Asian Pac. J. Health Sci., 2018; 5(4):210-220 e-ISSN: 2349-0659, p-ISSN: 2350-0964

Document heading doi: 10.21276/apjhs.2018.5.4.32 Research Article

Design and development of chronomodulated pulsincap delivery system of deflazacort

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Received: 08-05-2018 / Revised: 20-06-2018 / Accepted: 10-07-2018

Abstract

Aim of the present study was to formulate, evaluate and optimize the Pulsincap delivery system of deflazacort used in rheumatoid arthritis, based on the chronotherapeutic approach. The prepared pulsincap system consist of immediate release tablet sealed inside formaldehyde treated insoluble capsule body by hydrogel plug composed of polymer HPMC K15M and sodium alginate. Our target was to formulate a delivery system that could release the drug as per chronotherapeutic pattern of the disease (rheumatoid arthritis), so preliminary batches were prepared to study the effect of concentration of HPMC K15M and sodium alginate on the lag time of the drug release. Optimization of hydrogel plug was carried out by employing 3^2 full factorial design using Design expert 7 Software. The optimized batch of pulsincap sytem was found to release after a lag time of 366.66±2.887 minutes.

Keywords: chronothepary, Deflazacort, Rheumatoid arthritis, Pulsincap, 3^2 Full factorial design.

Introduction

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms**.** The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of drug delivery systems[1]. Chronotherapeutic delivery system have drawn a increasing interest over a last few decades. This type of delivery system is able to release drug according to pulsatile pattern[2]. Recent studies have revealed that diseases have predictable cyclic rhythms and outcomes in selected chronic conditions can be improved by taking in account the timing of medication regimens[3].

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease, associated with progressive disability, poor quality of life, and systemic complications.

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It has been studies that RA follow circadian pattern. Reduced production of cortisol in the early morning and increased production of melatonin in the night influence the severity of early morning symptoms of RA[4].

In the present study, Deflazacort was selected as the model drug. Deflazacort is a glucocorticoid. Glucocorticoids have been used in RA therapy due to their anti-inflammatory activities against symptoms such as joint stiffness and joint pain**.** Cortisol is an endogenous glucocorticoid, which reaches the peak in the morning in humans. Steroids are generally administered in the morning in order to prevent disturbances in the circadian rhythms of endogenous glucocorticoids[5,6].

In order to obtain an appropriate formulation with minimum experiments, optimization method was adopted in the present study. A 3^2 full factorial design was chosen to optimize the variables. The search for the optimum was carried out using desirability function as this technique involves a way of overcoming difficulty of multiple, sometimes opposing responses.

MATERIALS AND METHOD

Materials

Deflazacort, hydroxyl propyl methyl cellulose (HPMC K15M) and Avicel pH101 was obtained from Oscar Remedies Pvt. Ltd. Haryana, India, , sodium alginate,

sodium starch glycolate, talc and magnesium stearate was obtained from Nice Chemicals Pvt. Ltd. Kerala, India Ethylcellulose and ac-di-sol was obtained from Optica Pharmaceuticals, Haryana, India. Ethanol was obtained from modi mill, Yamuna nagar, Haryana.

Drug-Excepient compatibility study by FTIR

FTIR spectral analysis of physical mixture of drug and excipients was performed to assess drug excipients compatibility. Analysis was carried out by FTIR (Perkin Elmer 1600, USA) of Punjab University.

Preparation of cross-linked gelatin capsule

Hard gelatin capsules of size '1' were taken and their bodies were separated from the caps and then bodies were placed on a wire mesh, kept inside a desiccator containing 25ml of 15%(v/v) formaldehyde and a pinch of potassium permanganate. The vapors of formaldehyde formed were exposed to body of the capsule. Reaction was carried out for 12h after which the bodies were removed and dried at 50°C for 30 min to ensure completion of reaction between gelatin and formaldehyde vapors. Finally the bodies of the capsule were dried at room temperature to remove the excess of formaldehyde vapor[7,8]

Test for formaldehyde treated empty capsule bodies

Various physical tests, such as identification attributes, visual defects, changes in dimension were carried out.

Disintegration studies

Study was carried out in USP-27/NF-22 disintegration test apparatus. A removable wire cloth was attached to the upper plate of basket after placing one capsule in each tube assembled in the disintegration apparatus. Time required for disintegration was noted for each capsule[9].

