ORIGINAL ARTICLE

e-ISSN: 2349-0659 p-ISSN: 2350-0964
doi: 10.21276/apjhs.2018.5.2.32

Formulation and evaluation of controlled porosity osmotic pump-based tablet of tramadol hydrochloride

Singla Deepak*, Sharma Anjali, Kamboj Himanshu, Guarve Kumar

Department of Pharmacy, Guru Gobind Singh College of Pharmacy, Yamuna Nagar, Haryana, India

ABSTRACT

Introduction: Extended-release formulation of tramadol hydrochloride based on osmotic technology was developed and evaluated. The effect of different formulation variables, namely level of swellable polymer in the core and membrane weight gain, was studied. Drug release was found to be affected by the level of swellable polymer in the core formulation. Tramadol release was inversely proportional to the level of swellable polymer and membrane weight. Drug release from the developed formulations was independent of pH and agitation intensity. **Results:** The manufacturing procedure was found to be reproducible, and formulations were stable after 3 months of accelerated stability studies.

Key words: Extended release, osmotic pressure, osmotic pump, stability, tramadol hydrochloride

INTRODUCTION

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastrointestinal tract to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.[1-3] Tramadol hydrochloride, an oral opioid analgesic, is one of the most commonly prescribed drugs for the treatment of post-operative pain. It is highly water-soluble drug belonging to class 1 of the Biopharmaceutic Classification System.[4] Since tramadol hydrochloride is used for long term treatment for low back pain and osteoarthritis thereby requiring 3–4 times daily dosing in large number of patients which often leads to patient non-compliance. Thus, there is a strong clinical need and market potential for a dosage form that will deliver tramadol hydrochloride in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

The present study was aimed toward the development of extended-release formulations of tramadol hydrochloride based on osmotic technology. Different formulation variables were studied and optimized to achieve the desired release profile.

The manufacturing procedure was standardized, and the stability of the formulations was evaluated after 3 months of storage at accelerated stability conditions.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride (99.79% purity) a gift sample was purchased from Aar Ge Drugs Ltd., Parwanoo, India. Following chemicals and excipients were purchased from commercial sources and used as such. Cellulose acetate, mannitol, and microcrystalline cellulose (MCC) from Thomas Baker (Mumbai), polyvinylpyrrolidone (PVP) K 30, polyethylene glycol 400, methanol, and acetone (S.D. Fine Chem Ltd., Mumbai), and hydroxypropyl methylcellulose (HPMC), talc, and magnesium stearate (Central drug house (P) Ltd., New Delhi).

Formulation Development

Before initiating formulation development, compatibility of tramadol hydrochloride with different excipients was tested using the techniques of Fourier-transform infrared.[5]

Excipients used in the final formulation were found to be compatible with tramadol hydrochloride. Core tablets of tramadol hydrochloride were prepared by direct compression method, and batch size was kept as 100 tablets. Tramadol hydrochloride was mixed with HPMC for 10 min. After passing this mixture through #30 mesh sieves, osmotic agent (mannitol), MCC, and PVP were added and mixed continuously for additional 10 min. To this, talc and magnesium stearate were mixed and passed through #60 mesh sieve and mixing continued for additional 5 min. The blend was then compressed into tablets having an average weight of 300–320 mg using a tablet punching machine.

Coating of Core Tablet

Composition of coating solutions used for coating of core tablets is given in Table 1. 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. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process. Coating was applied to the

Address for correspondence:
Singla Deepak, Guru Gobind Singh College of Pharmacy, Yamuna Nagar, Haryana, India. E-mail: deepaksingla64@gmail.com

Received: 10-05-2018 **Revised:** 31-05-2018 **Accepted:** 07-06-2018

tablets by dipping them into the coating liquid. The wet tablets are dried in a conventional manner in coating pan. Alternative dipping and drying steps are repeated several times to obtain the desired coating.

Composition of Core Tablets

Osmotic tablet of tramadol is optimized using a varying amount of excipients, which are used in the formulation. Optimized final amount of all excipients is tabulated in Table 2.

Coating Composition of Core Tablet

Composition of coating solution is given in Table 1.

