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FORMULATION AND EVALUATION OF BUDESONIDE CONTROLLED RELEASE TABLETS BY USING NATURAL GUM

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ABSTRACT

The aim of present work was to develop 300mg control release budesonide tablets by using direct compression method. It is a potent glucocorticoid used for the treatment of ulcerative disease and wheezing and shortness of breath caused by asthma. In this work four formulations are selected for the design of budesonide controlled release formulations. In this formulations are prepared by using different concentrations gum karaya as a polymer and different ingredients are used as fillers to develop the formula. The granules and tablets are evaluated by FT-IR, DSC, pre-compression, post-compression parameters and *In-vitro* dissolution studies. Based on the dissolution studies F4 was selected as an optimized formula because of it gives best results in controlled by drug release manner and best fitted to order of kinetics.

KEYWORDS: Budesonide, Gum Karaya, Micro Crystalline Cellulose (MCC), Magnesium Stearate, Talc, Direct Compression Method, Controlled Release Tablets.

INTRODUCTION

The word "Drug Delivery" cover an extremely wide range of technique used to take therapeutic agents into the human body. Drugs are administered with a main intend of therapeutic patient ailments. Drugs are not at all administering in their pure form but are rehabilitated in a suitable dosage form so that it was intensity of action, duration of action can be checked. The oral route is the majority extensively used route of drug delivery.

Controlled release dosage form is defined as healthy characterize and reproducible quantity form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration.

CRDF has been progressed to new frontiers in which it can be formulated by combining (dissolve or disperse) the polymer(s) with active pharmaceutical ingredient (hereafter, API) such that the release of drug from dosage form is predesigned. Unprecedented developments in CRDF can be observed with a specific goal in order to maintain desired plasma concentration in systemic circulation using plethora of drugs. By releasing drug particles in a controlled manner over extended periods of time after single administration of rehashed dosage forms, CRDF have the potential to maintain drug concentrations within target ranges, diminish side effects caused by concentration extremes and repeated administrations, thereby, improve patient compliance as contrasted to conventional regimens.

Control release drug discharge from the dosage form. Once the rate of drug discharge from the dosage form is equal to the rate of drug absorption, reaches to unfaltering and the concentration of drug at site of absorption remains constant and leads to constant rate of absorption. Initially, plasma concentration is faster at absorption phase than elimination phase, then relentlessly increments until the rate of drug absorption equal to the rate of drug elimination. Given that the rate of drug absorption is consistent, however, the rate of drug absorption (ROA) and rate of drug elimination (ROE) equal over time and result in a flat plasma concentration (Cp) versus time (t) profile that persists until the dose of drug is completely discharged from the dosage form.

Budesonide is a corticosteroid that undergoes high first pass elimination by the liver so that systemic levels after oral administration are minimal. Budesonide has been used orally for several immune mediated gastrointestinal and liver diseases and as nasal spray or by inhalation for allergic rhinitis, asthma and chronic obstructive lung disease. Neither inhalant nor oral budesonide has been linked to serum enzyme elevations during therapy or to convincing instances of clinically apparent acute liver injury.

MATERIALS AND METHODS

Budesonide (SUN Pharma Pvt. Limited), Gum karaya (Chemiloids, Vijayawada), Micro crystalline cellulose (Chemiloids, Vijayawada) Talc (Reidel (India) Chemicals, Hapur) and Magnesium stearate (S.D. Fine-Chem. limited, Mumbai).

METHODS

Pre- formulation studies
Bulk Density (Db)
It is the ratio of the mass of powder to the bulk volume of powder. It was measured by pouring the weight powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$Db = M/Vb$

Where, M= mass of powder. Vb=bulk volume of the powder.

Tapped density (Dt)
It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$Dt = M/Vt$

Where, M=mass of powder. V_t=tapped volume of the powder.

Carr's Index (I)
It in dictates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$I = Dt- Db / Dt*100$

Where, D_t = tapped density of the powder. D_b = bulk density of the powder.

