Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : http://ijpsdr.com/index.php/ijpsdr

Research Article

Development of Water Transplant Based Single Core Osmotic Pump for Fluvoxamine Maleate Employing Quality by Design Principles

G. M. Umaretiya[1]*, J. R. Chavda[2], J. K. Patel[3]

[1]*School of Pharmacy, RK University, Rajkot-360020, Gujarat, India.*
[2]*B. K. Mody Government Pharmacy College, Rajkot-360003, Gujarat, India.*
[3]*Nootan Pharmacy College, Visnagar-384315, Gujarat, India*

ARTICLE INFO

Article history:
Received: 22 December, 2020
Revised: 22 January, 2020
Accepted: 24 January, 2020
Published: 30 January, 2020

Keywords:
Osmotic pump,
QbD,
Water transplant,
Zero order.

DOI:
10.25004/IJPSDR.2020.120114

ABSTRACT

The present study draw a bead on preparing single core osmotic pump with improved water transplant by employing Quality by Design (QbD) principles to achieve zero order drug release for prolonged period of time. QbD principles were employed in preparing single core osmotic pump by deriving quality target product profile (QTPP), critical quality attributes (CQA) followed by risk assessment using ishikawa diagram and risk estimation matrix. Box-Behnken design (BBD) was employed to study the effect of various independent parameters like concentration of Natrosol 250 HX (X1) and concentration of Xylitab (X2) no. of orifice (X3), on various dependent parameters like lag time (Y1) and time required for release 25, 50, 75 and 100% drug (Y2, Y3, Y4, and Y5). A controlled space was designed where each criteria or CQA was satisfied. Optimized formulation was further characterized for its efficiency. The results of design suggest the suitability of design for optimization of single core osmotic pump. In the initial period, drug release was driven by no. of orifice which on later stage depends on concentration of swellable polymer and concentration of osmogen. Optimized design was validated by preparing check point batch having less than 5% predicted error. Model fitting with drug release kinetics showed that optimized single core osmotic pump released drug in zero order. Stability data suggested that prepared formulation was stable for 3 month period without significant changes in the CQA. Single core osmotic pump using water transplant was successfully developed for a poorly soluble drug using QbD principles.

Introduction

To combat the drawbacks that the conventional drug delivery offers, modified delivery systems have to be developed which offer several advantages against making of a new drug entity. Due to advantages like maintenance of blood plasma concentration for a longer period of time, which in turn, results in fewer toxicity and better efficacy, modified release formulations have become more popular now a days. Moreover higher dosage frequency and patient compliance may be of added advantages while developing a controlled release formulation.[1]

The aim of fabrication of controlled delivery systems is to reduce dosing frequency or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Thus, controlled release dosage form is a design which releases one or more active pharmaceutical ingredient (APIs) unremittingly in a preset pattern for a fixed time, either systemically or to a specified target organ constant delivery, less side effect and dosing frequency.[2]

Amongst the US-Food and Drug Administration (US-FDA) recognized 112 distinct routes of administration, oral route have accounted for majority of small molecules. Oral controlled release (CR) drug delivery systems continue to be the most preferred ones among all the drug delivery owing to the ease of administration, patient compliance, ease, and versatility of fabrication. The conventional oral dosage forms show fluctuation in drug plasma concentration when pharmacokinetics of any drug is studied after oral administration. This

***Corresponding Author:** Mr. G. M. Umaretiya

Address: School of Pharmacy, RK University, Rajkot-360020, Gujarat, India.