EVALUATION OF FORMULATION OF TRAMADOL HYDROCHLORIDE

Evaluation for Pre-compressive Parameters

Bulk density[6]

a. Loose bulk density: An accurately weighed (2.5 g) quantity of powder was transferred to a 10 ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded.
   Loose bulk density = Weight of powder in g/Volume of packing in ml.
b. Tapped bulk density: The loosely packed powder in the measuring cylinder was too tapped 100 times on a plane hard wooden surface and volume occupied in ml was noted.
   Tapped bulk density = Weight of powder in g/tapped volume in ml

Hausner's factor[7]

Hausner found that the ratio D_F/D_0 was related to interparticle friction and, as such, could be used to predict powder flow properties.

Hausner's factor = Tapped bulk density/Poured bulk density

Table 1: Composition of coating solution

Ingredients	Quantity
Cellulose Acetate	4 g
PEG	400 mg
Acetone	90 ml
Methanol	10 ml

PEG: Polyethylene glycol

Table 2: Composition of core tablets

Ingredients used (mg/tab.)	Batch			
	I	II	III	IV
Tramadol HCL	100	100	100	100
Mannitol	136	136	136	136
HPMC	-	30	50	70
MCC	50	20	-	-
PVP	10	10	10	10
Talc	2	2	2	2
Magnesium stearate	2	2	2	2

MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methyl cellulose, PVP: Polyvinylpyrrolidone

Carr's compressibility index[8]

$$\text{Percent Carr's index}: \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Angle of repose[9]

It is measured to find frictional forces in loose powder or granules. It is the maximum angle possible between the surface of a pile of powder or granules and horizontal plane.

$\text{Tan } \theta = h/r \text{ or } \theta = \tan^{-1} [h/r]$

The values ≤30 indicate the free flowing powder.

Evaluation for Post-compressive Parameters

Weight variation test[10]

A total of 20 tablets were randomly selected from each batch and weighed on a electronic balance individually, and the average weight calculated was compared.

Hardness test[11]

Six tablets were randomly selected from each batch, and hardness of each tablet was determined using a hardness tester.

Friability test[12]

It is the ability of tablets to withstand mechanical shocks during handling and transportations. Six tablets were randomly picked from each batch and weighed and placed in the friability test apparatus and operated at a rate of 25 RPM for 4 min (or up to 100 revolutions); tablets were dedusted and weighed again. The loss of tablet weight due to abrasion and fracture was measured in terms of percentage friability (a value of <1% F is acceptable).

$$F = \frac{\text{Winitial} - \text{Wfinal}}{\text{Winitial}} \times 100$$

Drug content estimation[13]

The tablets were tested for their drug content. Five tablets were finely powdered and transferred to a 100 ml of volumetric flask. The flask was filled with phosphate buffer (pH 7.4) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 200 ml with phosphate buffer (pH 7.4) and measure the absorbance of the resulting solution at the maximum of 271 nm using a UV/Vis double beam spectrophotometer.

In vitro dissolution studies[14]

In vitro drug release studies of the prepared tablets were conducted for 12 h using an USP type 2 dissolution apparatus at 37.50°C, and the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media (pH-7.4). At different intervals, 10 ml of samples was withdrawn and filtered through a Whatman filter paper. The equivalent volume of the medium was added to the dissolution vessel. After filtration and appropriate dilution, the sample solutions were analyzed at 271 nm using U.V/VIS spectrophotometer and dissolution medium as blank. Experiments were performed in triplicates.

Formulation Aspects

Various formulation aspects that may affect the release rate are studied here.

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 were simulated gastric fluid (pH 7.4), acetate buffer (pH 6.8), and 0.1 N HCL. The samples (10 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45 mm nylon membrane filters.

Effect of agitational intensity

To study the effect of agitational 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-I (rotating basket) at 50 and 100 rev/min. Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45 mm nylon membrane filters. [15]

RESULTS AND DISCUSSIONS

Drug-excipient Compatibility Studies

The individual IR spectra of the pure drug and the combination spectra of the drug and polymer are shown in Figures 1-3 which indicate no interaction between tramadol and polymers when compared with infrared spectrum of pure drug, as all functional group frequencies were present. Peaks obtained for drug, excipients, and combination of drug and polymers are shown in Table 3.

EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF TRAMADOL HYDROCHLORIDE

Evaluation for Pre-compressive Parameters

The powdered blend of tramadol hydrochloride prepared for compression was evaluated for their flow properties [Table 4].

According to USP limits, values of the angle of repose of all formulation were <30° indicating free-flowing material. Hausner ratio values of all formulation were <1.25 indicating excellent flow as per USP limits. Carr's index values of all formulation were within limits (5–15) indicating excellent flow as per USP limits.