Angle of Repose (θ)
The friction force sin loose powder can be measured by the angle of repose θ. It is side fine das maximum angle possible between the surface of a pile of powder and the horizontal plane.

$Tan\ \theta = h/r$

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

Where θ = is the angle of repose, h = is the height, r = is the radius.
The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

FT-IR Spectral studies
The IR spectra for the formulation excipients and pure drugs were recorded on Jasco FT-Infrared spectrophotometer using KBr palette technique (1:100) at their solution rate of 4cm-1. Spectrum was integrated in transmittance mode at the wave number range 400-4000 cm-1utions were.

Differential scanning calorimetry
The Predictable DSC and MTDSC experiment be perform by means of DSC Q200 (TA instrument, NJ, USA) through a cooled assembly (RCS) and a modulate ability. The DSC compartment was purge with 50 ml/min dry nitrogen and the RCS be purge with 150 ml/min nitrogen. The DSC compartment was calibrate for baseline using empty pans of matched weight and for temperature using three temperature standards (cyclohexane, $T_m = 279.54^o$ K; indium, $T_m = 429.61^o$ K; tin $T_m = 504.93^o$ K). About 3-5 mg of samples was exposed to the desired heating rates from the desired starting temperature to above the melting point of Budesonide under dry nitrogen purging (50 ml/min) in hermetically sealed aluminum pans. The data was analyzed using Universal Analysis Software from TA Instruments.

Analytical method development for Budesonide
U. V Spectrophotometer
Calibration curve of the pure drug Budesonide was prepared in the concentration range from 2-10 µg/ml at the wave length of 246 nm by using 6.8 phosphate buffer solutions. Based on the Beer' lamberts law the graph was plotted between the absorbance vs concentration. The calibration curve showed good linearity and regression coefficient (r2) value is 0.999, and intercept 0.005.

Preparation of standard Stock solution of Budesonide
100 mg of Budesonide was dissolved in 100 ml of 6.8 phosphate buffer in a100 ml volumetric flask and made up to the volume with 6.8 phosphate buffer. From this 1 ml of solution was taken and made to 100 ml with 6.8 phosphate buffer.

Method
For the estimation of Budesonide in 6.8 phosphate buffer the stock solution has to be diluted subsequently with 6.8 phosphate buffer to get a series of dilutions containing 2, 4, 6, 8, 10 µg/ml of solution. The absorbance of the drug solution was measured at 246 nm. The calibration curve was constructed.

Formulation of Budesonide controlled release tablets
Budesonide controlled release tablets were prepared by direct compression method. Four formulations of tablets each containing 300 mg dose of Budesonide. Were prepared with different concentrations of various excipients which were shown in given below. Budesonide and natural gum such as karaya gum were accurately weighed, mixed uniformly and passed through # 40 meshes. Microcrystalline Cellulose is used as diluents were weighed accurately and passed through #40 meshes. Both were mixed properly and the mixture of Talc and magnesium stearate 1:1 ratio was added and mix for few minutes. Then the above mixture was compressed in to tablets by using station rotary compressed machine with punch size of 8 mm.

Table 1: **Formulation of Budesonide controlled release tablets.**

Ingredients mg/tab	Formulation			
	F1	F2	F3	F4
API (Budesonide)	200	200	200	200
Gum karaya	10	20	30	40
Microcrystalline Cellulose	86	76	66	56
Talc	2	2	2	2
Mg stearate	2	2	2	2
Total weight (mg)	300	300	300	300

Evaluation of Budesonide controlled release tablets
Physical appearance
The Physical emergence of tablets is resolute by visual inspection by which involve the quantity of number of

Table 2: Weight variation specifications (B.P).

Average Wt of the Tablets	Maximum difference allowed
Less than 130	5
130-324	7.5
More than 324	10

Table 3: Weight variation specifications (I.P).

Average weight of tablet(mg)	Percentage deviation
130 or less	10
130 to 324	7.5
More than 324	5

Thickness
The thickness of the tablets was calculated by vernier calipers. Take Five tablets from each batch and to evaluate average value are considered.

