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FORMULATION & EVALUATION OF BUDESONIDE CONTROLLED RELEASE CAPSULES BY SUSPENSION LAYERING METHOD

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ABSTRACT

The study was undertaken with an aim to formulate budesonide controlled release capsules. The drug budesonide is corticosteroid and used for the treatment of Crohn's disease. Before going to develop the formulation, a detail product literature review was carried out to know about the innovator's product and the patent status of the drug. Preformulation study involving drug -excipients compatibility was done initially and results indicated the compatibility with all the tested excipients. The study was carried out by solution/suspension matrix layering method. In this method first drug and polymer solutions were mixed, coating was done on the sugar spheres; further enteric coating was done on polymer matrix coated pellets. Different trials were conducted with various percentages of polymer in first stage and second stage (during enteric coating), and the formulation was finally optimized based on the drug release profile. Pellets were evaluated by *in vitro* dissolution. These studies revealed that the F6 pellets were found to be release the drug almost comparable to that of innovator's product. Further, the F6 formulation was subjected to release studies at different pH conditions and found to have similar release profile as that of innovator. The *in vitro* dissolution tests were performed and f2 values were calculated for all trials. Dissolution profile of formulation F6 matched with that of the innovator's product and f2 value was satisfactory. Stability studies were also performed; both accelerated and long term stability studies were conducted for two months. During this study, the formulation F6 was found to be stable and no differences in the assay and release characteristics were noticed.

Key words: Multiunit Pellet Systems, Suspension Layering Method, Budesonide, Controlled Release.

INTRODUCTION

Pharmaceutical oral dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical dosage forms today include tablets, capsules, granules and pellets [1-4]. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture and/or for providing a desired drug delivery system. Over the past 30 years as the expense and complications involved in marketing new drugs entities have increased with concomitant recognition of therapeutic advantage of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system [5-9].

Budesonide is a newer type of corticosteroid for treating Crohn's disease. Like other corticosteroids, budesonide is a potent anti-inflammatory medication. Unlike other corticosteroids, however, budesonide acts only *via* direct contact with the inflamed tissues and not systemically [10-12]. As soon as budesonide is absorbed into
the body, the liver converts it into inactive chemicals. Therefore, for effective treatment of Crohn's disease, budesonide, like topical 5-ASA, must be brought into direct contact with the inflamed intestinal tissue [13-17].

The main objective of the work is to do develop a pharmaceutically equivalent controlled release formulation of a corticosteroid, Budesonide comparable to innovator's formulation for the treatment of Crohn's disease.

EXPERIMENTAL

Materials

Hydroxy propyl methyl cellulose E5,Tween 80, Ethyl cellulose 7cps, Hydroxy propyl methyl cellulose pthalate 55s, Eudragit L-100 55, Aqua coat ECD, Diethyl phthalate, Triethyl citrate, Cetyl alcohol, Talc, Povidone, Isopropyl alcohol.

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METHODS

Solution/Suspension Layering By Matrix Layer Formulation

Solution/suspension layering involved only two steps,

1. Drug and polymer matrix layering
2. Enteric coating

i) Enteric coating of polymer coated pellets by using HPMCP-55s

ii) Enteric coating by using Eudragit L-100-55

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 triethyl citrate and polysorbate – 80 were dissolved in specified volume of water. Required volume of Aquacoat ECD (signet chem. Corp.) 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 and polymer matrix layered pellets were used for enteric coating.

Enteric Coating Of Polymer Coated Pellets By Using HPMCP-55s.

The required polymer coated pellets were loaded into the FBC and required quantity of diethyl phthalate and cetyl alcohol were dissolved in specified volume of isopropyl alcohol and acetone mixture. Later, Hydroxy propyl methyl cellulose phthalate 55s, dissolved in above solution and stirred for 20min. required quantity of talc was added to solution by stirring. The solution was sprayed on polymer coated pellets by bottom spray FBC.

