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Article

Optimization of Diltiazem hydrochloride osmotic formulation using QBD approach

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Diltiazem hydrochloride (DLH) is a calcium channel blocker useful for the treatment of angina pectoris, arrhythmia, and hypertension. DLH having a short half-life needs frequent administration for successful treatment but this poses a problem of poor patient compliance. These requirements are served by elementary osmotic pump tablets (EOP) based controlled-release (CR) systems. Quality by design (QbD) approach assists in screening various factors with subsequent assessment of critical parameters that can have a major impact on the scalability of EOP. Tablets were formulated using wet granulation method followed by osmotic coating. Factorial design based QbD strategy aided in defining the risk assessment of influential variables such as hydrophilic polymers and osmotic coat component on the in-vitro release kinetics of the designed EOP tablets. These formulated EOP systems followed zero-order kinetics, a characteristic feature of EOPs. EOP tablets were formulated applying a systematic QbD statistical approach. The formulated DLH EOP systems with improved concentration-independent behavior helped to address the challenges of IR formulation. Application of QbD strategy in ascertaining the scalability of DLH EOP formulation would help pharmaceutical industries in the translation of EOP based drug delivery systems from R&D to market.

Keywords: Elementary osmotic pump. QbD. Factorial design. Tablet. Zero order.

INTRODUCTION

Diltiazem Hydrochloride (DLH) is a calcium channel blocker approved by the United States Food and Drug Administration (USFDA) as an effective therapy for angina pectoris, arrhythmia, and hypertension (CARDIZEM® CD label). Owing to its short half-life (Prabakaran *et al.*, 2003) and the subsequent problem of frequent dosing makes osmotic drug delivery system (ODDS) a potential candidate. Reports indicated that the immediate release (IR) formulation caused adverse gastrointestinal (GI) reactions associated with abrupt fluctuations in the plasma level time profile. Also, the marketed extended release (ER) dosage forms are associated with the problem of burst release and thereby dose dumping (Huang, Brazel, 2001). This may lead to undesired and dangerous consequences of toxicity. Also, these dosage forms exhibit a first-order drug release profile. Considering the complexity and limitations of the current technology, such as food-intake or pH dependency there was a need for an alternative formulation strategy to address this issue (Malaterre *et al.*, 2009; Phaechamud, Darunkaisorn, 2016).

ODDS is better than other conventional controlled release drug delivery systems (CDDS) with advantages such as; (a) zero-order kinetics, (b) drug release independent of factors like gastric pH, food, hydrodynamic conditions (c) possible delayed or pulsed delivery, (d) higher release rates, (e) highly predictable programmable release, (f) high degree of *in vivo- in vitro* correlation (IVIVC), and (g) less inter-patient variability with improved in-vitro dissolution profiles (Malaterre *et al*., 2009). Considering the above attributes, although diltiazem undergoes first pass metabolism, the amount of drug that would be available in the gut mucosa at any point in time for absorption will be constant due to zero-order release mechanism of osmotic drug delivery system. Thus,

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in spite of the first pass metabolism, the amount of drug in the systemic circulation will be maintained constant.

Elementary osmotic pump (EOP) is the simplest type of ODDS, where a core containing drug and release modulating polymer is surrounded by a layer of semipermeable coating or osmotic coating (Naga, Madhusudan, 2016; Prabakaran *et al*., 2003). An osmotic agent is used to generate osmotic pressure inside the system (Shah, Prajapati, 2019). The drugs with high aqueous solubility themselves generate enough osmotic pressure to trigger the drug release and no additional osmotic agent is required (Naga, Madhusudan, 2016).

Quality by design (QbD) approach contributes to the drug design, development, and manufacture of high-quality drug products (Fukuda *et al*., 2018). The main idea for the wide recognition of QbD lies in the regulatory requirements for commercial compliance. Currently, pharmaceutical industries are capitalizing billions of dollars in the drug discovery and development of a quality product. Currently, QbD has become essential for product approval as the FDA evaluates the implementation and effectiveness of the process design as defined in the application along with risk management for successful technology transfer from lab to manufacturing level (Sangshetti *et al*., 2014; Zhang, Mao, 2016). QbD based formulation development involves the following three steps (Bonthagarala *et al*., 2019; Debnath, Aishwarya, Iranajan, 2018; International council for harmonisation of technical requirements for registration of pharmaceuticals for human use, 2009; Sangshetti *et al*., 2014; Yu *et al*., 2014):

(a) Defining Quality Target Product Profile (QTPP);
(b) dentification of Critical Quality Attributes (CQAs); and
(c) Initial and updated risk assessment (RAs) post-development (Lee *et al*., 2017).