Hardness (kg/cm^2)
Hardness test was conducted by using a Monsanto hardness tester. Each batch contains Five tablets are selected and then find out each tablet hardness.

% Friability
The Roche friabilator is used for the determination of %friability. In this test Ten tablets were weighed initially (w_1) and placed in the friabilator that revolves at a speed of 25 RPM, dropping those tablets at a distance of six inches height with each revolution and rotated in the friabilator for 100 revolutions. Behind achievement of rotations the tablets be dedusted and weighed (w_2).
% Friability = (IW-FW)/ IW × 100

Drug content
Ten tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to a 100 ml flask. The powder was dissolved buffer medium. The sample was mixed by using Sonicated for 5 minutes, after which it was filtered through what man's filter paper. The filtered solutions after appropriate dilution (1to10 ml) with P^H

factors such as size, shape, colour, odour, taste, surface touch and recognition symbols there on the tablet.

Weight variation test
The weight variation test is performed by taking 20 tablets from each formulation and weighing the individual tablets by using electronic balance. Their average weight was calculated as

% weight variation = (WA- WI) ×100/ WI
Where,
WI = Individual weight of the tablets
WA = Average weight of the tablet

6.8 phosphate buffer were analyzed by the validated UV Spectrophotometric method at λ_{max} 246 nm.

***In-vitro* dissolution studies**
In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of phosphate buffer of pH 6.8was used as the dissolution medium which was maintained at 37±0.5^{o}C. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1hr, 2hr, 4hr, 6hr, 8hr, 10hr and 12hr,) and were filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 246 nm.

RESULTS AND DISCUSSION

Formulations of Budesonide control release tablets are prepared by using natural gums like gum karaya was impact on *In- Vitro* dissolution rate.

Pre-formulation studies
The Active pharmaceutical ingredient (Budesonide**)** and excipients were blended and evaluated for different parameters as clarified before. Bulk density was found in the limit of 0.685 g/cm^3 and the tapped density between 0.0.578 g/cm^3. By using both density data Carr's compressibility was determined. The compressibility record was found between 12.06 % and the Hausner's

ratio was found to be 1.31. The result shows good flow properties of blend. The good flow properties of powder were also evident from angle of repose that range from 29.3°. In the present examination all powder mixes indicated excellent flow property.

Pre – Compression Parameters
Table 4: Micromeritic properties of the granules of Budesonide Formulation.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose(θ)	Compressibility Index (%)
F1	0.645	0.548	1.38	24.16	19.56
F2	0.635	0.564	1.36	24.59	19.89
F3	0.658	0.574	1.37	24.81	19.78
F4	0.678	0.587	1.39	26.12	20.35