Evaluation for Post-compressive Parameters

The weights and thicknesses were found to be ranging from 310.17 to 324.31 mg and 3.10 to –3.14 mm, respectively, and were considered to be uniform as per USP standard deviation values. The drug content was ranging from 96.89 ± 0.15 to 98.44 ± 0.18%,

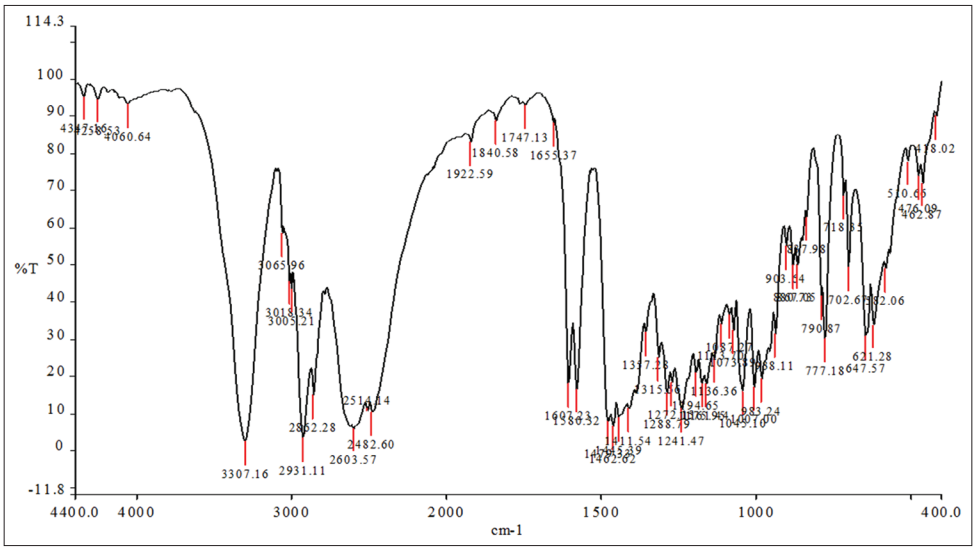

Figure 1: Fourier-transform infrared spectrum of tramadol hydrochloride (pure drug)

Table 3: Interpretation of FTIR spectra

Drug peak	Excipients peak	Drug+Excipients peak	Conclusion
4347.16, 4258.53, 4060.64, 3307.16, 2862.28, 2931.11, 1922.59, 1655.37, 1607.23, 1580.32, 1462.62	3305.62, 3067.46, 2916.32, 2629.06, 2351.59, 1607.89, 1530.07, 1356.84, 1018.45, 777.47, 670.10, 456.29	4335.62, 4013.06, 3896.15, 3402.18, 2838.32, 2888.30, 1961.86, 1659.01, 1529.87, 1511.42, 1468.05	No interaction

FTIR: Fourier-transform infrared

Table 4: Pre-compressive parameters of tramadol hydrochloride blend

Formulation code	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Carr's index (%)
F1	26.56±0.25	0.50±0.01	0.55±0.02	1.1±0.01	9.09±0.05
F2	27.92±0.30	0.51±0.02	0.54±0.01	1.05±0.02	5.55±0.05
F3	26.76±0.40	0.51±0.01	0.55±0.01	1.07±0.02	7.27±0.10
F4	28.89±0.35	0.49±0.02	0.54±0.01	1.1±0.01	9.25±0.05

