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Design and Development of Controlled Release Tablets of Deflazocort.

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ABSTRACT

The present investigation was undertaken to fabricate and evaluate the controlled release formulation of deflazocort matrix tablets by wet granulation technique. The matrix tablets were developed with 1:0.5, 1:1, 1:1.5, 1:2 ratios of drug:HPMC/HPC/HEC to determine the affect of polymer and its concentration on the release rate of Deflazacort. All the formulated preparations were subjected to weight variation, hardness, friability and drug content. All tablets complied I. P. weight variation test requirement. The rate of drug release from these matrix tablets followed zero order kinetics and mechanism of drug release was governed by peppas model. The exponential coefficient(n) values were found to be in between 1.0070 to 1.0544 indicating supercase –II transport diffusion mechanisam. These results indicated that the release rate was found to be decrease with increase in concentration of polymer. There was no change or shifting of characteristic peaks in drug loaded matrix tablets suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations. The Deflazacort matrix tablets were stored at 25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months and evaluated periodically at the regular interval of every month. Thus the drug release from Deflazacort matrix tablets was found be quite stable. Among the three polymers , controlled release matrix tablets prepared with HPMC at 1:2 ratio shown controlled release for a period of 12 hours.

Keywords: Deflazacort, HPMC, HPC, HEC, zero order, controlled release.

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INTRODUCTION

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. Drug release from these systems should be at a rate that is desirable, predictable and reproducible [1]. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Other advantages of using controlled release drug delivery systems include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug and increased patient compliance [2]. Many steroids, to be specific glucocorticoid, reduce inflammation or swelling by binding to glucocorticoid receptors. These drugs are often referred to as corticosteroids. Corticosteroids are involved in a wide range of physiological processes, including stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior [3]. Glucocorticoids such as cortisol control carbohydrate, fat and protein metabolism and are anti-inflammatory by preventing phospholipids release, decreasing eosinophil action and a number of other mechanisms. Deflazacort is a glucocorticoid with anti-inflammatory and immunosuppressive activities. It is administered in a dose of 6 mg for 3 to 4 times in a day. In acute conditions a dose as high as 120 mg is administered in a day. Deflazacort is having a half life of 1.1 -1.9 hrs. When administered chronically it is likely to cause gastrointestinal, ophthalmic and neuromuscular disturbances [4]. Administering deflazacort has to be done carefully in chronic therapy. In this regard, a controlled release dosage form of deflazacort is useful as it reduces the frequency of administration, improving the patient compliance and also avoids the side effects.

MATERIALES AND METHODS

Deflazacort was obtained as a gift sample from Avyukt Pharmaceuticals, Bengaluru. Hydroxy propyl methyl cellulose, Hydroxy propyl cellulose, Hydroxy ethyl cellulose were procured from Ronas Chemicals Ind. Co., Ltd,Mumbai. All other chemical reagents were of analytical grade. All materials were used as received.

Preparation of controlled release matrix tablets of Deflazacort

All the formulations were prepared according to Table no 1 . The tablets are prepared by wet granulation method. Deflazacort and polymer were triturated well and allowed to pass through sieve no. 80 and mixed thoroughly, the powders were granulated using povidone solution. The cohesive mass obtained was passed through sieve no. 12, and the granules were dried at 40 ^{O}C for 2 hours. The dried granules were reseived thorough sieve no.16 and are mixed with talc and magnesium stearate. The granules were punched to get tablets of average weight 150 mg using single punch tableting machine [5].

Table 1: Composition of Deflazacort controlled release matrix tablets

Ingredients (mg/tab)	CF1	CF2	CF3	CF4	CF 5	CF 6	CF 7	CF8	CF9	CF10	CF11	CF 12
Deflazacort	30	30	30	30	30	30	30	30	30	30	30	30
HPMC	15	30	45	60								
HEC					15	30	45	60				
HPC									15	30	45	60
Povidone K 30	5	5	5	5	5	5	5	5	5	5	5	5
MCC PH 101	95	80	65	50	85	85	85	85	85	85	85	85
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total tablet Weight	150	150	150	150	150	150	150	150	150	150	150	150

Evaluation of powder blend

The powder blend was evaluated for flow properties such as angle of repose,bulk density, tapped density, compressibility index, and Hausner ratio [6].

