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A Bharathi *et al.*
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Original Article

# Formulation and Evaluation of Budesonide Controlled-ileal Release Pellets

Bharathi Arigela*, Haritha Mandava,Chandra Sekhar Naik D, Ramakrishna Vemugunta
Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Pinnamaneni Polyclinic Road, Moghalrajpuram, Vijayawada-520010, Andhra Pradesh, India .

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ABSTRACT

**Objective:** The objective of the present study was to formulate and evaluate budesonide controlled-release ileal pellets different from the innovator's method of manufacturing, with the similar in-vitro release profiles. Budesonide controlled release ileal pellets are formulated by using combination of matrix coating method, barrier coating method and enteric coating method. The low efficacy of currently available oral BUDESONIDE formulations was because of readily absorbability by the gastrointestinal tract, which limits the amount of agent delivered to the ileum and colon. Hence few like controlled release systems and palletisation techniques are incorporated for its applications effective availability at ileum. **Results:** In this study the innovator was compared with regarding its pH solubility profile, post parameters and the dissolution profile of the optimised formulated product. **Conclusion:** The release was found similar to that of innovator product, so the prepared product was said to be equivalent with Entocort EC.

**Keywords:** Budesonide, controlled release, pellets, innovator product.

## 1. INTRODUCTION

Budesonide being a glucocorticoid with high topical anti-inflammatory activity has been used for many years in the treatment of inflammatory airway diseases for the low systemic activity of budesonide due to its rapid metabolism to biologically inactive. Systemic adverse effects, such as reduced bone density and disturbed adrenal function, which is associated with traditional glucocorticoid treatment, are less with long-term treatment with budesonide with improved safety profile led to its use as a locally acting agent in the treatment of inflammatory bowel diseases, such as Crohn's disease [22, 19] and collagenous colitis. Oral

**Corresponding author ***
**Bharathi. Agirela**
Department of Pharmaceutics,
KVSR Siddhartha College of Pharmaceutical Sciences,
Vijayawada-520010, Andhra Pradesh, India.
Email: bharathi.agirela004@gmail.com

budesonide though readily absorbed by the gastrointestinal tract, limits the amount of agent delivered to the ileum and colon. Controlled release (CR) [8] systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by design of its system itself. So it facilitates the availability of budesonide to ileum and colon [25]. Pellets [1, 3] are free-flowing spherical granules with narrow size distribution, varying between 500 and 1500 mm for pharmaceutical applications such as pellets smaller size can rapidly empty the stomach, uniform drug dispersion in gastrointestinal tract (GIT) can reduce the risk of side effect due to high drug concentration, reduction in intra and inter-subject variability in gastric emptying times, maximise drug absorption and reduce the peak plasma fluctuations, spherical shape exhibits a good flow property with narrow size distribution.

BUDESONIDE controlled-release capsules [17] (Entocort, AstraZeneca) contain small pellets (1.0–1.4 mm in diameter) which are coated to prevent dissolution in gastric juice, but which dissolve at pH > 5.5,in which BUDESONIDE dose being absorbed in the ileum and colon is more than 60%[(14)].

The objective of the study is to develop a method different from the innovator's method of manufacturing, with the similar in-vitro release profiles.

## 2. MATERIALS AND METHODS

**MATERIALS:** Sugar spheres, Ethyl cellulose [21], Tween 80, PVK 30, Isopropyl alcohol, Diethyl phthalate, Talc, HPMC E5 [2], Hypromellose phthalate 55S, Acetone, Purified water, Polysorbate 80 [4], Cetyl alcohol, Triethyl citrate[6, 5].

**METHODS:**

**pH SOLUBILITY PROFILE[18] OF BUDESONIDE**:

The procedure was carried out by method of HPLC.

**Chromatographic conditions:**

Column: Supelco C18 (4.6 X 250 mm), 5µm

Flow rate: 1.5ml /min

Wavelength: 240nm

Column temperature: $35^0$C

Injection volume: 100µl

Run time: 20 min

Instrumental conditions:

Medium: water , 0.1 N HCl, pH – 3 acetate buffer USP, pH 4.5 acetate buffer USP, pH 6.8 phosphate buffer USP, pH 7.2 phosphate buffer USP.

Orbital shaking: 45mins

Volume of medium: 250ml

Mobile phase preparation:

Mobile phase –pH 3.2 buffer: acetonitrile.

