) was a gift sample from AET Pharma, Hyderabad. Ethyl cellulose, hydroxypropyl methyl cellulose HPMC K4, and dibutylphthalate were gift samples from Dr. Reddy's labs Ltd., Hyderabad. Acetone, isopropyl alcohol, and poly(ethylene glycol) (PEG)-400 were purchased from Merck Ltd. All chemicals and reagents used were of analytical or pharmacopeial grade.

Methods

Formulation development

Preparation of core tablets

Core tablets of tramadol hydrochloride were prepared by wet granulation method. Tramadol hydrochloride was mixed with all the excipients and passed through 40-mesh sieve. The blend was mixed for 10 min and PVP K-30 was added. The mixture was granulated with water, and the resulting wet mass was passed through 18-mesh sieve. The granules were dried at 70°C to get a loss on drying (LOD) value between 0.96% and 0.99% after which they were again passed through 25-mesh sieve. These sized granules were then blended with magnesium stearate and talc, compressed into tablets having an average weight of 600 mg using 16 station rotary tablet compression machine (Riddhi, Ahmedabad, India) fitted with 10 mm round standard concave punches. Formulae of different core formulations of tramadol hydrochloride are listed in Table 1.

Coating of core tablets

Core tablets of tramadol hydrochloride were coated in a coating pan (VJ Instruments, India). The composition of coating solution used for coating of tramadol hydrochloride core tablets is given in Table 2. Various components of the coating solution were added to the solvent mixture in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of tramadol hydrochloride were placed in the coating pan along with 200 g of filler tablets (tablets made using 6 mm round deep concave punches and containing microcrystalline cellulose, starch, dibasic calcium phosphate, magnesium stearate, and talc). Initially, the pan was rotated at low speed (2-5 rev/min), and heated air was passed through the tablet bed. Coating process was started once the outlet air temperature reached 28°C. The revolutions per minute of the pan were kept in the range of 23-27 and coating solution was sprayed at the rate of 1-2 ml/min. Atomization pressure was kept at 1 kg/cm^2, and the outlet temperature was maintained above 28°C by keeping the inlet air temperature in the range of 50-55°C. Coating was continued until desired weight gain was obtained on the active tablets. In all the cases, active tablets were dried at room temperature for 24 h before further evaluation.

Drilling of coated tablets

For coated tablets, a small orifice was drilled through the one side by standard mechanical microdrills with various diameters (ranging from 400 to 600 µm). After drilling, the orifice size was controlled and measured microscopically (BAUSH and LOMB, Balplan microscope, USA) to make sure the right orifice size was used for dissolution studies. Any deviation in orifice size by more than 10 µm from the target orifice size was rejected and not used in dissolution studies.

Evaluation of the developed formulations

Evaluation of core tablets

Flow properties

Infrared moisture balance (PM 480, Mettler Toledo, Switzerland) was used to determine LOD of the granules. To determine bulk and tapped density of the granules, USP method II on a tap density tester (ETD-1020, Electrolab,

Table 1: Composition of core tablet formulations of tramadol hydrochloride EOPs

Ingredients	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10	FT11	FT12
Drug	100	100	100	100	100	100	100	100	100	100	100	100
Mannitol	-	50	100	200	300	400	50	25	-	-	-	-
Lactose	-	-	-	-	-	-	-	-	25	25	50	50
DCP	458	408	358	258	158	58	408	433	43	433	408	408
PVP K-30	18	18	18	18	18	18	18	18	18	18	18	18
Mg.st	12	12	12	12	12	12	12	12	12	12	12	12
Talc	12	12	12	12	12	12	12	12	12	12	12	12

EOPs: Elementary osmotic pumps, DCP: Dicalcium phosphate, PVP: Polyvinyl pyrrolidone, Mg.st: Magnesium stearate