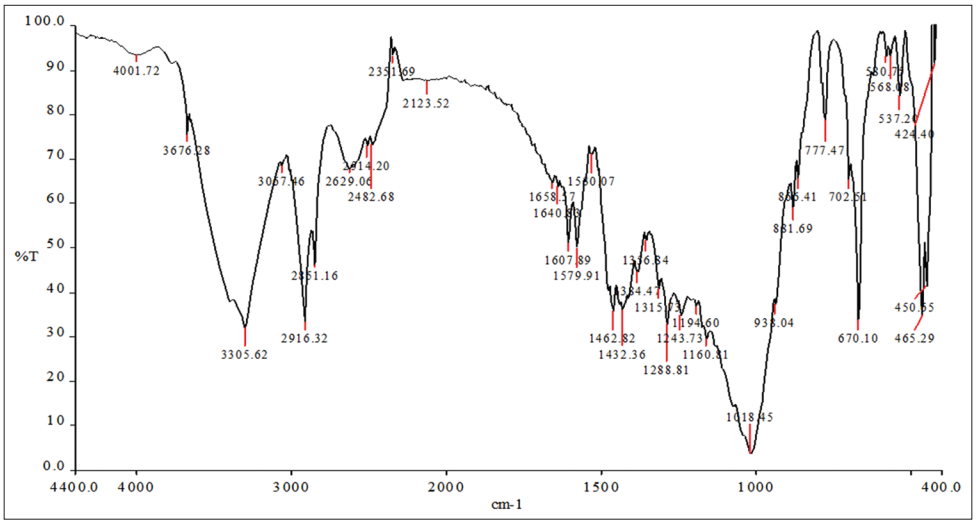

Figure 2: Fourier-transform infrared spectrum of mixture of excipients (68:35:5:1:1 = Mannitol:hydroxypropyl methyl cellulose:polyvinylpyrrolidone:talc:magnesium stearate)

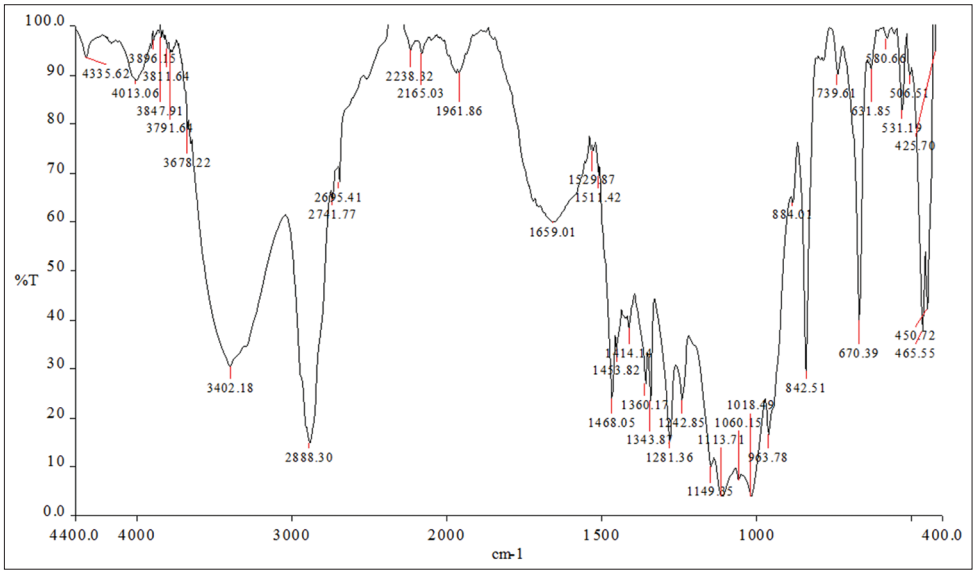

Figure 3: Fourier-transform infrared spectrum of drug + excipients (drug:excipients = 1:2)

Table 5: Post-compressive parameter of tramadol hydrochloride osmotic pump tablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Diameter (mm)	Thickness (mm)	Weight variation (mg)	Drug content (%)
F1	7.5±0.5	0.81±0.01	9.4±0.01	3.11±0.01	310.17±5.2	97.68±0.12
F2	6.5±0.5	0.84±0.01	9.5±0.01	3.14±0.02	312.28±5.8	98.44±0.17
F3	6.5±0.5	0.83±0.02	9.6±0.01	3.10±0.01	311.45±5.1	96.89±0.21
F4	7.5±0.5	0.88±0.02	9.5±0.01	3.10±0.01	324.31±6.5	97.96±0.16

indicating uniformity of drug content as per IP limits (85–115%). The hardness was ranging from 6 to 8 kg cm^2. The friability was found to be <1 which complies with IP limits [Table 5].

In Vitro Dissolution Study of Tramadol Osmotic Tablet

Cumulative percentage release profile of tramadol hydrochloride is given in Table 6.

In vitro release study of all batches was performed. Since the amount of release of drug of batch (F4) was best controlled, therefore batch (F4) was selected as optimized formulation of osmotic pump-based tablet [Figure 4].

