ORIGINAL ARTICLE

Amalgamation of Quality by Design and Convolution Concept for the Development of Oxcarbazepine Modified Release Granules

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Abstract

Introduction: The main objective of this study was to amalgamate quality by design (QbD) concept to develop oxcarbazepine modified release granules with pre-designed qualities. **Materials and Methods:** Modified release granules of oxcarbazepine were prepared using three different waxes. In this study, modified drug release was considered as quality targeted product profile; drug release at 2, 6, and 12 h was selected as critical quality attributes, type of wax and amount of wax were the critical material attributes. **Results and Discussion:** As per QbD, 3^2 full factorial batches were evaluated for effect on drug release at different time points. The optimized formulation was subjected to X-ray diffraction (XRD) study. The results of XRD showed that the crystal form of the drug remained unaltered after the melt granulation process. The robustness of the optimized formulation was checked by dissolution study considering different pH of dissolution medium, using hydroalcoholic medium and by simulating condition after meal. Based on the *in vitro* drug dissolution studies in different media, modified drug release is expected from the formulation. The dissolution studies in simulated dissolution media showed insignificance effect of food and combined food and alcohol on drug release. The convolution derived plasma concentration time profile indicated sustained release from modified release granules. From the result, design space was generated, and after implementation of control strategy, the risk factors were below critical level. **Conclusion:** The use of QbD and convolution approach makes it possible to develop formulation with desired qualities in short time.

Key words: Convolution, hydroalcoholic media, modified release granules, oxcarbazepine, quality by design

INTRODUCTION

Nowadays, the new concept quality by design (QbD) is favored over quality by testing (QbT) method. Because in the QbT process, only the quality of the product is assured by the testing and the quality is not guaranteed.[1] Thus, the Food and Drug Administration (FDA), strongly recommended QbD concept.[2-4] QbD has been receiving a lots of attention in the pharmaceutical industry because it saves time and money and ensure a high-quality product. QbD is based on continuous quality improvement which can yield safer and more efficacious product. The QbD concept is a systematic, scientific, risk-based, holistic, and proactive approach to pharmaceutical development to ensure the predefined quality.[5,6] The International Conference on Harmonisation defines QbD as: "It is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."[7]

The main objective of this study was to amalgamate QbD concept to develop oxcarbazepine modified release granules

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with pre-designed qualities. Here, modified drug release is considered as Quality Target Product Profile (QTPP); drug release at 2, 6, and 12 h was selected as critical quality attributes (CQAs), type of wax and amount of wax are the critical material attributes (CMA) for the modified release granules. Mathematical model and convolution approach were adopted to meet this requirements of QbD.

MATERIALS AND METHODS

Materials

Oxcarbazepine was obtained as a gift sample from Torrent Research Centre, India. Carnauba wax and glyceryl monostearate (GMS) were purchased from Otto Chemicals, India. Beeswax was purchased from ACS Chemicals, India. Sodium lauryl sulfate (SLS) was purchased from S. D. Fine Chemicals, India. All other solvents and reagents used were of analytical grade.

Identifying the QTPP and CQAs

It is the first step of QbD based product development. For the modified release system, the desired drug release is critical, so it was selected as QTPP. To meet the QTPP drug release at 1, 2, 6, and 12 h was selected as CQAs and the targets for these were decide by considering pharmacokinetic parameters of oxcarbazepine. Various elements of QTPP for modified release granules have been summarized in Table 1, while CQAs are enlisted in Table 2.

Ideal dissolution profile

In the development of modified release formulations, the drug release profile is an important criterion for selection of batch. For our work, ideal dissolution profile was generated considering pharmacokinetic parameters of oxcarbazepine, i.e., elimination rate constant (Ke) 0.3465 h^{-1}, dose of the drug (X_o) 150 mg and required time for drug release (τ) 12 h.[8]

Initial dose (Di) = $X_0/K_e*\tau$
=150/0.3465*12
=36.07 mg.

Desired rate of drug release (ks)=150−Di/11
=150−36.07/11,
=10.36 mg per h.