Table 2: Properties of granules

Formulation	LOD (%)	Bulk density (g/cm^3)	Tap density (g/cm^3)	CI (%)	HR^c
FT1	0.99	0.52	0.56	7.14	0.92
FT2	0.96	0.49	0.53	7.54	0.92
FT3	0.95	0.50	0.56	10.71	0.89
FT4	0.98	0.51	0.55	7.27	0.92
FT5	0.96	0.48	0.53	9.43	0.90
FT6	0.99	0.52	0.57	8.77	0.91
FT7	0.97	0.51	0.55	7.27	0.92
FT8	0.98	0.49	0.54	9.25	0.90
FT9	0.96	0.50	0.56	10.71	0.89
FT10	0.96	0.51	0.56	8.92	0.91
FT11	0.97	0.50	0.57	12.28	0.87
FT12	0.98	0.48	0.54	11.11	0.88

LOD: Loss on drying, CI: Compressibility index, HR: Hausner ratio

India) was used. From the data obtained, compressibility index (C.I.) and Hausner ratio (H.R) were calculated.

Weight and thickness variation of core

The weights of 20 core tablets of tramadol hydrochloride were measured using digital balance (Denver, Germany). The average values, standard deviation, and relative standard deviation were calculated. The thickness of core tablets and coated tablets was measured using a digital screw gauge (Mitutoyo, Japan). The percentage increase in weight on coating and increase in thickness upon coating were calculated.

Hardness test

Core tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks during tumbling action in the pan while coating. The hardness of core tablets was measured by Pfizer hardness tester, and results were expressed in kg/cm^2.

Friability

Friability is a measure of mechanical strength of tablets. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability. Preweighed core tablets (20 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 min (100 rotations). At the end of the test, the tablets were reweighed; and loss in weight was calculated and presented as percentage.

Determination of drug content

About 20 uncoated tablets were taken and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 ml of distilled water on a rotary shaker overnight. The solution was centrifuged, and the supernatant was filtered through 0.22 µ membrane filter. The absorbance of the filtrate was measured using an ultraviolet (UV)-Vis spectrophotometer (Elico, India) at 271 nm against distilled water as blank.

Evaluation of coated tablets

Weight and thickness variation of coated tablets

About 20 coated tablets were taken and their weight calculated individually and collectively on a digital weighing balance. Average weight was calculated along with percentage increase in weight. The increase in thickness upon coating was determined using digital screw gauge.

Hardness of the coated tablets

The coated tablets must be enough hard to maintain the integrity of the tablet during the dissolution process. Hardness of each batch of the formulation was determined using Pfizer hardness tester, and the average was calculated.

Determination of aperture diameter

After drilling, the orifice size was controlled and measured microscopically to make sure the right orifice size was used for dissolution studies. Any deviation in orifice size by more than 10 µm from the target orifice size was rejected and not used in dissolution studies.

In vitro release studies

The developed formulations of tramadol hydrochloride elementary osmotic pumps (EOPs) were subjected to *in vitro* drug release studies using USP-II dissolution apparatus (Disso 2000, Lab India) at 50 and 100 rev/min. Dissolution mediums used were 900 mL of distilled water (pH 7) and, 0.1 N HCl

for the first 2 h followed by 900 mL of 6.8 pH phosphate buffer for the remaining 10 h, maintained at a temperature of 37°C ± 0.5°C. The samples were withdrawn (5 ml) at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples were analyzed using the validated UV-Vis spectrophotometric method at 271 nm (Elico, SL-159 India).

Dissolution profile modeling

Dissolution data of the optimized formulation were fitted to various mathematical models (zero-order, first-order, Higuchi, and Korsmeyer–Peppas)[8-11] to describe the kinetics of drug release. An ideal osmotic system should be able to release a high percentage of drug content with a constant release rate (zero-order kinetics) during dissolution. Best goodness-of-fit test (R^2) was taken as a criterion for selecting the most appropriate model.[12]

Burst strength

Burst strength of the exhausted shells, after 12 h 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. Ultra test tensile tester, Mecmesin, U.K. with a 5 kg load cell was utilized for this purpose. Test speed of 0.8 mm/s was selected and the distance moved was set at 2 mm.