Qualitative chemical test for free formaldehyde

0.002w/v was used as the standard solution. Formaldehyde treated 25 body of the capsules were cut in to small pieces and taken into a beaker and dissolved with 40 ml of water. This was then stirred for 1 h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50 mL volumetric flask, washed with distilled water and volume was made up to 50 mL with the washings. From the prepared sample 1ml of sample was taken in a 10ml volumetric flask, 9ml of water was added to it; 1ml of the sample solution was taken into test tube and mixed with 4 ml of water and 5 ml of acetone. The test tube was kept in a water bath at 40 ^{0C} for 40 min. The same procedure was followed for 1 ml of standard formaldehyde solution. The color produced in the sample solution was compared with the color produced with the standard solution[10].

Preparation of immediate release tablets

The composition of the immediate release tablets is given in table 1. The immediate release tablets containing drug deflazacort, sodium strarch glycolate and ac di sol were prepared by weighing the drug, sodium strarch glycolate, ac di sol and mixing with Avicel pH 101. Magnesium stearate (1%) and talc (2%) were added to each blend and further mixed. The resultant blends were tableted to 30 mg using 3 mm round flat-faced punches using a single punch tablet press (single station tablet compression machine, Rolex scientific Eng. Haryana, India)

Evalution of immediate release tablets

The thickness and diameter of the tablets (n=10) were determined using micrometer[11]. The hardness of the tablets (n=10) was determined by using the pfizer hardness tester[12] Electrolab, Mumbai, India. The friability (%) of the tablets was determined by taking Sample of whole tablets corresponding to about 6.5gm placed in the friabilator and were subjected to 100 revolutions[13]. The tablets were taken out, de dusted and reweighed to determine the friability of all the batches. Weight variation test of the tablets (n=20) was carried out as per the official method[14]. The disintegration time of core tablets was determined by the Disintegration tester USP[15] (ED-2AL, Electrolab, Mumbai, India). For determining the drug content immediate release tablet was crushed in a glass mortar and transferred quantitatively with methanol in a stoppered conical flask. The flask was placed in a sonicator for 30 min. The mixture was filtered and an aliquot, following suitable dilution, was analyzed at 242 nm using a UV spectrophotometer. The drug content was determined using a calibration curve constructed in methanol. The drug content of each of the ten immediate release tablets was compared with the average drug content of the tablets[16]

Preparation of hydrogel plug

Hydrogel plugs (preliminary batches) were prepared by direct compression according to the formula mentioned in table 2. The average weight of hydrogel plug was found to be 100mg. HPMC/ sodium alginate polymers were properly blended with Avicel pH101 using a mortar and pestle. The resultant blend was lubricated with the addition of lubricant magnesium stearate and finally compressed into plug (100 mg) using 5 mm round flat punches.

Evaluation of hydrogel plug

Hydrogel plug containing HPMC and sodium alginate were evaluated for weight variation, thickness and hardness.

Development of pulsincap system

Prepared immediate release tablet was placed in the capsule size 1 and the prepared hydrogel plug was

introduced into the open end of the capsule body. Finally the soluble capsule cap was placed over the capsule body. The joint of formaldehyde treated capsule body and soluble cap was further sealed with 5% Ethylcellulose ethanolic solution.

***In vitro* dissolution study of the capsule**

The dissolution studies of prepared pulseincap formulations were carried out using USP type II dissolution test apparatus. The capsules were tied to paddle with a cotton thread so that the capsules get completely immersed in dissolution vessel containing containing 700ml of 0.1N HCl (pH 1.2 i.e gastric pH) and the study was carried out for 2h, taking 6ml sample at an interval of 30min. Then 200 ml of 0.2 (M) trisodium orthophosphate dodecahydrate solution was added quickly and pH was adjusted using a pH meter to pH 7.4(i.e small intestine pH). Samples (6 ml) were collected periodically at different time intervals.

Experimental design

A two factor, three level (3^2) FFD was used in the optimization of Hydrogel plug. The study design involved the investigation of the effect of independent variables viz concentration of HPMC (X_1) and concentration of sodium alginate (X_2) on the dependent variable lag time. The combination of these trials is presented in Table 3

The levels of the factors studied were chosen on the basis of results of preliminary studies, so that their relative difference was adequate to have a measurable effect on the response, along with the information that the selected levels are within practical use. After developing the experimental design nine batches of hydrogel plug were formulated. Nine formulations (Table 4) were prepared according to the experimental design.