The onset of clinical efficiency is dependent on the time required to release the loading (initial) dose of the drug. It was decided to develop a dosage form that releases 36.07 mg of drug (equivalent to 24.05%) in the 1st h to initiate the drug action and thereafter (i.e., from the 1st h onward) at a constant rate up to the remaining time period, i.e., 12 h for the maintenance of clinical efficiency. The expected ideal release profile is shown in Table 3.

In the dissolution test, variability has been reported considering variations due to men, dissolution apparatus or materials/components of dissolution medium. The US FDA allows 10% deviation in the calculation of similarity factor (f_2). This means the need to fix the boundary for control space. Design space is generally within the control space. It was therefore decided to adopt a ± 10% deviation at all sampling times.[9] According to the limits for drug dissolution at 1, 2, 6, and 12 h is 21.64-26.45%, 27.86-34.05%, 52.71-64.43%, and 90-110%, respectively. The midpoint values, shown in Table 3, shall be considered as the most desirable dissolution pattern.

Method for preparation of modified release granules

Modified release granules of oxcarbazepine were prepared by melt granulation. The wax was melted, and the drug was mixed with molten wax then the mass was cool at room temperature and passed through 20# sieve. Granules having size 20-40# were used for further evaluation. The hypromellose capsule was filled with modified release granules equivalent to 150 mg oxcarbazepine.

Evaluation parameters of modified release granules

In vitro drug release study

Oxcarbazepine release was determined using a dissolution apparatus USP Type II (Paddle type). The capsule containing modified release granules, equivalent to 150 mg

Table 1: Quality target product profile for modified release granules

QTPP elements	Target	Justification
Dosage form	Modified release system	Helps in minimizing side effects of oxcarbazepine
Dosage design	Modified release capsule (wax granules)	It provide good control on drug release and easy to manufacture and scale up
Route of administration	Oral	Most accepted route and available marketed product is extended release tablet for oral use
Dosage strength	150 mg	Lowest strength of oxcarbazepine extended-release formulation available in market
Packaging	Hypromellose capsule	Provide patient compliance and ease of manufacturing

QTPP: Quality Target Product Profile

Table 2: Critical quality attributes for modified release granules

Quality attributes of the drug product	Target	Is it CQAs	Justification
Physical attributes Color Odor Appearance	 Acceptable to patients No unpleasant order Acceptable to patients	 No	Physical attributes were not considered as critical, as these are not directly related to patient efficacy and safety
Drug content	100%	No	As modified-release granules are not the unit dosage form it was considered as moderately critical
Particle size	20-40#	No	Selected size ranged granules (20-40#) were used
Drug release at 1 h 2 h 6 h and 12 h	 21.64-26.45% 27.86-34.05% 52.71-64.43% 90-110%	Yes	This parameter is an indicator of sustained release profile of drug release, thus was considered as highly critical
Drug release alcohol-induced dose dumping	No dose dumping	Yes	The drug release profile in alcohol is critical to patient safety. Thus, it was selected as critical

Table 3: Ideal dissolution profile for oxcarbazepine modified release formulation

Time in h	Drug release in mg	% Drug release	Limits for % drug release
1	36.07	24.05	21.64-26.45
2	46.43	30.95	27.86-34.05
6	87.86	58.57	52.7-64.43
12	150	100	90-110

oxcarbazepine, was added with sinkers in 900 ml 0.3% SLS solution, stirred at 60 rpm and was maintained at 37 ± 0.5°C. 10 ml samples were withdrawn at defined time intervals and were replaced with the same volume of fresh dissolution medium. The samples were analyzed spectrophotometrically (UV-1700, Shimadzu Corp, Kyoto, Japan) at 256.0 nm.[10] Dissolution test was carried out for all formulations ($n = 3$) and the percentage drug released was calculated using standard calibration curve. The dissolution study in 0.3% SLS containing ethanol (20% and 40%) and in 0.1 N HCl and phosphate buffer pH 6.8 was performed for optimized formulation. These studies were conducted to check robustness of the formulation to sustain the oxcarbazepine release in the presence of alcohol and change in pH.