The present work was focused on formulating DLH EOP tablets by the QbD approach. Since the excipients in the core, as well as those in the SPM, affect drug release, optimization of both is of great importance to obtain the desired in-vitro release profile (zero order drug release over 24h). Adopting an appropriate statistical approach would help in analyzing various formulation parameters systematically along with the assessment of the release behavior.

MATERIAL AND METHODS

Materials

DLH was obtained from Sai Life Sciences Ltd., Pune, India. Hydroxypropyl methylcelluloses (HPMC E3), Opadry® clear YS-1-7006 were obtained from Colorcon, India. Lactose anhydrous was obtained from BASF, Germany. Microcrystalline cellulose (MCC) was obtained from Signet chemicals, India. Magnesium stearate was obtained from Peter graven, USA. Colloidal silicon dioxide was obtained from Evonik, India. Cellulose acetate (CA-398-10) was obtained from Eastman, India. Polyethylene glycol (PEG 400) was obtained from Clariant. Triacetin was obtained from Merck, India. All other reagents and solvents used were of analytical grade. Milli-Q water was used during the formulation and optimization studies.

Methods

Identification of QTPP and CQA's

The formulation should release DLH at zero-order over 24 hours. Thus, QTPP was configured accordingly and CQAs were identified. CQAs are the parameters that can affect purity, strength, drug release, etc. (Yu *et al*., 2014). Identification of CQAs helps in controlling the quality of the formulation. Table I summarizes QTPP and CQA's for DLH EOP tablets.

TABLE I - QTPP and CQA's for DLH EOP tablets

QTPP Element	Target		Is it CQA ?	Justification
Physical				
Route of administration	Oral		No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical.
Dosage form	Tablet			
Appearance	White/off-white tablet			
In vitro release profile				
Dissolution Profile: 0.1 N HCl, Apparatus: USP Type I (basket), Volume: 900mL, Speed: 100 rpm, Time points (hrs.): 1,2,4,6,8,10,12,15,18, and 24.	2 hrs.	5-10 %	Yes	To have dissolution profile of zero order release up to desired time
	15 hrs.	55-65 %		
	24 hrs.	NLT 70 %		

Drug excipient compatibility study

In drug-excipient compatibility studies, different polymers and excipients such as HPMC E3, lactose anhydrous, MCC, CA, PEG 400, triacetin, magnesium stearate, etc. were taken and mixed with the drug in 1:1 ratio individually. After 4 weeks storage at 40±2°C/ 75±5%RH (with and without water), 50°C (with and without water) and 2-8°C, physical evaluation like change in colour, formation of agglomerates, odor and state of these mixtures were done to check their compatibility. Further, the compatibility of drug with excipients were reinvestigated by preparing a physical mixture of drug with all excipients. This prepared physical mixture and pure drug was kept at 40±2°C/ 75±5% RH for 4 weeks which was then analyzed by using fourier transformed infrared spectroscopy (FTIR).

Risk assessment of formulation variables

Ishikawa fishbone diagram was employed to study the process and formulation variable that can influence CQAs (Figure 1) (Desai, Purohit, 2017; Kundawala, Sheth, Maheshwari, 2016). Various factors such as process, formulation, drug substance, and instruments were considered. The relative risk of each excipient attribute on the CQAs were ranked as high or low. The levels of HPMC and CA are less likely to have an impact on the physical attributes of the formulation, but as they are CQA's, the chances of their impact on the drug release rate are high. Thus, accordingly the risk statuses are assigned to the individual factors. High-risk parameters are optimized by response surface methodology.

