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Research Article

DESIGN AND CHARACTERIZATION OF DONEPEZIL HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The ultimate aim of the present study was to develop sustained release (SR) tablets of Donepezil Hydrochloride by employing natural polymers (Guar gum and Xanthan gum) as the matrix material in different proportion by wet granulation method. Initially drug-excipients compatibility studies were carried out using FTIR and DSC which showed no interaction between drug and excipients. Granules of prepared batches were evaluated for bulk density, tapped density, carr's index, hausner's ratio, angle of repose. Tablets were evaluated for various physicochemical parameters like hardness, thickness, friability, weight variation test, drug content and *in vitro* drug release. All the formulation showed compliance with pharmacopoeial standards. 3^2 full factorial design was applied in which Guar gum (X_1) and Xanthan gum (X_2) were taken as independent factor and %CDR at 2hr (Y_1) and at 12hr (Y_2) were taken as response. *In-vitro* drug release study revealed that as the amount of polymers increased, % CDR decreased. Contour plots as well as response surface plots were constructed to show the effect of X_1 and X_2 on %CDR and predicted at the concentration of independent variables X_1(40mg) and X_2(40mg) for maximized response. The kinetic release treatment showed that korsmeyer peppas equation has shown of r^2 0.9517 which was close to one indicating that the dissolution profile fits in Korsmeyer-Peppas model and the mechanism of drug release from these tablets was by non-fickian diffusion mechanism. The optimized batch was kept for stability study at 40 ± 2^oC/ 75 ± 5 % RH for a period of 1 month according to ICH guidelines and found to be stable after 1 month of study.

Keywords: Sustained release matrix tablet, Donepezil hydrochloride, Guar gum, Xanthan gum, 3^2 full factorial design.

INTRODUCTION

Oral route is the oldest and convenient way for the administration of therapeutic agents because of low amount of therapy and ease of administration leads to greater level of patient compliance. Approximately 50% of the drug products available in the market are administered orally and traditionally, oral drug administration has been the major route for drug delivery. Sustained release systems include any drug delivery system that achieves slow release of drug over an extend period of time. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by

gradual release of additional amounts of drug to maintain this effect over a predetermined period.[1,2]

Donepezil hydrochloride (DH) is a second-generation cholinesterase inhibitor (ChEI), used for the treatment of Alziemer's disease (AD) having greater specificity for the brain acetyl cholinesterase enzyme (AchE). This compound characterized by a long plasma half-life (70 hr) and a bioavailability of 100%. Donepezil hydrochloride currently formulated as film-coated tablets of 5 mg, 10 mg, 23 mg doses for once a day oral administration under trend name ARICEPT®. The immediate release of cholinesterase inhibitors results in a spike in the patient's blood plasma levels within 2 to 5 hours after administration of the drug. The most common adverse events from ARICEPT cholinomimetic effects include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, bradycardia, abdominal pain, and anorexia, resulting in a reduction of patient compliance. These undesirable effects are due to the initial spike in blood plasma levels. Therefore an initial therapeutic regimen is often recommended wherein donepezil is first introduced at low doses for several weeks followed by the gradual increase to the appropriate active dose for the patient. A sustained release formulation may be advantageous in reducing the undesirable side effects associated with the rapid increase in blood plasma concentration levels immediately after administration of the drug. Such sustained release formulations could provide a uniform and constant rate of release over an extended period of time, which may achieve a stable and desired blood level of donepezil without the initial spike in drug plasma level.[3] Therefore, the aim of the investigation is to develop, optimize and characterize the sustain release tablet of Donepezil hydrochloride using natural polymers.

MATERIALS AND METHODS

Donepezil hydrochloride was obtained as a gift sample from West Coast Pharmaceutical Works Ltd. Ahmedabad, Gujarat. Guar gum, Xanthan gum and Starch were procured as a gift sample from Chemdyes Corporation, Rajkot, Gujarat. Lactose was obtained as a gift sample from Finar chemicals, Ahmedabad, Gujarat. Magnesium stearate and Talc were purchased from S. D. Fine Chemicals, Mumbai, India. All other chemicals were of analytical reagent grade.

Drug-Excipients Compatibility Study by FTIR[4]

The Fourier transform infrared spectrum was obtained using an FT-IR spectrometer. The Donepezil hydrochloride and mixture of drug with other excipients were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:1 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5

tons for 5 min in a hydraulic press. Forty Scan were obtained at a resolution of 4 cm^{-1}, from 4000 to 600 cm^{-1} at Aum Research lab.

3^2 Full Factorial Design[5,6]

A 3^2 full factorial design was adopted and the amount of polymers, Guar gum (X_1) and Xanthan gum (X_2), were taken as independent variables and cumulative percentage drug release at 2 hr (Y_1), and 12 hr (Y_2) was taken as dependent variables as shown in Table 1. The factors were studied at three levels (-1, 0, +1) indicating low, medium and high, respectively, as represented in Table 2. The statistical optimization procedure was performed with the help of optimization software like Design Expert 11.0.4.0 demo version (Stat‑ Ease Inc.). The software performs the multiple regression analysis (MRA), analysis of variance (ANOVA) and statistical optimization.

The use of regression analysis in 3^2 full factorial design generates polynomial equations for different models, with interacting terms and regression coefficients, useful in evaluating the responses. The software generates two models, particularly, full model (non‑ significant terms included) and reduced model (excluding non‑ significant terms). In the full model study, the responses were analysed using the quadratic equation below:

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

where Y is the response evaluated, b0 is the arithmetic mean response of 9 runs and bi is the estimated coefficient of Xi. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term ($X_1 X_2$) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) were included to investigate nonlinearity. In the reduced model study, the non‑ significant terms in the quadratic equation are removed using backward regression procedure to generate a reduced model which is more important in studying the influence of factors on the responses evaluated. The value and sign of regression coefficient (bi) indicates the magnitude of influence of the particular term on the response. The regression coefficients give the average change in a response when the particular factor is changed by a unit, when all the other terms remain constant. A positive sign on the regression coefficient indicates the factor has a positive effect on the response and negative sign indicates a negative effect.