X-ray diffraction (XRD) study

Samples of oxcarbazepine and granules of optimized batch were studied by XRD technique (Xpert MPD, Philips, Holland). The powder was placed in a sample holder and scanned from 10 to 50° (2θ).

Effect of food and combined effect of food and alcohol on drug release

To simulate gastric fluid after meal phosphate buffer pH 6.8 containing hypromellose (0.5%) as viscosity enhancer and 0.3% SLS as surfactant was used as dissolution media. Because after food the pH of gastric fluid is in between 3 and 7 and the similar viscosity after food is produced by addition of 0.5% hypromellose and 0.3% SLS is added as surfactant (as oxcarbazepine is BCS Class II drug recommended dissolution media by USFDA is 0.3% SLS).[11] To study combined effect of food and alcohol the same medium containing 40% alcohol is used.

Convolution

Dissolution is one of the most important tools to predict the *in vivo* bioavailability. Using convolution approach, we can derive *in vivo* plasma profile from the dissolution data and pharmacokinetic parameters of the drug. The dissolution data set of optimized batch and the pharmacokinetic parameters such as volume of distribution, fraction of dose absorbed, and elimination rate constant were used to predict *in vivo* drug release profile as per back calculation Wagner-Nelson method reported earlier.[12]

RESULTS AND DISCUSSIONS

Initial risk assessment to identify variables affecting drug product quality

A systematic risk assessment is performed to identify CMAs and CPP whose variability may influence potential CQAs. The relative risk that each drug product formulation components present was ranked as high, medium, or low. Those attributes that could have a high impact on the drug product CQAs warranted further investigation whereas those attributes that had a low impact on the drug product CQAs required no further investigation. The same relative risk ranking system was used throughout the pharmaceutical development.

An overall risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product CQAs. Ishikawa fishbone diagram [Figure 1] was constructed to found the potential cause-effect relationship among the product and process variables employing Minitab 17 software (M/s Minitab Inc., Philadelphia, PA, USA). The results of the initial formulation risk assessment are presented in Table 4, and the justification for the risk prioritization is presented in Table 5. Each formulation component that has a high risk to impact the drug product CQAs is further evaluated in subsequent risk assessments to determine which formulation variables need to be studied to reduce the risk.

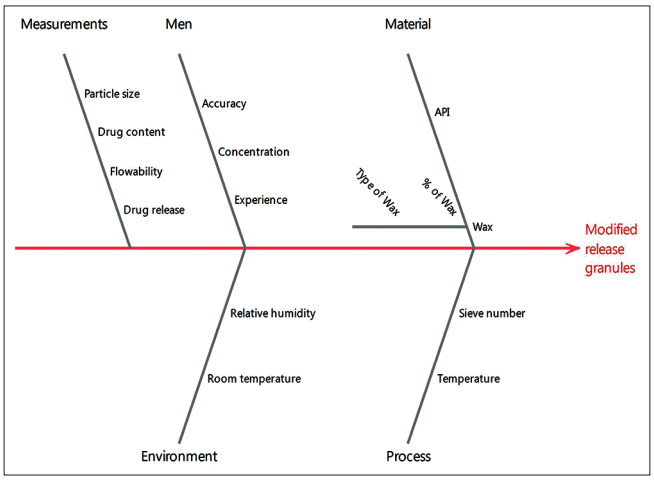

Figure 1: Ishikawa fishbone diagram for modified release granules

Table 4: Initial risk assessment to identify variables affecting drug product quality

Process and formulation variables		
Drug product CQAs;	**% of wax**	**Type of wax**
Drug release	High	High
Drug release – alcoholic induced dose dumping	High	High

CQA: Critical quality attributes

Based on the knowledge of initial risk assessment study, % of wax and type of wax were selected as CMA affecting QTPP. Preliminary trials were carried out using these waxes, and the levels of waxes were selected based on the results (data not shown here).