FT-IR Spectral studies
FT-IR studies
From the FT-IR spectra, it was concluded that similar characteristic peaks with minor difference for the drug and the FT-IR formulation. Hence, it appears that there was no chemical interaction between the drugs and excipients used**.** The IR Spectra of with, karaya gum shown. The following peaks were observed in as well as Budesonide with excipients.
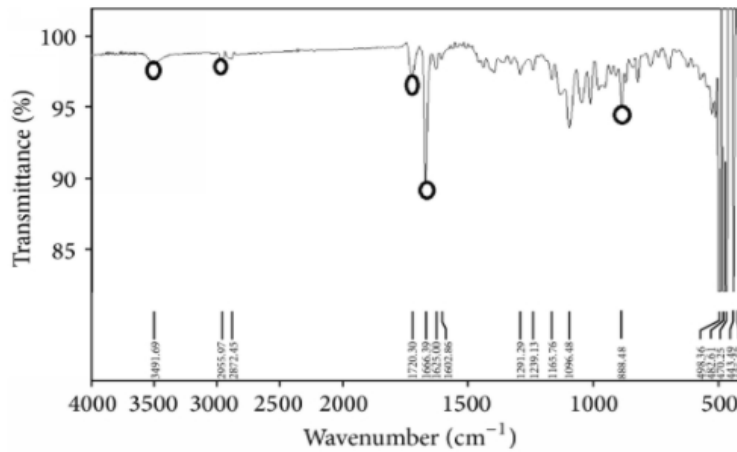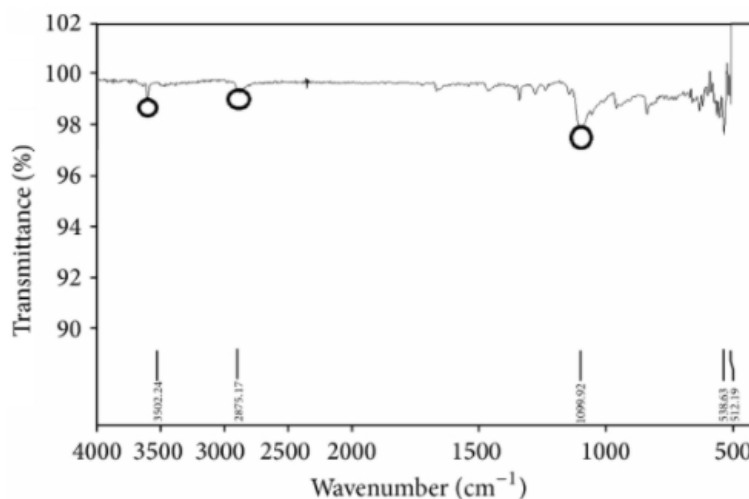

Fig. 1: FT-IR Reports of Budesonide.

Fig. 2: FT-IR Reports for Budesonide Optimized formula.

Differential scanning calorimetry

DSC indicated better drug stability presence of natural gum. A stronger drug amorphization and entrapment in natural gum was observed.
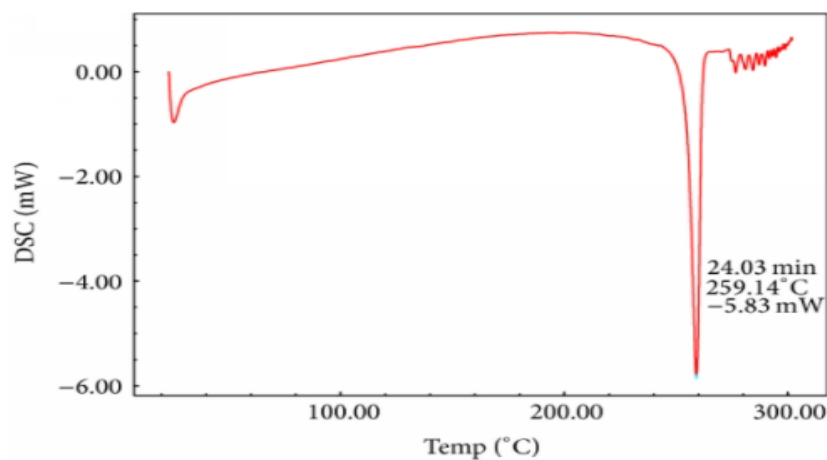