Email ✉**:** shyam.umaretiya@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

is not desirable because such changes significantly affect pharmacodynamic profile of API. So, it is always recommended to develop optimized dosage regimen which constantly release drug at fixed rate without any considerable variation in drug plasma concentration.[3]

In order to achieve zero order drug release for an extended period of time many novel drug delivery technologies have been developed so far. Out of which, osmotic controlled drug delivery systems is considered the best approach for achieving zero order dug release which is desirable for any controlled release delivery system. Osmotic delivery system uses osmotic pressure of an osmogen to expel drug from the unit which helps to maintain effective plasma concentration for a longer period of time without any fluctuation while remaining unaffected by all other physiological factors like pH, presence of food and diseased state.[4]

Many water soluble drugs are formulated in different forms of osmotic pump including (elementary OP, push pull OP, porosity controlled OP).[5-7] The key part in fabrication of optical discrimination evaluation study (ODDS) is pore formation and generation of osmotic pressure. It is challenging to delivery poorly water soluble drugs via ODDS, as poorly water-soluble drugs can not generate sufficient osmotic pressure and expelled out at low rates. The problem can be solved by improving water transport rate by preparing pores which may assist in improving water transport and improve release rate of poorly water soluble drug. Many researchers have contributed in this line of research and successfully delivery poorly soluble APIs.[8]

Fluvoxamine is selective serotonin reuptake inhibitor and pharmacologically classified as an antidepressant. The chemical name is 5-methoxy-4‟trifluoromethyl) valerophenone - (E)-O-(2-aminoethyl) oxime maleate and mostly used to treat obsessive-compulsive disorder. It is marketed by GlaxoSmithKline under registered trademark of Lotronex™. It is springly soluble in water (0.00734 mg/mL). Generally it is given bis in die (BID) (>100mg into 2 doses) in adults and (>50mg into 2 doses) in children. More change in FLV plasma concentration remarkably affects therapeutic response. So, it is justifiable to design early-onset periodontitis (EOP) for FLV which can deliver the drug in a constant rate.[9]

Thus, in the present study, structural classification of proteins (SCOP) was developed by preparing pores in the osmotic tablet which resulted in improved water transport and prepared SCOP was well characterized.

Materials and Methods

Materials

Fluvoxamine Maleate (FLV) was received as a gift sample from Ramdev Chemical Pvt. Ltd. (Boisar-Maharastra, India). Xylitab was kindly gifted by Roquette Pharma (France). Natrosol 250HX was received as a gift sample from DKSH India Pvt. Ltd. (Mumbai). Cellulose acetate phthalate was a kind gift from Eastman Chemical Company (USA) and Dibutyl pthalate was received as gift samples from Sigma–Aldrich (USA). Double distilled water was used wherever required. Other chemicals were of laboratory grade.

Quantification of FLV

Quantification of FLV was performed by double-beam UV spectrophotometer (Shimadzu-1800, Kyoto, Japan) in the present work. A known detectible amount of FLV (10 µg/mL) was taken and dissolved in the 0.1 N HCl and subsequently diluted with distilled water. The final solutions were analyzed at 246 nm. Standard concentrations were prepared in the range of 5–30 µg/mL and studied for 3 days for inter-day and intra-day variations. Other validation parameters were found for FLV.[10]

Application of QbD Tools[11,12]

Identification of Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQAs)

Considering desirable criteria of FLVSCOP and different factors impacting quality of formulation, QTPP and CQAs were finalized and properly justified.

Risk Assessment Studies

An Ishikawa diagram was delineated for proper interpreting the effect of different independent variables (IVs) on quality of product. A risk estimation matrix was outlined relating magnitude of risk on CQAs. The risk categorized into high, medium and low values and assigned to each factor accordingly.

Application of Box-Behnken Design[13]

After detail risk assessment study, the impact of risky factors on selected CQAs was done by employing BBD. The detail layout of BBD formulation batches are summarized in Table 1. The applied design was validated by standard