Optimization of formulation using 3^2 full factorial design

A two-factor, three levels full factorial design was used for the optimization. In this mathematical approach each experimental response Y can be represented by a quadratic equation of the response surface:

$$Y= b_0+b_1X_1+b_2X_2+b_{11}X_1^2+b_{22}X_2^2+b_{12}X_1X_2 \quad (1)$$

The equation facilitates the study of the effects of each variable and their interactions over the considered responses. Here X_1 and X_2 were selected as CMA (independent variables), and Y was CQA (dependent variable).

Table 6 shows independent and dependent variables with their levels and constraints. Constraints for dependent variables were decided by considering pharmacokinetic parameters of oxcarbazepine. The matrix of the factorial design is represented in Table 7.

In vitro drug release study

As oxcarbazepine is BCS Class II drug, thus 0.3% SLS solution is used as dissolution media (recommended by USFDA). *In vitro* drug release from the modified release granules is shown in Figure 2.

The lack of fit analysis (data not shown) showed that a quadratic model was appropriate for the description of all responses. The quadratic equations for the responses are shown below:

$$Y_2 = 23.16-3.02X_1 + 6.80X_2-0.78X_1X_2 +0.095X_1^2-11.79X_2^2 \quad (2)$$

$$Y_6 = 54.56-4.20X_1 + 3.94X_2 + 0.30X_1X_2 + 0.98X_1^2-17.65X_2^2 \quad (3)$$

Table 5: Justification for the initial risk assessment of the process and formulation variables

Components	Drug product CQAs	Justification
% of wax	Drug release	As amount of wax increase, their may be decrease in diffusion of drug and thereby drug release. The risk of % of wax to impact drug release is high
	Drug release – alcohol-induced dose dumping	Alcohol-induced dose dumping is primarily controlled by the wax. Amount of wax may affect retardation power of wax, so the risk of % of wax to impact alcohol induced dose dumping is high
Type of wax	Drug release	Property of wax may affect drug release retention power of wax. The risk of type of wax to impact drug release is high
	Drug release – alcohol-induced dose dumping	Solubility of wax in hydroalcoholic media affects the dose dumping. The risk of type of wax to impact alcohol induce dose dumping is high

CQA: Critical quality attributes

$$Y_{12} = 97.05 - 3.33X_1 + 5.89X_2 + 3.73X_1X_2 + 1.89X_1^2 - 26.01X_2^2 \quad (4)$$

The results of statistical analysis (data not shown) showed that the drug release at 1 h (Y_1) was not significantly affected by independent variables thus, it was not further considered for data treatment. From the result of statistical analysis, it was found that the independent variable X_1 and X_2 and X_2^2 had a significant effect on CQAs Y_2 and Y_6 ($P < 0.05$). The Y_{12} is significantly affected by X_2 and X_2^2 ($P < 0.05$). Type and amount of wax were critical variables for modified release granules. Amount of wax (X_1) had a negative effect on drug release at 2, 6, and 12 h. As the proportion of wax increased in the granules, the drug release decreased. It was found that the drug release at 2, 6, and 12 h is highest from GMS based granules and lowest in case of carnauba wax based granules and the sequence of rate retarding of the waxy materials is carnauba wax > beeswax > GMS. It is reported that the melting point of wax affects drug release from the wax matrix, higher the melting point lower the drug release. In this study, the carnauba wax having a highest melting point (81-86°C) among the selected wax thus less drug release compared to beeswax (61-65°C) and GMS (48-57°C).[13] This difference in the release profiles can also be attributed to the chemical nature and the relative hydrophobicity of the waxes.[14-16] GMS has two hydroxyl groups so more susceptible to hydration by the dissolution media. The relative hydrophobicities can be ranked depending on the length of carbon chains present in the waxes as follows: Carnauba wax > beeswax > GMS. As the hydrophobicity of the wax increased, oxcarbazepine release decreased. Therefore, the release rate of oxcarbazepine was found to be much higher for GMS when compared to the release rates obtained from other waxes.