The factorial design is a simplified representation in analytical form of a given reality. In this mathematical approach, each experimental response Y can be represented by a quadratic equation of the response surface: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2$, in which Y is the measured response associated with each factor-level combination; X1 and X2 are the factors studied; B0 is an intercept; B1– B5 are the regression coefficients. The equation enabled the study of the effects of each factor and their interaction over the considered responses.

Optimization of hydrogel plug

The optimization process was used to obtain a model equation that provides a means of evaluating changes in response due to changes in the independent variable levels. After application of full factorial design and with help of polynomial terms the optimized pulsincap system (H1) was produced. Pulsincap formulation was prepared as per the composition given in table 5. This batch targeted to lag time 360 min. the observed response for lag time was 366.66±2.887.

Stability studies

In order to assess stability, the optimum pulsincap of deflazacort were packed in an amber colored air tight vial and stored at (40 ± 2 °C and 75 ± 5% RH) for a period of 6 months. The formulations were withdrawn after a particular period of time, analyzed for physical appearance, weight, drug content, and lag time. At this point, the data was statistically analyzed using ANOVA to test the significance of difference at the level of significance 0.05.

RESULTS AND DISCUSSION

Preformulation studies

Drug and excipient studies were performed and FTIR studies revealed that there is no incompatibility between drug and excipients used in the study. FTIR spectra of DZ and physical mixture of (DZ:HPMC), and (DZ:SA) are shown in Fig. 1. Among the various bands obtained in the spectra of DZ, only important ones were identified. An IR band was obtained at 3455.8 which can be assigned to OH stretch vibration, 1746.4, 1730.1 and 1654 were assigned to 22-C=O the 20-C=O and the cyclic α–β unsaturated 3-ketone (3- C=O) respectively. All these functional groups indicate purity of the drug. In physical mixture of DZ and HPMC, the characteristic absorption peaks of DZ appeared at 3455.8 cm-1 indicating OH stretch vibration, 1746.6, 1730 and 1654.8cm-1 22-C=O the 20-C=O and the cyclic α–β unsaturated 3-ketone (3-C=O) respectively.

In DZ:SA physical mixture, all the above mentioned IR bands were identified and no significant shift in peak was observed with respect to drug and polymer, which signifies very less to no chemical interaction between drug and the polymers.

Physical test

It was found that after formaldehyde treatment the length and dimension of capsule bodies were decreased

Disintegration test of capsules

It was found that the untreated capsules and the caps of treated capsules were disintegrated within 20 min. whereas the treated capsules remained intact for 24 hours

Formaldehyde treatment of empty gelatin capsule

Formalin treatment has been employed to modify the solubility of the gelatin capsules. Exposure to formalin vapours results in an unpredictable decrease in solubility of gelatin owing to the cross-linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation. The solubility tests were carried out for untreated capsules and formaldehydetreated capsules for 24 h. It was observed that in all untreated capsules,

both cap and body dissolved within 30 min, whereas in formaldehyde-treated capsules, only the cap dissolved within 30 min, while the capsule body remained intact for about 24 h and hence indicates the suitability for colon targeting. The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensely coloured than the standard solution, inferring that less than 0.8 mg of free formaldehyde per capsule was present as residual amount.

Evaluation of prepared powder blend

Prepared powder blend of immediate release core tablet and hydogel plug was subjected to evaluate various micromeritic properties. It was found that the powder exhibit good flow property as evident from the table 6 and 7

Evaluation of prepared immediate release tablet

Prepared immediate release tablets were subjected to check various physico-chemical properties and the values were found within the limits. Results are depicted in table 8

Evaluation of compressed hydrogel plug and pulsincap system

After formulating preliminary batches of hydrogel plugs, the evaluation study of hydrogel plugs were carried out, and the results obtained are represented in Table 9. It was found that all the formulations exhibited uniform weight with low standard deviation values, indicating the uniformity of the weight in hydrogel plugs prepared by direct compression method. The weight of the hydrogel plug varied between 102.72 mg and 98.48 mg. Range of hydogel plug thickness was found to be between 5.92mm – 6.28mm.

Hardness of hydrogel plug was determined by Pfizer hardness tester taking average of ten hydrogel plugs. It was found that with the increase in concentration of polymer there was an increase in the hardness value of plug. Range of hardness for hydrogel plug was in between 2.68 kg/cm^2 – 3.93 kg/cm^2 with minimum standard deviation.

