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ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 10, Issue, 07, pp.9856-9860, July, 2019

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF BUDOSENIDE CONTROLLED RELAESE CAPSULES

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ARTICLE INFO

Article History:
Received 27th April, 2019
Received in revised form
24th May, 2019
Accepted 20th June, 2019
Published online 31st July, 2019

Key words:
Budosenide, Controlled release,
Aqua coat ECD, Talc,
Eudragit L30D55, Formulation.

ABSTRACT

The object of the present work is to formulate and evaluation of Budosenide controlled release tablets. The excipients were added in different concentrations with varying amount of rate controlling polymers. Sugar spheres, aqua coat ECD (30%), acetyl tri butyl citrate, talc, Eudragit L 30 D 55 and tween 80 were used as excipients for Budosenide formulation. The formulation blend was evaluated for various physicochemical properties and all the parameters were found to be within limits. The formulations F1-F9 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits. From the stability testing, the formulation F9 could show no difference in the release profiles and physical properties. Thus, the formulation was found to be stable.

***Citation: Sairam, N. Naganjanyelu, A. and Sreenivasa Prasanna, P.* 2019.** "Formulation and Evaluation of Budosenide Controlled Relaese Capsules", *Asian Journal of Science and Technology*, 10, (07), 9856-9860.

INTRODUCTION

The oral route of drug delivery is typically considered the preferred and most patient – convenient means of drug administration. The reality is that many compounds are either incompletely or ineffectively absorbed after oral administration (i.e. bioavailability is an issue), or that the required dosing frequency is too short to enable once or twice daily administration (ie. Pharmacokinetic half-life is an issue) (Gamlen, 1985)1. Modified release formulation technologies offer an effective means to optimize the bioavailability and resulting blood concentration – time profiles of drugs that otherwise suffer from limitations (David, 2007). Modified release refers to both delayed and extended release systems for oral administration as well as oral delivery systems designed specifically to modify the release of poorly water soluble drugs (Siepmann, 2007). Budesonide is a synthetic corticosteroid used in Crohn's disease to decrease the symptoms and inflammation associated with the disease, especially at times of flare up.Glucocorticoids bind to Cytosolic Glucocorticoid receptor (GR). GR is activated by ligand binding forming receptor ligand complex. This complex translocates itself into cell nucleus, where it binds to glucocorticoid response elements. (GRE) in the promoter region of target genes. Regulation of gene expression takes place. Proteins are encoded which cause anti-inflammatory action (Anju, 2005; Ewart, 2002).

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EXPERIMENTAL WORK

Materials used:

Equipment's used

Pre formulation Studies

Standard Calibration Curve of Budesonide: A 100 mg of Budesonide was transferred to a 100 ml of standard flask and then dissolved in to the required quantity of phosphate buffer pH 7.5 and then make up to the volume in 100 ml of standard flask.From this stock solution the aliquots of 5µg, 10µg, 15µg, 20µg, and 25µg/ml were withdrawn and volume made up to 10ml. The absorbance of the concentration was measured at 244nm using UV- spectrophotometer.

Drug- excipient compatibility study protocol: In this study the active pharmaceutical ingredients and excipients were mixed and stored at different conditions for variable time periods. Drug and excipients samples were mixed and were stored at 40˚c/75RH and 25˚c/60RH for one month duration. After one month the samples were collected and observed for any colour changes. In this study drug and excipients were mixed in following ratio's

Study of interaction of the drug with excipients used in the formula*:* Infrared spectrum of Budesonide with used polymers was recorded on FT-IR spectrophotometer using Potassium bromide disc method.

Table 1. List of Raw materials

S. No.	Name of the Raw material	Source of Materials
1.	Budesonide	MulBerry Chemical Pvt. Ltd., Mumbai
2.	Sugar Spheres	M.B. Sugars & Pharmaceuticals, Nashik
3.	Aqua coat ECD (30%)	Signet Chemical Corporation, Mumbai
4.	Acetyl Tributyl Citrate	Safine Chemicals Pvt. Limited, Hyderabad
5.	Talc	Mohanlal Dayaram Co., Hyderabad
6.	Eudragit L 30 D 55	Rohm Gmbh, Germany
7.	Triethyl Citrate	Vasco Scientific Pvt. Ltd., Mumbai
8.	Tween 80	Merck Chemical Limited, Mumbai