The software performs the individual analysis of responses and calculates the sum of squares (SS), mean square (MS), Fischer's ratio (F statistics) and *P* value. The F statistics and *P* value give the significance level of each term. The terms with a *P* value less than 0.05 are considered significant at a level of significance α = 0.05.

Table 1: Selection of Independent and Dependent Variables

Independent variables		Dependent variables	
X_1	X_2	Y_1	Y_2
Concentration of Guar gum (mg)	Concentration of Xanthan gum (mg)	% CDR at 2hr	% CDR at 12hr

Table 2: Selection of Levels for Independent Variables and Coding of Variable

Levels	Coded value	Independent variables	
		Concentration of Guar gum (mg) X_1	Concentration of Xanthan gum (mg) X_2
Low	-1	40	40
Intermediate	0	50	50
High	+1	60	60

Table 3: Composition of Factorial Design Batches D1 to D9

Ingredients (mg)	D1	D2	D3	D4	D5	D6	D7	D8	D9
Donepezil Hydrochlorie	23	23	23	23	23	23	23	23	23
Guar Gum	40	50	60	40	50	60	40	50	60
Xanthan gum	40	40	40	50	50	50	60	60	60
Lactose	139.5	129.5	119.5	129.5	119.5	109.5	119.5	109.5	99.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5	5	5	5
Total Weight (mg/tablet)	250	250	250	250	250	250	250	250	250

To select matrix polymer, a comparative study was carried out. In preliminary trial batches, different concentrations of Guar gum and Xanthan gum were screened. Donepezil Hydrochloride and other excipients are weighed accurately, transferred in mortar and pestle and thoroughly mixed for 15 min. The powder mixture was granulated with 10 % w/v starch paste. The wet mass was passed through 10# sieve and granules were dried at 50°C for 30 min. in hot air oven. The dried granules were passed through 20# sieve and lubricated with talc and magnesium stearate which was previously passed through 80# sieve. Tablets were compressed using 8 mm punch on 10 station rotary tablet punching machine (Karnavati Engineering). Composition of tablets is mentioned in Table 3. Hardness of the tablets was maintained between 5.0 to 6.0 Kg/cm^2 and tablet weight at 250 mg.[7]

Pre Compression Evaluations[8,9]

The evaluation of Pre compression parameters such as Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose of the granules.

Post Compression Evaluation

The prepared tablets were evaluated for physical and chemical characteristics.

Diameter[10]

Tablets of each batch were selected and measured for diameter using vernier caliper.

Thickness[10]

The thickness of five randomly selected tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

Weight Variation[11]

Uniformity of the weight test as described in the IP/BP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations was determined and recorded.

$$Percentage\ Deviation = \frac{Individual\ Wt - Average\ Wt}{Individual\ Weight}$$

Hardness[11]

The hardness of the tablets was determined by diametric compression using a Monsanto Hardness tester. A tablet hardness of about 5-6 kg/cm^2 is considered adequate for mechanical stability. Determinations were made in triplicate. The mean values and standard deviation for each batch were calculated.

Friability[11]

The friability of tablets was performed in a Roche Friabilator. Five tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed.

$$F = \frac{Winitial - Wfinal}{Winitial} X\ 100$$

Drug Content[4]

The drug content was carried out by weighing ten tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to 23 mg of Donepezil hydrochloride and dissolved in 100 ml volumetric flask containing 100 ml of dissolution media and volume was made to 100 ml with solvent. The volumetric flask was shaken using sonicator for 1 hr. and after suitable dilution with dissolution media, the drug content was determined using UV-Visible Spectrophotometer at 229 nm.

In-vitro Drug Release Study[4]

Release of the prepared tablets was determined using U.S.P type II paddle type dissolution rate test apparatus (TDT-06P, Electrolab) using 900 ml of 0.1 N HCl medium for 120 minutes, then in phosphate buffer pH 6.8 medium for 12hrs. as dissolution medium. The temperature of $37\pm1°C$ was maintained and paddle was adjusted at 25 rpm throughout the experiment. Withdrawn not less than 5 ml of the dissolution solution at 1, 2, 4, 6, 8, 10, 12, 14hr time interval and were replaced with 5 ml of fresh dissolution media after each withdrawal. Filtered each sample through a membrane filter with pore size of not more than 0.45 mm. The samples were analyzed after appropriate dilution by UV spectrophotometer at λ max 229 nm.

Statistical Analysis[5,6]

Statistical Analysis of the 3^2 full factorial design batches was performed by multiple regression analysis using Microsoft excel. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. To evaluate the contribution of each factor with different levels to the response, the two-way analysis of variance (ANOVA) was performed using the Design Expert 11.0.4.0 (STAT – EASE) trial version software. To graphically demonstrate the influence of each factor on the response, the response surface plots, Normal plot of residual, Two-Dimensional counter plot, 3-D graph, and overlay plot were generated using the Design Expert 11.0.4.0 (STAT – EASE) demo version software.

Check point Analysis[5,6]

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points and the theoretical values of %CDR at 2hr and %CDR at 12hr were calculated by substituting the values in the polynomial equation.

Optimization of Formulation[5,6]

The computation for optimized formulation was carried using software, Design Expert 11.0.4.0 (STAT – EASE). The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). The models were evaluated in terms of statistically significant coefficients and R^2 values. Various feasibility and grid searches were conducted to find the optimum parameters. Various 3D response surface graphs were provided by the Design Expert software. The optimized formulation factors were evaluated for various response properties.