**Standard preparation:**

40 mg of budesonide (working standard) dissolved in 100ml; 50 ml of acetonitrile was added, sonicated for 5 min,diluted to volume with acetonitrile and mixed. Transfer 5ml of solution into 50ml volumetric flask and diluted to volume with specific buffer and mixed.

**Sample preparation:**

Weigh 10 mg of budesonide into 500ml of volumetric flask and add 250ml of specific buffer. Shake in shaker for 45 min and after that collect samples and filter through 0.45µm of finer porosity. The filtrate the injected into chromatographic system and calculated the percent of drug in respective buffers.

Procedure:

Separately injected 100µl of standard and sample preparation into chromatograph and recorded the chromatograms. Calculate the per cent solubility of budesonide in different media by using below calculation.

**Sample peak area X standard weight (mg) X dissolution medium X % purity X 100**

**Standard peak area X sample weight (mg) X volumetric flask X 100**

**Mobile phase preparation:**

**a) pH 3.2 buffer preparation**: 6.34gm monobasic sodium phosphate was dissolved in water.0.3ml of phosphoric acid was added and diluted in water to 2000ml and mixed .pH was adjusted to 3.2 +/- 0.1 with orthophosphoric acid and filtered the buffer with 0.45 µm membrane filter and degas it.

**b) Mobile phase composition**: Buffer and acetonitrile in ratio 62:38 v/v respectively. Diluent preparation– pH 3.2 buffer.

Sample preparation: 50 mg drug was taken in 1000 ml volumetric flask, added 15 ml of acetonitrile and sonicated for 30mins and make up with different diluent (pH 3.2 buffer) and filter through 0.45 µm, then filtrate injected into chromatographic system.

Procedure: Compatibility studies are carried out by mixing definite proportion of drug excipient and kept in glass vials, which is stored at $55^0$C for 1 month. Afterwards separately injected100µl of sample preparation into chromatograph and recorded the chromatograms. Calculate the different impurities in samples.

**Table: 1 Formulation of budesonide Controlled Release Pellets**

| | Mg/capsule | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ingredients** | T-1 | T-2 | T-3 | T-4 | T-5 | T-6 | T-7 | T-8 | T-9 |
| Sugar spheres | 265.0 | 262.0 | 260.0 | 245.0 | 250.0 | 260.0 | 260.0 | 250.0 | 255.0 |
| Drug(BUDESONIDE ) | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 |
| PVP K 30 | 3.6 | 3.6 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Ethyl cellulose | 0.9 | 2.4 | 10.0 | 25.0 | 20.0 | 15 | 15.0 | 17.50 | 14.6 |
| Tween 80 | 0.3 | 0.3 | 0.9 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| Isopropyl alcohol | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

**EVALUATION** [1]: The controlled release capsules are evaluated by the following tests

1) **Weight variation**:

Individual weights of 20 capsules were taken and the average weight was determined.

The % deviation is represented as

Maximum deviation = $\frac{(WH - A) \times 100}{A}$

Minimum deviation = $\frac{(A - WL) \times 100}{A}$

Where,

A = average weight of capsules

$W_H$ = highest weight of capsule in 20 capsules

$W_L$=lowest weight of capsule in 20 capsules

2) **CONTENT UNIFORMITY**:

The content uniformity test is used to ensure that every capsule contains the amount of drug substance intended with very little variation among capsules in a batch. For content uniformity test, representative samples of 30 tablets are selected and 10 are assayed individually. At least 9 must lie within +/ - 15% of the declared potency and none may exceed +/- 25%.

3) **WATER CONTENT**:

Transfer 35 to 40 ml of methanol to the titration vessel and titrate vessel and titrate with Karl Fischer reagent to the electrometric point, to consume any moisture present (disregard the volume consumed, since it does not enter into the calculation). Use powder from five tables, ground to fine powder in an atmosphere of temperature and relative humidity known not to influence the results. Accurately weigh and transfer about 300mg of the powder into the titration vessel, mix and titrate with Karl Fischer reagent to the electrometric end point .calculate the water content by the formula

$$\frac{S \times F \times 100}{W}$$

The water content should be 1.5 +/- 0.5% w/w

3) **LOCK LENGTH**: it was tested by using Vernier callipers.

The lock length should be 19.0 +/- 0.5 mm.

**STABILITY STUDIES**:

The optimized trial batch i.e. ninth one was subjected to "ACCELERATED STABILITY TESTING" at 40 +/- 2°C / 75 +/- 5% RH , 30 +/- 2°C / 65 +/- 5% RH and 25 +/- 2°C / 60 +/- 5% RH for 3 months in HDPE containers.