Evaluation of tablets

Hardness

Hardness of tablet is determined by using the Monsanto hardness tester [7]. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. As the spring was compressed a pointer rides a long a gauge in the barrel to indicate the force. The hardness was measured in terms of Kg/cm^2.

Weight variation

Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula [7].

$$\%\ Weight\ variation = \frac{Average\ weight - individual\ weight}{Average\ weight} \text{X } 100$$

Friability

The Roche friabilitor apparatus was used to determine the friability of the tablets. About 44 tablets were selected, dedusted and weighed. Then they were placed in a drum and rotated at 25 rpm for 4 minutes. Then tablets were dedusted to remove dust and reweighed. The percentage friability was calculated by the formula [7].

$$\%\ FRIABILITY\ = \frac{INITIAL\ WEIGHT - \ FINAL\ WEIGHT}{INITIAL\ WEIGHT} \text{ X } 100$$

Drug content

Twenty tablets were collected and powdered. The powder equivalent to 143.5 mg of drug was weighed accurately, dissolved in 100ml of deaerated water. The solution was filtered, suitably diluted and an aliquot was analyzed at 224nm by using uv-spectrophotometer [8].

***In-vitro* dissolution test**

The release of Deflazacort from the tablet was studied using USP – Type II paddle apparatus. Drug release profile was carried out in 900 ml of deaerated water maintained at 37 ± 0.5°C temperature at 50 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples were analyzed at 265 nm by UV spectrophotometer [8].

Dissolution kinetics

The rate and the mechanism of release of Deflazacort from the prepared matrix tablets were analyzed by fitting the dissolution data into [9], zero-order equation, $Q=Q_0 - k_0t$(1),where Q is the amount of drug released at time t, and k_0 is the release rate. First order equation, $Ln\ Q=Ln\ Q_0 - k_1t$ (2), where k_1 is the release rate constant and Higuchi's equation, $Q= k_2t^{1/2}$ (3) where Q is the amount of the drug released at time t and k_2 is the diffusion rate constant. The dissolution data was further analyzed to define the mechanism of release by applying the dissolution data following the empirical equation , $M_1/M_\alpha=Kt^n$ (4), where Mt/M_α is the fraction of drug released at time t. K is a constant and n characterizes the mechanism of drug release from the formulations during dissolution process.

Fourier Transform Infra-Red (FT-IR) spectral analysis

Infrared spectra of pure drug, alone, HPMC and optimized tablet formulation were recorded using Fourier–Transformed Infrared (FT–IR) spectroscopy, Perkin Elmer, spectrum-100, Japan[10]. Potassium bromide was used as background and the scanning range was 400 to $4000cm^{-1}$.

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Stability studies of controlled release matrix tablets of Deflazacort

The optimized controlled release matrix tablets of Deflazacort tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 25±5°C/60% RH and 40±5°C/75% RH respectively for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated[11].

RESULTS AND DISCUSSION

The Deflazacort controlled release matrix tablets were prepared by wet granulation method. The matrix tablets were developed with 1:0.5, 1:1, 1:1.5, 1:2 ratios of drug:HPMC/HPC/HEC to determine the affect of polymer and its concentration on the release rate of Deflazacort. The granules were evaluated for angle of repose, bulk density and carr's index. The bulk density for all the formulations was ranged from 0.419 to 0.478. The angle of repose for all the formulations was ranged from $23^{0}12^{1}$-29^{0} 10^{1}. The carr's index for all the formulations was ranged from 13.94– 17.86%. The value of bulk density indicates good packing characters. The value of angle of repose (25^{0}-30^{0}) for all the formulations indicates good flow property. The values of carr's index (12-18%) indicates free flowing material.