Curve Fitting Analysis[12]

In order to describe the kinetics of drug release from sustained release formulation, various mathematical equations have been proposed namely, Zero order, First order, Higuchi model and Hixson–Crowell cube root law. To authenticate the release model, dissolution data can further be analyzed by Korsmeyer Peppas equation. The criteria for the selection of most suitable model were value of regression coefficient (R^2) nearer to 1,

smallest values of Residual sum of squares (SSR) and Akaike Information Criteria (AIC).

Similarity and Dissimilarity Study[4,12]

The similarity factor *f*2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products:

$$f2 = 50 * \log\left\{\left[1 + \left(1/n\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} * 100\right\}$$

Where, n is the number of dissolution time points, Rt and Tt are the reference and test dissolution values (mean of at least 12 dosage units) at time t.

When the two dissolution profiles are identical, f2 = 50 * log (100) = 100, and when the dissolution of one product (test or reference) is completed before the other begins, f2 = 50 * log {(1 + 1/n Σ (100) 2)-0.5 * 100} = -0.001, which can be rounded to 0. Thus the value of f2 ranges from 0* to 100. Two dissolution profiles are considered 'similar' when the f2 value is between 50 and 100. Thus FDA recognizes the profiles to be similar when the two drug profiles differ only by a difference of 10%. A higher f2 value indicates closeness between the two dissolution profiles.

Difference factor (f1) measures the percent error between two curves over all time points.

$$f_t = \frac{\sum_{j=1}^{n}|R_j - T_j|}{\sum_{j=1}^{n}R_j} \times 100$$

Where, n is the sampling number, R and T are the % dissolved of reference & test products at each time point j. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. It is generally accepted that values of f1 between 0- 15 do not indicate dissimilarity.

Stability Study[13]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of temperature, humidity, and light and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The storage conditions used for accelerated stability studies were accelerated condition (40 ºC ± 2°C / 75% ± 5 % RH) and Room temperature (30 ºC ± 2°C / 65 % RH ± 5 %). Stability study was carried out for the most satisfactory formulations. Tablets of optimized formulation were striped packed and kept in humidity chamber for 1 month on above mention temperature.

RESULTS AND DISCUSSION

Drug Excipients Compatibility Study by FT-IR

The FTIR spectra of pure drug and mixture of drug with excipient are shown in Figure 1. From this it is clear that the characteristic peaks at 1696.21 (C=O stretching),

1602.74 (C=C stretching), 1312.17 (C-N stretching) 748.14 (aromatic –CH Stretching) cm^{-1} are present in both the pure drug and mixture of drug with excipient, without any change in their positions, indicating no chemical interaction between drug and excipients.
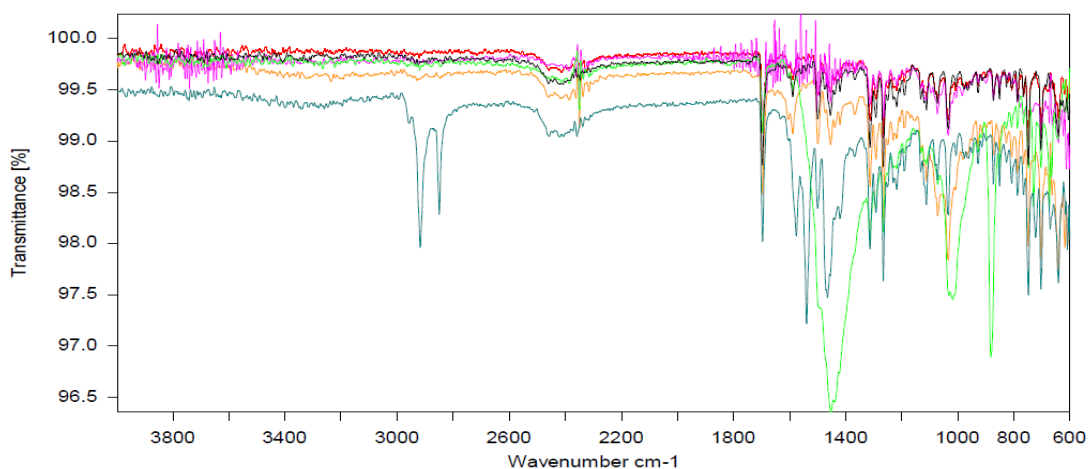

Figure 1: FT-IR Spectra of Donepezil Hydrochloride and all Excipient

Pre-compression Evaluation of Powder Blend of Batches D1 to D9

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table 4. Bulk density ranged from 0.572 ± 0.041 to 0.632 ± 0.025 gm/ml, tapped density ranged from 0.667 ± 0.049 to 0.739 ± 0.038 gm/ml, Carr's index ranged from 12.50 ± 1.25% to 14.74 ± 1.88%, Hausner's ratio ranged from 1.14 ± 0.17 to 1.17 ± 0.69 whereas Angle of repose ranged from 24.15 ± 2.27 to 27.75 ± 2.28. All these results indicated that, the powder blends possess excellent to good flowability and compressibility properties.

