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Research Article

FORMULATION AND IN-VITRO EVALUATION OF DEFLAZACORT PULSATILE DRUG DELIVERY

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ABSTRACT

The purpose of the present study was to design and evaluate an Oral, site specific, Pulsatile drug delivery system containing Deflazacort as a model drug, which can be time dependent manner, to modulate the drug level in synchrony is a member of the drug class known as corticosteroid prodrug with an active metabolite. It is used for treatment of Duchenne Muscular Dystrophy. The basic design consists of an insoluble hard gelatin capsule body, filled with powder blend and sealed with a hydrogel plug. The powder blend containing Deflazacort, Xanthan gum, Guar Gum, Lycoat, Ludiflash, Croscarmellose sodium, MCC and talc was prepared and evaluated for flow properties and FTIR studies. From the obtained results, F12 powder blend formulation was selected for further fabrication of pulsatile capsules. Hydrogel plug was formulated in a lone and in combination of hydrophobic polymer like ethyl cellulose with hydrophilic polymers like Ethyl Cellulose: HPMC K15M in 1:1, 1:2, and 2:1 ratio to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The prepared formulations were evaluated for drug content, weight variation and Invitro release studies. FTIR studies confirmed that there was no interaction between drug and polymers and Invitro release studies of pulsatile device revealed that increasing hydrophilic polymer content resulted in delayed release of Deflazacort from the pulsincap after a predetermined lag time of 6hrs. Based on invitro studies performed, P3F12 was found to be optimized formulation.

Key words: Pulsatile system; time dependent delivery; Deflazacort; Chrono pharmaceutics; In vitro release studies.

INTRODUCTION

Compared to traditional instant release systems, oral control medication delivery has several benefits. These systems are made to provide the medication at a regulated and predefined pace, preserving its therapeutic concentration in the bloodstream for extended periods of time.[1]

The idea behind time-controlled drug delivery systems is that the medicine is released at a predefined rate in order to maximize therapeutic impact and minimize harmful effect.[2] Two delivery systems for chronotherapeutics have been created to offer the most effective treatment plans, with the main goal being to guarantee the highest possible drug concentration at the moment of attack.[3]

The goal of the current project is to create a medicine delivery system that consistently delivers the necessary dosage at the appropriate moment. This issue is resolved by a pulsatile drug delivery method; a single tablet taken before bed delivers the medication early in the morning, protecting against cardiovascular problems. The most prevalent chronic ailment in medicine is high blood pressure, sometimes known as hypertension.[4-7]

Deflazacort is a prednisolone oxazoline derivative.[8] Deflazacort, a glucocorticoid prodrug, is converted into 21-desacetyldeflazacort, an active form. Deflazacort reduces the production of cytokines by preventing CD 4+ lymphocytes from growing in the culture. The decrease in CD4+ cells and subsequent rise in CD8+ cells exerts immunosuppressive and anti-inflammatory effects.[9] Deflazacort is thought to stimulate muscle cell proliferation and decrease muscle breakdown, which results in an increase in total muscle mass, however the precise

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mechanism by which it increases muscle potency and usefulness in people with Duchenne muscular dystrophy is yet understood. The capacity of deflazacort to alter transcription may have an impact on dystrophin protein and other proteins in a positive feedback loop with it.[10]

MATERIALS

Deflazacort procured from Joshi Agrochem Pharma Pvt. Ltd,Mumbai, Guar Gum, Lycoat, Hydrochloric acid from S d fine chemical Ltd, Mumbai, Microcrystalline cellulose, Talc from Loba chemie pvt.ltd, Ethyl Cellulose, XANTHAN GUM from Otto Chemicals, Mumbai, Magnesium stearate from Loba chemie pvt.ltd, Mumbai, Formaldehyde, Potassium permanganate from Qualigens fine chemicals, Mumbai, Potassium dihydrogen Phosphate from Qualigens fine chemicals, Mumbai

METHODOLOGY

PREFORMULATION STUDIES: [11-15]

Pre formulation testing is the first step in the rationale development of dosage forms of a drug substance. It is one of the important prerequisites in development of any drug delivery system. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Characterization of the drug is a very important step at the pre formulation phase of product development followed by studying the properties of the excipients and their compatibility. The overall objective of pre formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

The following are the various pre formulation studies:

Solubility: Solubility is defined as amount of substance that passes into solution to achieve a saturated solution at constant temperature and pressure. The solvents used are water and methanol. Solubility was determined by adding Deflazacort in small incremental amount to a test tube containing fixed quantity of different solvents. After each addition, the system was vigorously shaken and examined visually for any un dissolved solute particles.

Drug-Excipient compatibility studies:

To know the chemical compatibility of the drug spectroscopic technique that is FTIR studies were used. The FTIR spectra were recorded using an IR spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The IR spectra for the samples were obtained by KBr disk method. The samples were prepared by grinding the pure drug, polymer and physical mixture with KBr separately. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm^{-1}. FTIR study was carried on Deflazacort ,physical mixture of Deflazacort and for the best formulation.

UV spectroscopy:

The main step in pre formulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in ultraviolet wavelengths (190-400nm), since they are generally aromatic or contain double bonds. 10 mg of Deflazacort was accurately weighed on an electronic balance and dissolved in 2 ml methanol and volume was made up to 10ml with buffer which gives 1000µg/mL (stock solution-I). From the stock solution I, 1 ml is pippetted out then transfer to 10mL volumetric flask and volume was made up to 10mL with pH 7.4 phosphate buffer which gives 100 µg/mL. From 100 µg/mL, 1mL was pippeted out and volume was made upto 10ml with buffer to give 10 µg/mL and scanned on a UV scanner between 2000-400nm. The maxima obtained in the graph were considered as λ_{max} for the Deflazacort in respective buffers.

Standard calibration curve for Deflazacort:

Deflazacort standard calibration curve was plotted in pH 7.4 phosphate buffer. Accurately weighed amount of 10 mg of drug was transferred into a 10 ml volumetric flask and the primary stock solution was prepared by making up volume to 10 ml with pH 7.4 phosphate buffer. This gives a solution having concentration of 1000 µg/mL of Deflazacort in stock solution. From this primary stock solution 1 ml was transferred into another 10 ml volumetric flask and made up to 10 ml with pH 7.4 phosphate buffer, from this secondary stock 0.3, 0.6, 0.9, 1.2, 1.5, and 1.8ml was taken separately and made up to 10 ml with pH 1.2 buffer, to produce 3, 6, 9, 12, 15, and 18µg/ml solution respectively. The absorbance was measured at 247 nm using UV spectrophotometer. Similarly, Deflazacort standard graphs were plotted in pH 7.4 phosphate buffer by following the above procedure.