Enteric coating by using Eudragit L-100-55

The required quantity of drug-polymer matrix layered pellets were loaded into the FBC and required quantity of triethyl citrate and Eudragit L-100-55 were dissolved in specified volume of isopropyl alcohol and acetone mixture under continuous stirring for 20min. later required quantity of talc was added to above solution on drug-polymer matrix layered pellets in bottom spray FBC.

Table 1: Composition Of Drug And Polymer Matrix Coated Pellets For The Formulation Trials (F1-F6).

Name of the Excipients	Weight of the Excipients (gm)					
Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Budesonide (1%)	6.0	6.0	6.0	6.0	6.0	6.0
Sugar spheres	575	575	575	575	575	575
Aquacoat ECD	12.0	12.0	10.5	10.5	9.0	9.0
Polysorbate (10% of Drug)	0.60	0.60	0.60	0.60	0.60	0.60
Tri ethyl citrate (20% of polymer)	2.40	2.40	2.10	2.10	1.80	1.80
Water	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Composition of Material Used For Matrix Layering

Name of the excipients	Weight of the excipients(mg/gm)	FBC operation conditions
Budesonide	10	Atomizing air pressure-2lb/in^2(2bar) Inlet temperature – 50^{o}c Bed temperature – 43^{o}c Spray RPM – 3-8 Exhaust RPM (blower) – 299
Sugar spheres	834.66	
Aquacoat ECD	23.3	
Polysorbate 80	1	
Triethyl citrate	5	
Water	q.s	

Table 3: Composition of Material Used For Enteric Coating

Name of the excipients	Weight of the excipients (mg/gm)	FBC operation conditions
Hydroxy propyl methyl cellulose phthalate 55s	120	Atomizing air pressure-2lb/in^2(2bar) Inlet temperature – 48^{o}c Bed temperature – 43^{o}c Spray RPM – 8-10 Exhaust RPM (blower) – 299
Diethyl phthalate	12	
Cetyl alcohol	6	
Talc	5	
Acetone: Iso propyl alcohol	q.s	

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Table 4: Formulation Ingredients for Enteric Coating and Operation Conditions

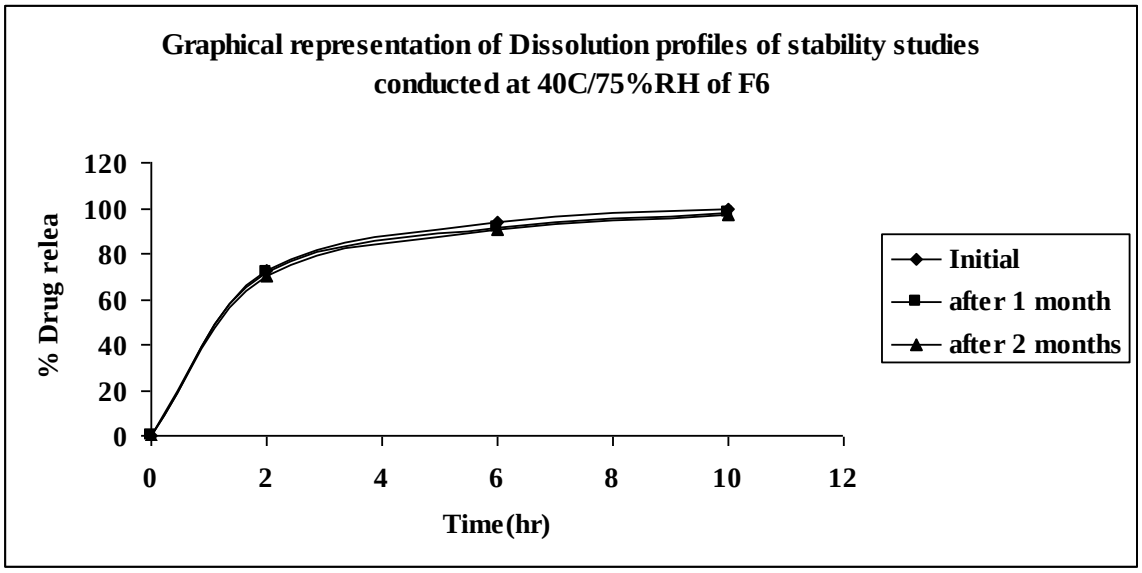
Name of the excipients	Weight of the excipients (mg/gm)	FBC operation Conditions
Eudragit L-100 55	120	Atomizing air pressure-2lb/in^2(2bar) Inlet temperature – 50^{o}c Bed temperature – 40^{o}c Spray RPM – 3-6 Exhaust RPM (blower) – 299
Triethyl citrate	12	
Talc	30	
Acetone: Iso propyl alcohol(3:1)	q.s	