Table 4: Pre-Compression Evaluations of Design Batches D1 to D9

Batch Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (Θ)
D1	0.588 ± 0.031	0.689 ± 0.024	14.70 ± 1.30	1.17 ± 0.69	27.75 ± 2.28
D2	0.579 ± 0.039	0.669 ± 0.031	13.45 ± 1.24	1.15 ± 0.21	25.46 ± 1.43
D3	0.584 ± 0.032	0.675 ± 0.028	13.48 ± 1.21	1.15 ± 0.25	26.56 ± 1.31
D4	0.630 ± 0.044	0.739 ± 0.038	14.74 ± 1.88	1.17 ± 0.27	24.15 ± 2.27
D5	0.575 ± 0.053	0.667 ± 0.049	13.79 ± 1.27	1.16 ± 0.05	27.34 ± 1.25
D6	0.625 ± 0.045	0.714 ± 0.042	12.50± 1.25	1.14 ± 0.17	25.32 ± 1.25
D7	0.594 ± 0.032	0.691 ± 0.028	14.03 ± 1.20	1.16 ± 0.21	25.30 ± 2.15
D8	0.632 ± 0.025	0.726 ± 0.021	12.94 ± 1.26	1.14 ± 0.57	24.30 ± 1.15
D9	0.572 ± 0.041	0.668 ± 0.036	14.43 ± 1.29	1.16 ± 0.35	25.82 ± 2.52

All values are expressed as mean ± standard deviation, n=3

Post Compression Evaluation of Batches D1 to D9

The tablets from all the batches were evaluated for various physical parameters before proceeding further. Table 5 includes the values (mean ± SD) of weight variation, hardness, thickness, friability and % drug content of batches prepared using different combinations of functional excipients. Weight of the tablets in all the 9 batches varied between 249.26 ± 0.47 to 251.24 ± 0.32mg. All the formulated (D1 to D9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight.

Diameter of all tablets was in the ranged from 7.97±0.002 mm to 7.99±0.004 mm. Thickness of all tablets was in the range between 3.20 ± 0.037 mm to 3.62 ± 0.028mm. Hardness of tablets was in range between 5.11 ± 0.023 to 5.91± 0.031 kg/cm^2. Friability was in range between 0.30 ± 0.04 to 0.58± 0.45%. Friability values were less than 1 % in all cases which shows good mechanical strength at the time of handling and transports. Drug content of all tablets was found in the range between 98.65 ± 2.20 to 99.82 ± 1.32%. Thus, all the physical parameters of the compressed tablets complies the standards.

Table 5: Post-Compression Evaluation Parameters of Full Factorial Design Batches

Batch Code	Weight variation (n=20)	Diameter (n=5)	Thickness (mm) (n=5)	Hardness (kg/cm²) (n=5)	% Friability (n=5)	% Drug Content (n=10)
D1	Pass	7.99 ± 0.002	3.28 ± 0.015	5.91 ± 0.031	0.46 ± 0.17	99.21 ± 1.30
D2	Pass	7.98 ± 0.003	3.62 ± 0.028	5.49 ± 0.014	0.47 ± 0.32	98.66 ± 1.87
D3	Pass	7.99 ± 0.004	3.37 ± 0.035	5.11 ± 0.023	0.58 ± 0.45	99.07 ± 0.71
D4	Pass	7.99 ± 0.003	3.42 ± 0.032	5.68 ± 0.091	0.30 ± 0.45	99.52 ± 1.42
D5	Pass	7.97 ± 0.002	3.37 ± 0.054	5.75 ± 0.072	0.50 ± 0.25	99.33 ± 1.52
D6	Pass	7.98 ± 0.002	3.28 ± 0.075	5.82 ± 0.055	0.58 ± 0.03	98.65 ± 2.20
D7	Pass	7.98 ± 0.004	3.45 ± 0.047	5.70 ± 0.058	0.45 ± 0.15	99.05 ± 1.15
D8	Pass	7.99 ± 0.004	3.60 ± 0.041	5.54 ± 0.039	0.30 ± 0.04	99.82 ± 1.32
D9	Pass	7.99 ± 0.001	3.20 ± 0.037	5.41 ± 0.015	0.52 ± 0.05	99.1 ± 0.32

All values are expressed as mean ± standard deviation

In vitro Drug Release Study of Batches D1 to D9

Batch D1 to D9 were developed using different concentration of Guar Gum (40, 50 & 60 mg) and Xanthan gum (40, 50 & 60 mg). Results of % CDR study are shown in Figure 2. From the figure, it was observed that as the concentration of polymers Guar gum and Xanthan gum increases, amount of drug release decreases. Results exhibited that batch D1 containing 40mg of guar gum and 40mg of xanthan gum have shown better drug release (99.74%) compared to other batches and it was similar to marketed product ALZIL SR23. Further this batch fulfills drug release as per the requirement at 2hr and 12hr. So, batch D1 was considered as optimized batch among all formulated batches on the basis of drug release.
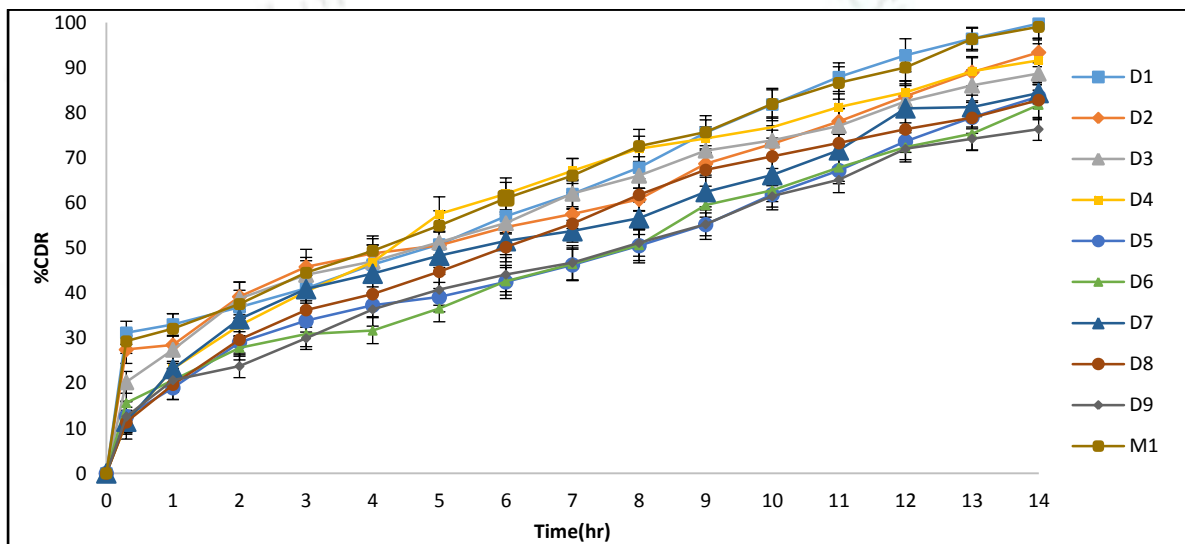