All the formulated preparations were subjected to weight variation, hardness, friability and drug content. All tablets complied I. P. weight variation test requirement. The hardness was found to be in between 4 - 5 kg. The tablets satisfied USP friability requirement, as the % friability values are less than 1%. The percent drug content was found to be within 98 - 102% of the labeled amount and hence complied drug content requirement.The matrix tablets were subjected to *In-vitro* release studies by employing deareated water and the data was shown in Figure 1-3. When the amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these matrix tablets followed zero order kinetics. To ascertain the mechanism of drug release from various matrix tablets plot of log %Released vs log time (peppas plots) were drawn. The plots were found to be linear with all matrix tablets. Release Kinetics of Deflazacort matrix tablets were shown in Table 2. The exponential coefficient(n) values were found to be inbetween 1.0070 to 1.0544 indicating supercase –II transport diffusion mechanisam. These results indicated that the release rate was found to be decrease with increase in concentration of polymer.

The prominent IR peaks of drug,excipients and optimized formulations weres hown in figures 4-6.IR spectra of Deflazacort showed characteristic peaks at 3294. 04 cm^{-1} (Broad intermolecular hydrogen bond,O-H stretch), 2970.01 cm^{-1} (Aliphatic C-H stretch), 1705.84 cm^{-1} (C=O of carboxylic group), 1435.35 cm^{-1} (C-N stretch), 1388.06 cm^{-1} (in plane O-H bend), 1043.12 cm^{-1} (ring C-O-C stretch). The optimized matrix tablets showed characteristic absorption peaks of Deflazacort at 3295.83 cm^{-1} (Broad intermolecular hydrogen bond,O-H stretch), 2969.82 cm^{-1} (Aliphatic C-H stretch), 1706.36 cm^{-1} (C=O of carboxylic group), 1436.30 cm^{-1} (C-N stretch), 1388.38 cm^{-1} (in plane O-H bend), 1043.39 cm^{-1} (ring C-O-C stretch). There was no change or shifting of characteristic peaks in drug loaded matrix tablets suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations.

The Deflazacort matrix tablets were stored at 25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months. Drug release from Deflazacort matrix tablets before and after storage under varying conditions were evaluated periodically at the regular interval of every month. The results indicated that the drug release from the Deflazacort matrix tablets was not changed significantly when stored at varying conditions and the release data was given in table 3. Thus the drug release from Deflazacort matrix tablets was found be quite stable.

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Table 2: Micromeritic properties of formulation blend of Deflazacort controlled release matrix tablets

Formulation	Evaluation parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (θ)
CF_1	0.419 ± 0.018	0.503 ± 0.20	14.16 ± 0.59	1.20 ± 0.012	28.04 ± 0.12
CF_2	0.429 ± 0.021	0.507 ±0.025	14.93 ± 0.46	1.18 ± 0.019	28.96 ± 0.17
CF_3	0.442 ± 0.023	0.511 ± 0.031	14.24 ± 0.51	1.18 ± 0.013	29.02 ± 0.18
CF_4	0.477 ± 0.019	0.571 ± 0.021	14.67 ± 0.44	1.16 ± 0.012	29.31 ± 0.15
CF_5	0.439 ± 0.018	0.512 ± 0.026	14.24 ± 0.71	1.16 ± 0.011	24.02 ± 0.22
CF_6	0.445 ± 0.011	0.522 ± 0.019	13.94 ± 0.52	1.17 ± 0.08	25.22 ± 0.16
CF_7	0.478 ± 0.017	0.580 ± 0.023	17.58 ± 0.45	1.21 ± 0.010	27.36 ± 0.15
CF_8	0.496 ± 0.015	0.594 ± 0.020	16.49 ± 0.56	1.19 ± 0.14	28.85 ± 0.18
CF_9	0.426 ± 0.016	0.502 ±0.021	15.13 ±0.57	1.17 ±0.010	23.12 ± 0.16
CF_{10}	0.452 ±0.019	0.543 ±0.023	16.75 ± 0.53	1.20 ±0.012	27.46 ± 0.13
CF_{11}	0.469 ± 0.021	0.571± 0.022	17.86 ±0.46	1.19 ± 0.013	28.12 ±0.12
CF_{12}	0.478 ±0.023	0.580±0.018	17.58 ±0.49	1.21 ±0.09	29.30 ± 0.18