STABILITY PROTOCOL

Table 5: Stability Conditions Applied in the Study

Storage conditions	Duration
40^{0}C±2^{0}C/75%RH±5%	1,2 Months
25^{0}C±2^{0}C/60%RH±5%	1,2 Months

Figure 1: Graphical Representation of Dissolution Profiles Of Stability Studies Conducted at 25^{0}C/60%RH OF F6



RESULTS AND DISCUSSION

Dissolution of pellets

Dissolution was conducted first two hours in pH 1.2 buffers and then followed by 10hrs in phosphate buffer pH 7.5.

Assay of enteric coated pellets

Assay standard preparation: about 50mg of budesonide working standard was accurately weighed in a 100ml volumetric flask. About 50ml of acetonitrile was added and sonicated for 10min. made up to 100ml with 3.2 pH buffer. Five ml of above standard was taken into 100ml volumetric flask and made up to 100ml with pH 3.2 buffer.

Assay test preparation: about 1.25gm of budesonide enteric pellets were taken into 100ml volumetric flask containing 50ml acetonitrile and sonicated for 30min. made up to volume with pH 3.2 buffer and filtered through 0.45µ membrane filter.

Five ml of above solution was taken into 100ml volumetric flask and diluted with pH3.2 buffer up to 100ml.

The following equation was used to calculate the assay value of given sample.

$$\frac{At \times 5 \times 100 \times 25 \times P \times 1000}{As \times 100 \times 100 \times Wt \times 5 \times 100}$$

Where,

At = Peak area of budesonide sample.

As = Peak area budesonide for working standard preparation

Wt = Weight of budesonide test sample taken for assay

P = Potency of budesonide

Stability Studies

In order to assess the stability of drug product, accelerated stability studies were conducted for the following development batches of budesonide CR capsules. The development batches were kept on stability

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in 60cc wide mouth HDPE container containing 1g silica gel canister and Pharma grade polyester cotton closed with CRC closure with HS123 printed liner.

CONCLUSION

Compatibility studies at different temperatures and relative humidity showed that drug itself was stable at higher temperature and relative humidity, as well as compatible with all above used excipients**.**

From the drug release profile and histograms, it was found that Eudragit L100 55 enteric coated formulation (F1) released more drugs in comparison with HPMC phthalate enteric coated formulation (F2). However, F1 and F2 were not matching in their release profile with that of innovator, failing at all time intervals. From the drug release profile and histograms, it was found that Eudragit L100 55 enteric coated formulation (F4) released more drugs in comparison with HPMC phthalate enteric coated formulation (F3). Thus, the nature of the enteric polymer could also affect the release rate from dosage form.

From the drug release profile and histograms, it was observed that Eudragit L100 55 enteric coated formulation (F5) released more drugs in comparison with HPMC phthalate enteric coated formulation (F6). Thus, the nature of the enteric polymer could also affect the release rate from dosage form. Drug release from F5 was not matching with that of innovator, failing at all time intervals as per innovator's profile. Drug release from F6 was matching with that of innovator at all-time points, and was considered as best formulation when with other formulations. Formulation F4 was also matching with that of innovator at 3rd and 4th time points, but F6 was matching with that of innovator at all time intervals. So, formulation F6 was found suitable for budesonide CR 3mg capsules preparation.

In Stability studies observed that both accelerated and long term stability studies were conducted for two months. During this study, the formulation F6 was found to be stable and no differences in the assay and release characteristics were noticed.

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