FLOW PROPERTIES OF API:

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve#20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

$$Db = m/Vo$$

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between the two tapped volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. . It is expressed in g/cc and is given by:

$$Dt = m/Vi$$

Angle of Repose (θ): This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

(Or)

$$\theta = \tan^{-1}(h/r)$$

Compressibility Index: The flow ability of powder can be evaluated by comparing the bulk density (Db) and tapped density (Dt) of powder and the rate at which it packed down. Compressibility index is calculated by:

$$\text{Compressibility index (\%)} = Dt - Db/Dt \times 100$$

Hausner's Ratio: It is the ratio of tapped density to the bulk density. It is given by:

$$\text{Hausner's ratio} = Dt / Db$$

PULSINCAP DESINGNING:

Designing or preparation of pulsincap capsules involves 3 steps:

1. Preparation of cross-linked gelatin capsule.
2. Preparation of powder blends for filling into capsules.
3. Formulation of pulsincap of Deflazacort.

PREPARATION OF CROSS-LINKED GELATIN CAPSULE:

Formaldehyde treatment:

About 100 hard gelatin capsules size '0' were taken. Their bodies were separated from the caps and placed on a wire mesh. The bodies which were placed on a wire mesh were spread as a single layer. 25 ml of 15% v/v of formaldehyde solution was prepared and placed in a desiccator. To this 5 g of potassium permanganate was added. The wire mesh containing the bodies of the capsules was kept on the top of desiccators' containing formaldehyde liquid at the bottom in equilibrium with its vapor and immediately the desiccators was tightly closed and sealed. The bodies of capsules were made to react with formaldehyde vapors by exposing them for varying periods of time viz., 2, 4, 6, 8, 10hrs. Then they were removed and kept on a filter paper and dried for 24 hrs to ensure completion of reaction between gelatin and formaldehyde vapors, afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated cap and stored in a polythene bag.

Use of Formaldehyde treatment:

The main aim of formaldehyde treatment was to modify the solubility of hard gelatin capsules. Cross-linking of gelatin molecules was achieved by exposing to formalin vapors. Cross-linking involves the reaction of amino groups in gelatin molecular chain with aldehyde groups of formaldehyde by a "Schiff's base condensation" so that the gelatin becomes water insoluble. Formaldehyde reacts with gelatin forming an irreversible complex. The primary amine group present in gelatin reacts with formaldehyde making it irreversibly bound. Potassium permanganate was added to formaldehyde solution so that formalin vapors were produced. When bodies of hard gelatin capsule were exposed to formaldehyde vapors for different periods of time in a closed desiccator, vapor gets equilibrated with formaldehyde liquid and therefore makes the gelatin water insoluble.

EVALUATION OF FORMALDEHYDE TREATED CAPSULES:

PHYSICAL TESTS:

Identification attributes: Suitable size capsules which are lockable were selected. Generally, the gelatin capsules when touched with wet hand they become sticky but upon formaldehyde treatment the capsules are observed for the stickiness.

Visual defects: Selected 100 treated capsules and observed for visual defects by physical observation and not more than 15-20 capsules must be distorted.

Dimensions: Variations in the dimensions between the formaldehyde treated and untreated capsules were studied. The length and diameter of the capsules were measured before and after formaldehyde treatment by using Vernier calipers.

OPTIMIZATION OF FORMALDEHYDE TREATED CAPSULE BODIES EXPOSED AT VARIOUS TIME INTERVALS VIZ., 2, 4, 6, 8, 10 hrs :-

Formaldehyde treated capsule bodies which were exposed at various time intervals viz., 2, 4, 6, 8, 10hrs were optimized by conducting Disintegration test. The test was performed on both untreated and treated capsules. Formaldehyde treated bodies joined with untreated caps and was tested for disintegration. Disintegration test was carried out by using Hiccon disintegration test apparatus. pH 1.2, pH 7.4 phosphate buffer, buffers were

used as medium and maintained at 37°C throughout the experiment. The time at which the capsules disintegrate are noted.

PREPARATION OF DEFLAZACORT TABLETS FOR FILLING INTO CAPSULES

All the ingredients were passed through # 60 mesh sieve separately. The drug & MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 4-5 kg/cm2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F12 (100 mg).

Table. 1 Formulae for preparation of blend for filling of Deflazacort Pulsincap

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Deflazacort	6	6	6	6	6	6	6	6	6	6	6	**6**
Croscarmellose sodium	3	6	12	15	--	--	--	--	--	--	--	**--**
Ludiflash	--	--	--	--	3	6	12	15	--	--	--	**--**
Lycoat	--	--	--	--	--	--	--	--	3	6	12	**15**
MCC	87	84	78	75	87	84	78	75	87	84	78	**75**
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	**2**
Talc	2	2	2	2	2	2	2	2	2	2	2	**2**
Total	100	100	100	100	100	100	100	100	100	100	100	**100**

FORMULATION OF PULSINCAP OF DEFLAZACORT:

The modified release pulsincaps containing 100mg of Deflazacort were prepared by using different excipients and polymers in varying ratios. The formaldehyde treated capsule bodies which were exposed to 6 hrs was optimized and chosen for the pulsincap formulation based on disintegration time. Optimized formulation of Deflazacort tablet was filed into the capsule body. For hydrogel plug formulation, the plug was prepared by using the combination of Ethyl Cellulose: HPMC K15M in varying ratios. Initially the total weight of the plug was taken as 100 mg alone and the ratio of hydrophobic & hydrophilic polymer as 1:1, 1:2, and 2:1.

Table.2 Pulsincap formulation

Ingredients	P1F12	P2F12	P3F12	P4F12	P5F12
Tablet	100mg	100mg	100mg	100mg	100mg
Ethyl Cellulose	100	100	200	100	-
HPMC K15M	100	200	100	-	100

Method of preparation of Pulsincap dosage form:

Preparation of powder blend:

Hard gelatin capsules of 'size 0' which were hardened with formaldehyde treatment for 6hrs were chosen for the formulation. The bodies and caps separated manually. Optimized formulation F12 was fitted at the bottom of the capsule body.