Table 3: *In-vitro* disssolution kinetics parameters of Deflazacort controlled release matrix tablets

Formulation	Correlation coefficient				Release kinetics			Diffusion Exponent value(n)
	Zero order	First order	Higuchi	Peppas	K_o (mg/hr)	T_{50} (hr)	T_{90} (hr)	
CF1	0.9999	0.9433	0.9877	0.9999	5.02	2.98	5.38	1.046
CF2	0.9999	0.9340	0.9879	0.9999	3.73	4.02	7.23	1.003
CF3	0.9998	0.9254	0.9877	0.9998	3.03	4.95	8.91	1.019
CF4	0.9997	0.9289	0.9862	0.9995	2.49	6.02	10.84	1.018
CF5	0.9998	0.9405	0.9883	0.9992	4.98	3.01	5.42	1.0212
CF6	0.9999	0.9396	0.9865	0.9999	3.98	3.76	6.78	1.0181
C F7	0.9997	0.9266	0.9860	0.9995	3.13	4.79	8.62	1.0188
C F8	0.9996	0.9233	0.9864	0.9992	2.74	5.47	9.85	1.0245
CF9	0.9991	0.9383	0.9901	0.9991	5.75	2.60	4.69	1.0368
CF10	0.9999	0.9369	0.9877	0.9998	4.67	3.21	5.78	1.0101
C F11	0.9996	0.9346	0.9852	0.9998	3.52	4.26	7.67	1.0070
C F12	0.9985	0.9267	0.9819	0.9990	2.95	5.03	9.15	1.0142

Table: 4. Stability studies of best formulation according to ICH guide lines.

S.NO	Time (hrs.)	% drug release (mg)						
		Initial	25±5°C/60% RH			40±5°C/75% RH		
			1st month	2nd month	3rd month	1st month	2nd month	3rd month
1	1	08.25	08.19	08.14	08.10	08.12	08.07	07.99
2	2	16.61	16.53	16.50	16.46	16.48	16.42	16.38
3	3	25.02	24.90	24.86	24.81	24.84	24.78	24.73
4	4	33.04	32.96	32.91	32.87	32.88	32.85	32.81
5	5	41.94	41.91	41.87	41.84	41.86	41.82	41.77
6	6	49.76	49.67	49.63	49.60	49.61	49.57	49.53
7	7	58.51	58.50	58.45	58.41	58.42	58.39	58.36
8	8	66.82	66.77	66.72	66.69	66.71	66.68	66.63
9	9	74.17	74.12	74.10	74.07	74.09	74.05	73.99
10	10	82.90	82.79	82.75	82.70	82.73	82.69	82.65
11	11	91.07	91.02	91.00	90.96	90.98	90.94	90.91
12	12	99.31	99.24	99.18	99.15	99.16	99.11	99.05