Release and Kinetic Study of Formulation (F1-F4)

From Table 7, all the values of release rate exponent (n) of Korsmeyer–Peppas release model were within the range of

Table 6: *In vitro* dissolution study of tramadol osmotic tablet

Dissolution media	Time (h)	F1	F2	F3	F4
pH 7.4 phosphate buffer	1	41.044±0.018	32.88±0.087	27.12±0.018	21.12±1.44
	2	46.329±0.065	40.32±0.073	34.56±0.001	24.60±1.94
	3	51.375±0.243	45.96±1.49	39.611±0.076	27.96±1.76
	4	55.941±0.365	51.12±1.44	43.81±0.435	33.35±1.48
	5	63.388±0.131	58.926±1.44	49.70±0.537	36.21±0.74
	6	71.316±0.150	63.24±1.57	57.60±0.849	41.40±0.79
	7	77.205±0.712	70.44±1.26	59.38±0.35	43.75±1.73
	8	82.855±0.215	76.56±1.95	60.07+0.209	47.90±1.54
	9	86.103±0.313	82.44±1.14	65.08±0.254	51.75±1.34
	10	90.433±0.124	86.88±1.34	67.01±0.321	54.64±0.98
	11	91.284±0.160	87.37±0.983	70.14±0.543	60.76±0.67
	12	92.494±0.432	88.10±0.542	71.11±0.657	63.17±0.450

Table 7: Mathematical models

Formulation code	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer–Peppas (n)
F1	0.970	0.978	0.979	1.565
F2	0.976	0.974	0.984	1.480
F3	0.957	0.987	0.989	1.419
F4	0.997	0.985	0.974	1.265

1.265–1.565 in phosphate buffered saline (PBS) (pH 7.4) (>1.0, Sajid *et al.,* 2010). Therefore, it can be concluded that drug release in PBS (pH 7.4) were mainly following super case II transport.

FORMULATION ASPECTS

Effect of pH on Drug Release

To study the effect of pH, best formulation (F-4) found after *in vitro* dissolution study was further studied for *in vitro* dissolution study in pH 6.8 buffer and 0.1 N HCL [Table 8].

In vitro release study shows that there is no effect of pH change on *in vitro* release of drug [Figure 5].

Effect of Agitation on Drug Release

To study the effect of agitation, best formulation (F-4) found after *in vitro* dissolution study was further studied for *in vitro* dissolution study at 50 rpm in pH 7.4 buffer [Table 9].

In vitro release of drug shows that there is no effect of agitation on *in vitro* release of drug [Figure 6].

Effect of Weight Gain due to Coating on Drug Release

In vitro drug release of final formulation at 6%, 10%, and 12% weight gain due to coating at 100 rpm in pH 7.4 buffer is shown in Table 10.

In vitro release of drug shows that release of drug decreased on increasing the weight due to coating [Figure 7].

RESULTS OF STABILITY STUDY

The results of stability study are shown in Table 11.

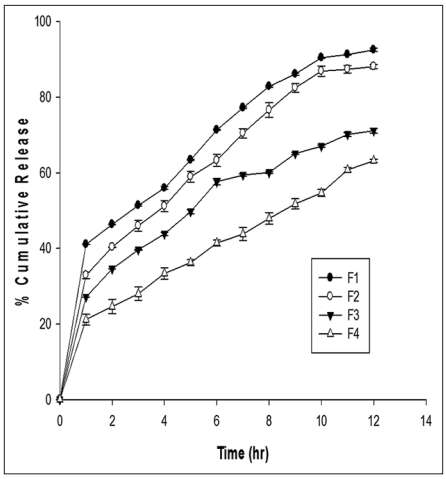

Figure 4: Cumulative release of drug in pH 7.4 buffer

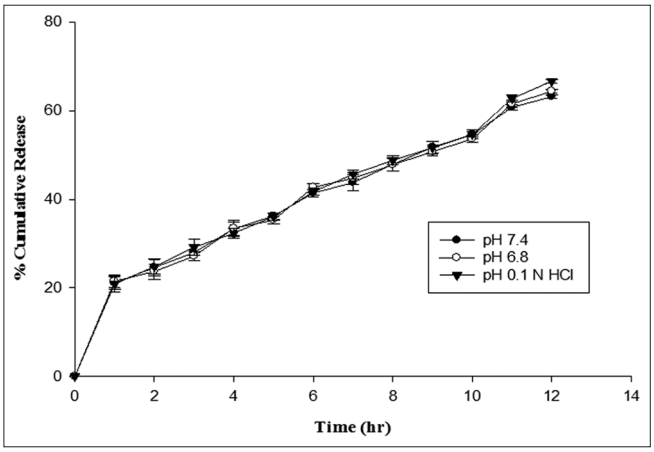

Figure 5: Effect of pH on drug release

Hardness, weight variation, and drug content were found stable after 3 months' storage [Table 12].

