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DEVELOPMENT AND CHARACTERIZATION OF DIACEREIN AND CHLORZOXAZONE PULSATILE RELEASE TABLET DOSAGE FORM

Richa Dayaramani[1], Sandeep V. Nathwani*[,2]

[1]Tolani Institute of Pharmacy, Adipur, Gujarat, India
[2]B. K. Mody Govt. Pharmacy College, Rajkot, Gujarat, India

***Corresponding author e-mail:** sannath_jay@yahoo.co.in

ABSTRACT

The aim of this study was to develop and characterize press coated tablet of Diacerein and Chlorzoxazone. The drug delivery system is based on the concept of chronotherapeutics where the drug is released rapidly after a well defined lag-time. A pulsatile-release profile is characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Diacerein (DMARD) and Chlorzoxazone (NSAID) combination has been used for obtaining synergistic effect in the management of arthritis. Drug polymer compatibility studies were carried out by FT-IR. Core tablet was prepared by direct compression using super disintegrant sodium starch glycolate. The core tablet was compression coated with different quantities of coating material containing different polymers. A 3^2 Full factorial design was used for optimization of the barrier layer. Total coat weight (X_1) and % HPMC K4M (X_2) were selected as independent variables. The lag time for Diacerein (Y_1), CPR at 1st hr after lag time for Diacerein (Y_2), time for 90% drug release for Diacerein (Y_3), the lag time for Chlorzoxazone (Y_4), CPR at 1st hr after lag time for Chlorzoxazone (Y_5) and time for 90% drug release for Chlorzoxazone (Y_6) were selected as dependent variables. Tablets were evaluated for various evaluation parameters. Comparative dissolution profiles of all the batches indicated drug release from tablet was inversely proportional to the coat weight. From the release profile it was deduced that delay lag time was observed for the press-coated tablet containing a higher amount of HPMC K4M in the outer shell. The press coated tablets coated with HPMC K4M:HPMC K100 in 64.39:35.61 ratios with 200 mg coat weight are most likely to provide the desired delivery of Diacerein and Chlorzoxazone.

Keywords: Diacerein, Chlorzoxazone, HPMC, Pulsatile release, rheumatoid arthritis, DMARD, NSAIDS

INTRODUCTION

In recent years, oral drug delivery systems with sustained-release kinetics have been developed for controlling drug release using various mechanisms, including matrices with controllable swelling, diffusion, erosion, and osmotic driven systems [1-3]. Novel systems have been developed in order to control drug release after specific lag time. Major disease conditions such as asthma, cardiac disorders, allergic rhinitis, and arthritis follow circadian rhythm. If disease symptoms occur during specific time of day or night, conventional dosage forms are unable to fulfill the necessities of the physiological conditions. Modified release dosage form preparations are expected to provide reduced dosing frequency and an improved patient compliance. This challenge has been met by pulsatile dosage forms [4-8]. Pulsatile release dosage forms are useful when constant plasma drug levels are not desired and an optimum therapeutic effect comes from a periodically fluctuating drug concentration. Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal drug delivery and increasing patient compliance. Pulsatile delivery systems are developed in order to fulfill the condition of rapid drug release after a lag time [9-12].
Chlorzoxazone, a non-steroidal anti-inflammatory drug, is used for the symptomatic relief of pain and joint stiffness in patients suffering from rheumatoid arthritis, Chlorzoxazone affects on levels of pro-

inflammatory cytokines, interleukin-6 and/or tumor necrosis factor-α and due to this, many signs and symptoms of active rheumatoid arthritis are manifested in the morning [13-20].

Diacerein act as DMARD (Disease Modifying Anti Rheumatic Drug) affecting on inflammation by mechanism of inhibiting IL 1.

The combination of a NSAID and DMARD is far better in treating rheumatoid arthritis than any other single drug. So, this combination pulsatile release tablet might be more effective in the treatment of arthritis [21-27].

Generally, the attack of rheumatoid arthritis peaks at early morning. If dosage form is designed such that it delivers drugs after proper lag time then it is convenient for patients to take dosage form at night time. Pulsatile release tablet will improve efficacy of combination and increase conveniences for patients [28-35].

Recently, factorial designs have gained a lot of interest because it provides more rapid and useful results than the conventional trial and error method. For this particular study, 3^2 full factorial design is applied [36].