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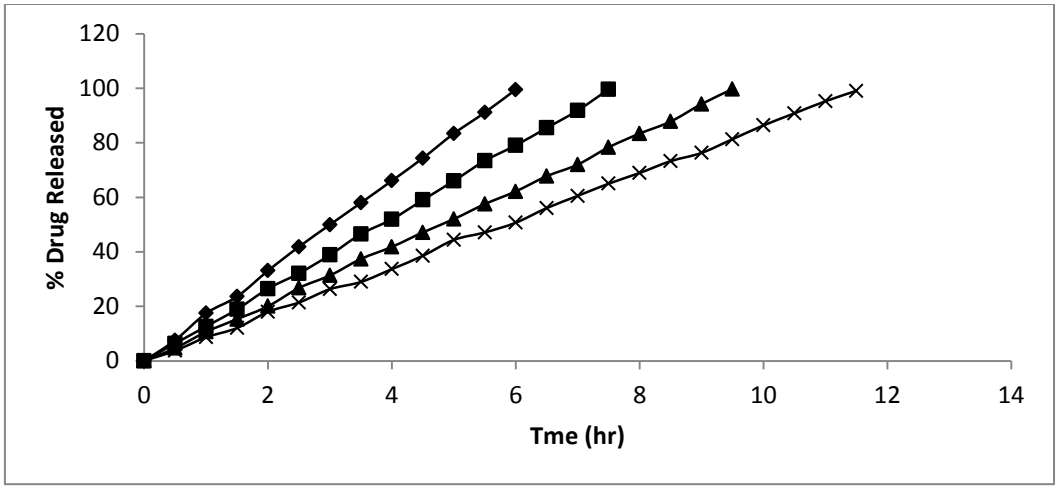
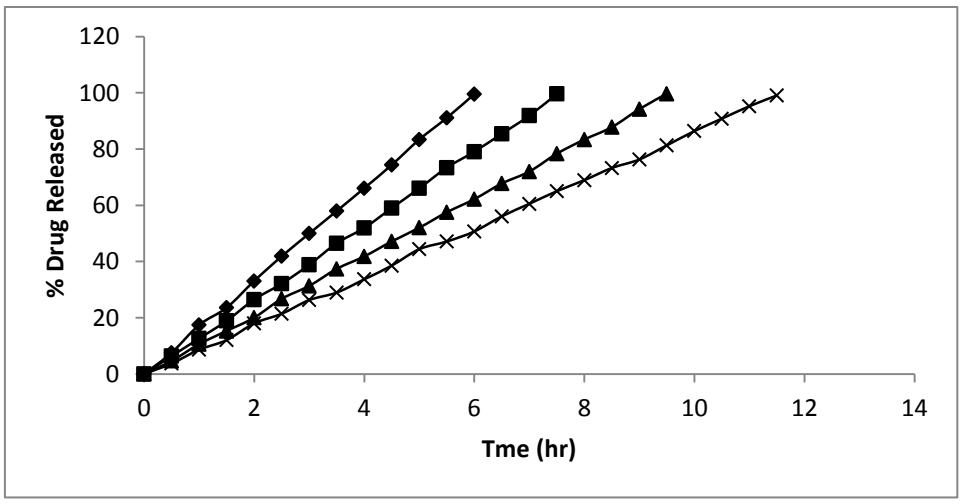
Figure 1: *In-vitro* drug release profile plot of Deflazacort controlled release matrix tablets prepared with HPMC in different ratios



(-■-)Deflazacort matrix tablets prepared with HPMC in 1:0.5 ratio
(-♦-)Deflazacort matrix tablets prepared with HPMC in 1:1ratio
(-▲-)Deflazacort matrix tablets prepared with HPMC in 1:1.5 ratio
(-×-) Deflazacort matrix tablets prepared with HPMC in 1:2ratio

Figure 2: *In-vitro* drug release profile plot of Deflazacort controlled release matrix tablets prepared with HEC in different ratios



(-■-)Deflazacort matrix tablets prepared with HEC in 1:0.5 ratio
(-♦-)Deflazacort matrix tablets prepared with HEC in 1:1ratio
(-▲-)Deflazacort matrix tablets prepared with HEC in 1:1.5 ratio
(-×-) Deflazacort matrix tablets prepared with HEC in 1:2ratio

