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Research

Formulation Development And In Vitro Characterisation Of Deflazacort Extended Release Matrix Tablets

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Abstract

The aim of the present study was to develop Extended release formulation of Deflazacort to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC K100M, HPMC (K4M) and Carbopol 71G were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 98.85% in 12 hours. It contains the HPMC (K4M) as Extended release material. It followed peppas release kinetics mechanism.

Keywords: Deflazacort, HPMC K100M, HPMC (K4M), Carbopol 71 G and Extended release system.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[1,2]

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug.[3] If one were to develop an ideal drugdelivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes orhypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.[4]

There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly

related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.[5,6]

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.[7]

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results.[8,9] Extended release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period.[10] The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the caregiver as well.[11]

MATERIALS

Deflazacort-Procured From Neon Laboratories Ltd, Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K100M-Merck Specialities Pvt Ltd, Mumbai, India, HPMC (K4M)- Merck Specialities Pvt Ltd, Mumbai, India, Carbopol 71 G-Merck Specialities Pvt Ltd, Mumbai, India, PVP K 30-Merck Specialities Pvt Ltd, Mumbai, India, MCC102-Merck Specialities Pvt Ltd, Mumbai, India, Mg. stearate-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development:

a) Determination of absorption maxima

100mg of Deflazacort pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100 ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve

100mg of Deflazacort pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 1, 2, 3, 4 and 5 ml of solution and make up to 10ml with 0.1N Hcl to obtain 10, 20, 30, 40 and 50 µg/ml of Deflazacort per ml of solution. The absorbance of the above dilutions was measured at 244nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Formulation development of Extended release Tablets:

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table 7.1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Deflazacort.

Procedure:

1) Deflazacort and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 1: Formulation of Extended release tablets

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Deflazacort	6	6	6	6	6	6	6	6	6
HPMC K100M	4	8	12	-	-	-	-	-	-

HPMC (K4M)	-	-	-	4	8	12	-	-	-
Carbopol 71 G	-	-	-	-	-	-	4	8	12
PVP K 30	10	10	10	10	10	10	10	10	10
MCC102	76	72	68	76	72	68	76	72	68
Mg. stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total Weight (mg)	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION

The present work was designed to developing Extended tablets of Deflazacort using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Deflazacort in 0.1N HCl

The scanning of the 10µg/ml solution of Deflazacort in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 244 nm. The standard concentrations of Deflazacort (10-50 µg/mL) prepared in 0.1N HCl showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

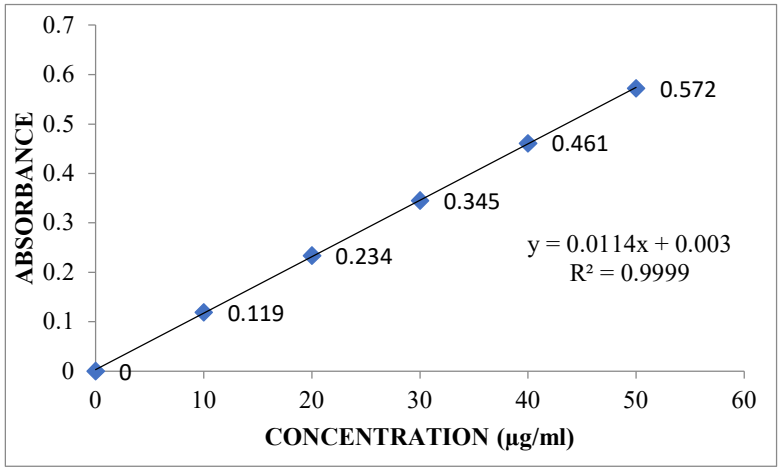

Fig 1: Calibration curve of Deflazacort in 0.1 N HCl at 244nm

Standard Curve of Deflazacort in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Deflazacort in the ultraviolet range (200-400nm) against 6.8 pH phosphate buffer as blank gave the λ_{max} as 244nm. The standard concentrations of Deflazacort (10-50µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