***In vitro* dissolution studies**

In vitro drug release from pulsincap delivery sytem containing hydrogelplug with varying polymer concentration is depicted fig 2. each formulation released the drug after a certain lag time and the lag time attained was dependant on type and concentration of polymer. It was found that maximium lag time (430 min) was shown by the formulation HG3 containing 60% of HPMC and minimum lag time (180 min) was shown by formulation HG4 containing 20% of sodium alginate. Lag time found in the formulation HG7 – HG9 containing HPMC and sodium alginate in combination was 330 min – 400 min.

On the basis of preliminary studies it was found that with increase in the concentration of the polymer the lag time of drug release was also increased. On the basis of values of hardness obtained it was observed that with decreasing the concentration of polymer value of hardness also decreased. In case of formulation HG7-HG9 improved hardness values were obtained. Based on these findings combination of polymer was selected for further studies.

Statistical and response surface analysis of models for lag time

Statistical analysis

It was investigated, lag time showed a wide variation with change in concentration of two factors. Table 10 describes effect of HPMC and sodium alginate. It was found that with increase in concentration of HPMC and sodium alginate lag time for drug release also increased. According to dissolution profile it was found that lag time OHG1-OHG9 (fig. 3) varied between 300-440 min. Formulation OHG2 released drug after a lag time of 370 min. and the percentage of drug released from the formulation was found to be 95.85%.

Optimization

Optimization was done employing a 32 FFD. The dependent and independent variables were related using quadratic equations obtained with the Design Expert software (Design Expert 7) For each dependent variable, a summarizing equation was generated as shown in Table 11. ANOVA was performed to identify insignificant factors. Model selection was based on lower p values than assigned significance level, high F value i.e. 26.961, absence of lack of fit, highest level of adjusted R^2 and predicted R^2, low standard deviation and lower PRESS value. All values are represented in Table 12. All values implies the model is significant. High value of R^2 for dependent variable was obtained, which indicate a good fit. Value of p less than 0.05 indicated that model terms are significant.

Response surface analysis

Response surface plot was generated for response to study the behavior of the system. Response surface plot for hardness in fig. 4 shows that with the increase in the concentration of HPMC lag time of drug increases in linear manner and with increase in concentration in SA the lag time value of the hydrogel plug also increases in a curvilinear manner.

Table 1: Composition of immediate release tablet

Batch	Ingredients (mg)					
	Deflazacort	Sodium starch glycolate	Ac-Di-Sol	Talc	Magnesium stearate	Avicel pH101
Immediate release tablet	6	1.8	1.974	0.6	0.3	19.36

Table 2: Trial batches of hydrogel plug

Batch	Hydrogel plug material (mg)			
	HPMC	Sodium alginate	Avicel pH101	Magnesium stearate
HG1	20	-	79	1
HG2	40	-	59	1
HG3	60	-	39	1
HG4	-	20	79	1
HG5	-	40	59	1
HG6	-	60	39	1
HG7	20	60	19	1
HG8	40	40	19	1
HG9	60	20	19	1

Table 3 Experimental plan of 3^2 full factorial design

Formulation Code	HPMC (X_1)	Sodium alginate (X_2)
OHG1	-1	-1
OHG2	0	-1
OHG3	+1	-1
OHG4	-1	0
OHG5	0	0
OHG6	+1	0
OHG7	-1	+1
OHG8	0	+1
OHG9	+1	+1

Table 4 Formulation of experimental batches of pulsincap formulation

Formulation code	Immediate release tablet (mg)	Hydrogel composition (mg)			
		HPMC	Sodium alginate	Avicel pH101	Magnesium stearate
OHG1	30	50	45	4	1
OHG2	30	40	45	14	1
OHG3	30	30	45	24	1
OHG4	30	50	40	9	1
OHG5	30	40	40	19	1
OHG6	30	30	40	29	1
OHG7	30	50	35	14	1
OHG8	30	40	35	24	1
OHG9	30	30	35	34	1

Table 5 Composition of optimum batch (mg) of pulsincap formulation

Batch	Immediate release tablet (mg)	HPMC	Sodium alginate	Magnesium stearate	Avicel pH101
H1	30	40	37.65	1	21.35