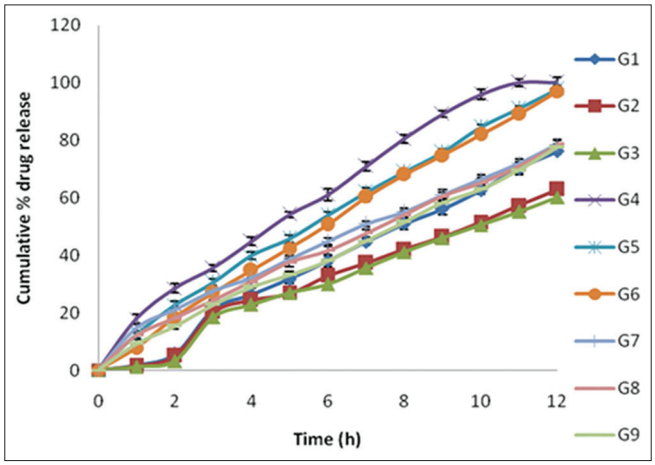

Figure 2: *In vitro* drug release from batches G1 to G9

Table 6: Independent and dependent variables with their levels and constraints

Independent variables		−1	0	1
X_1: % of wax		10	30	50
X_2: Type of wax		CW	GMS	BW
Dependent variables		**Constraints**		
Y_2	% drug release at 2 h	$27.86 \leq Y_2 \geq 34.05$		
Y_6	% drug release at 6 h	$52.71 \leq Y_6 \geq 64.43$		
Y_{12}	% drug release at 12 h	$90 \leq Y_{12} \geq 110$		

CW: Carnauba wax, GMS: Glyceryl monostearate, BW: Beeswax

Selection of best batch

The best batch was selected considering the required release profile. The sum of square residual (SSR) was calculated for each batch using required release profile (data not shown). The low value of SSR indicates similarity of release profile with that of required release profile. Batch G4 was selected as best batch because it had low SSR (396.51) and drug release at 2, 6 and 12 h was 28.55%, 61.05%, and 100.01%.

Evaluation of optimized batch

XRD study

Results of XRD study are shown in Figure 3. Pure oxcarbazepine is crystalline, as demonstrated by sharp and

Table 7: Experimental runs and observed values of responses for full factorial design

Run	Independent variables		Dependent variables		
	X_1	X_2	Y_2	Y_6	Y_{12}
G1	−1	−1	05.66±1.23	37.98±1.02	76.12±1.14
G2	0	−1	05.02±1.02	32.89±1.89	62.89±1.09
G3	1	−1	03.23±1.26	29.98±2.08	60.17±1.29
G4	−1	0	28.55±1.69	61.05±2.05	100.01±2.01
G5	0	0	22.68±1.34	53.90±1.04	97.87±1.14
G6	1	0	18.43±1.38	50.68±1.48	96.99±1.52
G7	−1	1	21.02±1.12	44.86±1.05	78.59±1.59
G8	0	1	18.20±1.36	41.58±1.49	78.36±1.53
G9	1	1	15.47±1.28	38.05±1.93	77.56±1.04

X_1=% of wax, X_2=Type of wax, Y_2=% drug release at 2 h, Y_6=% drug release at 6 h, Y_{12}=% drug release at 12 h

intense diffraction peaks at 14.13, 23.50, 24.83, 28.66, and 41.19 of 2θ. The XRD diffractograms of modified release granules showed the characteristic peaks of the drug with comparable intensity, indicating that the crystal form of the drug remained unaltered after the melt granulation process.

Effect of hydroalcoholic media on drug release from modified release granules

The results shown in Figure 4 reveal that the drug release was similar in hydroalcoholic media and in 0.3% sodium dodecyl sulfate (SDS). Higher f_2 value (72.82 and 66.5 for 20% and 40% alcohol) and result of *t*-test (t_{stat} = −0.2247 less than $t_{critical}$ 2.0639 and t_{stat} = −0.3071 less than $t_{critical}$ 2.0639 for 20% and 40% alcohol) indicated the similarity between dissolution profiles and thus confirms the robustness of formulation. This may be due to insolubility of GMS in 20% and 40% alcohol.