Selected formulation F4 was found stable after 3 months of period, as weight variation, hardness, drug content, and percentage cumulative drug release showed no significant changes and was within limits.

CONCLUSION

Sustained release formulations of tramadol hydrochloride were developed based on osmotic technology. The effect of different formulation variables was studied to optimize release profile. Drug release was inversely proportional to the level of swellable polymer and membrane weight. The release from the developed formulations was independent of pH and agitational intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. Developed formulations were found to be stable after 3 months of storage at accelerated stability conditions. The system was found to deliver pseudoephedrine at a

Table 8: *In vitro* dissolution study of tramadol in 6.8 buffer and 0.1 N HCL

Time (h)	F4 (7.4 buffer)	F4 (6.8 buffer)	F4 (0.1 N HCL)
1	21.12±1.44	21.52±1.34	20.88±1.76
2	24.60±1.94	23.70±1.74	24.80±1.64
3	27.96±1.76	27.16±1.06	29.16±1.76
4	33.35±1.48	33.45±1.8	32.35±1.08
5	36.21±0.74	35.31±0.84	36.11±0.84
6	41.40±0.79	42.70±0.89	41.70±0.79
7	43.75±1.73	44.75±1.3	45.65±1.03
8	47.90±1.54	47.80±1.4	48.80±1.04
9	51.75±1.34	50.75±1.03	51.65±1.34
10	54.64±0.98	53.64±0.88	54.64±0.67
11	60.76±0.67	61.56±0.77	62.76±0.87
12	63.17±0.450	64.37±0.450	66.67±0.40

Table 9: *In vitro* dissolution study of tramadol at 50 rpm

Time (h)	F4 (7.4 buffer) at 100 rpm	F4 (7.4 buffer) at 50 rpm
1	21.12±1.44	21.22±0.44
2	24.60±1.94	24.70±1.94
3	27.96±1.76	26.96±1.91
4	33.35±1.48	34.65±1.80
5	36.21±0.74	35.89±0.84
6	41.40±0.79	41.80±0.89
7	43.75±1.73	44.85±1.03
8	47.90±1.54	47.60±1.24
9	51.75±1.34	50.65±1.24
10	54.64±0.98	55.74±0.88
11	60.76±0.67	61.86±0.77
12	63.17±0.450	63.57±0.350