Effect of formulation variables on in vitro drug release

Various formulation factors such as nature of semipermeable membrane (SPM)-forming polymer, type and concentration of plasticizer, type and concentration of plasticizer, percentage increase in weight upon coating, and aperture diameter affect the drug release from an EOP. The effect of formulation variables on *in vitro* drug release kinetics is studied by varying the above-listed factors. The influence of pH and agitation intensity on release kinetics was studied by conducting the drug release in varying conditions of pH and agitation intensity.

RESULTS AND DISCUSSION

The oral osmotic drug delivery system was developed as an EOP containing a tablet core coated with a rate controlling membrane. Tablet core consists of the drug along with osmogen, and other conventional excipients to form the core compartment [Table 1]. All the ingredients are mixed thoroughly, and granules are prepared by wet granulation method. Various properties of granules such as LOD, bulk density, tap density, C.I., and H.R were found out [Table 2]. The results have shown that the granules formed had good flow properties with C.I. in the range of 7.14-12.28 (granules with C.I. between 5 and 12 are free flowing) and H.R in the range of 0.87-0.92 (granules with H.R between 0 and 1.2 are free flowing).

The core compartment is surrounded by a membrane consisting of an SPM-forming polymer, water-soluble additives (in case of ethyl cellulose coating), and a plasticizer capable of improving film-forming properties of the polymers [Table 3]. CA and ethyl cellulose were used as SPM-forming polymers, and water-soluble additive (HPMC) was added in case of ethyl cellulose coating. PEG-400 and dibutylphthalate were used as water-soluble and water-insoluble plasticizers, respectively.

Various process parameters such as weight variation, hardness, thickness, diameter of core and coated tablets, friability and content uniformity of the coated tablets were evaluated and were found to be with the limits as per USP specifications. The results are presented in Table 4.

Evaluation of core and coated tablets

Osmotic systems utilize osmotic pressure as the driving force to control the drug release from the core of the system. SPM-forming polymer has the main role in maintaining the osmotic pressure, controlling the drug release, and retaining the integrity of the device. To investigate the role of various formulation parameters effecting drug release from an EOP of tramadol hydrochloride, the following parameters were studied, and the results are presented hereunder.

In vitro drug release

The *in vitro* drug release profiles of formulations containing lactose and mannitol as osmogens, coated with 4% CA solution containing dibutylphthalate (15% of CA) as plasticizer in acetone with 8% increase in weight of the core tablet upon coating are shown in Figure 1. Formulations containing mannitol in the drug:osmogen ratio of 1:0.5 (FT2 and FT7), released 99.83% and 94.17% of drug, respectively, in a period of 10 h. Formulations containing lactose as osmogen in the drug:osmogen ratio of 1:0.25 and 1:0.5 (FT10 and FT12) released 93.52% and 95.78% of drug, respectively, in 10 h.

Table 3: Coating composition of tramadol hydrochloride EOPs

Ingredients	A	B	C	D	E
Cellulose acetate	4	4	4	-	-
Ethyl cellulose	-	-	-	5	5
PEG-400	0.6	-	-	0.4	-
DBP	-	0.4	0.6	-	0.6
HPMC	-	-	-	2	2
Acetone	95.4	95.6	95.4	-	-
IPA	-	-	-	93.6	93.4

EOPs: Elementary osmotic pumps, PEG-400: Poly (ethylene glycol) 400, DBP: Dibutylphthalate, HPMC: Hydroxypropyl methyl cellulose, IPA: Isopropyl alcohol

Dissolution profile modeling

The release profiles of the optimized formulations were fitted into various mathematical models, and the R^2 value was taken as the index of the release pattern of the drug. From the Table 5, it is evident that the formulations FT2 release 87.48% and FT7 released 86.16% of drug in zero-order for a period of 6 h and 8 h, respectively. Formulations FT10 and FT12 released 81.71% and 93.46% of drug, respectively, in zero-order for 8 h. The "n" values indicate that the drug was released by Fickian diffusion mechanism.