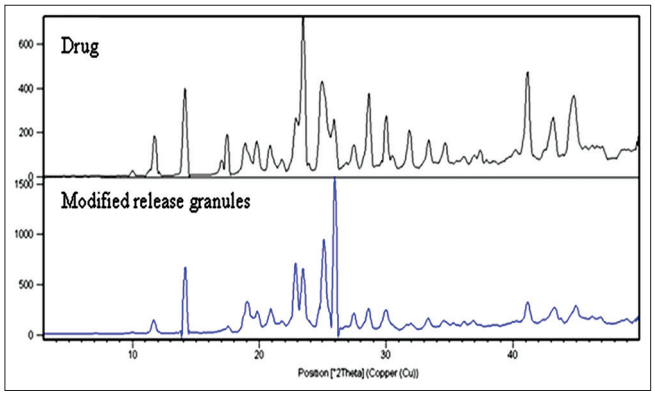

Figure 3: X-ray diffraction pattern of pure drug and modified release granules

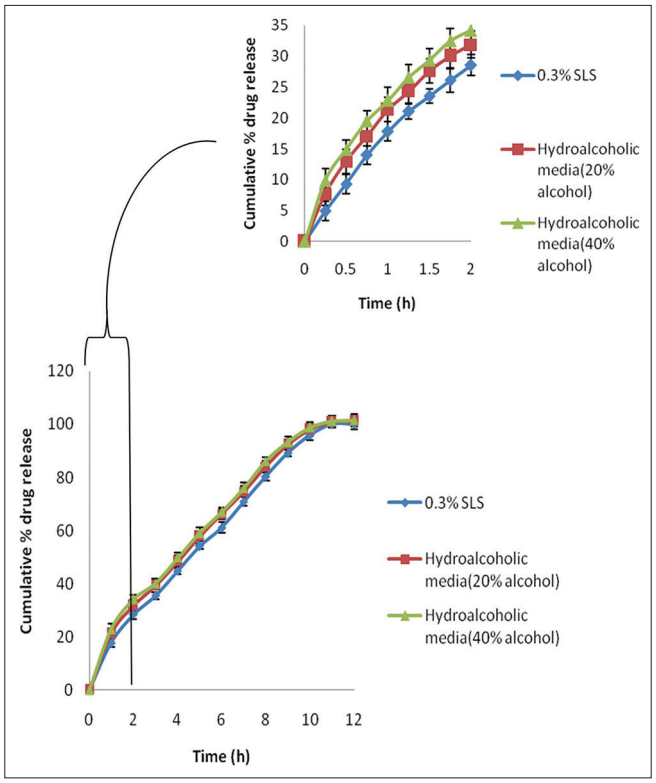

Figure 4: Effect of hydroalcoholic media on dissolution of **modified release granules**

Effect of pH on drug release from modified release granules

The effect of pH on drug release from the modified release granules is shown in Figure 5. High value of f_2 (75.92 and 70.32 for 0.1 N HCl and phosphate buffer pH 6.8, respectively) and the result of *t*-test (t_{stat} = −0.1932 less than $t_{critical}$ 2.0639 and t_{stat} = −0.2441 less than $t_{critical}$ 2.0639 for 0.1 N HCl and phosphate buffer pH 6.8, respectively) showed insignificant effect of pH on drug release from the granules. This is due to the pH-independent solubility of GMS. This indicated the pH independent drug release from the formulation.

