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Consequence of Wax Property on Drug Release Behavior of Oxcarbazepine Modified Release Granules

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Abstract: Now a day's various types of oral controlled release formulations have been developed to improve the efficacy of drugs as well as to increase patient compliance. Waxy materials are one of the materials to control the drug release from the formulations. Modified release granules of oxcarbazepine were prepared using three different waxes. Amount of wax and type of wax were selected as independent variables and drug release from the modified release granules at 2, 6 and 12 h were selected as dependent variables. Ideal drug release profile was generated using pharmacokinetic parameters of oxcarbazepine. Batch G4 was selected as best batch because it showed lowest sum of square of residue. SEM study of optimized batch of modified release granules shows that the drug particles are coated by glyceryl monostearate. The drug release from the modified release granules followed anomalous diffusion. The modified release granules were remained stable during stability study. The modified release granules can be a promising drug delivery for epilepsy.
Key Words : Modified release granules, Oxcarbazepine, Desired drug release, Bees wax, Carnauba wax and Glyceryl monostearate.

Introduction

Now a day's various types of oral controlled release formulations have been developed to improve the efficacy of drugs as well as to increase patient compliance. These formulations are designed to deliver drugs at a predetermined rate for a predetermined period. Various hydrophilic and hydrophobic materials have been used to develop these formulations. Waxy materials are one of them to control the drug release from the formulations (1).

A wax matrix system is a well developed matrix system used for sustained drug delivery because of its effectiveness, low cost, ease of manufacture and chemical inertness of wax (2). Most frequently used waxes are glyceryl palmitostearate, glyceryl behenate, glyceryl monostearate, beeswax, paraffin wax, carnauba wax, and stearyl alcohol. These waxes have some advantages like good stability at varying pH, chemical inertness and eliminate the effect of food present in GIT because of their water insolubility and non swellability (3; 4; 5).

Capsule containing waxy matrix system can be prepared by melt granulation technique. Several advantages of melt granulations are solvent free process, fewer processing steps, good stability at varying pH and moisture levels (6; 7). Moreover, due to simplicity and easy scale up, it is one of the most widely applied processing techniques in the pharmaceutical manufacturing operations (8; 9; 10). In recent years, melt granulation has also been successfully used to improve the dissolution rate and bioavailability of poorly soluble drugs (11; 12; 13; 14), and in the development of extended release formulations (15; 16; 17).

Oxcarbazepine, an antiepileptic drug, is used in the treatment of partial seizures and generalized tonic-clonic seizures in adults and children. The maximum dose administered per day is 2400mg and administered 2 to 3 times in divided doses. Different dosage strengths like 150, 300 and 600mg of immediate release (IR) and extended release (ER) tablets are available in market. Immediate release of high dose of oxcarbazepine leads to side effect such as dizziness, drowsiness, fatigue, nausea, vomiting, headache, sleeping trouble, acne, dry mouth or constipation which anticipate the modification of oxcarbazepine release from the formulation for better therapeutic efficacy and patient compliance. The available extended release formulation is tablet, unit solid dosage form. The objective of the presented investigation is to develop oral modified release granules of oxcarbazepine to overcome disadvantages associated with unit modified release solid dosage form.

The second objective of this study is to observe the effect of property of wax on drug release from modified release granules. For the preparation of modified release granules waxes were selected on the bases of their melting points. Three different waxes were selected having different melting points like carnauba wax (CW) (melting point = 81-86°C), bees wax (BW) (melting point = 61-65°C), and glyceryl monostearate (GMS) (melting point = 48-57°C).

Materials and Methods

Oxcarbazepine was obtained as a gift sample from Torrent Research Centre, India. Carnauba wax and Glyceryl monostearate were purchased from Otto chemicals, India. Bees wax was purchased from ACS chemicals, India. Sodium lauryl sulfate (SLS) was purchased from S. D. Fine Chemicals, India.

Method of 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 to room temperature and passed through 20 # sieve. Granules having size 20 # to 40 # were used for further evaluation. The hard gelatin capsule was filled with modified release granules equivalent to 150 mg oxcarbazepine.