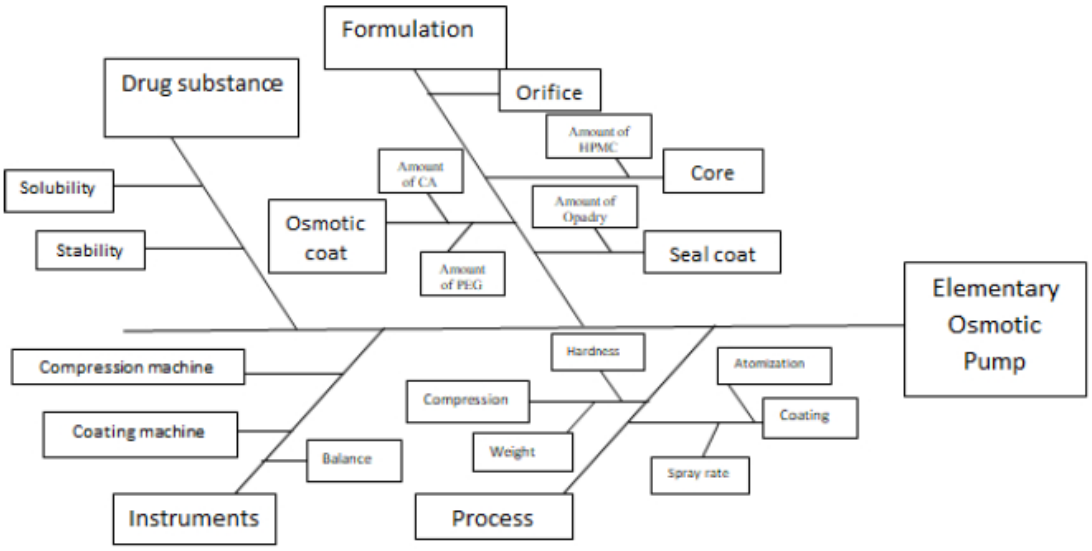

FIGURE 1 - Ishikawa Fishbone diagram.

Formulation of EOP tablets

DLH and excipients (viz. Lactose anhydrous, MCC PH 101, HPMC E3, CA, PEG 400, Triacetin) were passed through 30# mesh sieve. Granules were prepared by wet granulation technique using IPA as a solvent. The obtained granules were dried and further sieved through a #20 mesh. Above granules were then lubricated with colloidal SiO_2 and #60 passed magnesium stearate. The tablet was prepared using a tablet compression machine (Korsch XL100, Germany). Core tablets with optimum hardness were coated using a tablet coating machine (Neocoata 5D, Neomachine Pvt. Ltd, Kolkata, India).

MCC was used in the formulation owing to its hydrophobic nature. The active pharmaceutical agent used is itself highly soluble in water. Thus, to control the wetting and consequent swelling of the tablet core, MCC was added to the matrix core which will delay the interaction of water with the active. Lactose anhydrous is less hygroscopic than monohydrous lactose which will give advantage of delayed uptake of water in comparison with hydrous forms of the excipient (Listiohadi *et al.*, 2008). Hence, MCC and lactose anhydrate were used in the formulation of core tablets.

Initially, a seal coat consisting of 10% w/w Opadry® clear YS-1-7006 in water was sprayed on the core tablet to obtain 3% w/w weight gain. Tablets were preheated for 15 min at about 30-35°C. The osmotic coating solution was prepared by mixing PEG 400 as a pore forming agent and triacetin as a plasticizer in acetone. To the above solution CA was added and stirred to get a clear coating solution. Coated tablets were further dried at 25±0.5°C to remove the residual organic solvent if any. Mechanical drilling was done on one side of the tablet. Preliminary trials were conducted to determine the effects of different formulation excipients. From these trials, the significant formulation variables were identified. Thus, risk assessment and evaluation using optimization of formulation become important criteria.

TABLE II - Formulation composition

Sr. No.	Ingredients	Batch No				Functional category
		Batch 1	Batch 2	Batch 3	Batch 4	
	Core tablet composition (mg/tab)					
1	Diltiazem HCl	240	240	240	240	Antianginal drug
2	HPMC E3	-	7.5	-	145	Swelling polymer
3	Lactose anhydrous	-	26	80	80	Diluent
4	MCC (Avicel PH101)	50	30	30	30	Diluent, hydrophobic polymer
5	Lactose monohydrate	131	-	-	-	Diluent
6	PVP K30	25	-	-	-	Binder
7	PEO (WSR N10 LEO NF)	-	191	145	-	Swelling polymer
8	Magnesium stearate	4	5	4.5	4.5	Lubricant
9	Colloidal SiO_2 (Aerosil Pharma 200)	-	0.5	0.5	0.5	Glidant
	Core tablet weight (mg)	450	500	500	500	
	Seal Coat composition (%) (3% w/w wt. built up)					
10	Opadry® clear	15	15	15	15	Film coating polymer
	Osmotic Coat composition (%) (3% w/w wt. built up)					
1	Cellulose acetate 398-10	85	85	85	85	Osmotic polymer
2	Polyethylene glycol 400	10	10	10	10	Pore-former
3	Triacetin	5	5	5	5	Plasticizer

2^2 factorial design

2^2 factorial design with 2 center points was selected to screen the effect of formulation parameters on the CQAs. Two factors at two levels give us 4 runs and adding two center points we get total of six runs. Selected factors and their levels are given in Table II. Monograph for DLH osmotic tablet was not available in the compendia. Thus USP monograph of DLH ER capsule and dissolution data of osmotic system from US patent 4966769 (Guittard *et al.*, 1990) were used to design a zero-order drug release dissolution profile up to 24 hrs. To achieve desired cumulative percentage of drug release based on compendia and patent the drug release at the end of 2h, 15h, and 24h were selected as dependent variables Y_1, Y_2, and Y_3 respectively. Design expert software V. 11.0.3.0 (Stat-Ease Inc., Minneapolis, Minnesota) was used for design matrix construction and the statistical data analysis.