Equipment's used:

Table 2. List of Equipment's

S. No.	Process Equipment	Manufacturer
1.	Fluid bed processor	Umang Pharma Pvt. Ltd., Mumbai
2.	Mechanical Stirrer	Remi motors Pvt. Ltd., Chennai
3.	Capsule Filling Machine	Karnavati Engineering Limited, Gujarat
4.	HPLC	Waters USA
5.	Dissolution Tester USP	Electro lab, Mumbai
6.	Digitals Balance	Ohaus Carp Ltd., USA
7.	pH meter	Polmon Instruments Ltd., Hyderabad

Table 3. Drug and Excipients ratio

S.No.	Drug + Excipient	Ratio
1.	Drug + Aquacoat ECD (30%)	1:5
2.	Drug + Talc	1:1
3.	Drug + Acetyl tributyl citrate	1:1
4.	Drug + Eudragit L30 D55	1:5
5.	Drug + Triethyl citrate	1:1
6.	Drug + Tween 80	1:5

Table 4. Innovator's product details

S.No.	Parameter	Details
1	Brand name	Entocort EC
2	Strengths	3mg, 6mg, 9mg
3	Capsule size	Size 1
4	Total capsule weight	436.0 mg
5	Empty capsule weight	75.0 mg
6	Pellets weight	361.0mg
7	Pellets size	16/18#
8	Distributed by	Prometheus Labs Inc., Sweden.

Table 5. Stability conditions applied in the study

Storage conditions	Duration
40˚c ± 2˚c / 75% RH ± 5%	1,2 months
25˚c ± 2˚c / 60% RH ± 5%	1,2 months

Table 6. Calibration curve of Budesonide

S. No.	Concentration in(mcg/ml)	Absorbance at 274 nm
1	5	0.080
2	10	0.162
3	15	0.242
4	20	0.321
5	25	0.391

Table 7. Drug – Excipients Compatibility Study

S.No	Drug + Excipient	Initial	After 1 month at 40˚c / 75%RH	After 1 month at 25˚c / 60 % RH	Compatible
1.	Drug	White powder	NCC	NCC	Yes
2.	Drug +Aquacoat ECD	White suspension	NCC	NCC	Yes
3.	Drug+ Talc	White powder	NCC	NCC	Yes
4.	Drug+ Acetyl tri butyl citrate	White suspension	NCC	NCC	Yes
5.	Drug+ Eudragit L30 D55	White suspension	NCC	NCC	Yes
6.	Drug+ Triethyl citrate	White suspension	NCC	NCC	Yes
7.	Drug+ Tween 80	White powder	NCC	NCC	Yes

The absorption maxima in spectrum obtained with the substance being examined correspond in the position and the relative intensity to those in the IR spectra of budesonide and polymers respectively.

Particle size analysis: Determination of particle size of drug is done by Malvern Mastersizer 2000.Formulation development

Innovator product information:

Drug and polymer matrix layering on sugar spheres: The required quantity of sugar spheres (18/20#) were weighed and transferred into a fluidized bed processor and required quantity of acetyl tributyl citrate and talc were dissolved in specified volume of water. Required volume of aqua coat ECD was added to above solution under continuous stirring. Later required quantity of budesonide was dispersed in above suspension by stirring. This suspension was sprayed on sugar spheres by bottom spray technique. This drug-polymer layered pellets were further used for enteric coating.

Enteric coating by using Eudragit L30 D55: The required quantity of drug-polymer matrix layered pellets were loaded into the FBC and required quantity of triethyl citrate, tween 80 and eudragit L30 D55 were dissolved in specified volume of water under continuous stirring for 20 min. Later required quantity of talc was added to the above solution and sprayed on drug-polymer matrix layered pellets in bottom spray FBC.

Stability studies: In order to assess the stability of drug product, accelerated stability studies were conducted for the optimized formulation of budesonide MR capsules. The formulation was kept in 60^0c wide mouth HDPE container containing 1g silica gel canister and pharma grade polyester cotton closed with CRC closure with HS123 printed liner.

The products charged for stability were to be monitored for the following parameters:

- Appearance
- Assay
- Moisture determination (Mettler-toledo moisture analyser)
- Dissolution

RESULTS AND DISCUSSION

Drug – Excipients Compatibility Study: In this study, the active pharmaceutical ingredient and excipients were mixed separately and stored at different conditions for a time period of 1 month. The physical properties (colour change) was monitored regularly.