Evaluation parameters of modified release granules

Drug excipients compatibility study

Fourier transform infrared spectroscopy (FTIR) (FTIR 8400S, Simadzu) spectra of drug, wax, and formulations were captured. Discs consisting of 2 mg of the sample and 100 mg of potassium bromide (KBr) were prepared. Spectra were scanned between 4000 and 500 cm^{-1}.

Percentage yield

The yield was calculated by dividing the measured weight of modified release granules by the total weight of drug and wax. The % yield of modified release granules (size 20 # to 40 #) were calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Weight of modified release granules}}{\text{Weight of drug} + \text{Weight of wax}} \quad (1)$$

Drug content

Oxcarbazepine content of the prepared modified release granules was determined spectrophotometrically at 254 nm in triplicate (18). Modified release granules were crushed in a porcelain mortar and about 25 mg of the crushed modified release granules was dispersed in 100 ml of methanol. The supernatant was filtered through a Whatman filter paper with pores of 0.2 mm in diameter (Sartorius, Germany) and measured spectrophotometrically (UV-1700, Simadzu). Oxcarbazepine content was then calculated using a pre constructed calibration curve.

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 oxcarbazepine, was added with sinkers in 900 ml 0.3% sodium lauryl sulphate (SLS) solution. The dissolution medium was stirred at 60 rpm and was maintained at 37±0.5°C. Ten ml samples were withdrawn at defined time intervals, and were replaced with the

same volume of fresh dissolution media. The samples were analysed spectrophotometrically (UV-1700, Shimadzu Corp, Kyoto, Japan) at 256.0 nm (19). Dissolution tests were repeated three times for all formulations and the percentage drug released was calculated using standard calibration curve.

Morphology study

Morphological characteristics of modified release granules were observed by scanning electron microscopy (SEM). SEM image of the optimized batch modified release granules were recorded using a scanning electron microscope (ESEM EDAX XL-30, Philips) at the required magnification.

Mechanism of drug release

The exact mechanism of oxcarbazepine release from the modified release granules was studied by kinetic models. A FORTRAN software was used to fit zero order, first order, Higuchi, Korsmeyer Peppas, Hixson Crowell and Weibull models. The least value of Fisher's ratio (F) was employed to select the most appropriate kinetic model.

Accelerated stability study

Stability study is an integral part of formulation development. From the stability study we can determine the storage condition of the formulation. Accelerated stability study at 40°C and 75 % RH was performed for optimized batch. The formulations were characterized for various parameters after six months.

Results and Discussions

Desired drug release profile

In 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 drug (X_o) 150 mg and required time for drug release (τ) 12h (20).

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 first h to initiate the drug action and thereafter (i.e. from the first h onward) at a constant rate up to the remaining time period i.e. 12h for the maintenance of clinical efficiency. The expected ideal release profile is shown Table1.

Table 1 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	52.71 - 64.43
12	150	100	90 - 110

In the dissolution test, variability has been reported considering variations due to men, dissolution apparatus or materials / components of dissolution medium. The USFDA 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 (21). According to the limits for drug dissolution at 1, 2, 6 and 12 h are 21.64 - 26.45, 27.86 - 34.05, 52.71 - 64.43 and 90 - 110 % respectively. The midpoint values, shown in Table 1, shall be considered as the most

desirable dissolution pattern. The formulation with lowest sum of square residual (SSR) will be selected as best batch of developed formulation.

Drug excipients compatibility study

The FTIR spectroscopic analysis was performed to confirm the compatibility of oxcarbazepine with waxes. The FTIR spectra are shown in Figure 1. In the case of oxcarbazepine (pure drug) the characteristic peak at 3342 $cm^{-1}$was due to stretching vibration of NH group bending, peak at1650 cm^{-1} was due to C=O stretching, while Stretching vibrations of C=C in aromatic ring was observed at 1562 cm^{-1}. The oxcarbazepine granules had significant characteristic peaks of oxcarbazepine in the FTIR spectra of oxcarbazepine granules, suggesting, there was no interaction between oxcarbazepine and the waxes used. The FTIR analysis confirmed the compatibility of the oxcarbazepine with waxes.