The orifice diameter was not selected as critical quality attribute because unlike the concentrations of excipients, it is not a continuous factor but a discrete factor. It would be easier and statistically appropriate to select continuous variables which can be studied at various intermediate levels and fine tunes to get optimized formula. On the other hand discrete variables cannot be adjusted on micro-levels and thus they cannot help us in achieving optimized formulation.

TABLE III - Representation of 2^2 factorial design

Coded levels (%w/w)	-1	+1
A (HPMC)	19	39
B (Coating ratio)	75	95

Dissolution

The in-vitro dissolution test was performed using USP I (basket) apparatus. It was set at 100 rpm with 900 ml of 0.1NHCl as a drug release medium for 24 h at 37±0.5°C. Samples were collected and absorbance was measured using a UV spectrophotometer (UV-2401PC, Shimadzu Co., Ltd., Jiangsu, China) at 237 nm.

Design Space

The operating ranges of critical material attributes were defined by knowledge obtained through risk assessment and design of experiment for its effects on CQAs. The effect of each parameter on drug release was estimated and operating ranges for each parameter were selected as design space to obtain robust formulation.

RESULTS AND DISCUSSION

Drug excipient compatibility study

Physical observation of the samples after one-month storage in various conditions of temperature and humidity viz., 2-8°C, 40°C/75%RH, and 50°C; with and without 10%w/w water showed no detectable change in odor, color, state, etc. indicating no drug-excipient interaction. Further, FTIR spectra of pure drug and physical mixture (pure drug + excipients) demonstrated that there was no interaction of drug with other excipients and are compatible with each other (Figure 2). From the comparative DSC thermograms of pure drug and physical mixture, it can be inferred that there is very little or no interaction between the drug and the excipients. (Figure 3).

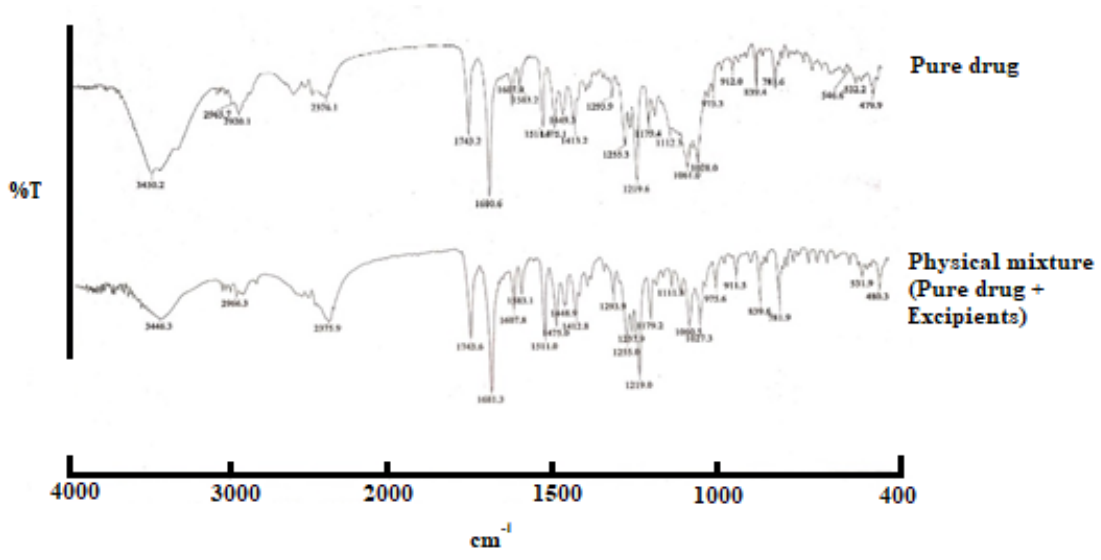

FIGURE 2 - FTIR spectra of Pure drug and Physical mixture (pure drug + excipients).