Preparation of Hydrogel plug:

- Plug was prepared as a compressed tablet and placed at the opening of capsule body. The capsule body was closed by a cap.
- Hydrogel plug was prepared by using different polymers like Ethyl Cellulose, HPMC K15M at different concentrations.
- A combination of hydrophobic and hydrophilic polymers was used viz., Ethyl Cellulose: HPMC K15M, in different ratios like 1:1, 1:2, and 2:1.
- A tight fit between the plug and impermeable capsule shell is essential to regulate water penetration into the capsule content and the drug release prior to complete erosion of plug material. Ideally plug should erode only from the surface exposed to the release medium.
- Plug ejection can be done by swelling on contact with aqueous fluids (or) pushing out by increased internal pressure (or) erosion (or) by enzyme degradation.

Capsule filling:

- Homogeneous mixture of drug and excipients were filled into the 6th hr formaldehyde treated capsule body manually by filling method.
- Then, hydrogel plug in the form of a tablet is placed above the mixture i.e., at the opening of capsule body
- The capsule body was closed by a cap.

Capsule sealing:

The joint of the treated capsule body and untreated cap of the capsules was sealed with a small amount of 1% Ethyl Cellulose ethanolic solution.

Evaluation of tablets:[16,17] Tablet Dimensions:

Thickness and diameter were measured using a calibrated vernier caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability test:

The friability of tablets was determined by using electro lab Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_I) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_F). The % friability was then calculated by –

$$\%F = 100\ (1-W_I/W_F)$$

% Friability of tablets less than 1% was considered acceptable.

Weight Variation Test:

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S.Pharmacopoeia. The following percentage deviation in weight variation was allowed.

Test for Content Uniformity:

Tablet containing 10mg of drug was dissolved in 50ml of pH 7.4 phosphate buffer in volumetric flask. The drug was allowed to dissolve in the solvent. The solution was filtered, 2ml of filtrate was taken in 10ml of volumetric flask and diluted up to mark with distilled water and analyzed spectrophotometrically at 247 nm . The concentration of Deflazacort was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch.

In vitro Disintegration Time:

Tablet was added to 900ml of distilled water at 37±0.5ºC. Time required for complete dispersion of a tablet was measured.

In vitro Dissolution Study:

In vitro dissolution of Deflazacort tablets was studied in USP XXII dissolution test apparatus 900ml pH pH 7.4 phosphate buffer (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 100RPM. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 247 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Deflazacort released was calculated and plotted against time.

EVALUATION OF PULSINCAP DOSAGE FORM:[101,102,103.]

In vitro release studies:

Dissolution study was carried out to measure the release rate of the drug from the pulsincap formulation. Invitro dissolution profile of each formulation was determined by employing USP I apparatus by rotating basket method. In order to stimulate the pH changes along GI tract 2 different dissolution media with pH 1.2, pH 7.4 phosphate buffer, 2 buffers were sequentially used, and therefore referred to as "Sequential pH change method". The dissolution media were maintained at a temperature of 37 ± 0.5ºC throughout the experiment and the speed of rotation of basket maintained at 100 rpm. 900ml of dissolution medium was used at each time. Deflazacort Pulsincaps was placed in basket in each dissolution vessel to prevent floating. While performing experiments, stimulated gastric fluid (SGF) pH 1.2 buffer was first used for 2 hrs (since the average gastric emptying time is 2hrs) and then removed and the fresh stimulated intestinal fluid (SIF) pH 7.4 phosphate buffer was added and used for remaining hours. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with the help of a syringe. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at same temperature. The filtered

samples were suitably diluted whenever necessary and assayed for Deflazacort by measuring absorbance at 247 nm , by UV absorption spectroscopy. %CDR was calculated over the sampling times.

Table.3 Dissolution specifications of Deflazacort

Vessel temperature	37 ± 0.5°C
Bath temperature	38 ± 0.5°C
Dissolution media	pH 1.2, pH 7.4 phosphate buffer
Volume of dissolution media	900 ml
Aliquot withdrawn	5 ml
Aliquot replaced	5 ml of the fresh solution
Dissolution apparatus	USP type I (Basket)
Speed	100RPM

RELEASE KINETICS:

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient(R) value in various models. The models with high 'R-value is considered as the best fit on the release data.

Various mathematical models are:

1. Zero order release model
2. First order release model
3. Higuchi release model
4. Korsmeyer – peppas release model

RESULTS AND DISCUSSION

PREFORMULATION STUDIES:

Solubility: It was determined as per standard procedure.

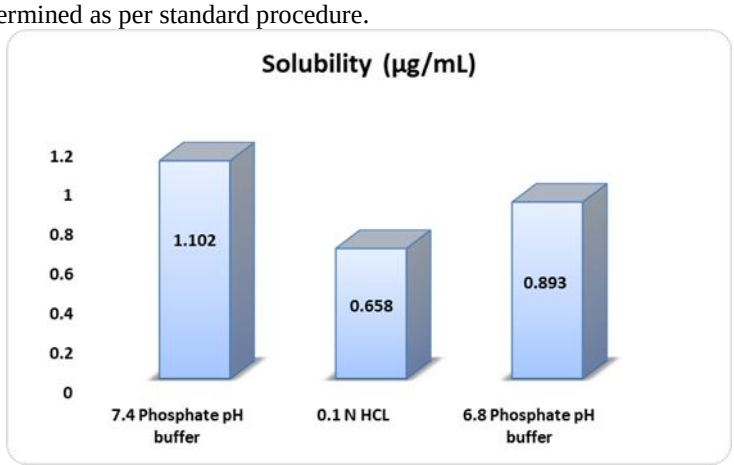

Figure.1 Solubility studies of Deflazacort in various solvents

Discussion: From the above conducted solubility studies in various buffers we can say that pH 7.4 phosphate buffer has more solubility when compared to other buffer solutions.

Drug-Excipient compatibility studies: The IR spectrum of pure drug was found to be similar to the standard spectrum of Deflazacort.