Effect of food on drug release from modified release granules

The most reliable method to study food effect is clinical food effect studies. However, it is expensive and time-consuming and is use in the final phase of drug development. To simulate

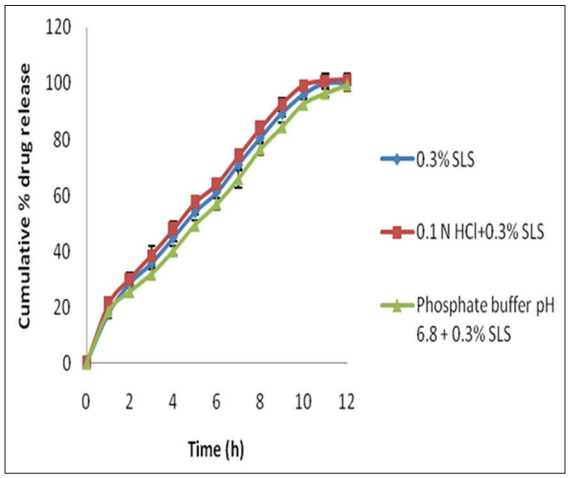

Figure 5: Effect of pH on drug release from the modified release granules

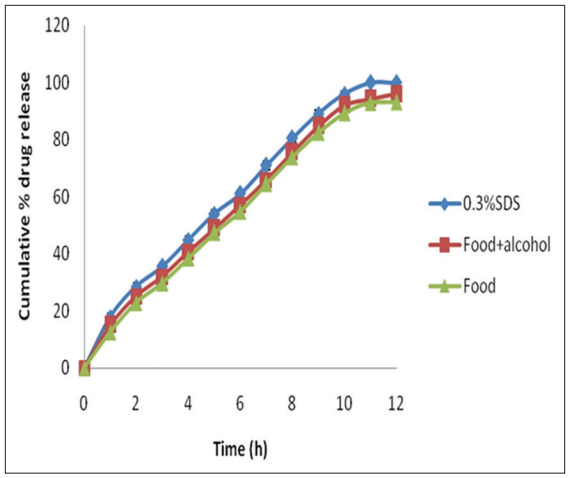

Figure 6: Effect of food and combined effect of food and alcohol on drug release from modified release granules

food effect, various dissolution media have been used, but they do not consider the viscosity of gastric fluid after food consumption. Hence, the aim of this study is to check the effect of viscosity on drug dissolution using simulated dissolution medium. The effect of food on drug release is shown in Figure 6. The high value of f_2 (59.46) and results of *t*-test (t_{stat} = 0.4627 less than $t_{critical\ (24,\ 0.05)}$ 2.0639) showed that the food insignificantly affects drug release from the modified release granules. The slight decrease in drug release was probably due to the high viscosity of medium, which could retard drug diffusion from the modified release granules.

The combined effect of alcohol and food has not been explored in earlier studies. We proposed a novel dissolution test in a medium containing alcohol (40%), hydroxypropyl methylcellulose and 0.3% SLS. The combined effect of food and alcohol is represented in Figure 6. High f_2 value (67.5) indicates the combined food and alcohol showed the insignificant effect on drug release. The result of *t*-test also supports the same outcome (t_{stat} = 0.3093 less than $t_{critical\ (24,0.05)}$ 2.0639).

Convolution

Predicted plasma concentration time profile of pure drug, required plasma concentration time profile and predicted plasma profile for modified release granules are shown in Figure 7. The lower C_{max}, prolonged T_{max} [Table 8] as compare to pure drug indicates sustained release drug delivery from modified release granules.

Updated risk assessment

During process development, CMAs having high risks were addressed. After detailed experimentation, the initial manufacturing process risk assessment was updated in-line with this process understanding. Tables 9 and 10 shows the risk reduction and its justification for the modified release granules as a result of the formulation development work.

Control strategy

The control strategy for modified release granules is result of extensive product and process understanding studies. These studies investigated the material attributes and process parameters that were deemed high risk to the CQAs of the drug product during the initial risk assessment. Through these systematic studies, the CMAs and CPPs were identified, and the acceptable operating ranges were established. The control strategy may be further refined based on additional experience gained during the commercial lifecycle of the product. Table 11 summarizes the proven acceptable ranges for each CMA in the granulation unit operation for the modified release granule. The predicted (obtained using the evolved mathematical models) and the practically obtained values of percentage drug released (observed % cumulative drug release) were in good agreement with each other. Hence, it is concluded that the evolved mathematical models have good predictive ability within the design space. The cumulative percentage drug release at 2 h (as per the very narrow release limit set) shall be in between 27.8% and 34%. The test batch with a coded value of $X_1 = -1$ and $X_2 = 0$ showed marginally slower drug release (26.27%) in the initial phase of drug release, i.e., at 2 h [Table 12]. This difference may not have any clinical significance since for the establishment of bioequivalence a limit of 80-125% is permitted. It is worthwhile to note that as per the guidance document of similarity factor ±10% difference is permitted. The drug release at the other sampling times, i.e., at 6 h (52-64%) and 12 h (90-100%) met with the set narrow criteria. Considering