Figure 2: Cumulative % Drug Release Study of D1 to D9 Batches

Statistical Analysis

Preliminary investigations of the process parameters revealed that factors concentration of Guar gum (X_1) and concentration of Xanthan gum (X_2) highly influenced the rate of *in vitro* dissolution and, hence, were used for further systematic studies.

Effect of Polymers on %CDR at 2hr

Mathematical relationships generated for the studied response variables concentration of Guar gum (X_1) & concentration of Xanthan gum (X_2) for %CDR at 2hr (Y_1) is as follows:

$$Y_1 = 30.07 - 2.24X_1 - 4.54X_2 - 3.09X_1X_2 - 0.2567X_1^2 + 3.85X_2^2, \ R^2 = 0.9884$$

The high values of correlation coefficients for %CDR at 2hr indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e positive or negative. Multiple linear regression analysis revealed that coefficient b_1 and b_2 is negative. This indicates that as the concentration of polymer decreases, %CDR increases. Low levels of X_1 and of X_2 were found to be favorable conditions for obtaining better dissolution. Table 6 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. The coefficients b_1, b_2, b_{12} and b_2^2 were found to be significant at P is less than 0.05 and thus, were retained in the reduced model equation.

$$Y_1 = 30.07 - 2.24X_1 - 4.54X_2 - 3.09\ X_1X_2 + 3.85\ X_2^2, \ R^2 = 0.9878$$

Table 6: ANOVA Response Surface Quadratic Model for %CDR at 2hr

Source	SS	Df	MS	F Value	p-value prob > F
Model	221.77	5	44.35	51.30	0.0042
X_1	30.02	1	30.02	34.72	0.0098
X_2	123.67	1	123.67	143.04	0.0013
X_1X_2	38.25	1	38.25	44.24	0.0069
X_1^2	0.1318	1	0.1318	0.1524	0.7223
X_2^2	29.70	1	29.70	34.35	0.0099
Residual	2.59	3	0.8646	-	-
Cor Total	224.36	8	-	-	-

The 2D and 3D response surface for responses Y_1 was also drawn to study the effect of variables on response and it was shown in Figure 3.
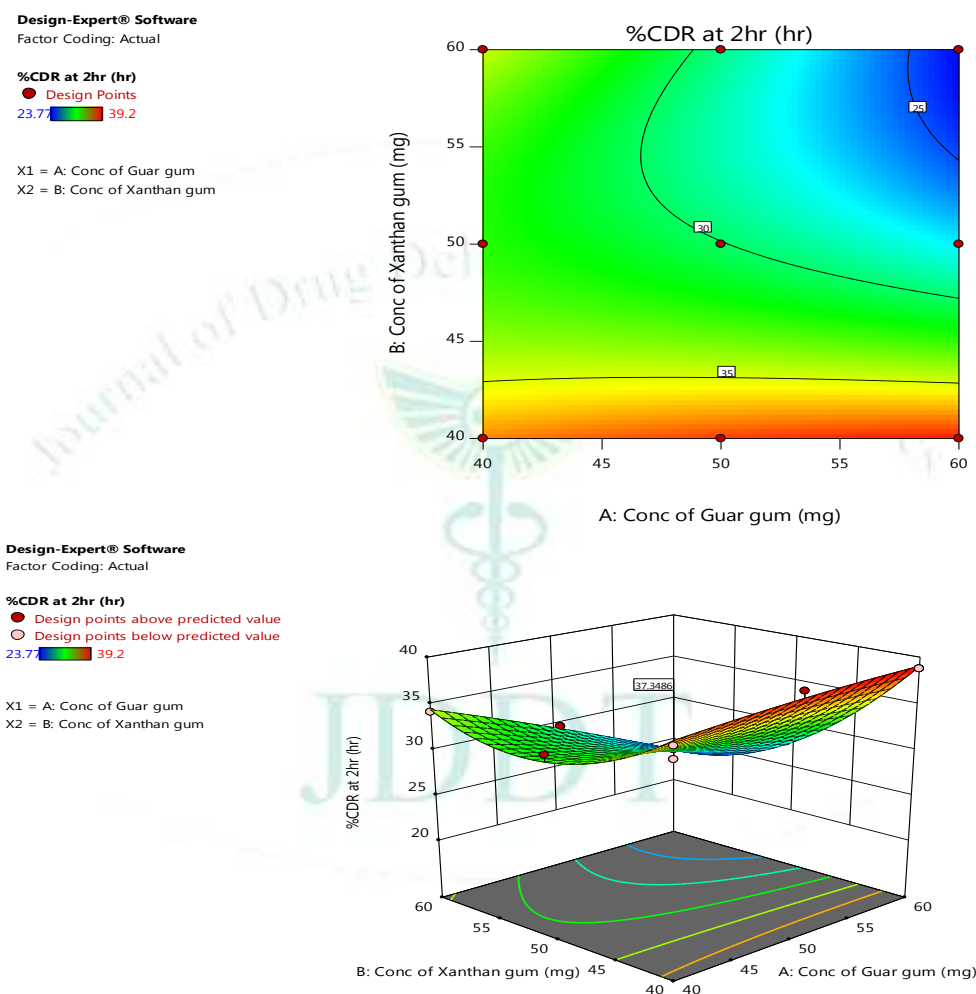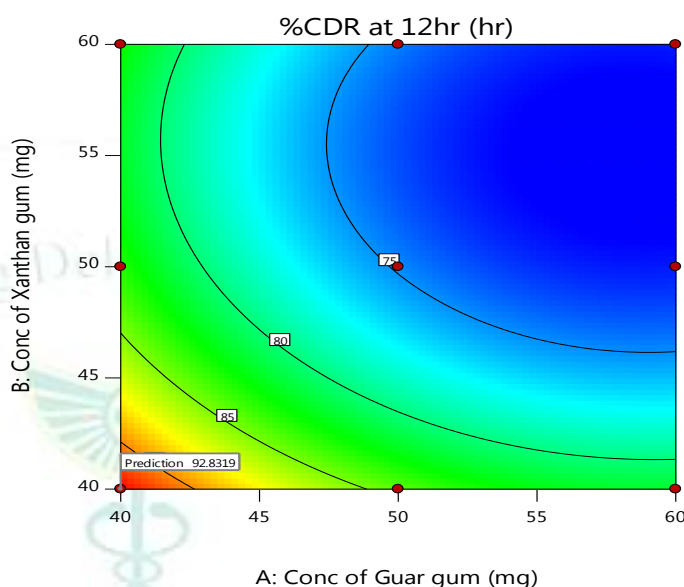