MATERIALS AND METHOD

Materials: Diacerein was obtained as a gift sample from Ami Lifesciences Pvt. Ltd, Baroda, India, and Chlorzoxazone was obtained from Espee Pharma. Pvt. Ltd., Rajkot. HPMC K4M and K100 were obtained from ACS chemicals. All other chemicals used were of pharmaceutical grade.

Method:

Preparation of Press coated pulsatile release tablets: Press coated pulsatile release tablet was prepared by using compression coating method. Initially, core tablet of Diacerein and Chlorzoxazone was prepared and coated on compression machine.

A. Preparation of core tablets [37-39]: All ingredients of core tablet given in table 1 were weighed and passed through 60 # sieve. Finally resultant powder was mixed using mortar and pestle. The powder mixture lubricated with magnesium stearate (0.5 % w/w) and talc (0.5 % w/w). 200 mg of this powder mixture was weighed and transferred manually in to die and compressed by using 6 mm punch on a rotary tablet compression machine.

B. Preparation press coated tablets [40-45]: Formulation compositions of coating layer (B1 to B9) are shown in table 2. The ingredients of coating layer were mixed in mortar and pestle. Required weight of coating powder was weighed and used in two steps.

For first half coating, the powder was filled in to die and core tablet was placed in the centre of die. Core tablet was slightly pressed and other half quantity was filled and compressed by using 12 mm concave punch tooling. From the developed formulations best formulation was chosen using response optimization.

Evaluation of tablet characteristics

Thickness [46] : Thickness of tablets was determined using vernier caliper. Three tablets were evaluated and an average value was calculated. The thicknesses were measured in mm.

Hardness test [46]: Hardness was measured using Monsanto hardness tester. For each batch ten tablets were tested. The force required to break the tablet was recorded. The hardness of tablets of each batch was measured in kg/cm^2.

Friability test [46]: Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were de-dusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X } 100$$

Drug content [47-48]: Amount of the powder equivalent to 10 mg each of Diacerein and Chlorzoxazone was dissolved in 100 ml of phosphate buffer pH 6.8, filtered, diluted suitably. Chlorzoxazone was analyzed at 228.4 nm and Diacerein was analyzed at 249.11 nm using UV-spectrophotometer.

In vitro disintegration time [49]: In vitro disintegration time of three tablets was determined by using digital tablet disintegration apparatus. In vitro disintegration test was carried out at 37 ± 2°C in 900 ml phosphate buffer pH 6.8.

In vitro dissolution study [50-52]: In-vitro dissolution study of optimized core tablet was performed using USP Type II dissolution apparatus (Paddle type) at speed of 50 rpm. 900 mL of phosphate buffer pH 6.8 was used as dissolution medium. The temperature of the medium was maintained at 37 ± 0.5°C. 5 mL aliquots of dissolution medium were withdrawn at specific time intervals (5, 10, 15, 20, 30, 45, & 60 min) and each of them was filtered using Whatman filter paper no. 20. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amount of drug present in each sample was determined using UV-Visible

spectrophotometer at 249.11 nm for Diacerein and 228.4 nm for Chlorzoxazone.

RESULTS AND DISCUSSION

Core tablets are evaluated for weight variation, thickness, hardness, friability, drug content, disintegration time and in vitro dissolution test.
Results of physicochemical evaluation of core tablets (C) are given in Table 3. Results of in vitro disintegration time are given in table 4. Results of physicochemical evaluation of press coated tablets (B1 –B9) are given in Table 5.

In-vitro dissolution study

A. In vitro dissolution of core tablets: In case of core tablets in vitro dissolution test was carried out in phosphate buffer pH 6.8 for 60 min. Results of in vitro dissolution test presented in Table 6 and figure 1. In order to perform different release kinetics, depending upon different release mechanism involved, effect of Sodium starch glycolate level on drug release profile from uncoated tablet (Formulations CT1 to CT4) were determined.

As amount of sodium starch glycolate level decreased from formulations C-1 to C-4 it was observed that the formulation containing highest amount of sodium starch glycolate (C-3) showed fast disintegration and fast release because of swellable disintegrant present in it. As the amount of swellable disintegrant decreased, the amount of drug release also decreased. Without the disintegrant sodium starch glycolate in formulation C-4 showed a significant decrease in disintegrantion. As shown in figure1 significant change in release profile C3 shows drug release initially faster compare to C 4 which was without the disintegrant.