Table 6: Characterization of powder blends of immediate release tablet

F.Code	Bulk Density* (g/cc)	Tapped Density* (g/cc)	Hausner's Ratio**	Compressibility Index (%)**	Angle of Repose* (º)
F1	0.492±.003	0.558±.011	1.134	11.827	15.844±0.805
F2	0.498±.008	0.581±.008	1.166	14.285	14.248±0.602
F3	0.559±.009	0.652±.011	1.166	14.263	15.093±0.92
F4	0.556±.010	0.662±.010	1.191	16.012	14.676±0.606
F5	0.551±.011	0.682±.011	1.238	19.208	10.506±0.833
F6	0.559±.012	0.612±.007	1.023	8.660	13.929±1.113
F7	0.549±.013	0.622±.013	1.133	11.736	14.844±0.702
F8	0.561±.012	0.619±.008	1.103	9.369	10.248±0.501

F9	0.553±.006	0.633±.013	1.145	12.638	11.093±0.620
F10	0.545±.007	0.617±.004	1.132	11.669	14.676±0.416
F11	0.564±.009	0.629±.013	1.115	10.333	12.506±0.723
F12	0.541±.014	0.614±.010	1.135	11.889	13.929±1.113

* n=3; ** Calculated from average values of tapped density and bulk density.

Table 7: Characterization of powder blends of hydrogel plug

F.Code	Bulk Density* (g/cc)	Tapped Density* (g/cc)	Hausner's Ratio**	Compressibility Index (%)**	Angle of Repose* (º)
HG1	0.416±0.006	0.488±0.01	1.17	14.73	15.47±0.815
HG2	0.481±0.014	0.526±0.011	1.094	8.63	15.62 ±0.91
HG3	0.460±0.013	0.515±0.01	1.12	10.714	14.956±0.701
HG4	0.510±0.013	0.564±0.009	1.104	9.498	16.57 ±0.52
HG5	0.526±0.014	0.570±0.009	1.083	7.691	16.82 ±0.82
HG6	0.561±0.011	0.669±0.013	1.192	16.107	16.64 ±0.53
HG7	0.575±0.018	0.619±0.011	1.078	7.243	16.494± 0.71
HG8	0.575±0.017	0.635±0.012	1.104	9.448	15.83±0.63
HG9	0.487±0.014	0.556±0.006	1.141	12.41	15.364±0.612

* n=3; ** Calculated from average values of tapped density and bulk density

Table 8: Characterization of immediate release tablets

Batch	Average Weight (gm) *	Thickness (mm)***	Hardness (Kg/cm^2)***	Disintegration Time (s)*****	Friability (%)****	Drug content (%)**
Immediate release tablets	30.86±2.634	3.26±0.071	3.0±0.15	64.167±3.502	0.598	99.36

*Each value is average of twenty independent determinations; **Each value is average of five tablets; ***Each value is average of ten independent determinations; ;******** Each value is average of two hundred sixteen tablets. ***** Each value is average of six independent determinations

Table 9: Characterization of Hydrogel plugs

Formulation Code	Weight variation (mg) (Mean±SD)***	Thickness (mm) (Mean±SD)***	Hardness**** (Kg/cm^2)
HG1	100.25±4.989	6.044±0.089	3.57±0.199
HG2	99.6±3.072	6.1576±0.086	3.65±0.133
HG3	100.15±3.531	6.0953±0.112	3.93±0.134
HG4	101.4±3.627	6.006±0.128	2.68±0.175
HG5	102.74±4.701	6.1608±0.074	2.72±0.171
HG6	98.48±2.988	6.0313±0.097	2.78±0.177
HG7	102.36±3.423	6.28±0.103	2.91±0.231
HG8	100.15±2.901	5.920±.154	3.31±0.148
HG9	102.72±3.86	6.21±.099	3.62±0.206

*** Each value is average of twenty independent determinations; **** Each value is average of ten independent determinations.

Table 10: Effect of polymer concentration on the characteristics of the prepared pulsincap formulations

F. Code	Conc. of HPMC (%)	Conc. of sodium alginate (%)	Lag Time* (min)
OHG1	50	45	440±3.65
OHG2	40	45	370±4.37
OHG3	30	45	330±5.31
OHG4	50	40	410±6.188
OHG5	40	40	380±4.51
OHG6	30	40	330±5.58
OHG7	50	35	390±2.70
OHG8	40	35	340±4.67
OHG9	30	35	300±2.54

* n=3

Table 11: The quadratic equations relating lag time with independent variables in pulsincap formulation

Response	Experiment Parameters					
	β_0	β_1	β_2	β_3	β_4	β_5
Lag Time	371.1111	46.66667	18.33333	5	3.333333	-11.6667