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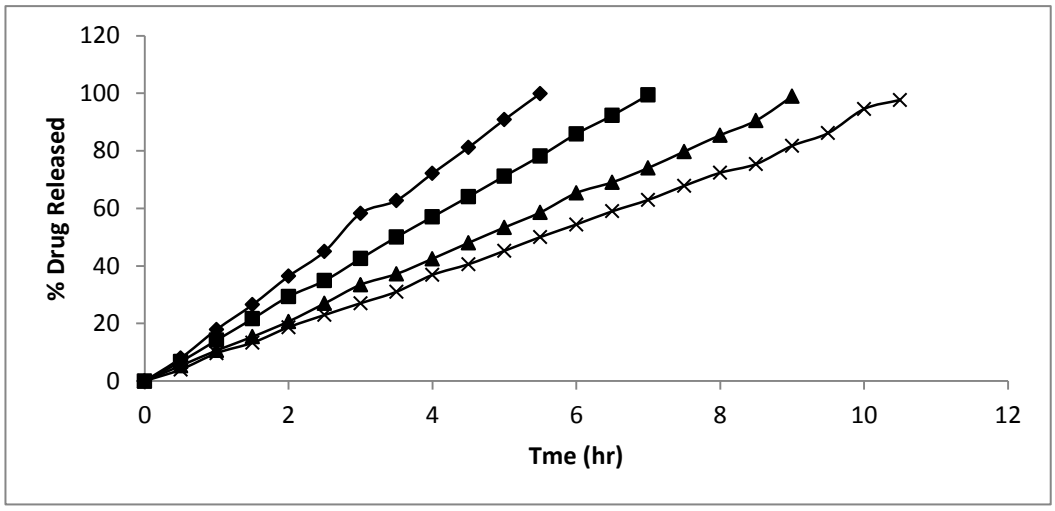
Figure 3: *In-vitro* drug release profile plot of Deflazacort controlled release matrix tablets prepared with HPC in different ratios



(-■-)Deflazacort matrix tablets prepared with HPC in 1:0.5 ratio
(-♦-)Deflazacort matrix tablets prepared with HPC in 1:1ratio
(-▲-)Deflazacort matrix tablets prepared with HPC in 1:1.5 ratio
(-×-) Deflazacort matrix tablets prepared with HPC in 1:2ratio