Table 1: Layout of Box-Behnken design

	Coded values			*Actual values*		
Batch	X_1	X_2	X_3	X_1	X_2	X_3
F1	–1	–1	0	4	10	3
F2	+1	–1	0	12	10	3
F3	–1	+1	0	4	20	3
F4	+1	+1	0	12	20	3
F5	–1	0	–1	4	15	1
F6	+1	0	–1	12	15	1
F7	–1	0	+1	4	15	5
F8	+1	0	+1	12	15	5
F9	0	–1	–1	8	10	1
F10	0	+1	–1	8	20	1
F11	0	–1	+1	8	10	5
F12	0	+1	+1	8	20	5
F13	0	0	0	8	15	3
BBK1	–0.387	0.28	+1	6.45	17.10	5
BBK2	–0.471	0.224	+1	6.115	16.680	5

error graph (SEG) and its standard error was found. Independent variables were fixed as amount of water swellable polymer (X_1) and amount of osmogen (X_2) and no. of orifice (X_3). Dependent variables were fixed as Lag time (T_L), time required for 25% drug release (T_{25}), time required for 50% drug release (T_{50}), time required for 75% drug release (T_{75}), and time required for 100% drug release (T_{100}).

Also to confirm the evolved model, different check point batches (BBK1 and BBK2) were formulated. % PE was also determined to assess the accuracy of evolved model. Detail ANOVA study was performed to under the significant and non-significant impact of factors.

Percentage error (%PE) = [(Experimental value-Predicted value)/Experimental value]*100

Preparation of Core Tablet

Core tablets were prepared by direct compression. All the ingredients are weighed accurately on electronic balance (Lab Intelligence, India). The drug and water swellable polymer (Natrosol 250HX) were mixed according to geometrical dilution method and were triturated to remove any coarse particles. After passing this mixture through 20# sieve, osmogen (Xytilab) was added in geometric dilution and mixing continued for additional 10 minutes. The blend was then compressed with a hardness of 4-5 kg/cm^2 using 10 mm round flat faced punches on 12 station tablet machine (Rimek Mini Press II). Tablet of each batch contained 150 mg of FLV.

Coating of Core Tablet and Drilling[14,15]

The core Tablet was coated by homogenous mixture of cellulose acetate phthalate (CAP) and dibutyl phthalate (DBT) (6:4). The ratio was selected based on prior studies (results not included). Spray solution was prepared using Remi's stirrer. Each batch of 100 convex shaped core Tablets were coated in a conventional standard coating pan (Labtronik, India) with conditions (Inlet air temperature, 45°C; air flow rate, 1.4 kg/cm^2; coating spray rate, 4-5 mL/min and pan speed 25 rpm). Prepared tablets were drilled using laser driller with an orifice size of 0.5mm. Numbers of orifice were generated as per the matrix of design.

Physical Evaluation

The dry blend of core tablet was evaluated for various pre-compression parameters. The prepared core Tablets and coated Tablets were inspected manually for any sign of defects. The core tablet and coated tablet were evaluated for weight variation, drug content, thickness, diameter, hardness and friability.

In vitro Drug Release Study[15]

In vitro release studies of different formulations were performed according to USP apparatus II, paddle method. Paddle speed was maintained at 50 rpm and 900 mL of water used as the dissolution medium. Samples (10 mL) were collected at predetermined time intervals (0, 0.2, 0.5, 0.7, 1, 1.2, 1.5, 1.7, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours) and replaced with equal volume of fresh medium, filtered through a 0.45 µm filter and analyzed with a UV-visible spectrophotometer at 246nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved.

Drug release Kinetics[16]

In vitro release profile of the optimized batch FLVSCOP was fitted in various *In-Vitro* release kinetic models. Amongst them best fitting model was selected on the basis of R^2 value, sum of squared residuals (SSR) value and F value. The study was assisted by DD solver.

Effect of Variables on Drug Release

With the aim to achieve independent, constant and uniform drug release, FLVSCOP was developed. To determine the robustness of drug release behavior from FLVSCOP and independent release from system, effect of different variables including effect of pH, agitation and ionic strength on dissolution was studied.

Stability Study[15]

The optimized batch (OB) of FLVSCOP was submitted to stability chambers (Model-TH 90 S, Thermolab, India) for short term stability study as per ICH guidelines (40 ± 2°C and 75 ± 5% RH; 3 months). The FLVSCOP was packed in flint vials and sealed hermetically with rubber plugs and aluminum caps. Samples were taken out at 1, 2, and 3 months and checked for different performance and physicochemical parameters.