Figure 3: 2D and 3D Curve Concentration of Guar gum (X_1) & Xanthan gum (X_2) for %CDR at 2hr (Y_1)

Effect of Polymers on %CDR at 12hr

Mathematical relationships generated for the studied response variables concentration of Guar gum (X_1) & concentration of Xanthan gum (X_2) for %CDR at 12hr (Y_2) is as follows:

$$Y_2 = 74.83 - 5.23X_1 - 4.94X_2 - 0.3075X_1X_2 + 2.96X_1^2 + 4.55X_2^2, \ R^2 = 0.9734$$

The high values of correlation coefficients for %CDR at 2hr indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e positive or negative. Multiple linear regression analysis revealed that coefficient b_1 and b_2 is negative. This indicates that as the concentration of polymer decreases, %CDR increases. Low levels of X_1 and of X_2 were found to be favorable conditions for obtaining better dissolution. Table 7 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. The coefficients b_1, b_2 and b_2^2 were found to be significant at P is less than 0.05 and thus, were retained in the reduced model equation.

$$Y_2 = 74.83 - 5.23X_1 - 4.94X_2 + 4.55X_2^2, \ R^2 = 0.9262$$

Table 7: ANOVA Response Surface Quadratic Model for %CDR at 12hr

Source	SS	Df	MS	F Value	p-value prob > F
Model	370.14	5	74.03	21.98	0.0144
X_1	164.12	1	164.12	48.74	0.0060
X_2	146.62	1	146.62	43.54	0.0071
X_1X_2	0.3782	1	0.3782	0.1123	0.7596
$X_1{}^2$	17.56	1	17.56	5.22	0.1066
$X_2{}^2$	41.47	1	41.47	12.31	0.0392
Residual	10.10	3	3.37	-	-
Cor Total	380.25	8	-	-	-

The 2D and 3D response surface for responses Y_2 was also drawn to study the effect of variables on response and it was shown in Figure 4.
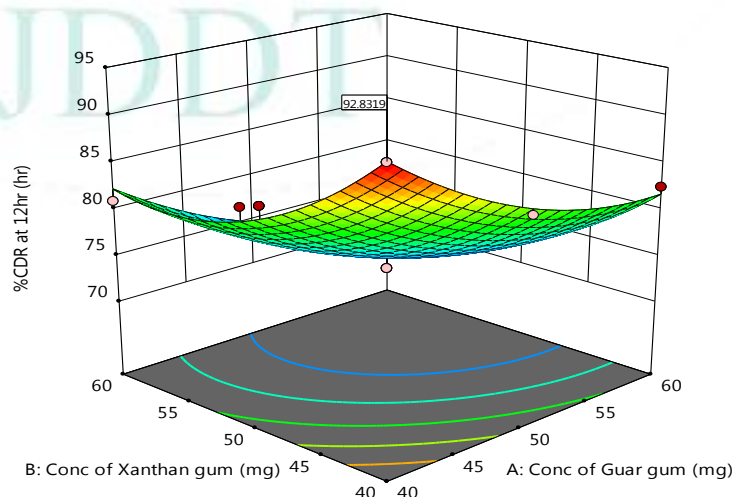

Figure 4: 2D and 3D Curve Concentration of Guar gum (X_1) & Xanthan gum (X_2) for %CDR at 12hr (Y_2)

Check Point Analysis

Three check point batches were prepared and evaluated for %CDR at 2hr and %CDR at 12hr as shown in table 8. When measured % CDR values were compared with predicted % CDR, the differences were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicted values.