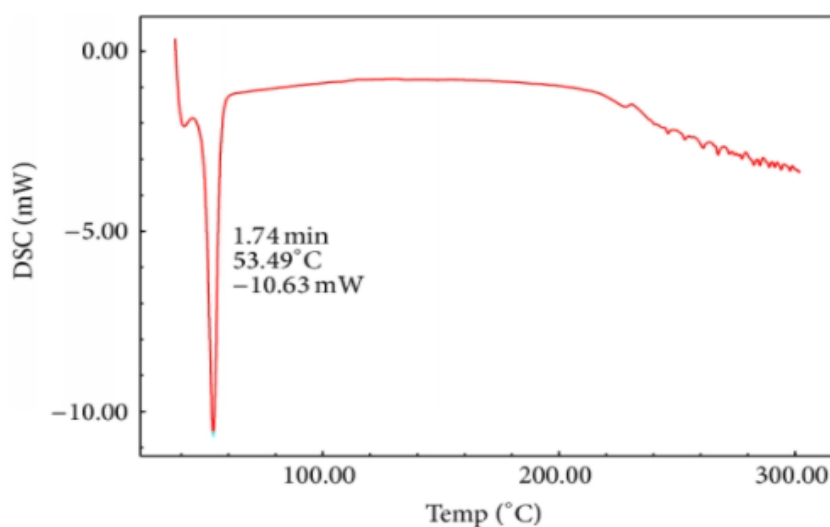**Fig. 3: DSC Reports for Budesonide.**

Fig. 4: DSC Reports for Budesonide Optimized Formula.

Analytical method development

Budesonide was estimation using UV/VIS spectrophotometer method. It was found that under UV/VIS spectrophotometer standard absorbance of the peak of Budesonide was 0.311 µg/ml,

Table: 5 Standard Calibration Curve for the Budesonide in 6.8 pH phosphate buffer.

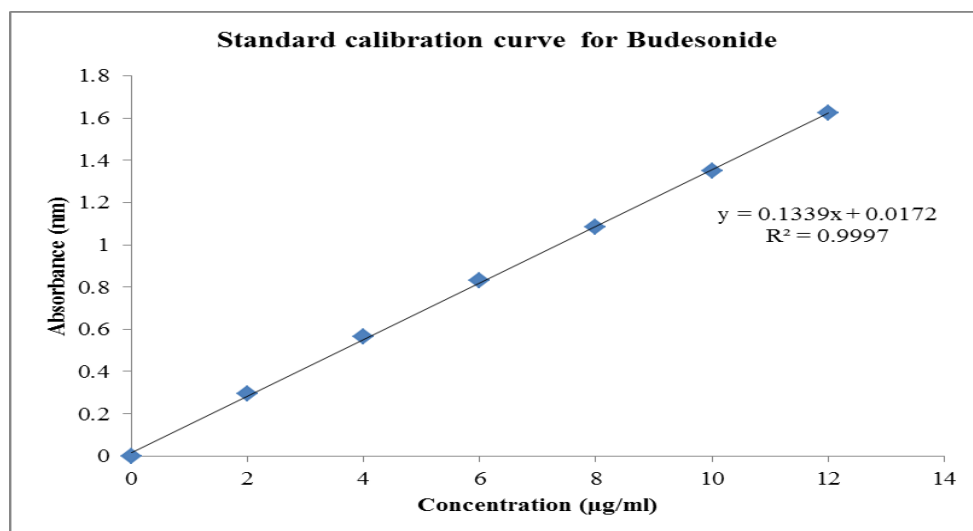| S. No	Concentration (µg/ml)	Absorbance
1	2(µg/ml)	0.102
2	4(µg/ml)	0.206
3	6(µg/ml)	0.311
4	8(µg/ml)	0.424
5	10(µg/ml)	0.538

Fig. 5: Standard Calibration Curve for the Budesonide in 6.8 pH phosphate buffer.

Evaluation of post-compression parameters Budesonide controlled release tablets

The preliminary studies were carried out by preparing various formulations with different process variable and subjecting the formulation to all post-compression parameters has fulfilled according to IP standards.

Weight variation

Average weight of 20 tablets of Budesonide was calculated for each formulation which varied from mg 291±1to 303 ±3 mg. the complied the official requirements as per IP.

Tablet thickness

The thickness of the Budesonide formulation varied from 2.14±0.06 mm to 2.68±0.06mm.

Tablet hardness (kg/cm^2)

The hardness of the tablet developed formulation shows 4.6. ±1.0 kg/cm^2.

%Friability

The friability of the developed formulation varied from 0.231±0.1% to 0.248±0.01% loss which was less than 1% as per official requirement of IP.

Drug content

The drug content of the developed formulation shows 92.34%

Post – compression parameters

Table 6: Post compression parameters of Budesonide controlled release tablets.

Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability (% loss)	% DC
F1	303	2.14	4.6	0.245	91.21
F2	301	2.53	4.8	0.235	93.42
F3	298	2.68	4.7	0.248	92.41
F4	295	2.48	4.8	0.239	91.14

***In-Vitro* Dissolution studies of Budesonide controlled release tablets**

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of phosphate buffer of pH 6.8was used as the dissolution medium which was maintained at 37±0.5°C. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr) and were filtered. The amount of drug dissolved was determined by UV- spectrophotometer by measuring the absorbance of the sample at 246 nm. The formulation F1,F2,F3 and F4 contains the gum karaya (different

concentration) was prepared in Budesonide controlled release tablets the drug released in formulation f1 is 89.45 % in 12hr, f2 formulation drug released is 71.56 % in 12hr,f3 formulation drug released is 78.12 % in 12hr and f4 formulation drug released is 99.67 % in 12hr. The optimized formulation F4 the prepared with gum karaya (40 mg) the dissolution medium was the P^H 6.8 phosphate buffer the drug released in formulation F4 is 99.67 % in 12hr.

Table 7: Dissolution studies for Budesonide controlled release tablets.

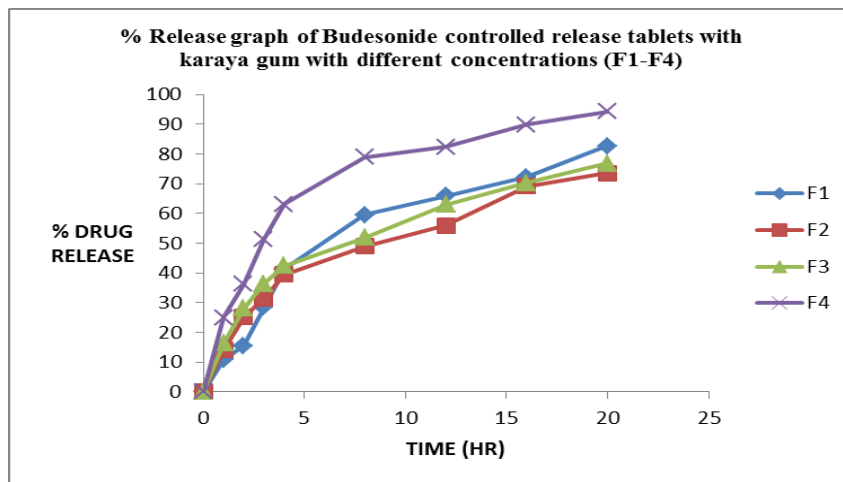|	Dissolution with pH 6.8 phosphate buffer, 900ml, RPM 100, λ max 246 nm				
% Cumulative Drug Release					
S.NO	Time (hr)	F1	F2	F3	F4
1	0	0	0	0	0
2	1hr	14.07	10.61	12.20	16.43
3	2hr	28.47	21.36	27.21	31.14
4	4hr	39.57	36.45	34..56	57.50
5	6hr	49.67	49.65	47.68	69.47
6	8hr	61.58	58.64	59.64	79.48
7	10hr	78.45	68.68	67.24	89.67
8	12hr	89.45	71.56	78.12	99.67