Result and Discussion

Quantification of FLV

The drug solution in 0.1 N HCl exhibited a λmax at 246 nm. Calibration curves (5–30 µg/mL) were made using freshly prepared solutions for 3 consecutive days. The coefficient of variation (CV) determined on the basis of the absorbance for six triplicate measurements were found to be 0.416 and 0.385% for *intra* and *inter* day assay precision respectively. The % recovery was found to be varying from 98.75 ± 0.6148 to 101.19 ± 0.4915 indicate that proposed method was accurate. A high degree of correlation was established between concentrations and respective absorbance (R^2 = 0.999).

Application of QbD Tools

Identification of Quality Target Product Profiles and Critical Quality Attributes

QTPP for FLVSCOP are summarized in Table 2. All QTPPs were justified considering osmotic pump design of FLV satisfying zero order drug release pattern. The CQAs were identified for FLVSCOP considering its impact on safety and efficacy. All quality attributes (QAs) are summarized in Table 3 and out of them, selected CQAs were studied further using dyspnea on exertion (DoE).

Table 2: Quality target product profile (QTPP) for flvscop

Quality Target Product Profiles	*Target*	*Justification*
Dosage form	Tablet (osmotic pump)	Suitable drug delivery system which provides constant release and not affected by variables.
Route of administration	Oral	Recommended route for efficacy
Dosage strength	150 mg	Pharmaceutical equivalence
Expected drug release	Zero order	To achieve constant drug plasma level in blood without major fluctuation
Impurity	Below safety threshold	To avoid any chance of toxicity
Assay	Acceptable limit	To achieve proper pharmacological response
Content uniformity	Acceptable limit	To maintain uniformity from batch to batch and consequently uniform therapeutic response
Stability	At least 24 months	To maintain therapeutic integrity of API for stipulated storage period
Container closure system	System qualified as suitable for this drug product	Needed to achieve the targeted shelf life

Table 3: Critical quality attributes (CQAS) for flvscop

Quality attributes of the drug products	*Target*	*Is this a CQA?*	*Justification*
Physical attributes • Color • Odor • Appearance	Transparent No unpleasant odor Acceptable to patients	No	They are not directly associated to efficacy and safety
Assay and content uniformity	100%	No	Proper mixing and direct compression method helps to maintain desired assay and CU in acceptable range.
Lag time	0.2–0.5	Yes	To maintain minimum effective concentration (MEC) as early as possible
T_{25} (time required to achieve 25% drug release)	1.5–3.5	Yes	Time required to achieve 25% drug release to obtain for zero order profile
T_{50} (time required to achieve 50% drug release)	11.25–12.75	Yes	Time required to achieve 50% drug release to obtain for zero order profile
T_{75} (time required to achieve 75% drug release)	17–19	Yes	Time required to achieve 75% drug release to obtain for zero order profile
T_{100} (time required to achieve 100% drug release)	23–25	Yes	Time required to achieve 100% drug release to obtain for zero order profile
Microbial limits	Meets relevant pharmacopoeial requirements	No	Noncompliance to microbial limits will affect safety profile of formulation. Though critical care during development may reduce bio-burden in final product.
Water content	NMT 4.0% w/w	No	Generally, water content may affect stability but FLV is not moisture sensitive and so stability may not be affected.

Risk Assessment

Ishikawa diagram as shown in Fig. 1 indicates list of various factors which may affect the quality of FLVSCOP with an intensity of minor to major. Moreover, the Risk Estimation Matrix (REM) was outlined (Table 4) and the factors having high risk on selected CQAs were further studied in optimization section.

Validation of Box-Behnken Design

Fig. 2 shows standard error graph (SEG) of applied BBD. Value of X_3 is constant at 5 orifices. This graph represents over all standard error which is less than unity proving rationalized selection of BBD for given data set in formulation of FLVSCOP.