The change in the colour in any mixture was the basis for disregarding the study.Compatibility studies at different temperatures and relative humidity showed that the drug itself was stable at higher temperature and relative humidity, as well as compatible with all the above excipients.

Particle Size Analysis: Particle size analysis of the powder indicated that 90% of the particles were below 4.927 µm.

Dissolution: In-Vitro dissolution profiles of budesonide modified release capsules (3mg) prepared in different trails and comparison of dissolution profiles of innovator's and optimized formulation.

Stability study: After two months storage at 40°C/75%RH and 25°C/60%RH in stability testing, the formulation F9 could show no difference in the release profiles and physical properties. Thus, the formulation was found to be stable.

Table 8. Results of particle size analysis

D(0.1)	D(0.5)	D(0.9)
0.72µm	1.59 µm	4.53 µm

Table 9. Cumulative% drug release of budesonide MR Capsules in the formulation trails and Innovator product

FORMULATION	pH 7.5 phosphate buffer					0.1N HCl
	1 hr	2 hr	4hr	6hr	8hr	2hr
F1	70.12	78.91	79.81	86.23	89.61	1.01
F2	68.21	77.22	82.13	86.81	90.12	0.71
F3	67.72	75.91	84.31	88.23	91.73	0.65
F4	67.13	75.43	84.91	89.45	92.94	0.40
F5	64.10	74.81	90.12	91.32	94.33	0.93
F6	64.61	78.32	92.42	93.14	94.83	0.82
F7	63.92	78.81	93.11	94.62	95.52	0.59
F8	64.12	79.22	93.60	95.92	96.14	0.38
F9	63.51	81.01	96.23	98.51	99.33	0.23
INNOVATOR	62.01	81.91	93.51	97.13	99.24	0.27

Table 10. Dissolution profile of stability data

Buffer	Time interval (hrs)	Cumulative% drug release				
			At 40˚c/75%RH		At 25˚c/60%RH	
		Initial	1 month	2 month	1 month	2 month
0.1N Hcl	2	0.23	0	0	0	0
	1	63.5	63.0	62.6	63.4	63.1
	2	81.0	81.3	81.2	80.9	80.8
pH 7.5 phosphate buffer	4	96.2	96.4	95.8	95.9	96.1
	6	98.5	98.3	98.3	98.4	98.1
	8	99.8	99.9	99.9	99.5	99.5