B. In vitro dissolution of press coated tablet: *In-vitro* drug release profile of all nine formulations is shown Figure 2. The release profiles from the press coated tablets were found to be typical sigmoidal curves with a lag time. For drug delivery systems designed for pulsatile delivery, it is desirable that the system remains intact and shows minimal drug release in the physiological environment of the stomach and triggers drug release in the lower GIT. From the release profile influence of change in the ratio of HPMC K4M to HPMC K100 and coat weight on drug release was demonstrated. It showed that lag time increases with increasing concentration of HPMC K4M. This might be due to the greater degree of hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway. The viscous HPMC gel deposited might prolong the time lag.

It was observed that the higher amount of drug was released from batches containing lower level of polymer weight in coating layer. From release profile of all nine batches it was observed that drug release from tablet was inversely proportional to coat weight. Drug release rate was highly retarded in formulation B7, B8 and B9 which contained a higher level of coat weight (200 mg). From all the batches, formulation B1 shows >90 % of drug released before the lag time of 6 h. The intermediate drug release retardation was observed from the batches B2,B3 and B6 while significant retardation was observed from the batches B4 and B5 containing higher amount of HPMC K4M in the outer shell. Formulation B4 and B5 show less than 10% of drug release at the end of 6h and nearer 99% of drug release at the end of 9 h. Hence, it can be said that the batches B4 and B5 showed desirable drug release.

STATISTICAL ANALYSIS OF FACTORIAL DESIGN: From statistical analysis it was conclude that as amount of HPMC K4M increases drug release decrease and as amount of coating layer increase drug release decrease.

Based on the criteria for optimized batch, pulsatile tablets should release minimum amount of drug at 6 hours. Ideally, release should start after 6 hours of dissolution study. Difference of drug release between 6 to 9 hours should be the maximum and 90% of drug release would be desirable within 9 hours. Drug release at 6 hours: 0-10%, Drug release after lag time provide burst release: 70-80%, Time required for releasing 90% of drug: 8-9 hours various dependent variables were chosen.

Here, amount of coating as X_1 independent variable, % of HPMC K4M as X_2 independent variable and Y1 (Lag time for Diacerein), Y2 (CPR at 1st hr after lag time for Diacerein), Y3 (Time for 90% drug release for Diacerein), Y4 (Lag time for Chlorzoxazone), Y5 (CPR at 1st hr after lag time for Chlorzoxazone) and Y6 (Time for 90% drug release for Chlorzoxazone) are considered as dependent variables.

$Y1= 6.90 + 1.08\ X_1 + 0.97\ X_2 - 0.56\ X_1^2 - 0.38\ X_2^2 - 0.44\ X_1X_2$
$Y2= 51.6 – 35.81\ X_1 – 11.86\ X_2 - 2.66\ X_1^2 - 6.55\ X_2^2 - 2.2\ X_1X_2$
$Y3= 9.03 + 1.84\ X_1 + 0.92\ X_2 + 0.40\ X_1^2 + 0.25\ X_2^2 - 0.68\ X_1X_2$
$Y4= 6.73 + 1.16\ X_1 + 0.93\ X_2 - 0.56\ X_1^2 - 0.32\ X_2^2 - 0.46\ X_1X_2$
$Y5= 55.09 - 35.81\ X_1 - 12.54\ X_2 - 5.40\ X_1^2 - 6.89\ X_2^2 - 3.90\ X_1X_2$
$Y6= 9.33 + 2.10\ X_1 + 0.88\ X_2 + 0.15\ X_1^2 + 0.058\ X_2^2 - 0.41\ X_1X_2$

On the basis of the optimization technique few experiments and statistical analysis of the results can provide an efficient and economical method for the prediction of the optimal composition. Best batch was selected according to different criteria which were fulfilled by prepared batch.

To validate evolved model a checkpoint batch B10 was prepared at X_1 = -1(Coded value) and X_2 = 0.9 (Coded value) levels means X_1= 200 mg and X_2= 64.39%. Dependent parameters were determined and compared with predicted values as shown in Table 8.

Batch B 10 was prepared using defined level of total amount of coating (200 mg) and % HPMC K4M (64.39%). Results obtained with check point batch were very close to predicted values. Thus, it can be concluded that the statistical model is mathematically valid.