Application of Box-Behnken Design

The results of BBD batches are presented in Table 5. The results show that remarkable variation in data confirming sensitivity of selected independent variables (X_1, X_2, and X_3) on CQAs. The analysis of variance analysis of selected dependent and independent variables is shown in Table 6. The significant and non-significant level of main, interaction and polynomial effect are denoted as 'S' and 'NS'.

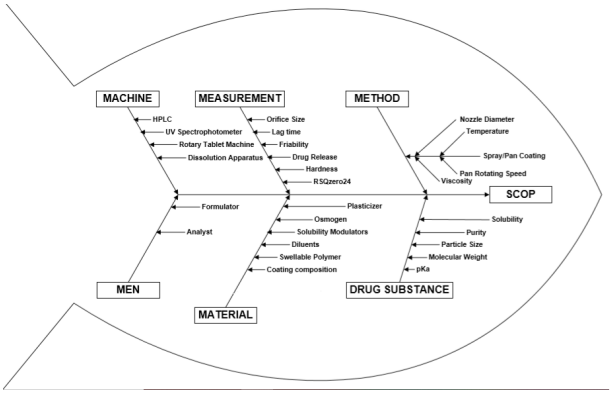

Fig. 1: Ishikawa diagram

Table 4: Risk estimation matrix

Critical quality attributes	*Conc. of osmogen*	*Water swellable polymer*	*Coating polymer*	*No of orifice*	*% Weight gain*
T_L	Medium	High	Medium	High	Medium
T_{25}	High	High	Low	High	Medium
T_{50}	High	High	Low	High	Medium
T_{75}	High	High	Low	High	Medium
T_{100}	High	High	Low	High	Low

Table 5: Results of critical quality attributes of Box-Behnken design batches

Batch	T_L	T_{25}	T_{50}	T_{75}	T_{100}
F1	1.2	2.88	13.4	19.1	25.9
F2	1.12	2.6	14.2	16.2	22.1
F3	0.25	1.98	16.6	17.6	23.2
F4	0.7	1.99	11.2	21.1	27.3
F5	1.08	2.1	10.2	18.1	24.1
F6	1.18	2.8	11.7	18.2	24.9
F7	1.3	3	15.4	17.4	23.1
F8	0.8	2.5	18.6	20.0	26.1
F9	1.01	2.4	11.9	18.1	24.2
F10	0.6	2.4	11.3	19.9	25.3
F11	0.2	1.56	12.6	17.6	23.1
F12	0.45	1.68	12.3	19.1	25.0
F13	1.5	2.7	13.0	20.2	26.2

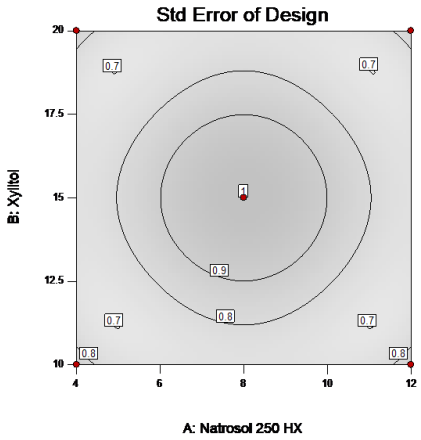

Fig. 2: SEG plot of applied BBD for FLVSCOP

Table 6: Anova analysis of intravaginal slingplasty and critical quality attributes for FLVSCOP

	Y1		*Y2*		*Y3*		*Y4*		*Y5*	
Source	*p-value*	*S/ NS*	*p-value*	*S/ NS*	*p-value*	*S/ NS*	*p-value*	*S/ NS*	*p-value*	*S/ NS*
Model	0.0012	S	< 0.0001	S	0.0439	S	0.0454	S	0.0454	S
X_1	0.8142	NS	0.0209	S	0.0073	S	0.0894	NS	0.0894	NS
X_2	0.3117	NS	0.0767	NS	0.6263	NS	0.0298	S	0.0298	S
X_3	0.0002	S	< 0.0001	S	0.7445	NS	1.0000	NS	1.0000	NS
X_1X_2	-		-		-		0.1367	NS	0.1367	NS
X_1X_3	-		-		-		1.0000	NS	1.0000	NS
X_2X_3	-		-		-		0.0139	S	0.0139	S