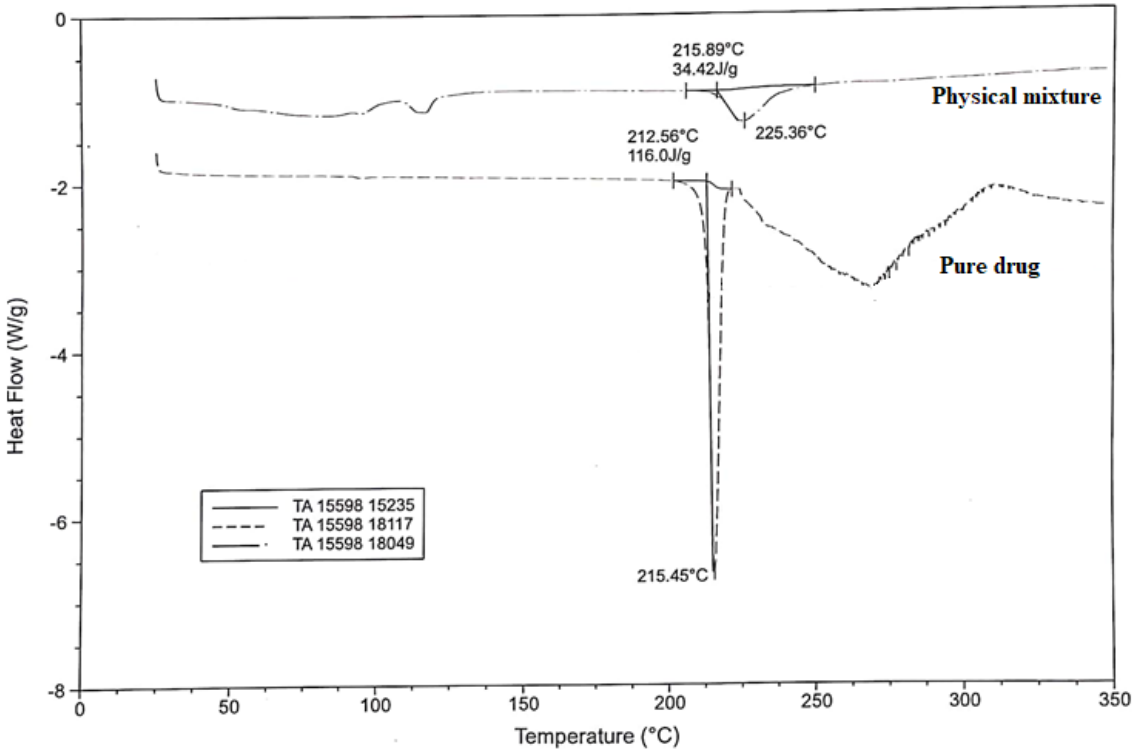

FIGURE 3 - DSC thermograms of pure drug and Physical Mixture.

Quality by design (QbD) - Factorial design

Based on the evaluation of preliminary batches HPMC in the core and CA in the osmotic coating has shown impact on the dissolution profile of DLH EOP tablets (Figure 4). The responses selected as the dependent variables were Y_1 (% drug release at the end of 2h), Y_2 (% drug release at the end of 15h) and Y_3 (% drug release at the end of 24h) with aforementioned dissolution parameters. In this design, the significance of the coefficient and their impact on the responses were studied. The interaction terms were determined based on p values and the polynomial model equations (i), (ii) and (iii). Lesser the p-value ($p < 0.05$), more significant is the respective coefficient and the effect of the corresponding independent variable(s) is significant. A positive value in the quadratic equation indicated a direct relation (synergistic effect), and a negative value indicates an inverse relation (antagonistic effect) with the dependent variable.

$$Y_1 = 7.1667 - 4.25B \quad (i)$$

$$Y_2 = 61.25 - 6.25A - 7.25B - 2.75AB \quad (ii)$$

$$Y_3 = 81.334 – 12.5A \quad (iii)$$

As seen in the above equations, average drug release was found to be 7.1667%, 61.25% and 81.334% at the end of 2, 15 and 24 hrs. respectively. βB in eq.(i) with negative sign indicates the effect of the level of CA on drug release. While the high negative value of βB in eq.(ii) shows the predominant impact of the level of CA as compared to that of HPMC pertaining to the low negative value of βA. Also, the greater value of βA with negative in eq.(iii), indicates a greater antagonistic impact of the level of HPMC in the core tablet.