Table 8: Checkpoint Batches with Predicted and Measured Value of %CDR at 2hr and at 12hr

Batch Code	X_1	X_2	%CDR at 2hr (Y_1)		%CDR at 12hr (Y_2)	
			Measured	Predicted	Measured	Predicted
D10	0	0.5	28.31	28.76	73.48	73.53
D11	0.5	1	26.50	26.65	72.36	72.41
D12	1	0.5	24.51	24.42	71.02	71.07

Optimization of Formulation

The overlay plot of responses generates an optimized area as per desired criteria (Figure 5). This was the most important part of the response surface methodology. The formulation of the drug which released the drug in controlled and complete manner was selected for optimum formulation. After studying the effect of the independent variables on the responses, the levels of these variables that give the optimum response were determined. The optimum formulation was selected based on the criteria of attaining complete and controlled drug release. Batch D1 having 40 mg of Guar gum and 40 mg of Xanthan gum fulfilled maximum requisites of an optimum formulation because of better regulation of release rate. The said formulation released 37.35% of drug in 2 hr. and 92.84% in 12 hr., however, the drug completely got released i.e. 99.74% in 14 hours, which were in close agreement with the theoretical values.
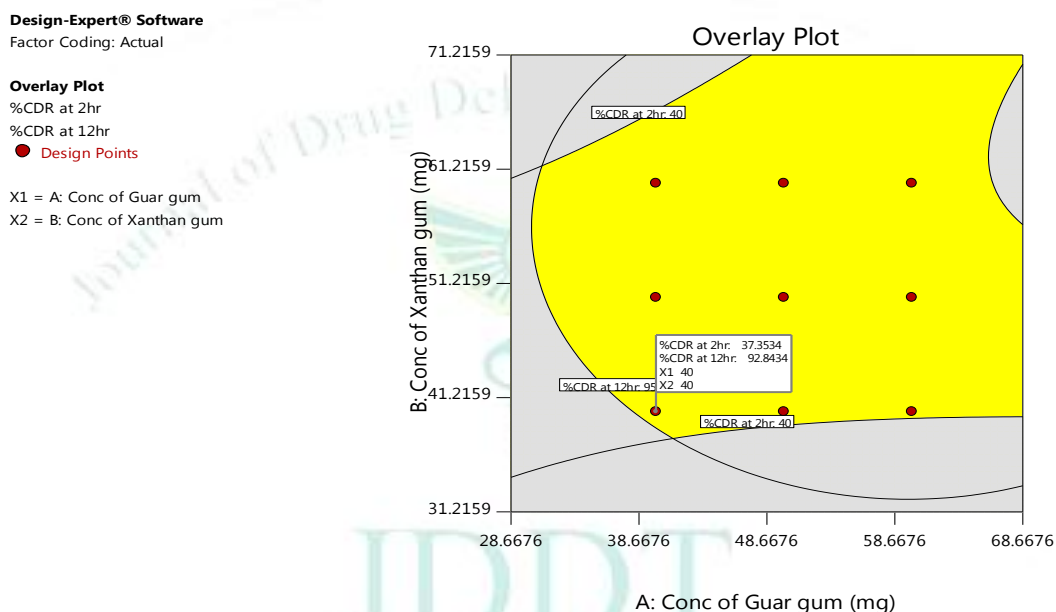

Figure 5: Overlay Plot of Batch D1

Drug Release Kinetic Study

In order to examine the kinetic of drug release from prepared sustained release tablets, the dissolution data of optimized formulation D1 was fitted into different kinetic models i.e. Zero order, First order, Higuchi model, Hixson- Crowell and Korsemeyer-Peppas model (Figure 6 to 10). The criteria for the selection of most suitable model were value of regression coefficient (R^2) nearer to 1, smallest values of Residual sum of squares (SSR) and Akaike Information Criteria (AIC). Table 9 shows the data obtained. The optimized formulation fitted well into Korsemeyer-Peppas, it was confirming the desired release profile. The calculated R^2 value for Korsemeyer-Peppas was 0.9517. According to Korsemeyer-Peppas equation, the release exponent "n" value is between $0.45 < n < 0.89$, which indicates that drug release is non-fickian diffusion type and states that release followed the diffusion controlled mechanism.

Table 9: Fitting of Release Profile of Optimized Formulation to Kinetic Models

Batch	Model	Parameters Used				
		R^2	R	K	SSR	AIC
D1	Zero-order	0.7592	0.9743	8.102	2858.1321	129.326
	First-order	0.8785	0.9532	0.171	1442.0205	118.380
	Higuchi	0.9317	0.9770	25.584	574.4741	105.627
	Korsemeyer –Peppas	0.9517	0.9772	25.378 n=0.504	573.2614	103.621
	Hixson Crowell	0.8755	0.9639	0.045	1477.8248	118.773

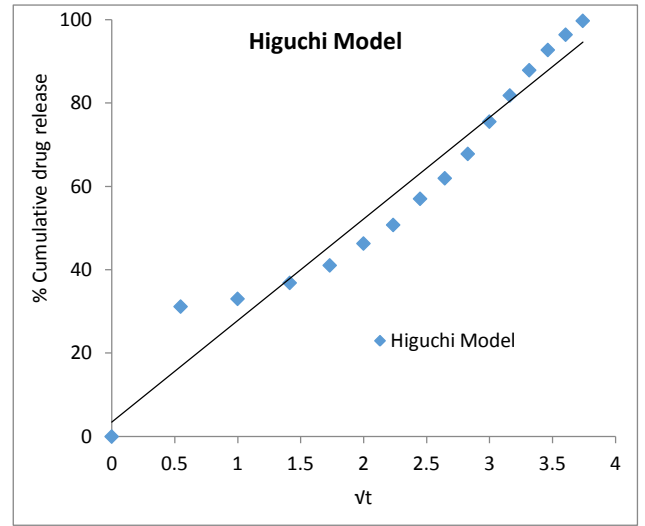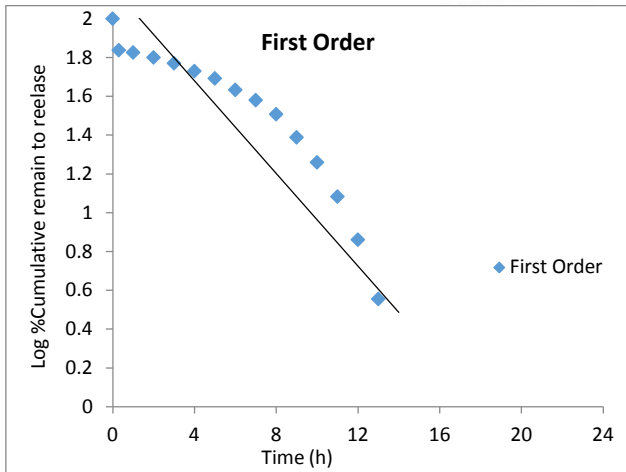Figure 6: Zero-order Release Kinetic Model