(S = significant, NS = non significant)

Non-significant terms were omitted from full medical loss ratio (MLR) equation and further reduced MLR equations were derived. The detail ANOVA study reveals that the model best fits for all selected five responses (Y1-Y5). Further, factor X_3 has significant effect on lag time and drug release in initial hours. Though factor X_3 is considerable in the initial release, but the impact of X_2 and X_3 is also observed during later phases of drug release. The reduced MLR equations for Y1-Y5 are summarized as below.

$Y1\ (T_L) = +1.279+0.4375E\text{-}003X_1+0.015500X_2-0.22375X_3$

$Y2\ (T_{25}) = +3.15370+0.31875X_1-0.018250X_2-0.26063X_3$

$Y3\ (T_{50}) = +10.22308+0.51250X_1-0.0600X_2-0.100X_3$

$Y4\ (T_{75}) = +11.000-0.40625X_1+0.575X_2+2.25X_3-0.037X_1X_2+0.0005X_1X_3-0.150X_2X_3$

$Y5\ (T_{100}) = +11.000-0.40625X_1+0.575X_2+2.25X_3-0.037X_1X_2+0.0005X_1X_3-0.150X_2X_3$

Furthermore, the impact of independent variables (X_1, X_2 and X_3) on selected CQAs (Y1–Y5) was studied by contor plots and response surface plots. The response surface plots and overlay plot of all contour plots are show in Fig. 3. The curvature in surface response plot itself indicates the sensitivity of X_1, X_2, and X_3 on Y1-Y5. All physico chemical parameters of BBD batches were in pharmacopoeial limit.

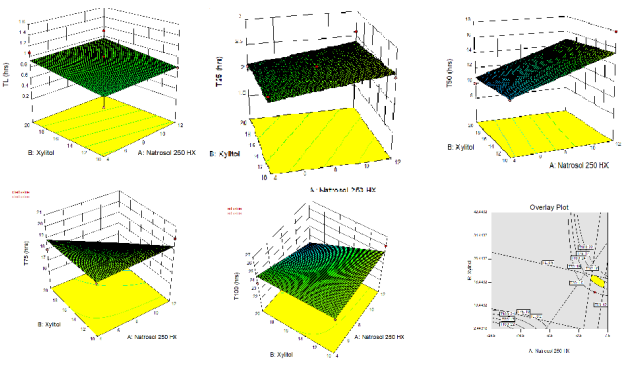

Fig. 3: Response surface plots and overlay plot

Check point batches were defined from the yellow region of overlay plot to find the validity of reduced MLR evolved models. The value for X_3 (no. of orifice) was kept constant for each graph. % PE of check point batches were calculated and were found below 5% (Table 7), which proves the legitimacy of acquired models.[17]

Based on control space (Fig. 4) revised risk assessment study was performed and revised REM (Table 8) was prepared where all IVS revealed low risk on CQAs.

The results of physical evaluations were performed and they were under pharmacopoeial limit. Also the dissolution of FLVSCOP was performed in different variables. In all varying conditions, non-significant deviation was observed amongst all dissolution profiles. This indicates that SCOP is robust design which release drug without being affected by different variables (pH, agitation, ionic strength).

Drug Release Kinetics

Drug release kinetic model fitting parameters (R^2, SSR and F-value) for FLVSCOP are enlisted Table 9. *In vitro* drug release of FLVSCOP was best explicated by Zero order model release kinetics; which was concluded from highest R^2 value and lowest SSR and F value. This confirms the constant release from FLVSCOP with uniform release rate.