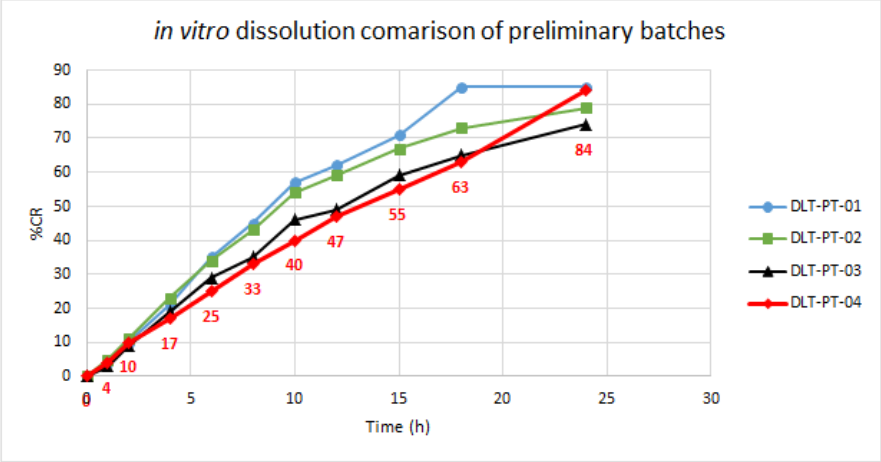

FIGURE 4 - In-vitro release profiles of Preliminary batches.

The individual and collaborative effects of HPMC (A) and CA (B) concentration on Y_1 (% drug release at the end of 2h) (Figure 5-a), Y_2 (% drug release at the end of 15h) (Figure 5-b) and Y_3 (% drug release at the end of 24h) (Figure 5-c) were clearly observed with their corresponding 3D response surface plots and contour plots. 3D response surface graphs help understand the main and interaction effects of the independent variables while the contour plot highlights the comparative effects by the visual illustration of the response values. The factorial design suggested the predominant effect of HPMC in the core and CA in the osmotic coat on drug release profile over other parameters. The coating process and concentration of the coating agent had a striking effect on the drug delivery as it forms the semi-permeable membrane for outlining the release kinetics.

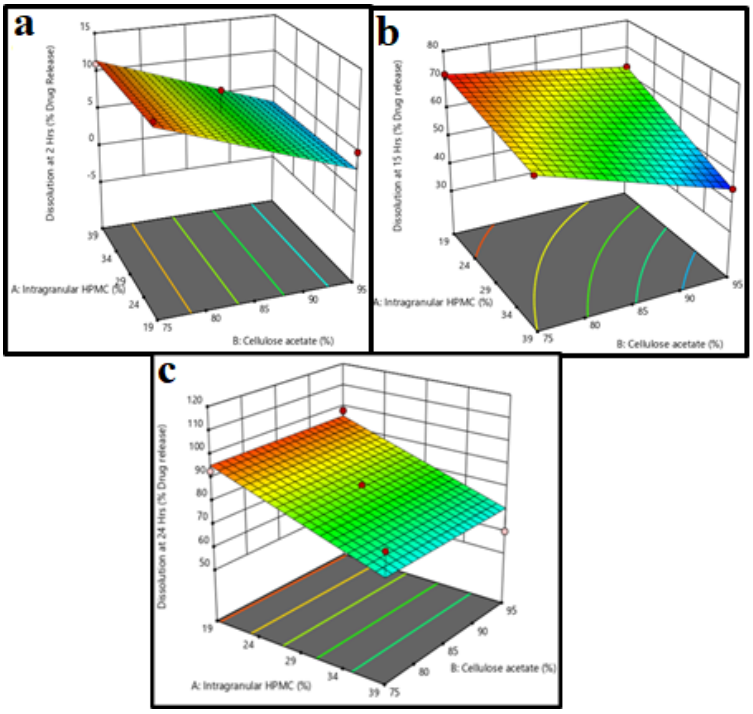

FIGURE 5 - 3D response surface plots and corresponding contour plots indicating the effect of independent variables on (a): Y_1 (% drug release at the end of 2h), (b): Y_2 (% drug release at the end of 15h) and (c): Y_3 (% drug release at the end of 24h).

Factorial design was used to determine factors with the highest impact. The recommended concentrations of the independent variables were evaluated by the Design Expert software (V. 11.0.3.0) from the overlay plot of the design space. The yellow region of the plot indicates the optimized design space (Figure 6a). This optimization helped to find the level of factors A and B which gives Y_1 in the range of 5-10%, Y_2 in the range of 55-65% and Y_3 NLT 70% drug release. The yellow portion suggests the simultaneous effects of independent variables on dependent variables (Figure 6a) (Lee *et al*., 2017; Patel *et al*., 2016).