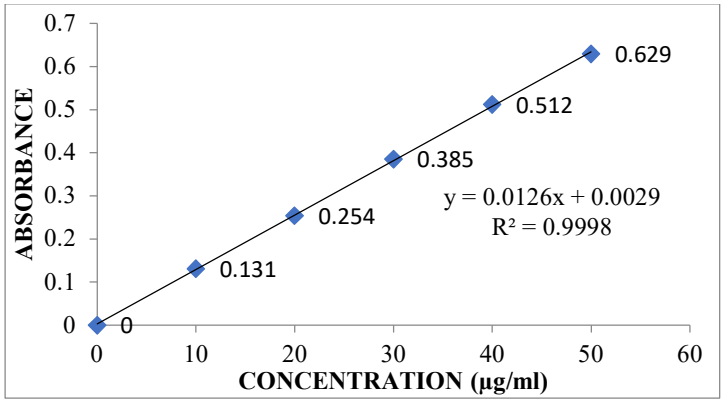

Fig 2: Calibration of Deflazacort in Phosphate buffer pH 6.8

EVALUATION PARAMETERS

Pre-compression parameters

Table 2: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)	Hausner's Ratio
F1	25.01	0. 59	0.57	14.03	1.16
F2	26.8	0. 46	0.67	16.41	1.19
F3	27.7	0. 32	0. 54	18.75	1.23
F4	25.33	0.54	0.64	15.62	1.18
F5	25.24	0.52	0.65	18.46	1.22
F6	28.12	0. 46	0. 56	15.15	1.17
F7	27.08	0.58	0.69	15.94	1.18
F8	25.12	0.48	0.67	15.78	1.18
F9	26.45	0.54	0.65	16.92	1.25

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25.01 to 28.12; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.32-0.59 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54-0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14.03 to 18.75 which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 1.16 to 1.25 indicating the powder has good flow properties.

Post Compression Parameters For tablets

Table 3: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	98.62	5.9	0.52	3.16	96.35
F2	96.35	**5.1**	0.34	3.56	99.61
F3	99.21	5.6	0.62	3.41	98.52
F4	97.49	5.2	0.41	3.22	97.42
F5	95.32	5.8	0.26	3.61	97.12
F6	99.58	5.1	0.39	3.25	99.33
F7	97.96	5.7	0.65	3.42	98.64
F8	99.67	5.9	0.73	3.13	95.78
F9	98.32	5.5	0.15	3.24	96.41

Weight variation and thickness

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.4. The average tablet weight of all the formulations was found to be between 95.32 to 99.67**.** The maximum allowed percentage weight variation for tablets weighing >100.5 mg is 1.5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.13 to 3.61.

Hardness and friability

All the formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown in table 8.4. The average hardness for all the formulations was found to be between **(**5.1 to 5.9**)** Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using roche friabilator and the results were shown in table 8.4. The average percentage friability for all the formulations was between 0.15 and 0.73, which was found to be within the limit.

Drug content

All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 7.4. The drug content values for all the formulations were found to be in the range of **(**95.78 to 99.61**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In Vitro* Drug Release Studies**

The formulations prepared with different natural polymers by wet granulation method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 4: Dissolution Data of Deflazacort Tablets Prepared With HPMC K100M In Different Concentrations

TIME	CUMULATIVE PERCENT DRUG RELEASED								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	25.32	20.04	18.63	15.17	13.90	10.49	20.56	17.58	10.62
1	34.53	27.56	21.63	22.12	19.45	16.63	26.45	23.20	15.28
2	49.90	34.35	28.52	36.64	25.02	27.55	31.23	27.35	20.95
3	54.96	43.52	31.31	42.20	31.31	33.21	40.54	34.14	25.51
4	59.14	48.75	38.25	48.56	37.82	40.96	49.73	39.75	29.32
5	62.85	52.54	45.78	55.43	43.47	45.11	56.46	43.09	33.96
6	73.92	59.26	50.17	58.01	50.74	55.28	58.12	46.16	39.78
7	80.41	65.95	57.79	67.57	54.05	61.71	62.59	55.75	44.35
8	89.61	70.14	62.27	73.91	57.93	67.34	71.41	60.11	50.62
9	93.17	73.45	69.64	79.41	63.26	74.98	78.98	64.67	56.43
10	96.33	81.57	74.87	83.72	75.45	80.74	83.24	68.34	60.02
11		98.18	84.10	86.02	80.36	86.12	89.72	76.40	64.10
12			98.64	90.14	95.47	98.85	90.14	85.18	70.16

From the dissolution data it was evident that the formulations prepared with HPMC K100M as polymer were retarded the drug release more than 12 hours.

Whereas the formulations prepared with higher concentration of HPMC (K4M) retarded the drug release up to 12 hours in the concentration 12 mg. In lower concentrations the polymer was unable to retard the drug release.