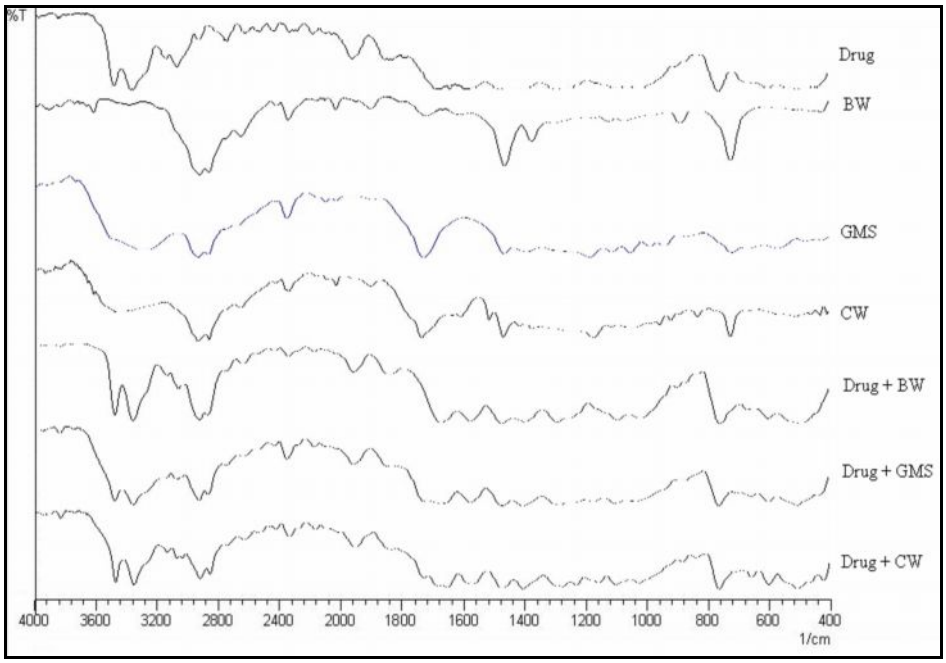


Figure 1 FTIR of pure drug, bees wax, glyceryl monostearate, carnauba wax, physical mixture of physical mixture of drug and bees wax, physical mixture of drug and glyceryl monostearate and drug and carnauba wax

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:

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

The equation facilitates the study of the effects of each variable and their interactions over the considered responses. Here X_1 and X_2 are selected as independent variables and Y is dependent variable. Table 2 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 3.

Table 2 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 hr		$27.86 \leq Y_2 \geq 34.05$	
Y_6	% drug release at 6 hr		$52.71 \leq Y_6 \geq 64.43$	
Y_{12}	% drug release at 12 hr		$90 \leq Y_{12} \geq 110$	

CW= Carnauba wax, GMS = Glyceryl monostearate and BW= Bees wax

Table 3 Matrix of the factorial design and results of % Yield and % drug content of modified release granules

Batch Number	X_1	X_2	% Yield	% Drug Content
G1	10	CW	85.20	80.33 ± 1.23
G2	30	CW	88.56	91.59 ± 2.36
G3	50	CW	90.22	89.58 ± 2.15
G4	10	GMS	92.45	91.56 ± 2.58
G5	30	GMS	95.56	95.26 ± 1.89
G6	50	GMS	96.12	94.28 ± 2.38
G7	10	BW	85.15	89.46 ± 1.38
G8	30	BW	89.92	87.54 ± 1.68
G9	50	BW	95.19	84.38 ± 2.05

%yield and drug content

The % yield of modified release granules varies from 85.15 to 96.12%. The result showed that the drug content of all the batches were good and ranges from 80.33 % to 95.26 % (Table 3).

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 were shown in Figure 2. Nine batches of modified release granules were prepared according to factorial design (Table 3). The experimental results for responses of nine runs are presented in Table 4.