The risk reduction and control strategy include quality assertion measures based on the knowledge of the product and the process. Levels of the parameters within the yellow region of design space suggest that they satisfy QTPP. Due to this, the risk of the HPMC level in the core and CA in the osmotic coat on the drug release from EOP was reduced to low (Figure 6a). Figure 6b reflects the desirable ranges ranging from zero to one (least to most desirable, respectively) for set objectives responses. Keeping levels of all parameters within the yellow region would ensure adherence to QTTP. The control strategy was established based on the design space.

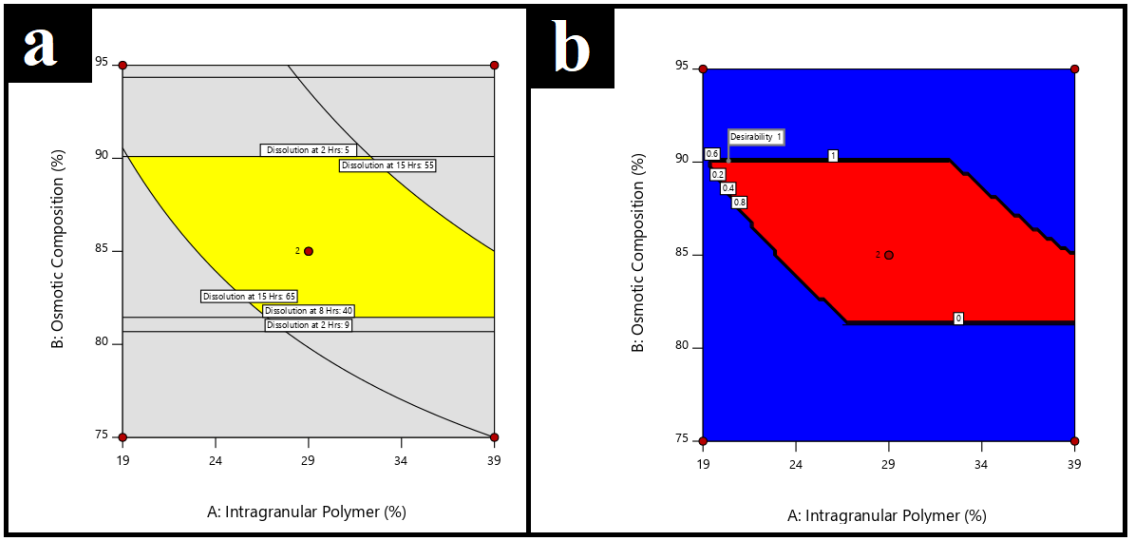

FIGURE 6 - a) Optimized design space for independent variables A and B; **b)** Desirability plot for independent variables.

Release mechanism of the optimized formulation

The possible drug release mechanism from prepared optimized formulation was depicted from the visual observations during in-vitro drug release studies. The in-vitro dissolution performance of the formulated DLH EOP tablets was evaluated as per the dissolution criteria discussed in earlier section. Optimized batch exhibited cumulative percent drug release within the specified limits. The model dependent method was employed to compare the drug release mechanism from prepared DLH EOP. The regression coefficient (R^2) values of the optimized batch with respect to different kinetic models were calculated as shown in Table IV. According to the R^2 values of various models of drug release, the value of R^2 is the highest for zero order model. Thus, it can be derived that the desired zero order release rate was achieved by the optimized batch. EOPs are intended to deliver the drug in a zero-order kinetic manner for a prolonged period. Such zero-order models indicate the applicability of DLH EOPs in maintaining the peak plasma concentration within the therapeutic window with a reduced possibility of side effects.

TABLE IV - Model fitting kinetics for optimized batch of DLH EOP tablets

Sr. No.	Kinetic model	R^2 value
1	Zero order	0.9735
2	First order	0.6571
3	Higuchi	0.9609
4	Hixon Crowell	0.6563
5	Korsemeyer Peppas	0.9129

During dissolution tests, the DLH EOP tablet release was observed at different time points. Semipermeable membrane played a vital role in determining the drug release mechanism from the osmotic systems. The coating layer controls initial burst release by the preventing preliminary diffusion of media across the membrane (time required for water/media diffusion and hydration of the outer layer). This continued up to 15 hours where the effect of the semi-permeable membrane was still seen but the additional impact of polymer in the core was also witnessed. The introduction of the level of the polymer as a governing factor at 15 hours can be attributed to the time required by the HPMC to get fully hydrated and for the gel layer to control the release. At 24 hours the rate-controlling completely shifted to the concentration of the polymer as it was now completely hydrated and diffusion controlled drug release to over. It was also seen that the additional layer of Opadry® clear (YS-1-7006) in the form of seal coat contributed to the shift of kinetics towards controlled release zero-order (Siepmann *et al*., 2007; Siepmann, Siepmann, 2012).