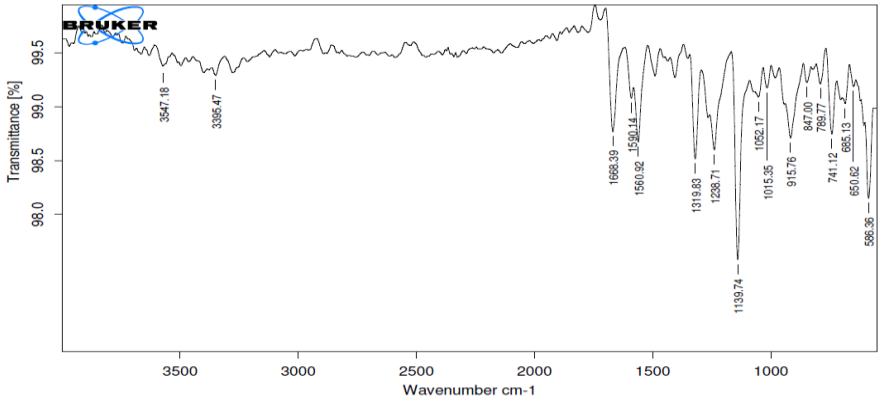

Figure.2 FTIR spectrum of Deflazacort

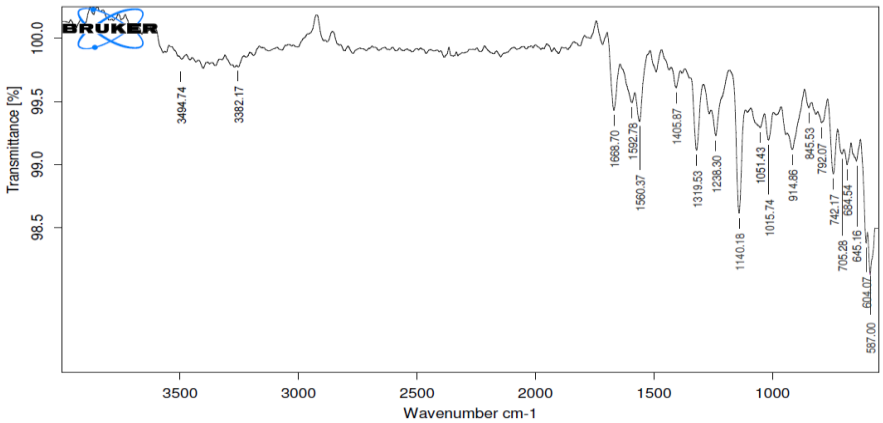

Figure.3 FTIR Spectrum of optimized formulation

Discussion: The FTIR spectrum of pure Deflazacort, prepared colon Targeted Pulsincap of Deflazacort formulation are shown in Figure respectively. The units are represented as cm^{-1}. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Deflazacort) and optimized formulation (Deflazacort + Excipients) which indicates there are no physical changes.

λ_{max} Determination of Deflazacort

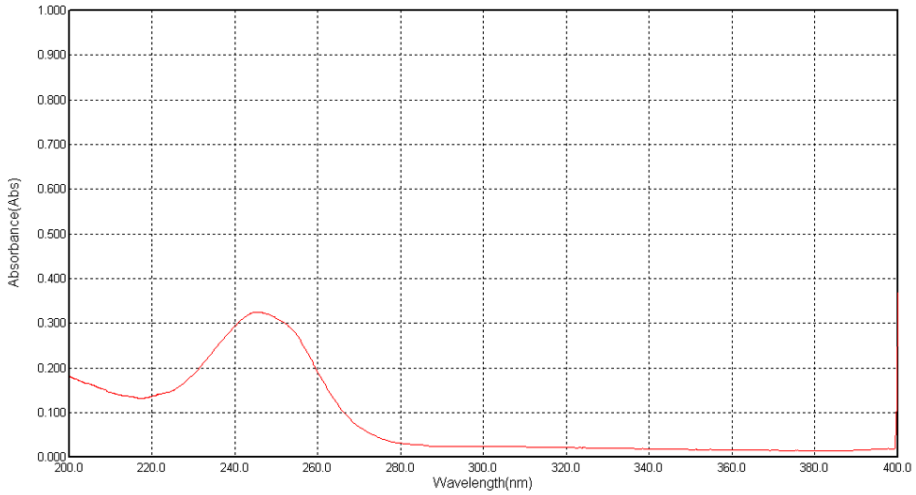

Figure.4 λ_{max} Determination of Deflazacort

Discussion: The λ-max of Deflazacort of 100% solution i.e 12ppm (µg/ml) by using Single Beam Spectrophotometer (YIS-294) was found to be at 247.0 nm by using 7.4 pH Phosphate Buffer.

Standard Calibration Curve:

The standard calibration curve of Deflazacort was developed in different pH media such as pH 1.2, and pH 7.4 phosphate buffer. Two buffers were selected in order to mimic the in-vivo conditions of the GIT.

Standard Calibration Curve in 1.2 pH:

Standard graph of Deflazacort showed linearity at the concentration range of 3-18µg with correlation coefficient of 0.999. Table 7.2 gives the data of the standard graph and Figure shows the standard graph in pH 1.2.

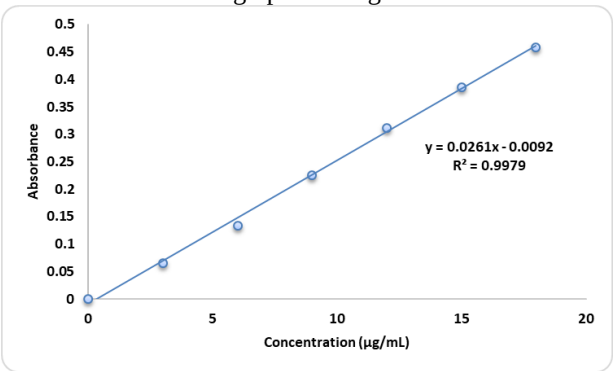

Figure.5 Standard Calibration Curve of Deflazacort in pH 1.2 HCl Buffer at 247 nm

Discussion: The linearity was found to be in the range of 3-18µg/ml in acetone, pH 1.2 HCl buffer. The regression value was found to be 0.997 which less closer to 1 indicating the method obeyed Beer-lamberts' law.