CONCLUSION

To conclude, the compression coating technique can be applied to obtain flexible drug delivery systems based on time controlled release. Drug release of compression-coated tablets can be modified by the adjusting the release controlling parameters to achieve programmable drug release for site specific drug delivery in GI tract. The present investigation was aimed to develop pulsatile release press coated tablet of Diacerein and Chlorzoxazone for treatment of arthritis. A press coated tablet, taken at bedtime with delayed start of drug release in the early mornings, a time when arthritic attacks exacerbates and thus this type of drug delivery can provide adequate protection against it. Diacerein and Chlorzoxazone pulsatile release tablets were prepared by compression coating technique. Initially core tablets were prepared by direct compression. These tablets were compression coated with polymeric powder (different combinations of HPMC K4M and HPMC K100). Press coated tablets of Diacerein and Chlorzoxazone was optimized using 3^2 full factorial designs. Total amount of polymer (X_1) and % of HPMC K4M (X_2) were taken as independent variables. Lag time for Diacerein (Y1), CPR at 1st hr after lag time for Diacerein (Y2), Time for 90% drug release for Diacerein (Y3), Lag time for Chlorzoxazone (Y4), CPR at 1st hr after lag time for Chlorzoxazone (Y5) and Time for 90% drug release for Chlorzoxazone (Y6) were taken as dependent variables. From optimized batch, 200 mg of total polymer coating with 64.39 % HPMC K4M was found to be best compression coat formula to achieve the desired drug release profile.

Table 1 Composition of core tablet

Ingredients(mg)	Batch C1	Batch C2	Batch C3	Batch C4
Chlorzoxazone	150	150	150	150
Diacerein	50	50	50	50
Sodium starch glycolate	4	6	8	-
Microcrystalline Cellulose	38	36	34	42
PVP K30	6	6	6	6
Mg. stearate	1	1	1	1
Talc	1	1	1	1
Total	200	200	200	200

Table 2 Composition of coating material

Sr no.	Amount of coating X_1 factor	% HPMC K4M X_2 factor
1	200 mg	25%
2	200 mg	50%
3	200 mg	75%
4	250 mg	25%
5	250 mg	50%
6	250 mg	75%
7	300 mg	25%
8	300 mg	50%
9	300 mg	75%

Table 3 Physicochemical evaluation of core tablets (C)

Core tablet	Weight variation (mg)	Thickness	Hardness (kg/cm^2)	Friability test (%)	Drug content (%)	
					CLZ*	DCN*
Batch C1	200 ±1.23	3.20±0.1	3.10 ± 0.0305	0.23	99.45±1.61	99.38±1.23
Batch C2	200 ±1.14	3.21±0.1	3.20 ± 0.0312	0.12	99.21±1.45	99.28±1.87
Batch C3	200 ±1.48	3.20±0.1	3.10 ± 0.0298	0.28	100.10±1.87	100.12±1.78
Batch C4	200 ±1.08	3.20±0.1	2.90 ± 0.0310	0.25	100.28±1.98	99.92±1.46

*CLZ – Chlorzoxazone, DCN - Diacerein

Table 4 In disintegration time of core tablets (C)

Core tablet	Disintegration time(sec.)
Batch C1	72 ±0.02
Batch C2	60 ±0.02
Batch C3	54 ±0.01
Batch C4	230 ±0.02

Table 5 Physicochemical evaluation of press coated tablets (B)

Batches	Uniformity of weight (mg)	Thickness (mm)	Hardness test (kg/cm^2)	Friability (%)	Drug contents			
					CLZ		DCN	
B1	400 ± 1.25	5.10 ± 0.12	5.30 ± 0.017	0.012	99.24 ± 0.025	±	99.78 ± 0.05	±
B2	400 ± 1.38	5.12 ± 0.40	5.40 ± 0.026	0.015	100.21 ± 0.1	±	99.21 ± 0.01	±
B3	400 ± 1.12	5.02 ± 0.30	5.10 ± 0.018	0.011	98.91 ± 0.18	±	99.32 ± 0.023	±
B4	450 ± 1.45	5.65 ± 0.23	5.80 ± 0.016	0.010	99.37 ± 0.023	±	100.14 ± 0.025	±
B5	450 ± 1.58	5.69 ± 0.40	5.60 ± 0.028	0.012	100.01 ± 0.03	±	99.20 ± 0.05	±
B6	450 ± 1.61	5.64 ± 0.35	5.20 ± 0.021	0.014	99.12 ± 0.001	±	99.14 ± 0.014	±
B7	500 ± 1.32	5.87 ± 0.12	5.40 ± 0.018	0.012	99.25 ± 0.02	±	99.35 ± 0.012	±
B8	500 ± 1.12	5.85 ± 0.14	5.80 ± 0.016	0.014	100.02 ± 0.05	±	99.92 ± 0.025	±
B9	500 ± 1.25	5.12 ± 0.12	5.80 ± 0.021	0.010	99.89 ± 0.03	±	99.21 ± 0.05	±