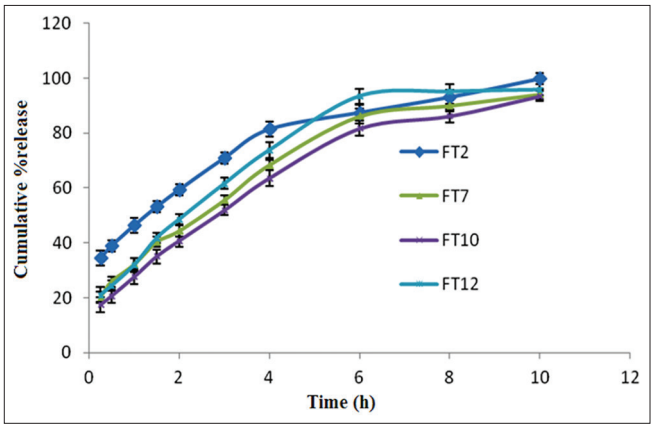

Figure 1: *In vitro* drug release profile of tramadol hydrochloride elementary osmotic pumps (mean ± standard deviation, $n = 3$)

Burst strength

The strength of mechanical destructive forces in the GIT of humans has been reported to be 1.9 N (approximately 190 g).[13,14] With % increase in weight on coating from 4% to 8%, the burst strength of the osmotic pumps was found to increase [Table 6 and Figure 2]. 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.

Influence of formulation parameters on drug release

The effect of type and polymer concentration on the release rate from osmotic devices

The choice of a rate controlling membrane is an important aspect in the formulation development of oral osmotic systems. The delivery of the agent from oral osmotic systems is controlled by the influx of solvent across the SPM, which in turn carries the agent to the outside environment. The SPM must possess certain performance criteria such as sufficient wet strength and water permeability. Moreover, it should be

Table 4: Process parameters of core and coated tablets

Code	Weight variation (%)		Thickness (mm)		Hardness (kg/cm²)		Friability (%)	Content uniformity
	Core tablet	Coated tablet	Core tablet	Coated tablet	Core tablet	Coated tablet	Core tablet	Core tablet
FT1	2.3±0.10	3.7±1.21	5.76±0.03	6.16±0.03	7.5±0.5	13.2±0.6	0.096	96.6±2.82
FT2	2.3±0.27	4.1±1.50	5.81±0.03	6.21±0.02	6.7±1.2	14.0±0.5	0.089	97.2±1.56
FT3	1.8±0.12	4.3±1.02	5.80±0.05	6.26±0.04	8.1±0.4	12.9±1.6	0.091	99.2±0.52
FT4	2.2±0.13	3.8±1.33	5.87±0.04	6.17±0.04	7.8±0.3	15.2±0.3	0.098	95.9±2.89
FT5	2.7±0.21	4.5±1.11	5.79±0.08	6.09±0.06	6.9±0.8	12.6±0.8	0.097	96.4±1.50
FT6	2.5±0.12	3.9±0.98	5.85±0.05	6.15±0.05	7.2±0.6	13.5±0.4	0.092	95.4±2.51
FT7	2.2±0.26	4.2±1.09	5.82±0.06	6.28±0.04	6.5±1.0	12.8±0.9	0.099	96.8±1.70
FT8	2.4±0.11	3.6±1.05	5.83±0.04	6.03±0.06	8.2±0.2	13.1±1.5	0.093	94.7±1.19
FT9	1.9±0.11	3.5±1.23	5.79±0.06	6.19±0.05	7.6±0.5	13.8±1.1	0.097	97.3±2.71
FT10	2.6±0.25	3.8±1.52	5.82±0.05	6.22±0.05	7.9±0.3	12.9±1.5	0.094	98.4±1.02
FT11	2.2±0.18	3.7±1.63	5.86±0.04	6.16±0.04	7.4±0.7	13.9±1.2	0.094	96.8±2.50
FT12	2.4±0.22	3.9±0.97	5.80±0.04	6.13±0.07	6.9±1.3	14.0±0.9	0.098	97.8±1.09