Table 12: ANOVA results model in pulsincap formulation

Measured Response	SS	DF	MS	F-Value	Prob > F	SD	R^2
Lag Time	15477.78	5	3095.556	26.961	0.0107	10.715	0.978

SS- sum of squares, DF- degree of freedom, MS- Mean square, SD- Standard deviation

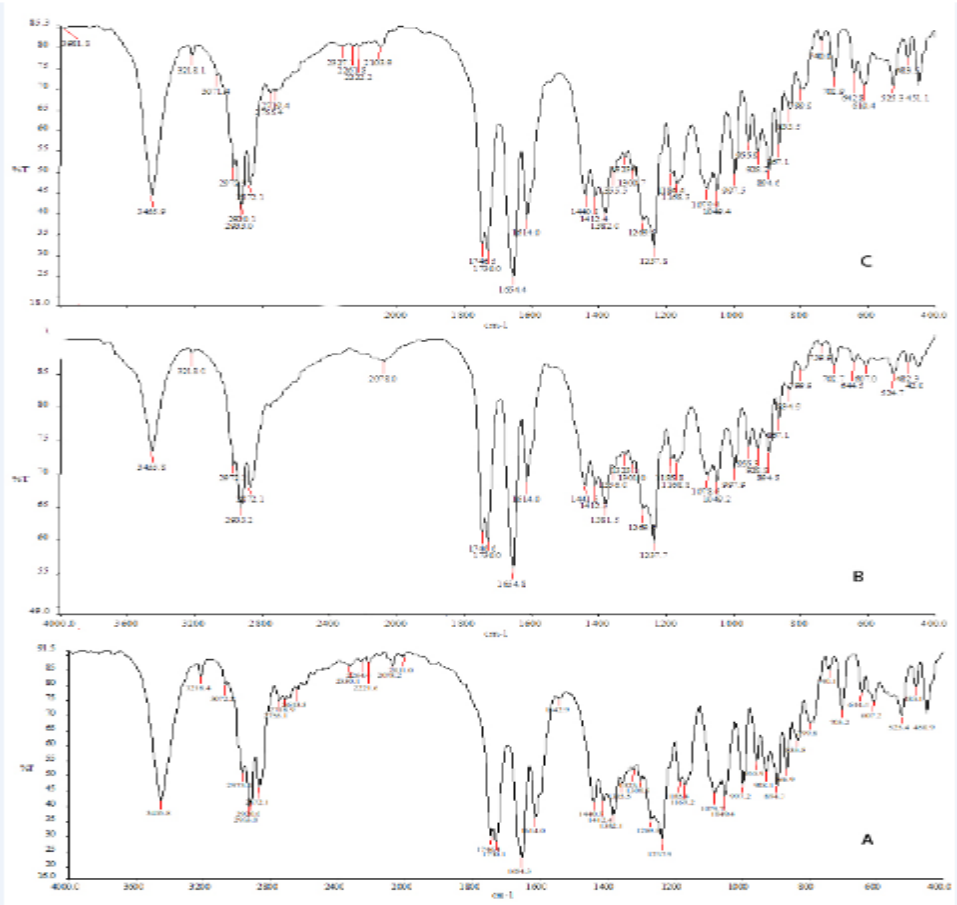

Figure 1 Scanned FTIR spectra of (a) Deflazacort (b) Physical mixture of Deflazacort and HPMC K15M (C) Physical mixture of deflazacort and sodium alginate