The formulations prepared with Carbopol 71G showed very less retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that F6 formulation was considered as optimised formulation because good drug release (98.85%) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Deflazacort release from Extended tablets. The data was fitted into various kinetic models such as Zero, First order kinetics; Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table

Table 5: Release kinetics data for optimised formulation (F6)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
10.49	**0.5**	0.707	1.021	-0.301	1.952	20.980	0.0953	-0.979	89.51	4.642	4.473	0.168
16.63	**1**	1.000	1.221	0.000	1.921	16.630	0.0601	-0.779	83.37	4.642	4.369	0.273

27.55	**2**	1.414	1.440	0.301	1.860	13.775	0.0363	-0.560	72.45	4.642	4.169	0.473
33.21	**3**	1.732	1.521	0.477	1.825	11.070	0.0301	-0.479	66.79	4.642	4.057	0.584
40.96	**4**	2.000	1.612	0.602	1.771	10.240	0.0244	-0.388	59.04	4.642	3.894	0.748
45.11	**5**	2.236	1.654	0.699	1.739	9.022	0.0222	-0.346	54.89	4.642	3.800	0.841
55.28	**6**	2.449	1.743	0.778	1.651	9.213	0.0181	-0.257	44.72	4.642	3.550	1.092
61.71	**7**	2.646	1.790	0.845	1.583	8.816	0.0162	-0.210	38.29	4.642	3.371	1.271
67.34	**8**	2.828	1.828	0.903	1.514	8.418	0.0149	-0.172	32.66	4.642	3.196	1.445
74.98	**9**	3.000	1.875	0.954	1.398	8.331	0.0133	-0.125	25.02	4.642	2.925	1.717
80.74	**10**	3.162	1.907	1.000	1.285	8.074	0.0124	-0.093	19.26	4.642	2.681	1.961
86.12	**11**	3.317	1.935	1.041	1.142	7.829	0.0116	-0.065	13.88	4.642	2.403	2.238
98.85	**12**	3.464	1.995	1.079	0.061	8.238	0.0101	-0.005	1.15	4.642	1.048	3.594

Drug and Excipient Compatability Studies

FTIR study

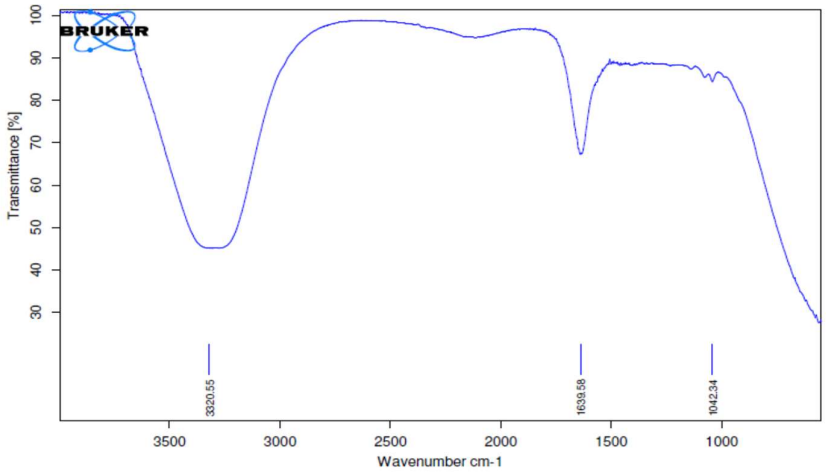

Fig 3: Ftir Graph Of Pure Drug Of Deflazacort

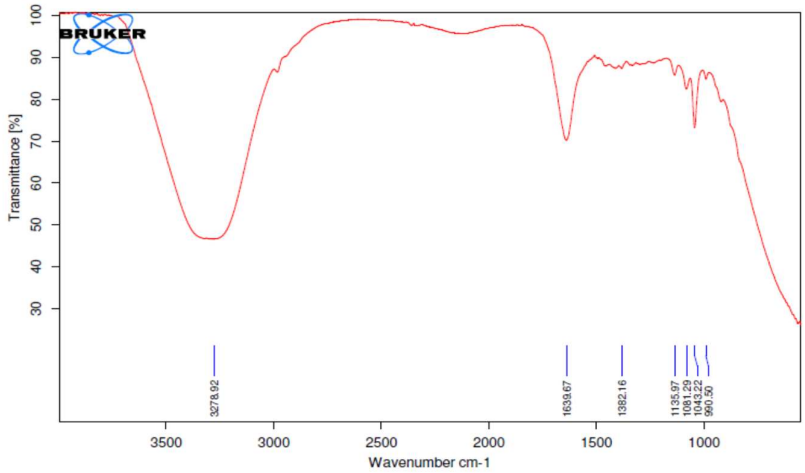

Fig 4: Ftir Graph Of Pure Drug Of Deflazacort Optimised Graph

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION

The present study concludes that Extended drug delivery of Deflazacort tablets can be a good way to prolong duration of action of drug by reducing the frequency of dosing of Deflazacort. Present study concludes

that extended drug delivery system should be a suitable method for Deflazacort administration. The optimised formulation was found to be F6 formulation.

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