Table 5: Mathematical models explaining release kinetics from optimized formulations

Formulation	% release	Time of zero-order drug release (h)	R^2 value				"*n*" value
			Zero-order	First-order	Higuchi	Korsmeyer-Peppas	
FT2	87.48	6	0.9941	0.9596	0.9909	0.9686	0.3102
FT7	86.16	8	0.9907	0.9108	0.9854	0.9841	0.4540
FT10	81.71	8	0.993	0.9118	0.9842	0.9772	0.4983
FT12	93.46	8	0.9884	0.9052	0.9874	0.9750	0.4878

Table 6: Effect of percentage increase in weight upon coating on burst strength

Percentage increase in weight (%)	Burst strength (N)
4	3.5
6	7.5
8	9.0

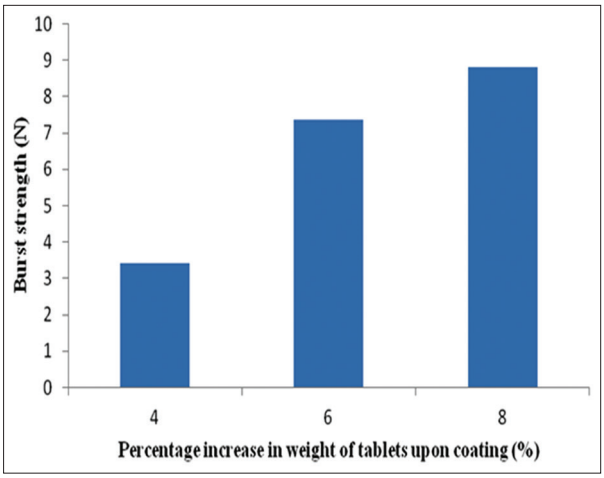

Figure 2: Effect of % increase in weight (on coating) on burst strength of exhausted elementary osmotic pumps of tramadol hydrochloride after dissolution (mean ± standard deviation, *n* = 3)

selectively permeable to water and should be biocompatible. Drug release from osmotic systems is independent of the pH and agitation intensity of the GIT to a large extent. This is because of selectively water permeable membrane and effective isolation of dissolution process from the gut environment.[1,15]

To select suitable polymer(s) for the formulation of osmotic devices, various SPM-forming polymers were incorporated in the coating solution. Ethyl cellulose is completely impermeable to water.[16] Semipermeability and thus drug release from osmotic systems coated with ethyl cellulose membrane can be enhanced by the incorporation of water-soluble additives such as HPMC. Upon contact with dissolution media, the water-soluble HPMC leaches out of the coating membrane leaving a porous structure. Through these pores, the drug solution from the core of the EOP enters the dissolution medium. The results showed that coating with ethyl cellulose showed dose dumping after 4 h of dissolution because of the detachment of the coating. The burst strength of the ethyl cellulose coating was not sufficient to withstand the hydrodynamic pressure of the dissolution medium, due to the formation of porous structure.

CA films are insoluble, yet semipermeable to allow water to pass through the tablet coating. The water permeability of CA is relatively high and can be easily adjusted by varying the degree of acetylation. The permeability of CA film can be further increased by the addition of hydrophilic flux enhancer (necessary in case of poorly water-soluble drugs). Incorporation of a plasticizer in CA coating formulation generally lowers the glass transition temperature, increases the polymer-chain mobility, enhances the flexibility, and affects the permeability of the film.[17] The SPM formed from CA possesses sufficient wet strength and wet modulus so as to retain its dimensional integrity during the operation and the reflection coefficient (σ), leakiness of the membrane (i.e., leakage of solute through the membrane) is near to 1 which is desired. The polymer is also biocompatible.

CA coating remained intact even after 12 h of dissolution. The 4% w/w of CA in acetone had excellent spray properties. CA coating improved the elegance of osmotic pump along with controlling the release of the drug from the core formulation.