Figure 4: FTIR of pure Deflazacort

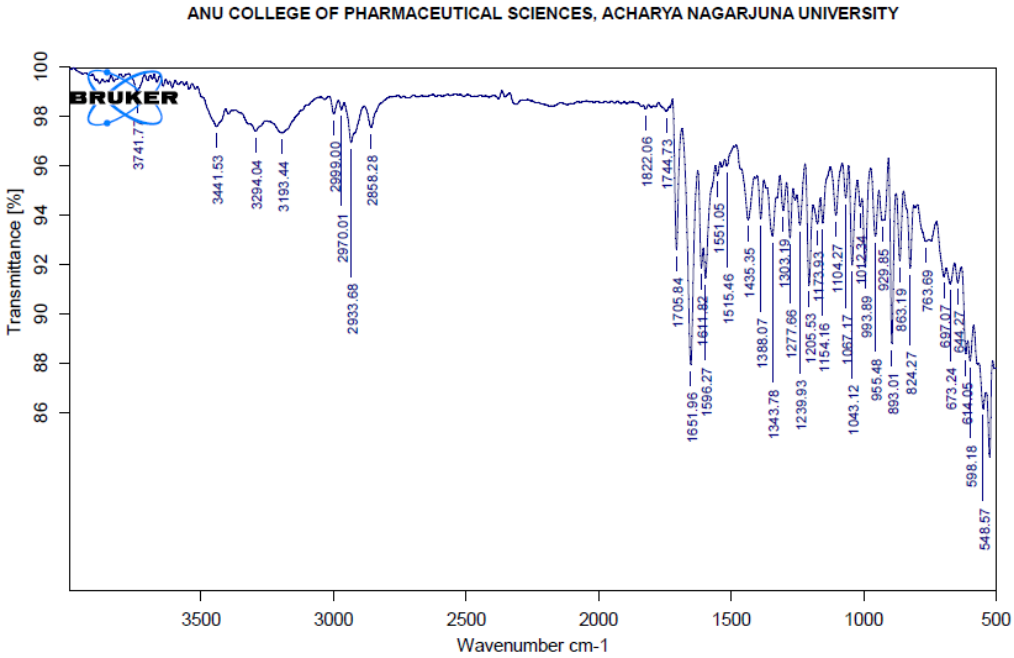


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Figure 5: FTIR of HPMC

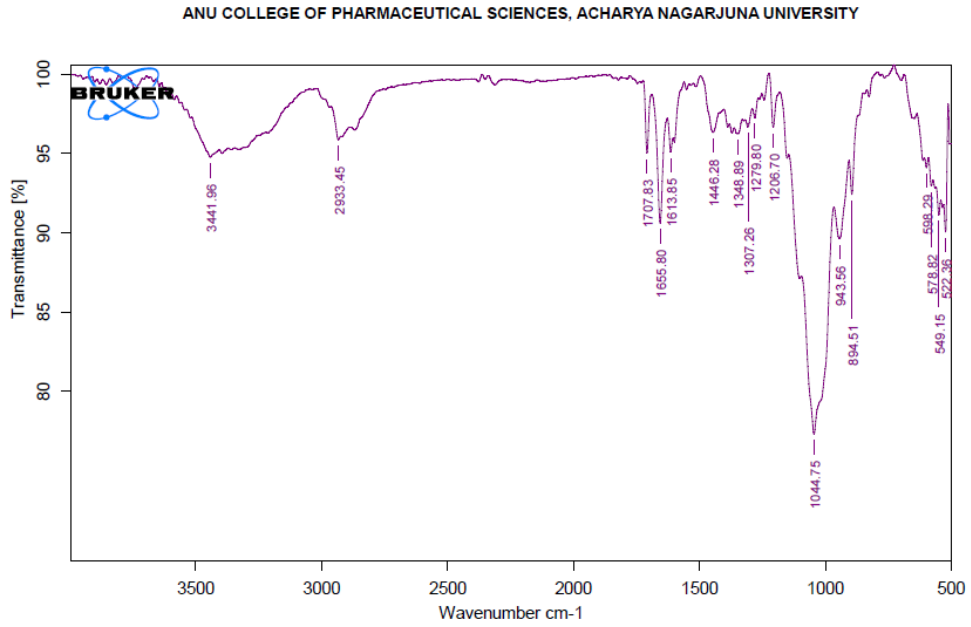
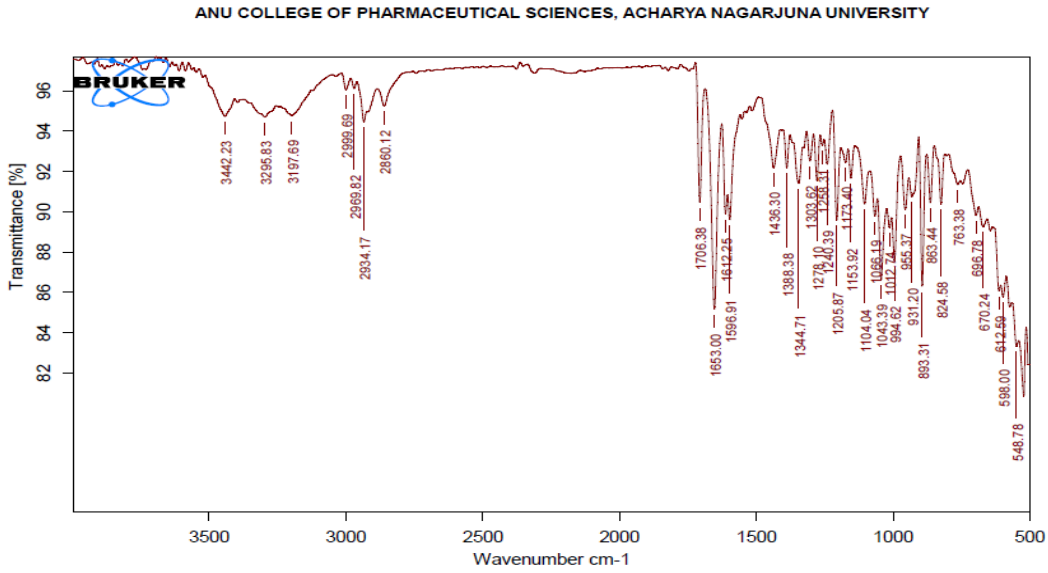


Figure 6: FTIR of optimized formulation



CONCLUSION

The Deflazacort controlled release matrix tablets release rate was found to be decreased with increase in concentration of polymer.Among the three polymers , controlled release matrix tablets prepared with HPMC shown slow release compared with other polymers. Deflazacort release from the matrix tablets formulated employing HPMC at 1:2 ratio shown controlled release for a period of 12 hours.

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