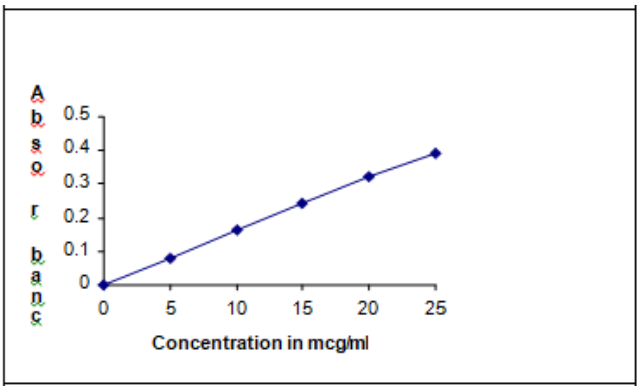

Fig 1:Calibration curve of Budesonide in Phosphate Buffer in pH 7.5

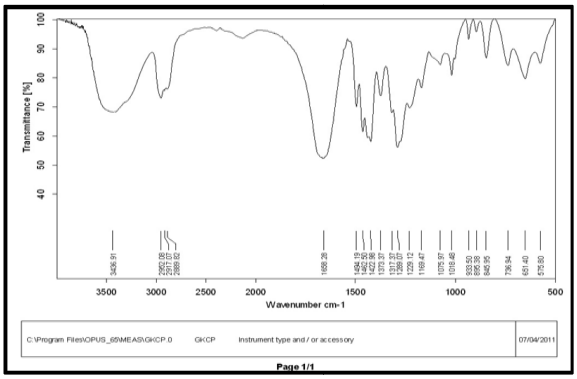

Fig 2: FT-IR spectrum of Budesonide

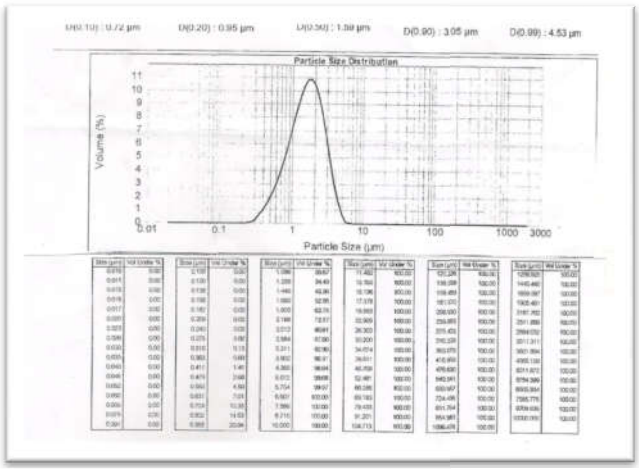

Fig. 3. Determination of particle size of drug is done by Malvern mastersizer 2000

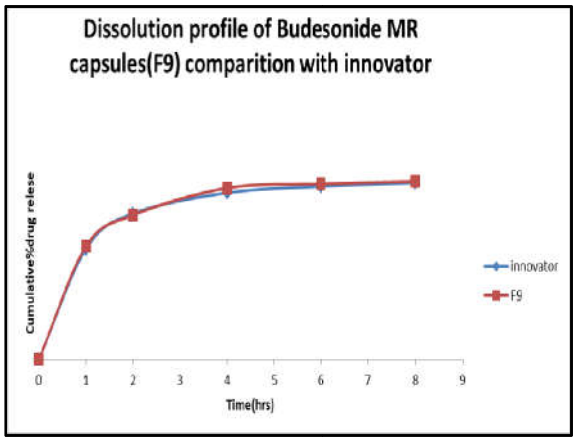

Fig. 4. Dissolution profile of Budesonide MR capsules(F9) comparison with innovator

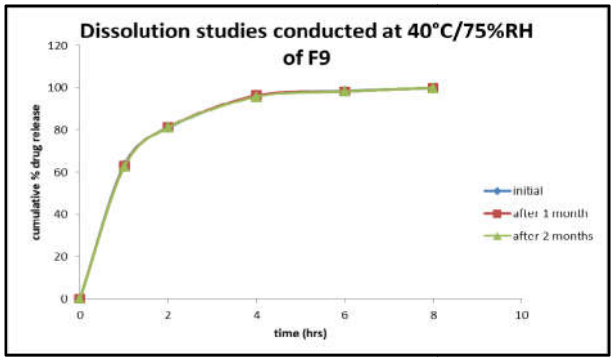

Fig 5. Dissolution studies conducted at 40°C/75%RH of F9

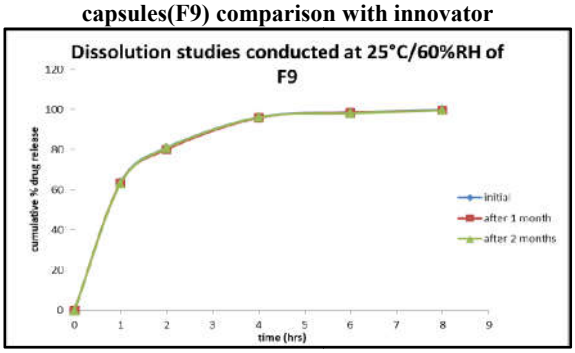

Fig 6. Dissolution studies conducted at 25°C/60%RH of F9

Conclusion

The study was undertaken with an aim to formulate budesonide modified release capsules. The drug budesonide is corticosteroid and currently used for the treatment of Crohn's disease. was carried out by solution/suspension matrix layering , first drug and polymer solutions were mixed, coating was done on the sugar spheres; further enteric coating was done on the polymer matrix coated pellets. Different trails were conducted with various percentages of polymers and other excipients in the first (drug loading) and second stage (during enteric coating) and the formulation was finally optimized based on the Cumulative % drug release. The in-vitro dissolution tests were performed for all trails. Dissolution profile of formulation F9 matched with the innovator's product and was found to be satisfactory. Stability studies were conducted for two months.

During this study, the formulation F9 was found to be stable and no differences in the assay, moisture content and release characteristics were noticed.

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