The effect of type and plasticizer concentration on the release rate

Plasticizers are added to modify the physical properties and improve film-forming characteristics of polymers.[18] As plasticizers will also affect the permeability of polymer films, it is important to investigate the effect of plasticizer on the release rate of drug from osmotic devices. The coating containing PEG-400 were found to release the drug by diffusion rather than by zero-order as the drug is freely water soluble. As PEG-400 is a hydrophilic plasticizer, it could be leached easily and leave behind an entirely porous structure, which increases membrane permeability and thus rapid drug release. In contrast, as dibutylphthalate (DBP) is insoluble in water, it is difficult to leach. Because of its hydrophobic character, the residual DBP would resist water diffusion and, as a consequence, the drug release was controlled. The more DBP incorporated into the membrane, the more difficult it was to leach, and in turn, the lower permeability of the membrane, the lower the drug release rate obtained. DBP in the concentration of 10% of CA or ethyl cellulose in the coating solution formed brittle coating with low burst strength. DBP at concentration of 15% w/w of the polymer was found to form a film with good flexibility, elegant appearance, controlling the imbibition of water from the dissolution media and thus the drug release.

Type and amount of osmotically active agents

The type and amount of osmotically active agent in the core formulation affected the drug release from osmotic devices. Tramadol hydrochloride is a freely water-soluble drug. Thus, it also contributes to the osmotic pressure of the core along with the osmogens. The formulation (FT1) without osmogen showed drug release by diffusion rather than by zero-order and also the drug release was incomplete, proving the role of osmotic pressure created by the osmogen as the driving force for the zero-order drug release. NaCl was eliminated from the study, as it is having a high osmotic pressure of 356 atm, which could lead to faster drug release by diffusion rather than by zero-order. Therefore, mannitol and lactose with

osmotic pressures of 38 atm and 23 atm, respectively, were chosen as the osmogens of choice to release the drug by zero order for a longer period.

The amount of osmogen affects the drug release form an EOP as the osmotic pressure that develops within the core depends on the concentration of osmotic agent in the core [Table 7].[19] Formulations containing mannitol in the drug:osmogen ratio of 1:0.5 released 87.48% of drug, and lactose in the drug:osmogen ratio of 1:0.25 and 1:0.5 released 81.71 and 93.46% of drug in zero-order for 6 h.

Effect of aperture diameter

Aperture diameter is one of the critical parameters that greatly influences release rate, lag time and release kinetics of the osmotic drug delivery devices.[20] Thus, the size of delivery orifice must be optimized to control the drug release from osmotic systems. The formulations containing mannitol in the drug:osmogen ratio of 1:0.5 (FT2 and FT7) showed zero-order drug release with the aperture diameters of 480 µm and 565 µm, respectively [Figure 3]. With the aperture diameter of 565 µm, FT2 showed zero-order release only for 6 h, whereas reducing the aperture diameter to 480 µm increased the time of zero-order release to 8 h.

Lactose has less osmotic pressure of 23 atm to that of mannitol (38 atm). Thus, formulations with drug:osmogen ratio of 1:0.25 (F10) and 1:0.5 (F12) showed zero-order release with an aperture diameter of 565 µm. Among the formulations of lactose, formulations with drug:osmogen ratio of 1:0.25 (FT10) showed CR, as was evident from the R^2 value.

Effect of weight gain upon coating on in vitro drug release

The delivery of the agent from oral osmotic systems is controlled by the influx of solvent across the SPM, which, in turn, carries the agent to the outside environment. Water influx into EOP can be described by the following equation:

$$\frac{dv}{dt} = \frac{A}{h} Lp\left(\sigma\Delta\pi - \Delta p\right)$$

Where, $\frac{dv}{dt}$ = Water influx
A =Membrane surface area
h = SPM thickness
Lp = Mechanical permeability
σ = Reflection coefficient
$\Delta\pi$ =Osmotic pressure difference
Δp = Hydrostatic pressure difference.