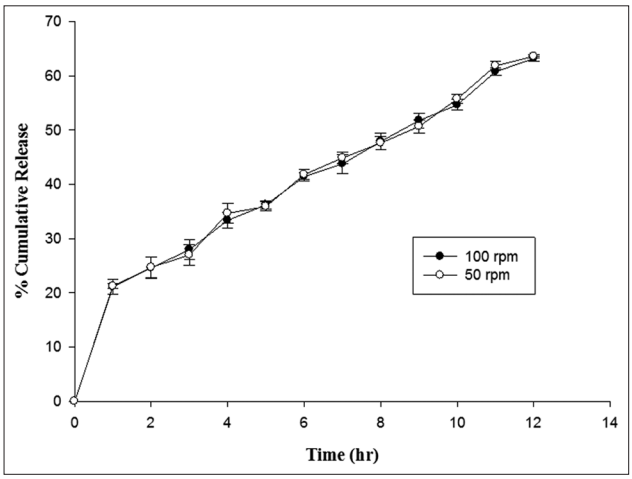

Figure 6: Effect of agitation on drug release

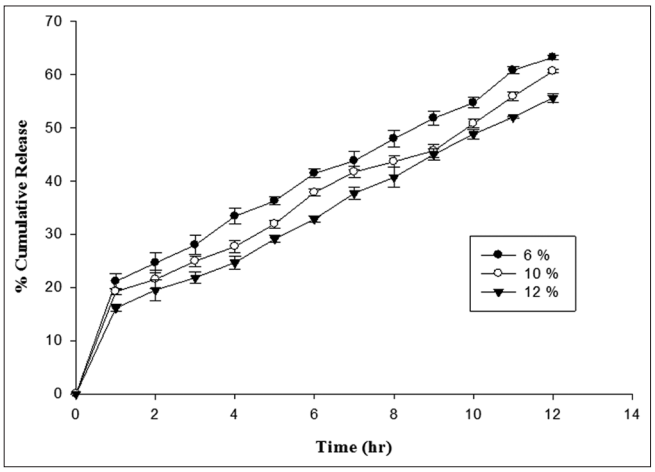

Figure 7: Effect of weight gain

Table 10: Drug release at 6%, 10%, and 12% weight gain

Time (h)	F4 (6% weight gain)	F4 (10% weight gain)	F4 (12% weight gain)
1	21.12±1.44	19.22±0.54	16.12±0.64
2	24.60±1.94	21.50±1.74	19.50±1.94
3	27.96±1.76	24.91±1.01	21.81±1.1
4	33.35±1.48	27.65±1.10	24.65±1.19
5	36.21±0.74	31.89±0.74	29.09±0.64
6	41.40±0.79	37.80±0.69	32.80±0.59
7	43.75±1.73	41.65±1.03	37.65±1.13
8	47.90±1.54	43.60±1.04	40.65±1.84
9	51.75±1.34	45.65±1.24	44.95±1.04
10	54.64±0.98	50.74±0.78	48.74±0.88
11	60.76±0.67	55.86±0.77	51.96±0.17
12	63.17±0.450	60.57±0.30	55.57±0.80

Table 11: Characteristics of tramadol osmotic pump tablet

Initial			3 months		
Hardness (kg/cm^2)	Weight-variation (mg)	Drug content (%)	Hardness (kg/cm^2)	Weight variation (mg)	Drug content
8.3	324.3	97.96	8.2	323.2	97.12

Table 12: *In vitro* CDR of final formulation (F4) initially and after 3 months

Time (h)	%CDR	
	Initial	3 month
1	21.12	21.36
2	24.60	24.12
3	27.96	29.16
4	33.35	33.37
5	36.21	36.69
6	41.40	40.80
7	43.75	42.43
8	47.90	48.38
9	51.75	51.03
10	54.64	53.03
11	60.76	59.31
12	63.17	62.09

CDR: Cumulative drug release

zero-order rate for 12 h independent of the environmental pH. This system is simple to prepare with no drilling required, and hence, it can be used in the field of controlled delivery of drugs.

REFERENCES

1. Theeuwes F, Swanson DR, Guittard G, Ayer A, Khanna S. Osmotic delivery systems for the b-adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration. Br J Clin Pharmacol 1985;19:69S-76.
2. Verma RK, Mishra B, Garg S. Osmotically controlled oral drug delivery. Drug Dev Ind Pharm 2000;26:695-708.
3. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Control Release 2002;79:7-27.
4. Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Glipizide: A review of its pharmacological properties and therapeutic use. Drugs 1979;18:329-53.
5. Guidance, Waiver of *in vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2000.
6. Lechman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Vol. 3. Mumbai: Varghese Publishing House Bombay; 1987. p. 297.
7. Martin A. Lippincott Williams & Wilkins. Phys Pharm 2006;1:333.
8. Subramanyam CV. Text Book of Physical Pharmaceutics, Thoroughly Revised and Enlarge. CBS Publishers; 2005. p. 258.
9. Subramanyam CV. Text Book of Physical Pharmaceutics, Thoroughly Revised and Enlarge. CBS Publishers; 2005. p. 202.
10. Lechman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Vol. 3. Mumbai: Varghese Publishing House Bombay; 1987. p. 313.
11. Lechman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Vol. 3. Mumbai: Varghese Publishing House Bombay; 1987. p. 249.
12. Lechman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Vol. 3. Mumbai: Varghese Publishing House Bombay; 1987. p. 297.
13. Sastri P, Kalra R, Mahalaxmi R, Narkhede R. Enhancement of dissolution of glipizide from controlled porosity osmotic pump using a wicking agent and a solubilizing agent intern. J PharmTech Res 2009;1:707.
14. Sastry VS, Reddy KI, Khan AM. Atenolol gastrointestinal therapeutic system: Optimization of formulation variables using response surface methodology. J Control Release 1997;45:121.
15. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms: Tablet. J Pharm Sci 2005;79:252.

How to cite this Article: Deepak S, Anjali S, Himanshu K, Kumar G. Formulation and evaluation of controlled porosity osmotic pump-based tablet of tramadol hydrochloride. Asian Pac. J. Health Sci., 2018;5(2):170-176.

Source of Support: Nil, **Conflict of Interest:** None declared.