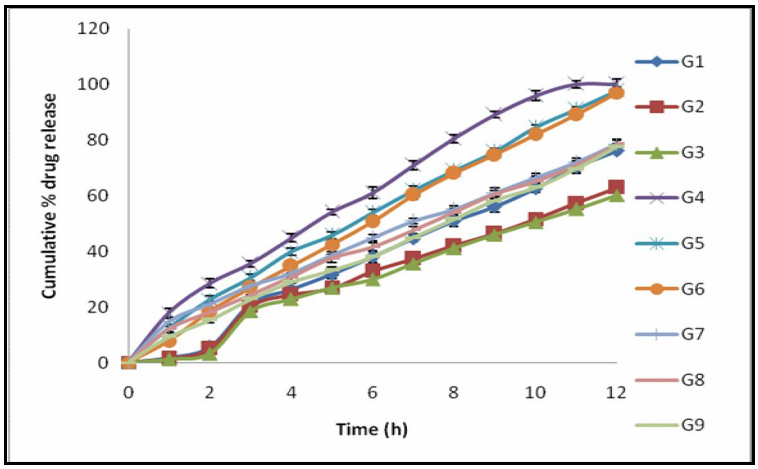


Figure 2 In vitro drug release from modified release granules

Table 4 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

Various models, such as linear, two factor interactions (2FI), quadratic and cubic were fitted to the data for three responses simultaneously using Design Expert® software version 7. Analysis of variance (ANOVA) test was used to draw conclusions. The multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS) were used for selection of adequate models. The lack of fit analysis (data not shown) showed that a quadratic model was appropriate for the description of all responses. Coefficient of model terms and statistical parameters obtained for quadratic equations for the studied Y_2, Y_6 and Y_{12} are shown in Table 5.

Table 5 Coefficient of model terms and statistical parameters obtained for quadratic equations for the studied response

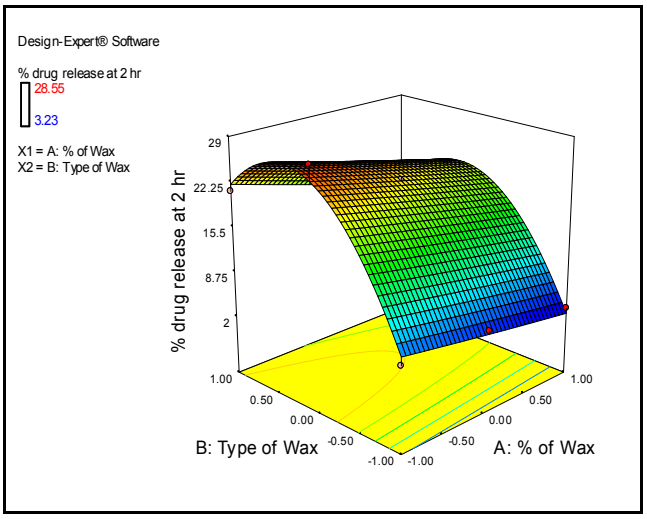
Co efficient code	Coefficients and p value for response					
	Y_2		Y_6		Y_{12}	
	Co efficient	P value	Co efficient	P value	Co efficient	P value
X_1	-3.02	0.0387	- 4.20	0.0034	-3.33	0.0562
X_2	6.80	0.0042	3.94	0.0041	5.89	0.0127
X_1X_2	-0.78	0.5105	0.30	0.6569	3.73	0.0695
X_1^2	0.093	0.9537	0.98	0.3368	1.89	0.3990
X_2^2	-11.79	0.0041	-17.65	0.0002	-26.01	0.0008
R^2	0.9789		0.9947		0.9873	
PRESS	158.09		48.99		257.69	

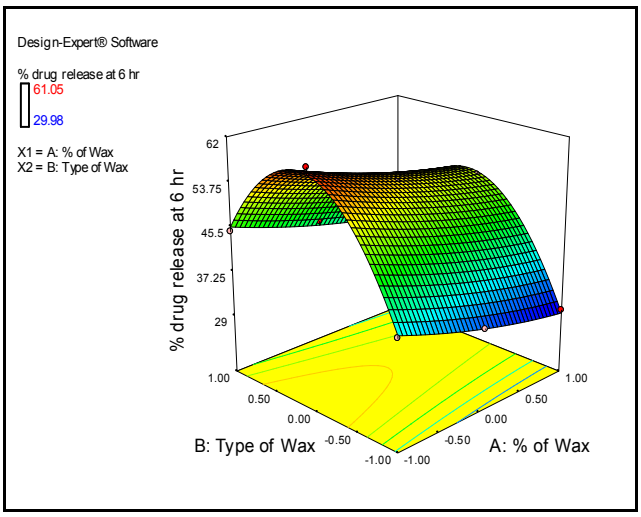
The quadratic equations for the responses are shown below:

$$Y_2 = 23.16 - 3.02X_1 + 6.80X_2 - 0.78X_1X_2 + 0.095\,X_1^2 - 11.79X_2^2 \quad (3)$$
$$Y_6 = 54.56 - 4.20X_1 + 3.94X_2 + 0.30X_1X_2 + 0.98\,X_1^2 - 17.65X_2^2 \quad (4)$$
$$Y_{12} = 97.05 - 3.33X_1 + 5.89X_2 + 3.73X_1X_2 + 1.89X_1^2 - 26.01X_2^2 \quad (5)$$