Stability Study

The results of short term stability study of FLVSCOP are depicted in Table 10. The data indicates that there is no any sign of instability after stipulated time of stability study. The values of all five CQAs were remained unaltered which confirms consistence performance of developed FLVSCOP.

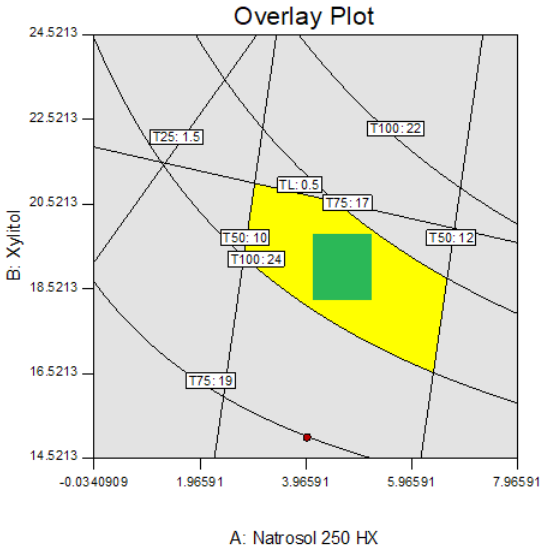

Fig. 4: Derivation of control space

Table 7: % pulmonary embolism of check point batches

Check point batches	*CQAs*	*Observed*	*Predicted*	*%PE*
	Y1	0.45	0.445	1.111111111
	Y2	1.82	1.752	3.736263736
BBK1	Y3	12.53	12.00	4.229848364
	Y4	17.96	18.00	0.222717149
	Y5	23.75	24.00	1.052631579
	Y1	0.44	0.450	2.272727273
	Y2	1.8	1.71	5
BBK2	Y3	12	11.48	4.333333333
	Y4	18.23	17.891	1.859572134
	Y5	24.25	23.981	1.109278351

Table 8: Updated risk assessment for flvscop

	Risk estimation matrix				
Drug product CQAs	*Conc. of osmogen*	*Solubility modulator*	*Coating polymer*	*No. of orifice*	*% Weight gain*
T_L	Low	Low	Low	Low	Low
T_{25}	Low	Low	Low	Low	Low
T_{50}	Low	Low	Low	Low	Low
T_{75}	Low	Low	Low	Low	Low
T_{100}	Low	Low	Low	Low	Low

Table 9: *In-Vitro* release kinetic model fitting parameters

	FLVSCOP (OB)		
Model	R^2	*SSR*	*F value*
Zero order	0.995	50.780	7.233
First order	0.979	345.11	45.30
Higuchi	0.961	183.18	26.305
Hixson-crowell	0.981	121.42	20.23
Weibull	0.989	159.89	46.21

Table 10: Result of stability study of FLVSCOP (OB)

	OB			
Parameters	*Initial*	*1 month*	*2 months*	*3 months*
Assay (%)	98.24 ± 0.078	99.02 ± 0.042	98.47 ± 0.039	99.88 ±0.049
Physical degradation	No	No	No	No
T_L	0.45	0.44 ± 0.001	0.48 ± 0.023	0.46 ± 0.0098
T_{25}	1.82	1.78 ± 0.011	1.99 ± 0.024	1.88 ± 0.038
T_{50}	12.53	12.45 ± 0.012	12.12 ± 0.015	12.00 ± 0.028
T_{75}	17.96	17.88 ± 0.033	17.55 ± 0.037	17.68 ± 0.051
T_{100}	23.75	24.12 ± 0.029	23.98 ± 0.032	24.01 ± 0.042

Conclusion

In order to achieve zero order release profile, role of water swellable polymer, presence of osmogen and no. of orifice in core Tablet were considered as key factors. Different principles of QbD and BBD were successfully employed for robust development of water transplant based SCOP for FLV to provide zero order drug release which delivers drug in a controlled manner for longer period of time.