Standard Calibration Curve in pH 7.4 Phosphate Buffer:

Standard graph of Deflazacort in pH 7.4 Phosphate Buffer phosphate buffer shows linearity in the concentration range of 3-18 µg with correlation coefficient of 0.999. Table 7.3 gives the data of the standard graph and Figure 7.6 shows the standard graph in pH 7.4 phosphate buffer.

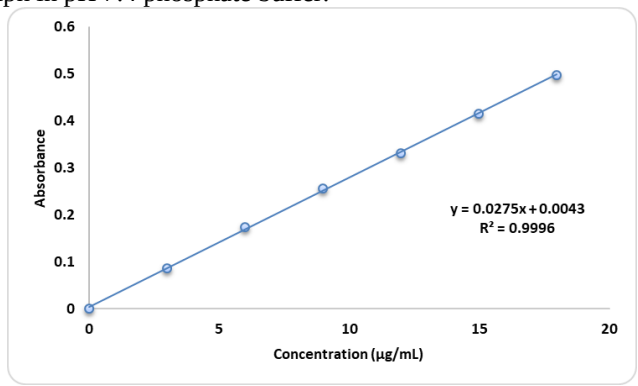

Figure.6 Standard Calibration Curve of Deflazacort in pH 7.4 Phosphate Buffer at 247.0 nm

Discussion: The linearity was found to be in the range of 3-18µg/ml in acetone, pH 7.4 Phosphate Buffer. The regression value was found to be 0.999 which is more closer to 1 indicating the method obeyed Beer-lamberts' law.

Flow properties of powder blend:

Table.4 Flow properties of powder blend

Formulation Code	Angle of Repose±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	29.12±1.14	0.227±0.002	0.335±0.001	19.14±1.17	1.21±0.02
F2	28.46±1.20	0.235±0.001	0.349±0.003	18.20±1.26	1.19±0.01
F3	27.27±1.34	0.249±0.003	0.361±0.004	18.46±1.45	1.18±0.01
F4	27.79±1.19	0.252±0.004	0.368±0.009	17.75±1.38	1.16±0.02
F5	28.15±1.02	0.236±0.002	0.346±0.004	18.69±1.20	1.18±0.01
F6	28.20±1.14	0.251±0.003	0.367±0.005	17.15±1.45	1.17±0.01
F7	27.36±1.45	0.245±0.004	0.359±0.006	15.42±1.05	1.16±0.02
F8	26.14±1.17	0.262±0.002	0.373±0.009	14.20±1.75	1.15±0.01
F9	27.20±1.20	0.241±0.005	0.354±0.005	16.34±1.10	1.17±0.02
F10	25.43±1.34	0.259±0.001	0.367±0.004	15.45±1.25	1.15±0.02
F11	25.28±1.57	0.267±0.004	0.376±0.008	13.85±1.69	1.14±0.01
F12	24.26±1.12	0.275±0.003	0.385±0.004	12.75±1.45	1.12±0.01

Discussion: The angle of repose of different formulations was ≤ 29.12±1.14, which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.227±0.002 g/cm^3 to 0.275±0.003 g/cm^3.Tapped density was found between 0.335±0.001 g/cm^3 to 0.385±0.004 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 12.75±1.45-19.14±1.17 and Hausner's ratio from 1.12±0.01-1.21±0.02 which reveals that the blends have good flow character.

Characterization of Tablets

Post Compression parameters

Table.5 Characterization Deflazacort Tablets

Formulation code	%Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	100.48 ±1.75	2.17 ±0.14	5.75 ±0.10	6.14 ±1.57	0.95 ±0.02	25±1.15	94.20 ±1.21
F2	99.26 ±1.57	2.24 ±0.20	5.29 ±0.11	6.26 ±1.45	0.86 ±0.05	23±1.24	95.24 ±1.45
F3	101.15 ±1.37	2.49 ±0.45	5.68 ±0.10	6.37 ±1.25	0.75 ±0.08	19±1.18	97.06 ±1.08
F4	102.45 ±0.14	2.61 ±0.30	5.45 ±0.09	6.45 ±1.42	0.69 ±0.06	16±1.28	98.28 ±1.65
F5	101.48 ±1.68	2.27 ±0.45	5.29 ±0.08	6.61 ±0.97	0.56 ±0.09	21±1.42	95.36 ±1.67
F6	98.20 ±1.37	2.35 ±0.75	5.76 ±0.07	6.75 ±1.48	0.49 ±0.02	18±1.45	96.35 ±1.26
F7	99.11 ±1.45	2.49 ±0.10	5.55 ±0.05	5.36 ±1.25	0.63 ±0.08	17±1.15	97.15 ±1.17
F8	100.27 ±1.45	2.61 ±0.35	5.75 ±0.04	6.27 ±1.45	0.48 ±0.05	15±1.21	98.85 ±1.65
F9	101.15 ±1.38	2.37 ±0.48	5.34 ±0.02	6.31 ±1.45	0.55 ±0.07	16±1.25	96.22 ±1.48
F10	102.45 ±1.12	2.46 ±0.51	5.27 ±0.05	6.45 ±0.45	0.68 ±0.03	14±1.43	97.36 ±1.29
F11	99.57 ±1.16	2.64 ±0.75	5.45 ±0.06	6.75 ±1.84	0.45 ±0.05	12±1.12	98.37 ±1.28
F12	100.20 ±1.46	2.71 ±0.69	5.69 ±0.07	6.97 ±1.22	0.43 ±0.01	12±1.06	99.45 ±1.15

Discussion:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 5.26±1.84-6.78±1.22 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeia limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 –F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The drug content values for all the formulations (F1-F12) was found to be in the range of 97.06±1.08-99.87±1.15%.

Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table .6 % Cumulative drug release of formulations F1-F6

Time (mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	19.48±1.24%	25.14±1.18	48.14±1.75%	45.12±1.20%	20.48±1.05%	29.17±1.21%
10	27.82±1.45%	49.27±1.54%	59.45±1.02%	63.42±1.45%	35.25±1.45%	43.27±1.37%
15	35.45±1.06%	60.34±1.67%	67.27±1.54%	79.36±1.27%	48.48±1.67%	59.38±1.16%
20	52.21±1.58%	69.12±1.06%	75.69±1.20%	87.45±1.69%	57.65±1.20%	67.46±1.16%
30	66.48±1.46%	78.42±1.04%	86.10±1.34%	92.45±1.02%	69.82±1.74%	76.12±1.12%
40	79.82±1.30%	86.37±1.51%	92.42±1.49%	98.89±1.45%	76.45±1.02%	88.47±1.43%
50	88.49±1.42%	92.49±1.20%	98.35±1.20%		84.28±1.34%	95.20±1.12%
60	98.17±1.20%	99.14±1.36%			97.14±1.45%	98.64±1.45%

Table .7 % Cumulative drug release of formulations F7-F12

Time (mins)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	39.14±1.42%	56.45±1.02%	30.19±1.45%	38.85±1.25%	45.42±1.42%	69.18±1.43%
10	50.67±1.35%	69.29±1.75%	38.27±1.18%	46.42±1.57%	53.21±1.32%	76.20±1.12%
15	65.12±1.46%	77.57±1.06%	46.34±1.27%	59.35±1.24%	67.36±1.12%	87.45±1.37%
20	77.39±1.12%	85.48±1.49%	60.18±1.12%	66.63±1.49%	74.75±1.45%	95.12±1.45%
30	89.45±1.17%	93.26±1.20%	69.43±1.24%	75.49±1.75%	89.15±1.37%	99.37±1.15%
40	95.37±1.12%	98.67±1.37%	76.16±1.27%	83.31±1.02%	92.28±1.14%	
50	98.42±1.37%		88.43±1.20%	89.53±1.34%	99.14±1.10%	
60			98.49±1.24%	98.76±1.45%		

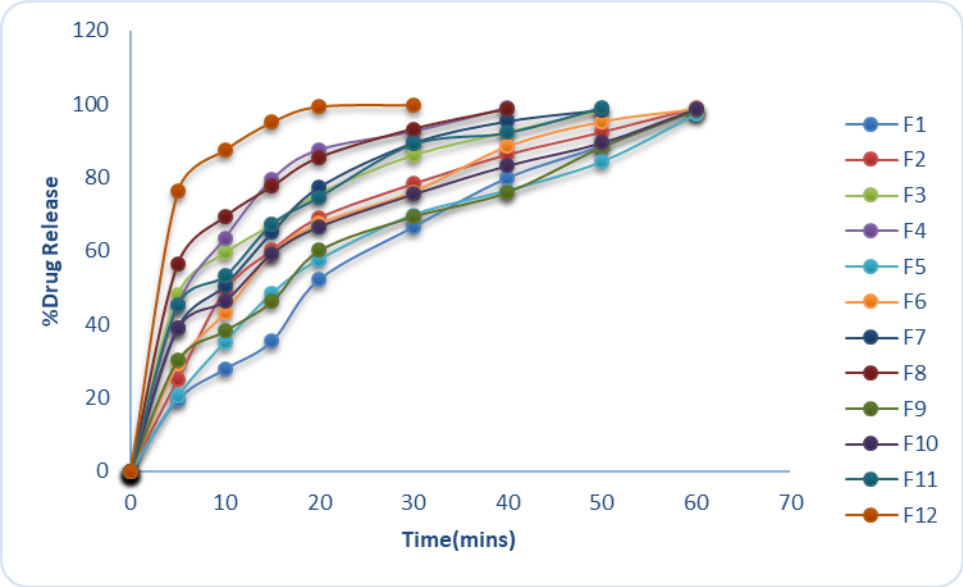

Figure.7 In vitro drug release of formulations F1-F12

Discussion: From the in vitro drug release in studies, it was observed that the formulations containing Croscarmellose sodium as a super disintegrant in different concentrations like 3mg, 6mg, 12mg, 15mg, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F12 formulation containing Croscarmellose sodium 15 mg concentration shows maximum amount of drug release (99.37±1.15%) at the end of 40mins. So, F12 formulation containing 15mg in concentration of ludiflash shows max. Release 99.37±1.15% within 40mins so that it is chosen as optimized formulation.

EVALUATION OF FORMALDEHYDE TREATED CAPSULES:

Physical tests:

Identification attributes: The size '0' capsules chosen were opaque, with white colored body and red cap. The normal capsule bodies were soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the physical appearance of the capsules except for the stickiness. The body of capsule was hard and non-sticking even when touched with wet hand due to treatment with the formaldehyde.

Visual defects: Among 100 capsules body which were treated with formaldehyde, about 15 to 20 capsule bodies showed visual defects. They were found to be shrunk and distortion into different shapes due to the complete loss of moisture.

Dimensions: Dimensional examination was done by using vernier calipers.

Average capsule length:

Before formaldehyde treatment (untreated cap and body) : 25.8 mm

After formaldehyde treatment (treated body and untreated cap) : 24.5 mm

Average diameter of capsule body:

Before formaldehyde treatment : 8.9 mm

After formaldehyde treatment : 7.7 mm

Average length of capsule body:
Before formaldehyde treatment : 20.4 mm
After formaldehyde treatment : 18.6 mm
Discussion: On formaldehyde treatment, the "0" size capsules bodies showed a significant decrease in length and diameter and attained hardness.
Chemical test:
Qualitative test for free formaldehyde: The formaldehyde treated capsules were tested for the presence of free formaldehyde by comparing color of sample solution with standard solution. It was found that the sample solution was not more intensity colored than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies.
Discussion: Limit test for the presence of residual formaldehyde, indicated that the amount of formaldehyde present in treated capsules was well within limits.
Discussion: Basing on the disintegration studies, it was observed that the 3rd capsule 6th hr treated capsule remained intact for 7 hrs so lag time was maintained. 4th and 5th remain intact for 9, 12 hrs respectively and therefore they were not selected for the formulation because the required lag time was 6hrs. As the required lag time is 6hrs, (6th hr treated capsule) was selected as optimized time for formaldehyde treatment for further studies.
In vitro release studies:
Dissolution study was carried out to measure the release rate of drug from prepared pulsincap formulation using USP I dissolution apparatus at 37^{0}C using 2 different dissolution media of pH 1.2, pH 7.4 phosphate buffer in order to mimic in vivo GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 10hrs of dissolution study in pH 7.4 phosphate buffer.