Independent variables having p value greater than 0.05 indicates non significant terms. Thus, such terms were eliminated from the equation (Equation 3, 4 and 5) and the reduced model equations (Equation 6, 7 and 8) for the various responses are shown bellow.

$$Y_2 = 23.16 - 3.02X_1 + 6.80X_2 - 11.79X_2^2 \quad (6)$$
$$Y_6 = 54.56 - 4.20X_1 + 3.94X_2 - 17.65X_2^2 \quad (7)$$
$$Y_{12} = 97.05 - 3.33X_1 + 5.89X_2 - 26.01X_2^2 \quad (8)$$





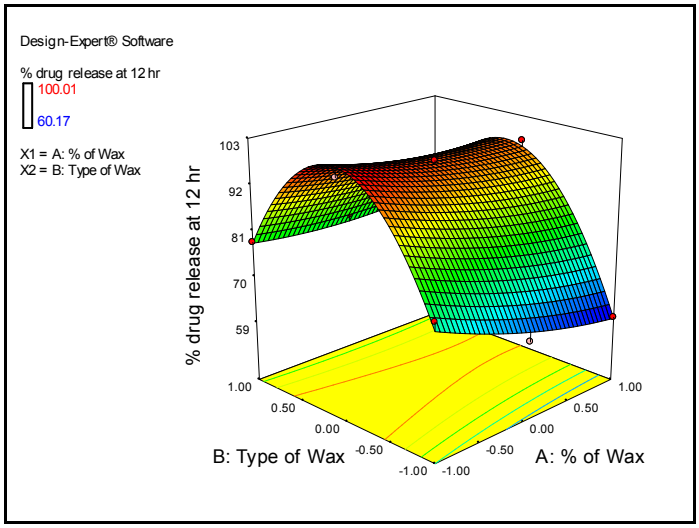


Figure 3 Response surface plot showing effect of independent variables on dependence variable (a) Y_2 (b) Y_6 and (c) Y_{12}

From the result of statistical analysis (Table 5; Figure 3 (a), (b) and (c)) it was found that the independent variable X_1 and X_2 and X_2^2 had significant effect on Y_2 and Y_6. The Y_{12} is significantly affected by X_2 and X_2^2 ($p < 0.05$). A positive or a negative sign before a coefficient in quadratic equation indicates positive and negative effect of independent variables on dependent variables. Type and amount of wax were critical variables for modified release granules. Amount of wax (X_1) had negative effect on drug release at 2, 6 and 12h. As the proportion of wax increases in granules they retard drug release from the granules. It was found that the drug release at 2, 6 and 12 h is highest from glyceryl monostearate 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 > glyceryl monostearate. It is reported that the release from the wax matrix is affected by melting point of wax. Higher the melting point lowers the drug release. Carnauba wax having highest melting point (81-86°C) so less drug release compared to bees wax (61-65°C) and glyceryl monostearate (48-57°C) (22). This difference in the release profiles can also be attributed to the chemical nature and the relative hydrophobicity of the waxes (23; 24; 25). Carnauba wax consists mostly of aliphatic esters (40 wt %), diesters of 4-hydroxycinnamic acid (21.0 wt %), ω-hydroxycarboxylic acids (13.0 wt %), and fatty acid alcohols (12 wt %). The compounds are predominantly derived from acids and alcohols in the C26-C30 range. Beeswax primarily consists of various esters of straight chain monohydric alcohols with even numbered carbon chains (C24–C36) esterified with straight chain acids. GMS is a monoglyceride of stearic acid (C22) and has two free hydroxyl groups. GMS has hydroxyl groups so more susceptible to hydration by the dissolution media. Therefore, release rates of oxcarbazepine were found to be much higher for GMS when compared to the release rates obtained from other waxes. 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.