References

1. Thombre AG, Wu XY, am Ende MT. Chemical Engineering in the Pharmaceutical Industry: Active Pharmaceutical Ingredients, A John Wiley & Sons Publication, Second Edition, 2019;p381-407.
2. Bruck SD, editor. Controlled Drug Delivery: Volume 1 Basic Concepts. CRC Press; 2019 Jun 4.
3. Tomar A, Wadhwani S, Bhadauria RS. An overview on oral controlled release matrix Tablet. International Journal of Pharmaceutical Erudition. 2019;4:10-21.
4. Jahromi AK, Shieh H, Saadatmand M. Theoretical study of diffusional release of a dispersed solute from cylindrical polymeric matrix: A novel configuration for providing zero-order release profile. Applied Mathematical Modelling. 2019;73:136-145.
5. Malaterre V, Ogorka J, Loggia N, Gurny R. Approach to design push–pull osmotic pumps. International journal of pharmaceutics. 2009;376(1-2):56-62.
6. Theeuwes F. Elementary osmotic pump. Journal of pharmaceutical sciences. 1975;64(12):1987-1991.
7. Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LA, Sutton SC. Osmotic drug delivery using swellable-core technology. Journal of Controlled Release. 2004;94(1):75-89.
8. Azharshekoufeh B L, Javadzadeh Y, Jalali MB, Nokhodchi A, Shokri J. Design and formulation of nano-porous controlled porosity osmotic pumps (CPOPs) containing a poorly water soluble drug, glibenclamide. Pakistan Journal of Pharmaceutical Sciences 2019;32(5):1979-1986.
9. Tyagi Y, Madhav NS. Smart innovative approach for designing fluvoxamine loaded bio-nanosuspension for the management of depression. International Journal of Applied Pharmceutics. 2019; 11(1):191-197.
10. Diva A A, Fathi S, Chekin F. Determination of Fluvoxamine in Real Samples using Carbon Paste Electrode Modified by Electrodeposition of Nickel. Journal of Analytical Chemistry. 2019; 74(8):809-815.
11. Xu X, Costa AP, Khan MA, Burgess DJ. Application of quality by design to formulation and processing of protein liposomes. International journal of pharmaceutics. 2012;434(1-2):349-359.
12. Rathod M, Suthar D, Patel H, Shelat P. Parejiya P. Microemulsion based nasal spray: A systemic approach for non-CNS drug, its optimization, characterization and statistical modelling using QbD principles. Journal of Drug Delivery Science and Technology. 2019;49:286-300.
13. Banerjee A, Verma PRP, Gore S. Application of Box–Behnken Design to Optimize the Osmotic Drug Delivery System of Metoprolol Succinate and its In-vivo E valuation in Beagle Dogs. Journal of Pharmaceutical Innovation. 2016;11(2):120-133.
14. Waterman KC, MacDonald BC, Roy MC. Extrudable core system: development of a single-layer osmotic controlled-release Tablet. Journal of Controlled Release. 2009;134(3):201-206.
15. Verma RK, Garg S. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. European Journal of Pharmaceutics and Biopharmaceutics. 2004;57(3):513-525.
16. Cheng X, Sun M, Gao Y, Cao F, Zhai G. Design and evaluation of osmotic pump-based controlled release system of Ambroxol Hydrochloride. Pharm Dev Technol. 2011;16(4):392-399.
17. Parejiya PB, Barot BS, Patel HK, Shelat PK, Shukla A. Innovation of novel 'Tab in Tab'system for release modulation of milnacipran HCl: optimization, formulation and in vitro investigations. Drug development and industrial pharmacy. 2013;39(11):1851-1863.

HOW TO CITE THIS ARTICLE: Umaretiya GM, Chavda JR, Patel JK. Development of Water Transplant Based Single Core Osmotic Pump for Fluvoxamine Maleate Employing Quality by Design Principles. Int. J. Pharm. Sci. Drug Res. 2020;12(1):87-93. **DOI:** 10.25004/IJPSDR.2020.120114