Fig. 6: % Release graph of Budesonide controlled release tablets with karaya gum with different concentrations (F1-F4).
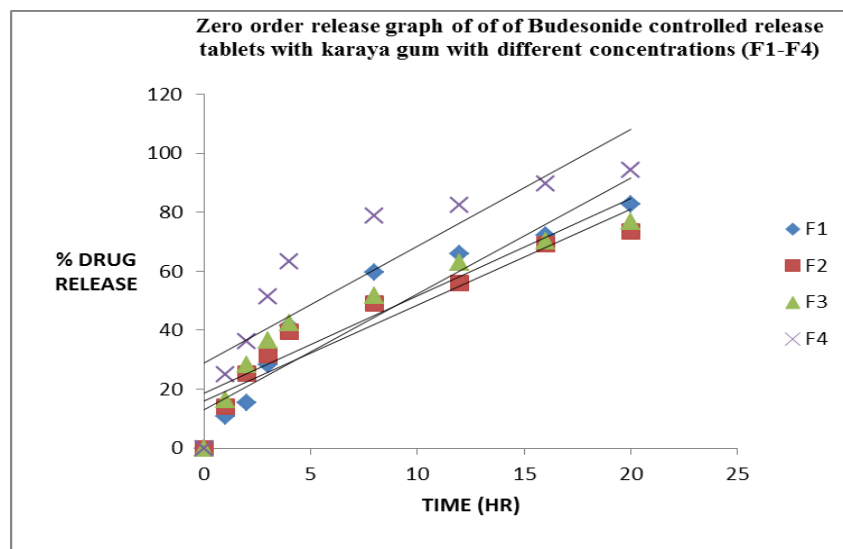

Fig. 7: Zero order release graph of Budesonide controlled release tablets with karaya gum with different concentrations (F1-F4).
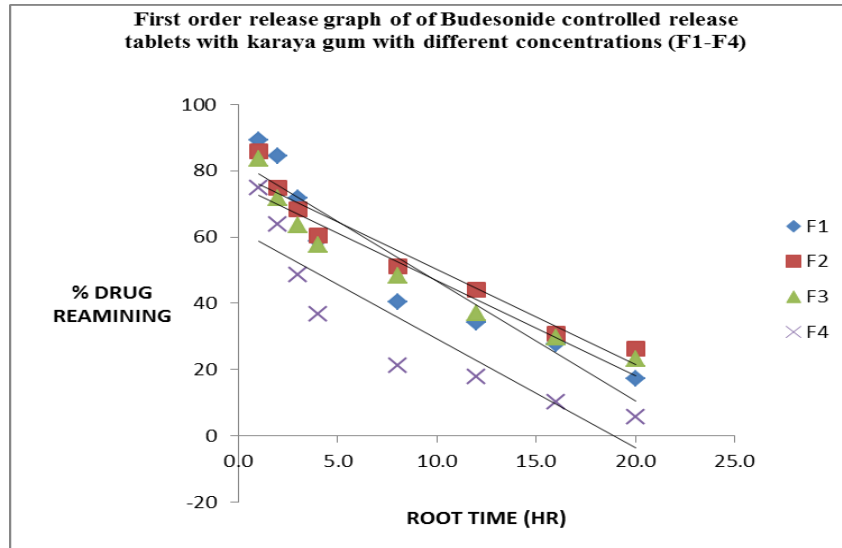
Fig. 8: First order release graph of Budesonide controlled release tablets with karaya gum with different concentrations (F1-F4).
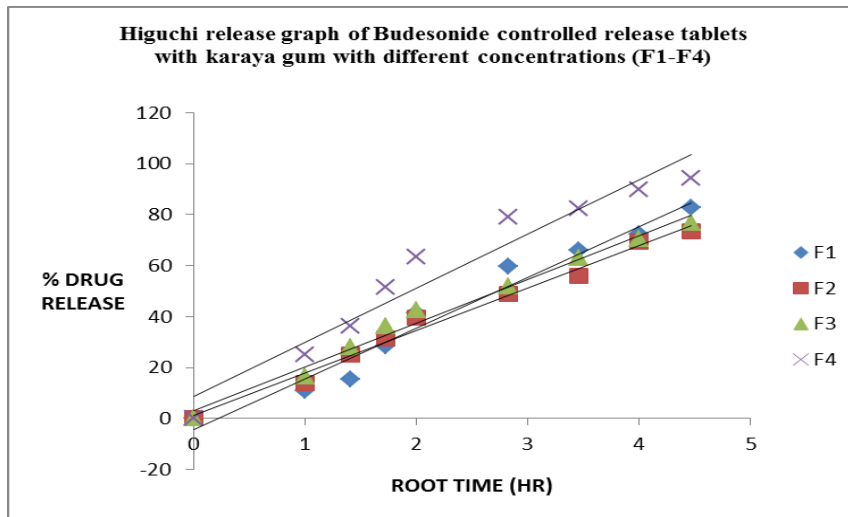