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. The lowest value of SSR indicates similarity of release profile with that of required release profile. Batch G4 was selected as best batches because it had low SSR (396.51) and drug release at 2, 6 and 12 h were 28.55%, 61.05% and 100.01%.

Evaluation of optimized batch

Morphology study

SEM image of optimized batch (Batch G4) of modified release granules (Figure 4) shows that the drug particles are coated by glyceryl monostearate.

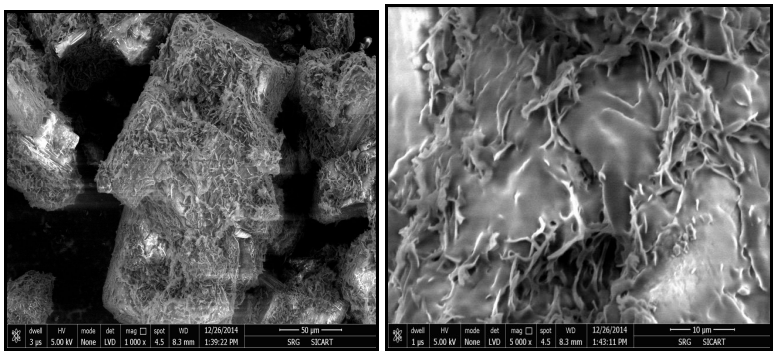


Figure 4 SEM images of modified release granules and surface of modified release granules

Mechanism of drug release

The release data of the optimized formulation (Batch G4) was fitted to different kinetic model. The Korsmeyer and Peppas model shows good fit (0.9947) to the drug release data (Table 6). The drug release from the modified release granules followed anomalous diffusion (n= 0.7322; 0.45 < n < 0.89).

Table 6 Results of mathematical modeling of modified release granules

Model	Batch B5	
	R^2	F
Zero order	0.9801	23.691
First order	0.6446	19315
Higuchi	0.9653	41.290
Hixson crowell	0.9045	202.24
Korsmeyer Peppas	0.9947	8.4234
Weibull	0.8345	105.19

Accelerated Stability study

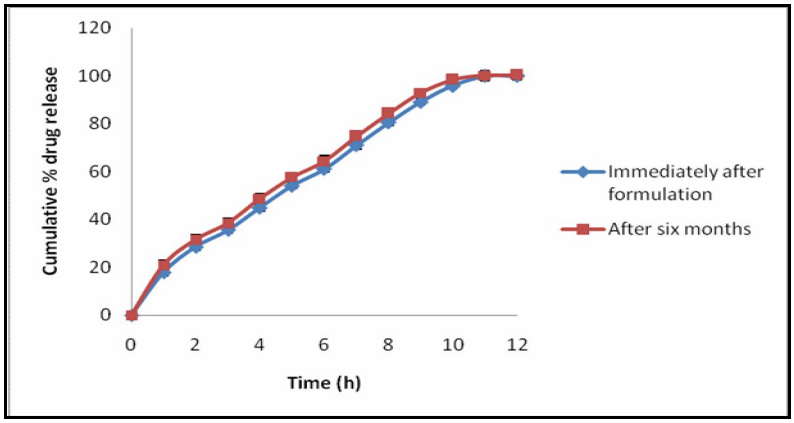


Figure 5 Dissolution after accelerated stability study of modified release granules

The appearance and drug content of modified granules remained same after stability study. Dissolution was performed after six month of accelerated stability study results are shown in Figure 5. The high value of similarity factor (f_2 value = 74.39) and result of t test (t_{stat} = -0.2014 less than $t_{critical}$ 2.0639) indicates that the modified release granules were remain stable during stability study.

Conclusion

Modified release granules of oxcarbazepine were prepared using three different waxes. To study consequences of wax property on drug release from granules amount of wax and type of wax were selected as

independent variables and drug release from the modified release granules at 2, 6 and 12 h were selected as dependent variables. Ideal drug release profile was generated using pharmacokinetic parameters of oxcarbazepine. Batch G4 was selected as best batch because it showed low sum of square of residue. SEM study of optimized batch of modified release granules shows that the drug particles are coated by glyceryl monostearate. The drug release from the modified release granules followed anomalous diffusion. The modified release granules were remained stable during stability study. The modified release granules can be a promising drug delivery for epilepsy.

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