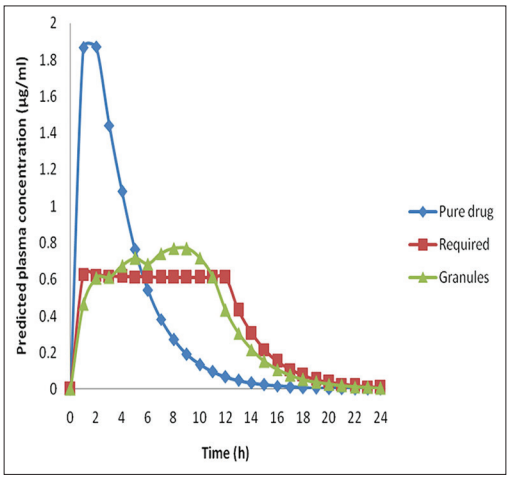

Figure 7: Comparison of predicted plasma concentration profile of modified release granules with required plasma profile and predicted plasma concentration profile of pure drug

Table 8: T_{max} and C_{max} and AUC for pure drug, required plasma concentration, and modified release granules

Batch	T_{max} (h)	C_{max} (µg/ml)	AUC (µg ml/h)
Pure drug	2	1.8728	25.5733
Required plasma parameters	1	0.6274	25.4628
G4	8	0.77017	25.4740

AUC: Area under the curve

Table 9: Updated risk assessment to identify variables affecting drug product quality

Process and formulation variables		
Drug product CQAs	**% of wax**	**Type of wax**
Drug release	Low	Low
Drug release alcohol-induced dose dumping	Low	Low

CQA: Critical quality attributes

Table 10: Justification for the updated risk assessment of the process and formulation variables

Components	Drug product CQAs	Justification
% of wax	Drug release	The drug release from the granules was significantly influence by the amount of wax. Amount of wax was optimized to achieve the desired drug release. Thus, the risk of % of wax to impact drug release is reduced from high to low
	Drug release – alcohol-induced dose dumping	GMS was selected as wax. GMS is insoluble in alcohol. Thus, the risk to impact alcohol-induced dose dumping is reduced from high to low
Type of wax	Drug release	The type of wax significantly affects drug release. Type of wax was optimized. Thus, the risk of type of wax to impact drug release is reduced from high to low
	Drug release – alcohol-induced dose dumping	As the wax is insoluble in 20% and 40% alcohol the drug release in the presence of alcohol was not affected. Thus, the risk of type of wax to impact alcohol induce dose dumping is reduced from high to low

CQA: Critical quality attributes

Table 11: Acceptable values for each critical material attribute

Factor	Proposed value
% of wax	10
Type of wax	GMS

GMS: Glyceryl monostearate

Table 12: Summary of calculation for range of critical material attributes

X_1	X_2	X_1X_2	X_1^2	X_2^2	Y_2=27.86-34.05	Y_6=52.71-64.43	Y_{12}=90-110
−1	0	0	1	0	26.27	59.74	102.27

the above-mentioned points, the batch G4 may be considered as an appropriate batch.

CONCLUSION

This study demonstrates the applicability of QbD approach in the early stage of formulation development of modified release granules of oxcarbazepine. The chosen model helps to visualize the different effects of the CMAs on the CQAs. Mathematical model and convolution approach were adopted to meet these requirements of QbD. From the above findings, it can be concluded that QbD and convolution could be successfully applied for the development of oxcarbazepine modified release granules with desired quality attributes in short time.

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