Updated risk assessment

After study of various factors of the formulation at various levels was complete the results indicated changed risk assessment from prior risk assessment. As the rate of drug release from the system was studied and controlled using QbD strategies, the impact of level of HPMC and CA on rate of drug release reduced to low. The response predicted by the software after keeping the desired independent variables was found comparable with the actual response observed (optimized batch) (Figure 7). These results confirm the reproducibility of the formulation as well as validation of the software (Kenjale *et al*., 2019).

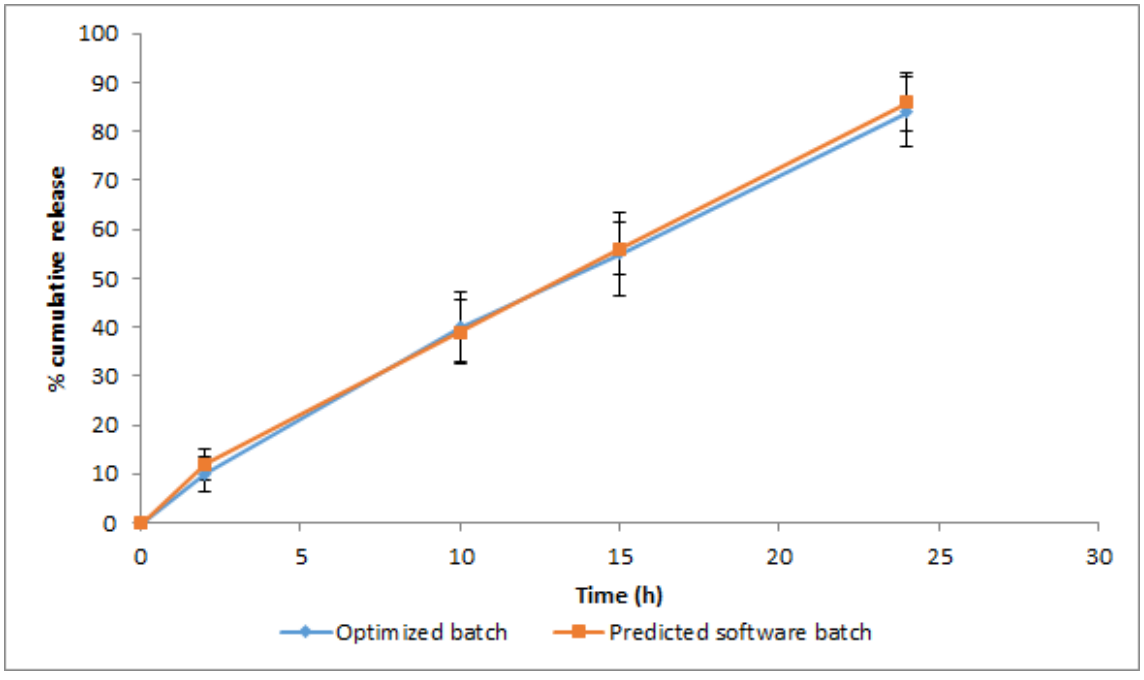

FIGURE 7 - Release profile for the Optimized batch and Predicted software batch of DLH EOP tablets.

CONCLUSIONS

DLH EOPs were formulated by using QbD approach to improve quality of ODDS. The design of experiments used in this study helped to understand the variables influencing the design of the tablet. DLH EOP tablets were formulated by evaluating different formulation variables with high risk on drug product CQA's. Drug and other excipients of EOP formulation were compatible with each other. The factorial design suggested the predominant effect of HPMC in the core and CA in the osmotic coat on drug release profile over other parameters. The coating process and concentration of the coating agent had a striking effect on the drug delivery as it forms the semi-permeable membrane for outlining the release kinetics. The optimized design space signifies all the selection criteria for DLH EOP. The risk assessment study helped in the evaluation of high influence variables on product quality and establishing safe design space for their variation. The optimized EOPs showed zero-order release similar to typical ODDS.

CONFLICT OF INTEREST STATEMENT

The authors confirm that this article content has no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are based on this research.

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