Table.8 In vitro dissolution data of formulations P1F12 to P5F12

Time (hrs)	P1F12	P2F12	P3F12	P4F12	P5F12
0	0	0	0	0	0
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	42.26	0
5	62.24	0	0	69.16	48.95
6	80.19	73.24	0	85.21	70.36
7	97.45	86.48	67.24	98.58	87.48
8		98.52	86.54		98.86
9			99.52		
10					

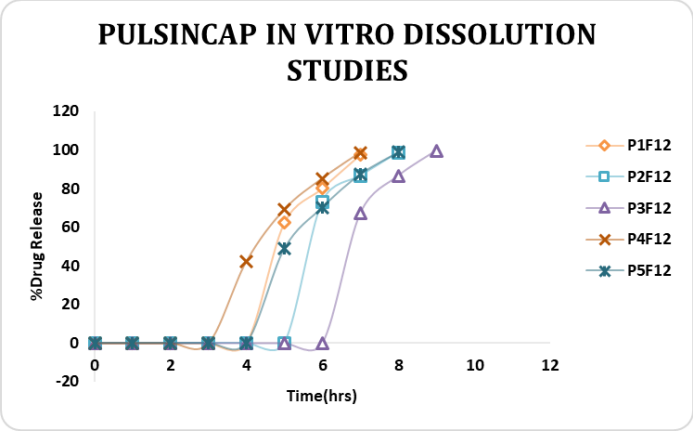

Figure.8 Dissolution plots for formulations P1F12 to P5F12

Discussion:
All the 5 formulations of Deflazacort pulsincaps were subjected to dissolution studies. Formulations P1F12, P2F12, P3F12, P4F12 & P5F12, contain the hydrogel plug with alone and combination of hydrophobic polymer and Hydrophilic polymer i.e Ethyl Cellulose: HPMC K15M in the ratio of 1:1, 2:1 & 1:2 of total 100mg weight

of the plug. It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl Cellulose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So, basing on these observations, of all the 5 pulsincap formulations, P3F12 formulation containing hydrogel plug of Ethyl Cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

RELEASE KINETICS:

Dissolution data was fitted in Zero order, First order, Higuchi's and koresmayer peppas equations. The regression coefficient "R" values for zero order, first order, higuchi's and peppas for formulation P3F12 was found to be 0.660, 0.521, 0.450 and 0.456 respectively.

Table.9 Correlation coefficient "R" values of P3F12 optimized formulation

Models	R values
Zero order	0.660
First order	0.521
Higuchi	0.450
Koresmayer peppas	0.456
Peppas 'n'	1.776