Increasing the weight gain and SPM thickness resulted in the enhanced resistance of the membrane to dissolution medium diffusion followed by a reduction in the liquefaction rate of the tablet core which ultimately leads to the reduced and controlled drug release rate from an osmotic device. It is evident from the equation that drug release decreases with an increase in weight gain of the membrane.[3]

To study the effect of weight gain of the coating on drug release, core tablets of tramadol hydrochloride (F10) were coated (coating composition C) so as to get tablets with different weight gains (4.30%, 6.52%, and 8.25% w/w). Release profile of tramadol hydrochloride from these formulations is shown in Figure 4. The results were found to be in accordance with the equation. The formulations with

Table 7: Effect of type and amount of osmogen on *in vitro* drug release

Osmogen	D:O ratio	Percentage drug released in zero-order	Time for which drug is released in zero-order (h)
Mannitol	1:0.5	87.48	6
Lactose	1:0.25	81.71	6
	1:0.5	93.46	6

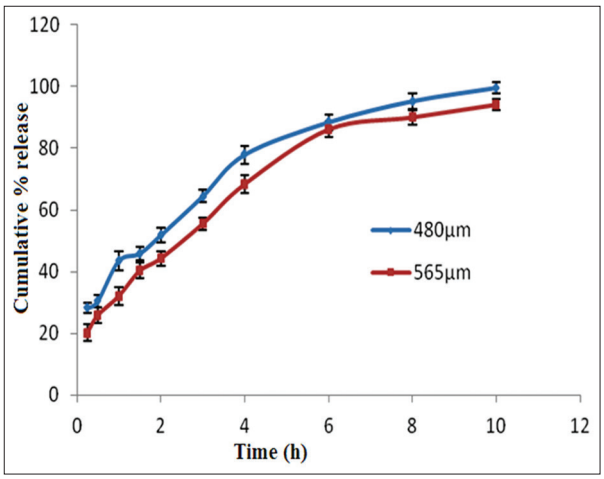

Figure 3: Effect of aperture diameter on *in vitro* drug release (mean ± standard deviation, *n*=3)

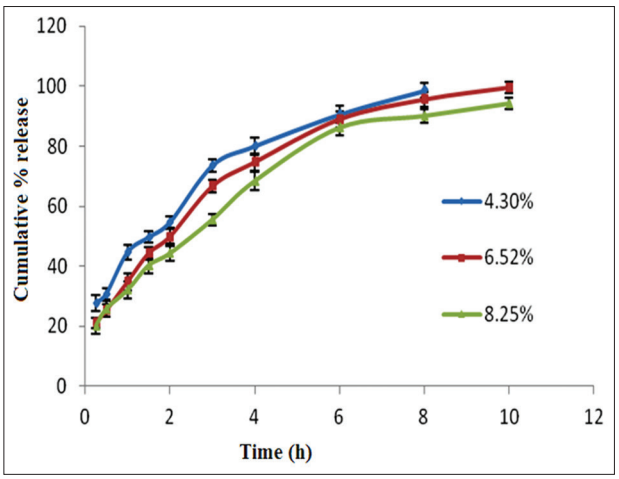

Figure 4: Effect of % increase in weight of tablet upon coating on *in vitro* drug release (mean ± standard deviation, *n* = 3)

Table 8: Effect of percentage increase in weight on *in vitro* drug release

Percentage increase in weight (%)	% drug release	R^2 value				"*n*" value
		Zero-order	First-order	Higuchi	Korsmeyer-Peppas	
6.52	88.95	0.9601	0.9926	0.9931	0.9928	0.5234
8.25	86.16	0.9907	0.9108	0.9854	0.9841	0.454

4.30% increase in weight released 98.56% of drug in <8 h. The formulations with 6.52% and 8.25% increase in weight upon coating released 88.95% and 86.16% of drug, respectively, by non-Fickian and Fickian diffusion mechanism in 10 h [Table 8]. Formulations with 8.25% increase in weight released the drug in zero-order for 6 h.

Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted according to pH change method. The release media used were 900 ml of distilled water (pH 7) and 900 ml of 0.1 N HCl (pH = 1.2) for the first 2 h followed by 900 ml of phosphate buffer (pH 6.8) for the remaining 8 h. The samples (5 ml) were withdrawn at predetermined intervals and analyzed using the UV-Vis spectrophotometer (Elico, India) at 271 nm. The results obtained [Figure 5] showed that there was no significant difference in the cumulative percentage drug release form osmotic systems in different pH conditions.

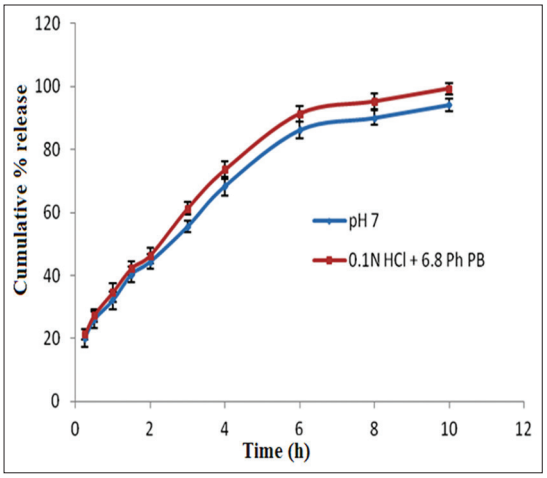

Figure 5: Effect of pH on *in vitro* drug release from an elementary osmotic pump of tramadol hydrochloride (mean ± standard deviation, *n* = 3)

Effect of agitation intensity

To study the effect of agitation intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP Type II at 50 and 100 rpm. The *in vitro* drug release profiles at various agitation rates are presented in Figure 6. It showed that a change in agitation rate did not significantly affect the drug release. Therefore, the mobility of the GIT might scarcely affect the drug release.

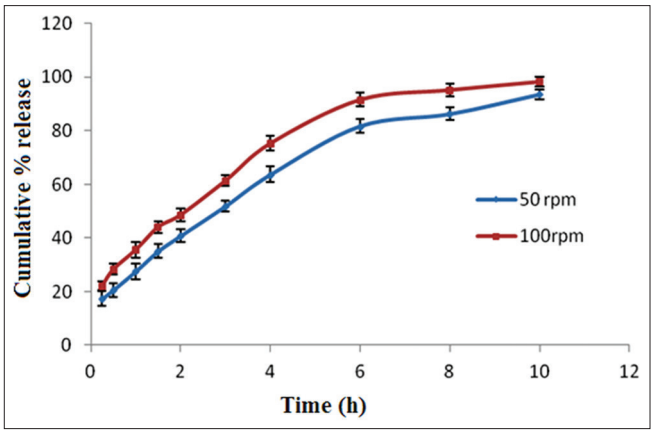

Figure 6: Effect of agitation intensity on *in vitro* drug release (mean ± standard deviation, *n* = 3)

CONCLUSION

EOPs of tramadol hydrochloride were developed based on osmotic technology. The effects of different formulation variables were studied to optimize release profile. The type and amount of osmogen, nature and concentration of plasticizer, the nature of SPM-forming polymer, and aperture diameter were found to control the drug release from the osmotic pumps. 8% increase in weight of osmotic pumps upon coating with CA was found to attribute desirable release pattern to the osmotic system. Dibutylphthalate as a plasticizer at a concentration of 15% of polymer concentration was found to control the imbibitions of water at a desirable rate to control the drug release. Lactose was found to produce osmotic pressure along with the freely soluble drug tramadol hydrochloride sufficient to release more than 80% of drug in a zero-order pattern for 8 h with a formulation containing drug:osmogen at a ratio of 1:0.25 and 1:0.5 and aperture diameter of 565 µm. The release of the drug was not affected by the agitation intensity and pH of the release media. The zero-order release pattern was further confirmed by mathematical treatment of the *in vitro* drug release profiles of the optimized formulations and from "n" values it was found that the drug was released by Fickian diffusion mechanism. The formulation produced had sufficient burst strength to withstand the hydrodynamic pressure both in the dissolution media and GIT.

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