Fig. 9: Higuchi release graph of Budesonide controlled release tablets with karaya gum with different concentrations (F1-F4).
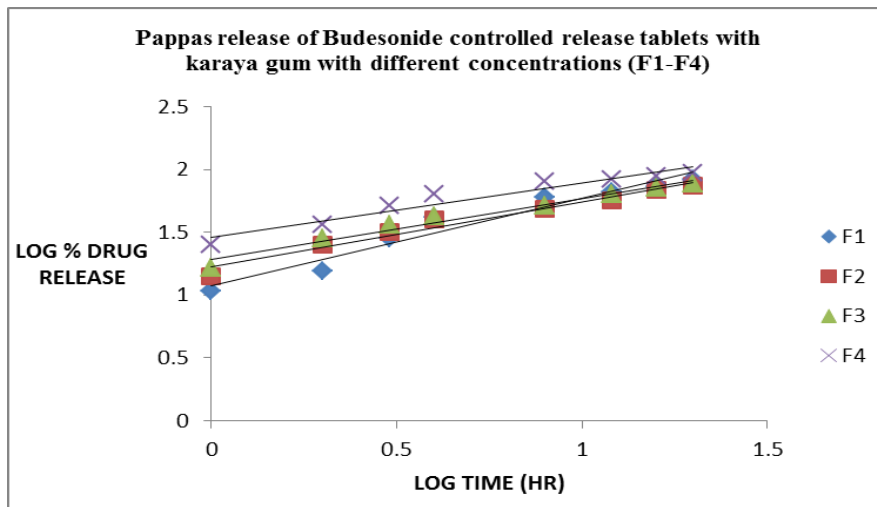

Fig. 10: Pappas release graph of Budesonide controlled release tablets with karaya gum with different concentrations (F1-F4).

Curve-Fitting Analysis

According to different kinetic models, the kinetics of the f1 and f4 drug release was evaluated by drug release rate models namely zero order, first order kinetics, and higuchi, papas mechanisms. The dissolution kinetics data was defected and the comparative dissolution profile**.** The optimized formulation F4 showed highest R^2 value

i.e. 0.986 for zero order plots indicating that release of drug follows zero order kinetics, and mechanism of release was fitted to higuchi equation with the r value of 0.987 indicating anomalous non-fickian diffusion mechanisms and may indicate that the drug release is controlled by more than one process.

Table 8: Dissolution kinetics of Budesonide controlled release tablets with karaya gum with different concentrations.

Formulation	Correlation co-efficient			
	Zero order	First order	Higuchi	Pappas
F1	0.963	0.892	0.981	0.946
F2	0.978	0.889	0.988	0.969
F3	0.940	0.866	0.985	0.970
F4	0.986	0.859	0.987	0.936

CONCLUSION

Budesonide was chosen as the model candidate for this study since it possess near ideal characteristics that a drug must have in formulating a controlled drug delivery system. It has high lipid solubility, effective in low plasma concentration and high degree of first pass metabolism. In this present study the tablets were prepared by using direct compression technique. All the formulations were evaluated for physical characteristics, pre-compression and post-compression*, In-vitro* dissolution studies, Drug – excipients compatibility studies were conducted by FT-IR spectroscopy results indicated that the Budesonide and polymers were found to be compatible and DSC studies are also conducted. The pure drug Budesonide % drug release was found to be 99.67% at the end of 12th hour. Finally we have found that from all the formulations (F1-F4) only F4 formulation has successfully attained the controlled drug release for 12th hour. The optimized formulation F4 showed highest R^2 value i.e. 0.986 for zero order plots indicating that release of drug follows zero order kinetics, and mechanism of release was fitted to higuchi equation with the n value of 1.3 indicating anomalous non-fickian diffusion mechanisms and may indicate that the drug release is controlled by more than one process.

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