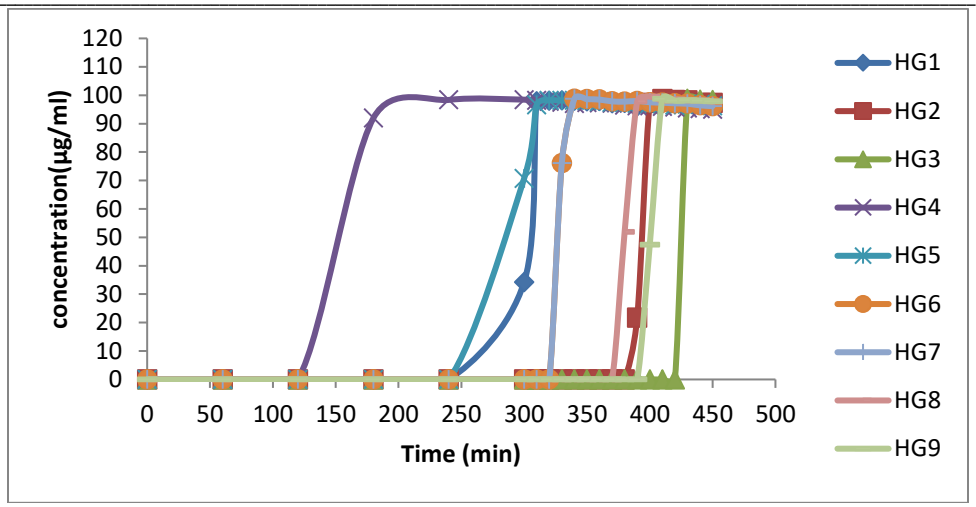

Figure 2: Percent released of Deflazacort from pulsincap system (preliminary batch)

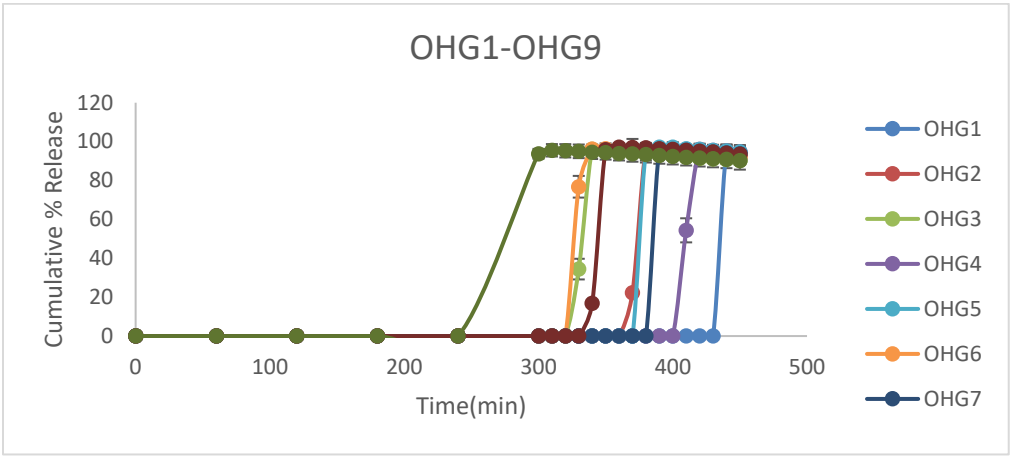

Figure 3 Percent released of Deflazacort from pulsincap system (Experimental batch)

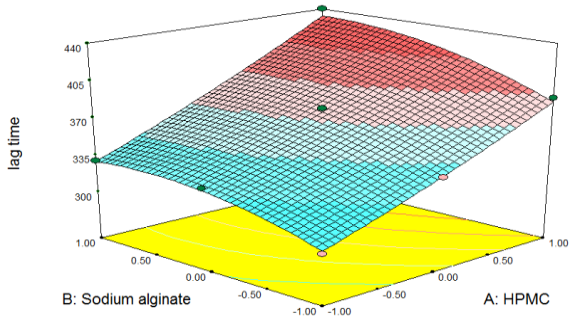

Figure 4: Response surface graph showing the influence of X_1 and X_2 on the Lag time of pulsincap system of deflazacort

Accelerated stability studies

Accelerated stability studies on the optimized promising formulation of pulsincap (H1) was carried out by storing the formulations (in amber colored rubber stoppered vials) at 40±2^{0}C and 75±5% RH for 6 months. At regular intervals the formulation was characterized for different parameters. It is shown that there was no change in physical appearance, weight, hardness, drug content during the study period and at the end of the six months. Also no significant change was shown in the percent drug release, before and after storage. Thus, results imply good stability of the formulation on six month storage. Since the accelerated data showed little or no change over time and little variability, a statistical analysis was considered unnecessary.

Conclusion

It was concluded that, implementation of a suitable experimental design results in achievement of an appropriate formulation, in the shortest time with minimum efforts. Pulsincap formulation of deflazacort prepared by using polymer HPMC and sodium alginate was found to be better alternative for the patients having rheumatoid arthritis that follows the circadian pattern because the prepared formulation released the drug according to the need of disease. Lag time for the release of drug from the optimized formulation was found to be 366.66±2.887 which was in close proximity to the desired value. Thus it can be said that our prepared formulation might be beneficial in a diseased state to provide relief at its worst condition.

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Conflict of Interest: None
Source of Support: Nil