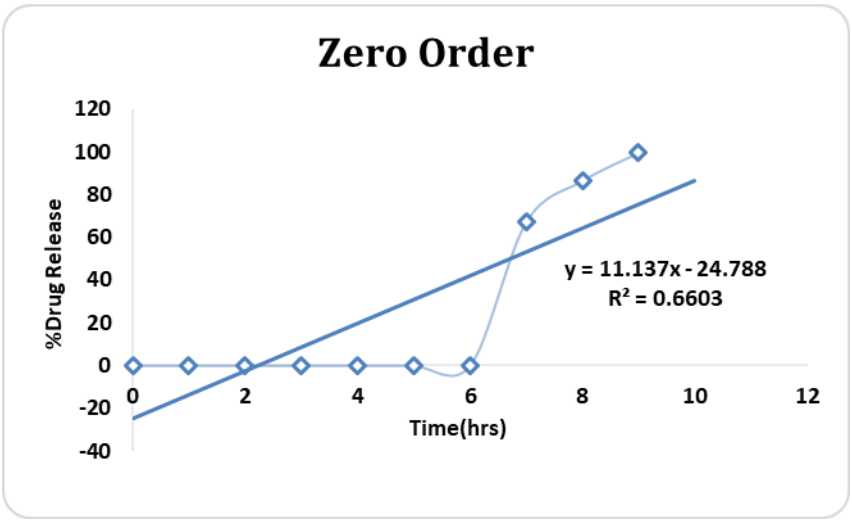

Figure.9 Zero order plot for optimized formulation P3F12

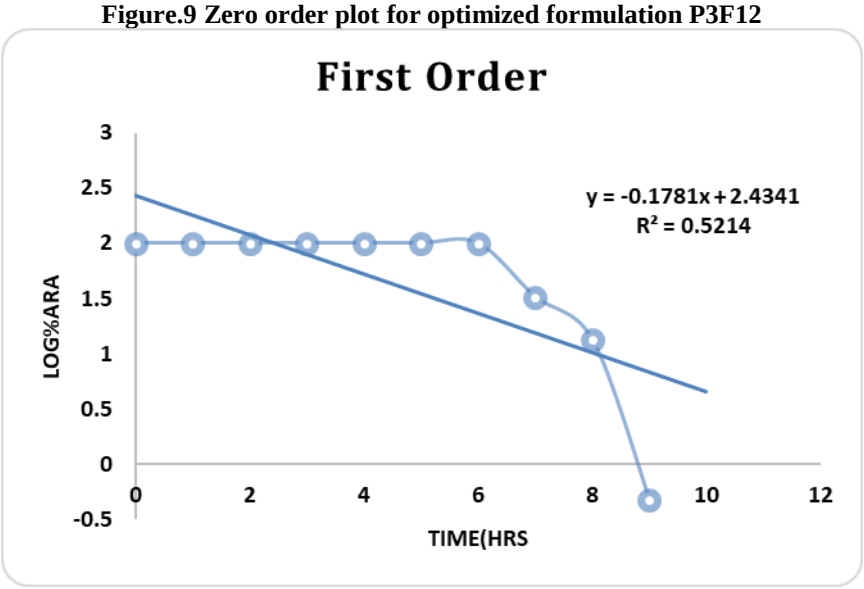

Figure.10 First order plot for optimized formulation P3F12

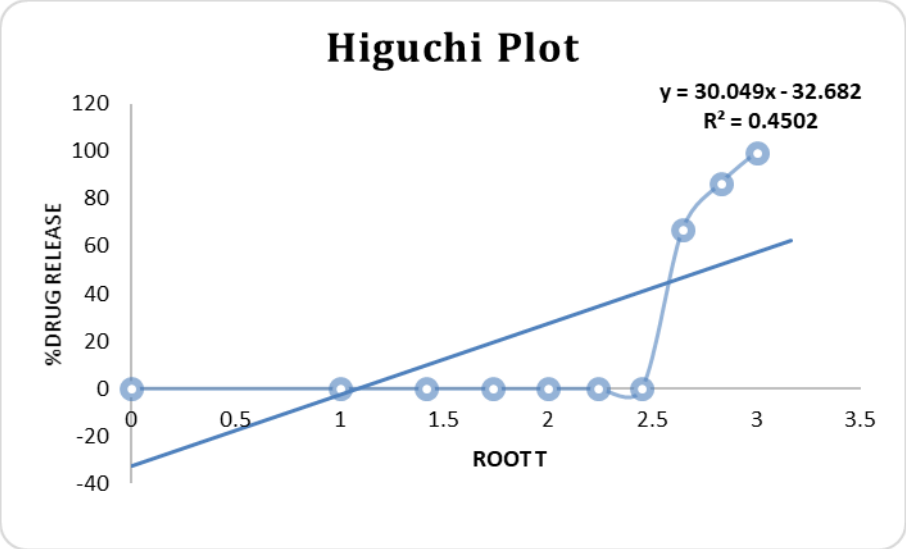

Figure.11 Higuchi's order plot for optimized formulation P3F12

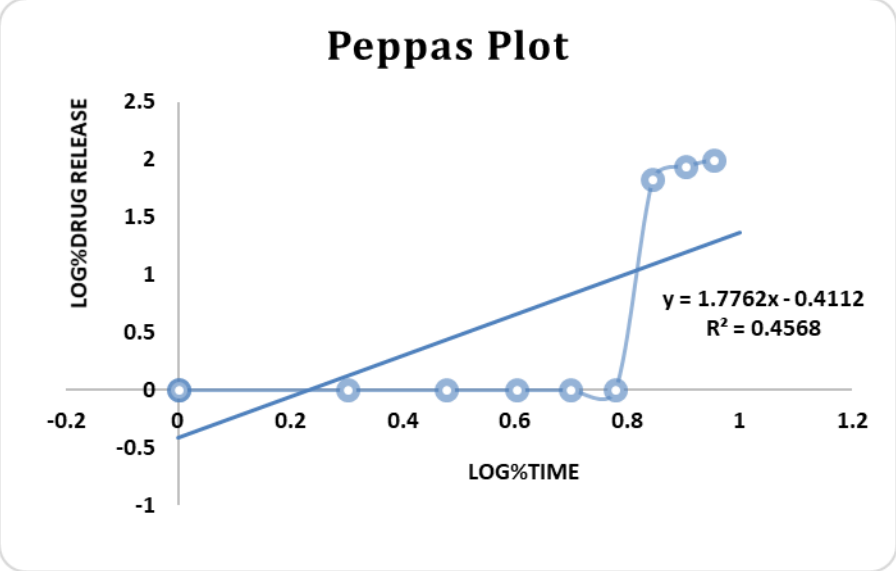

Figure.11 Koresmayer peppas order plot for optimized formulation P3F12

Discussion:

To analyze the mechanism of drug release from optimized P3F12 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R) was used as indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation P3F12 followed the Zero order and Peppas follows super case II transport mechanism.

SUMMARY AND CONCLUSION

SUMMARY:

Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of the drug administration on resultant pharmacodynamic and pharmacokinetics parameters. The significance of these day-night variations has not been over looked from the drug delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in development of time delayed drug delivery systems to address emerging Chronotherapeutic formulations.

Prior to formulation, Pre formulation studies were carried out in order to establish compatibility between Deflazacort and excipients by FTIR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of Deflazacort.

The capsule bodies were made insoluble by formaldehyde treatment by exposing at various time intervals viz., 2, 4, 6, 8, 10 hrs and then optimized by using disintegration studies and finally the optimized treated capsule

bodies were then subjected to various physical and chemical tests such as identification attributes, visual defects, dimensional studies and qualitative test for free formaldehyde.
Total 12 formulations were formulated by using super disintegrant in different ratios by direct compression method.
The formulations were subjected to flow properties and FTIR study. Based on the results obtained F12 containing 15mg Lycoat was considered as the optimum powder blend for fabrication of pulsincap capsule.
Different concentration of the polymers like Ethyl Cellulose and HPMC K15M alone and in combination were used for the preparation of hydrogel plug to maintain the suitable lag period and it was found that the drug release was controlled by the proportion of polymers used.
The powder blend F4 was filled into the 6th hr formaldehyde treated capsule bodies and plugged with hydrogel polymers, 100mg hydrogel plug. The ratios of hydrophobic polymer like Lactose and HPMC were taken in alone and 1:1, 2:1, and 1:2. Finally after arranging the plug, the joint of the capsule body and cap was sealed with a small amount of 1% 1% lactose ethanolic solution. The prepared pulsincaps were evaluated for Invitro studies.
All the 5 formulations of Deflazacort pulsincaps were subjected to dissolution studies. Formulations P1F12, P2F12, P3F12, P4F12 and P5F12, contain the hydrogel plug with alone and in combination of hydrophobic polymer and Hydrophilic polymer i.e., Lactose: HPMC in the ratio of 1:1, 2:1 & 1:2 of total 100mg weight of the plug.
It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl Cellulose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So, basing on these observations, of all the 5 pulsincap formulations P3F12 formulation containing hydrogel plug of Ethyl Cellulose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

CONCLUSION

The aim of this study was to explore the feasibility of time specific pulsatile drug delivery system of Deflazacort to treat short-term treatment.
From the results obtained from executed experiments it can be concluded that:
The Pre formulation studies like pH, solubility and UV-analysis of Deflazacort were compiling with BP standards.
The FTIR Spectra revealed that, there was no interaction between polymer and drug.
The solubility studies of empty gelatin capsule bodies, which were cross linked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting.
The polymers like HPMC K15M and Ethyl Cellulose can be used as hydrogel plugs to delay the release of Deflazacort.
The result of micromeritic properties showed good flow property of the powder blend indicating uniform distribution of drug within the various batches of capsule with negligible loss during the formulation stage.
In conclusion, this system can be considered as one of the promising formulation technique for preparing time specific drug delivery systems and in Chronotherapeutic management. From the preliminary trials it was concluded that it is possible to formulate the pulsatile drug delivery system by the design of time modified chrono pharmaceutical formulation.

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