Table 6 In vitro dissolution of core tablets

Time(min)	Batch C1		Batch C2		Batch C3		Batch C4	
	CLZ	DCN	CLZ	DCN	CLZ	DCN	CLZ	DCN
0	0	0	0	0	0	0	0	0
5	30.45	35.40	29.23	28.30	30.14	32.11	5.2	4.1
10	48.21	47.12	50.21	51.14	56.23	56.78	8.3	7.8
15	58.14	54.23	61.13	63.24	62.14	69.11	10.45	9.34
20	63.23	65.21	65.24	66.21	76.18	75.23	30.43	12.23
30	74.12	75.34	75.26	78.28	83.12	88.12	45.21	23.28
45	83.16	84.14	89.12	90.47	94.25	93.28	56.78	33.17
60	99.25	97.24	99.19	99.12	99.79	99.08	65.29	51.16

Table 7 Relationship between Dependent and independent variables

X_1	X_2	X_1X_1	X_2X_2	X_1X_2	Y1	Y2	Y3	Y4	Y5	Y6
-1	-1	1	1	1	3.17916	95.76	5.92	3.11583	98.02	5.8695
-1	0	1	0	0	5.9955	62.16	8.6315	5.42016	64.62	8.519
-1	1	1	1	-1	5.82716	83.21	8.73416	5.834	80.12	7.872
0	-1	0	1	0	5.84	58.73	8.5795	5.77016	62.22	8.70316
0	0	0	0	0	5.97416	79.08	7.8375	5.99666	82.14	7.78283
0	1	0	1	0	8.12083	3.88	11.1941	7.785	7.15	11.6165
1	-1	1	1	-1	6.50283	10.89	11.4028	6.4115	11.23	11.2613
1	0	1	0	0	7.61666	8.23	11.4425	7.6475	7.74	11.992
1	1	1	1	1	7.40233	7.14	11.4875	7.2865	8.92	11.6121

Table 8 Observed value and predicted value for dependant variables

Dependant variable	Observed value	Predicted value
Y1	6.01	5.99
Y2	74.12	73.17
Y3	8.60	8.55
Y4	5.80	5.78
Y5	74.78	73.25
Y6	8.50	8.11

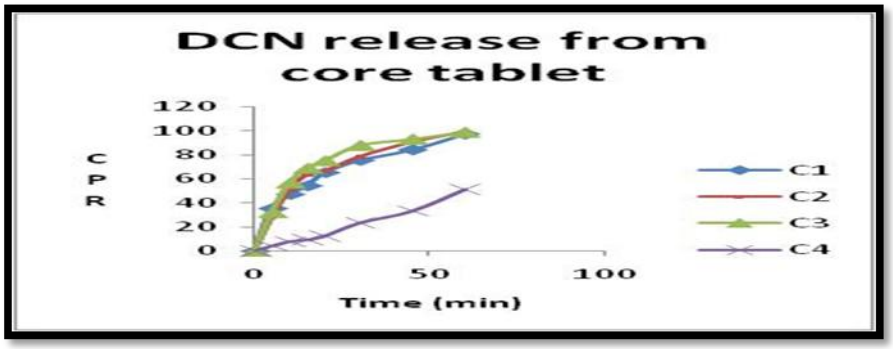

Figure 1: In vitro dissolution of core tablets

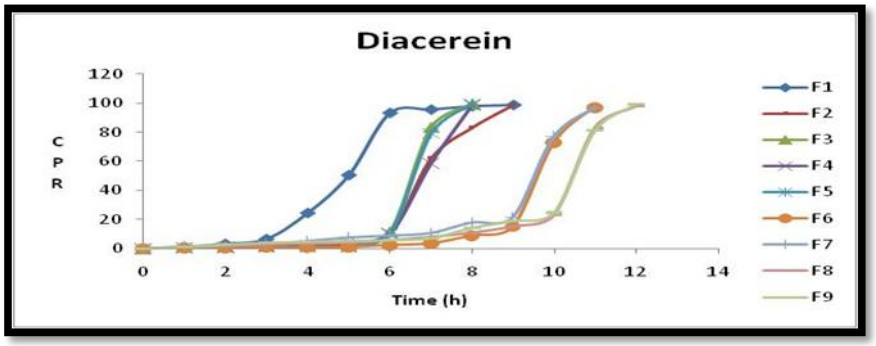

Figure 2: In vitro dissolution profile of coated tablets

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