Figure 9: Higuchi Kinetic Model

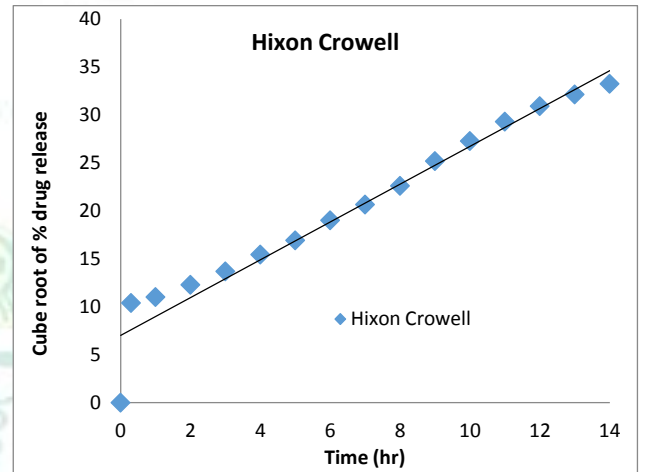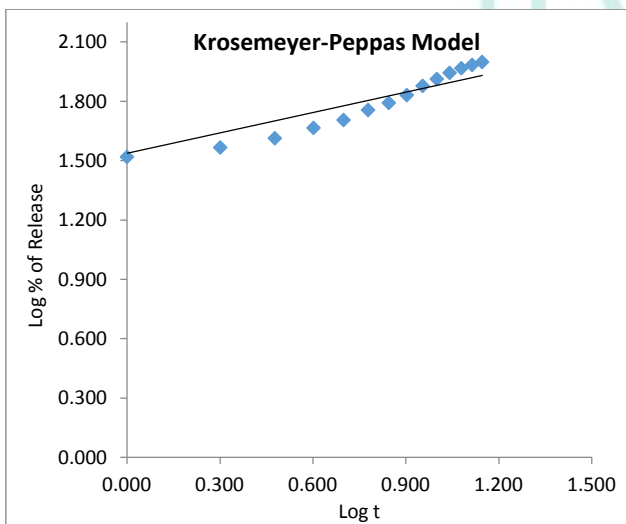Figure 7: First-order Kinetic Model

Figure 10: Hixon Crowell Kinetic Model

Similarity and Dissimilarity Study

Similarity factor (F2) and dissimilarity factor (F1) were calculated for optimized batch D1 and values were found to be 76.80 and 1.73 respectively. F2 value was within 50 to 100 and F1 value was within 0 to 15. This indicates that sustained release matrix tablets prepared using guar gum and xanthan gum (Batch D1) is similar to the marketed tablet formulation (ALZIL SR-23).

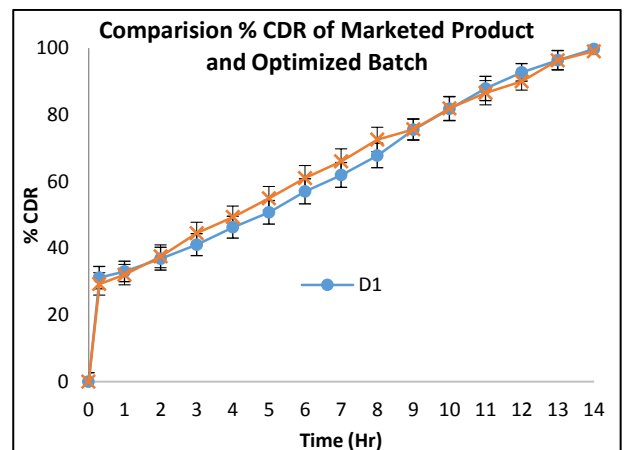Figure 8: Krosemeyer-Peppas Kinetic Model

Figure 11: Comparison % CDR of Optimized Batch with Marketed Product

Comparison %CDR of marketed product and optimized formulation was presented in Figure 11.

Stability Study

Stability study of sustained release matrix tablet of Donepezil hydrochloride (batch D1) was carried out for

1 month at specified condition. All data are mentioned in table 10. The stability studies of the optimized formulation (batch D1) shown no significant changes in the % drug content and % drug release at 14 hr. when stored at $40 \pm 2^{o}C/ 75 \pm 5$ % RH.

Table 10: Stability Study of Optimized Formulation (D1) carried out at $40 \pm 2^{o}C/ 75 \pm 5$ % RH

No. of Months	%Drug Content (n=3)	% Drug release at 14 hr. (n=3)
0	99.21 ± 1.30	99.74 ± 3.24
1	99.36 ± 1.47	99.49 ± 3.72

All values are expressed as mean ± standard deviation, n=3

CONCLUSION

The matrix type of tablets is potential to be an effective sustained release drug delivery system over a prolong period of time. The type and level of polymer used are important factors that can affect the drug release and also the physicochemical properties of this sustained release matrix tablets. 3^2 full factorial design was applied to achieve controlled drug release up to 14 hr. Among all the developed formulations, D1 formulation which contained the mixture of two polymers Guar gum and Xanthan gum sustained drug release for 14 hr. when compared with other formulations and also similar as marketed formulation. So, D1 was selected as the best formulation. The drug release kinetics follows Korsemeyer-peppas and the mechanism was found to be

non Fickian and shows continuous and uniform drug release for extended period of time. The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product.

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