## 3. RESULTS AND DISCUSSION

**Table 2: pH Solubility Profile of budesonide**

| Shaking time(in min) | % SOLUBILITY | | | | | |
|---|---|---|---|---|---|---|
| | Water | 0.1 N HCl | pH -3 (USP) | pH - 4.5(USP) | pH - 6.8(USP) | pH- 7.5(USP) |
| 45min | 39.1 | 40.8 | 46.1 | 38.5 | 35.3 | 33.8 |

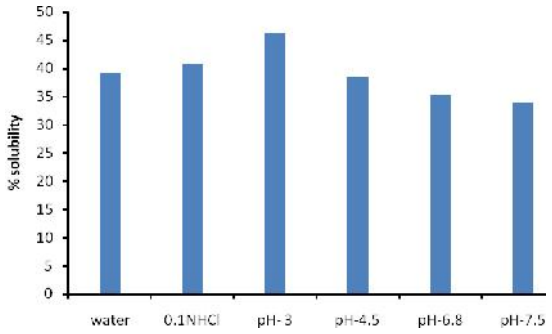


**Fig 1: solubility profile**

The capsules are evaluated for the following tests:

**Table: 3 Evaluation of capsules for weight variation, content uniformity, water content, lock length.**

| Trial batches | Evaluation parameter | | | |
|---|---|---|---|---|
| | Weight variation | Content uniformity | Water content (% w/w) | Lock length (mm) |
| 1 | Within limits | Complies | 1.85 | 18.8 |
| 2 | Within limits | Complies | 1.8 | 19 |
| 3 | Within limits | Complies | 1.75 | 19 |
| 4 | Within limits | Complies | 1.8 | 19.1 |
| 5 | Within limits | Complies | 1.8 | 19 |
| 6 | Within limits | Complies | 1.76 | 19 |
| 7 | Within limits | Complies | 1.7 | 18.9 |
| 8 | Within limits | Complies | 1.75 | 19 |
| 9 | Within limits | Complies | 1.75 | 19 |

## DISSOLUTION PROFILE [16]

**Table: 4 In-vitro dissolution of all trial batches**

| pH | Time (min) | % drug released | | Trial -1 | Trial-2 | Trial-3 | Trial-4 | Trial-5 | Trial-6 | Trial-7 | Trial-8 | Trial-9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Limits | Innovator product | | | | | | | | | |
| 1.2 | 120 | LT 10% | --- | -- | -- | -- | -- | --- | -- | -- | -- | -- |
| 7.5 | 240 | 15-50% | 37% | 99.4 | 95.4 | 65 | 20.4 | 33 | 45 | 41.5 | 39 | 36.5 |
| | 360 | 35-50% | 47% | 99.9 | 96.7 | 79.5 | 40.7 | 36.2 | 65.9 | 58 | 48 | 46.5 |
| | 480 | 50-70% | 65% | 101.2 | 99.6 | 88 | 45 | 57 | 87.7 | 75.6 | 68 | 65 |
| | 600 | NLT 60% | 78% | 103 | 99.8 | 95 | 45 | 60.1 | 90.8 | 80.4 | 78.3 | 78 |
| | 720 | NLT 80% | 87.2% | 103.1 | 101.1 | 98.1 | 46.9 | 65 | 95.2 | 92.3 | 90.7 | 87.1 |

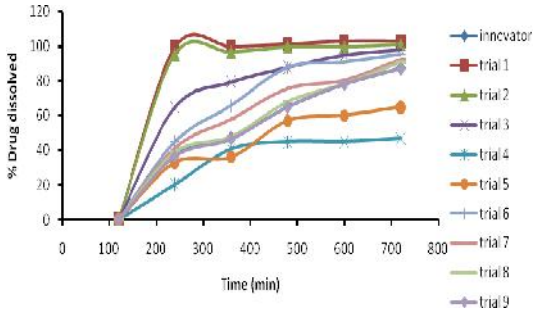


**Fig 2: dissolution profile of all trial batches**

**STABILITY STUDIES DATA:**

Stability studies were conducted for the optimized batch and the results were found satisfactory.

At 40°C +/- 2°C /75 +/- 5% RH

**Table 5: stability studies data at 40ºC +/- 2ºC /75 +/- 5% RH**

| Parameter | Initially | First month | Third month |
|---|---|---|---|
| Description | White spherical pellets | White spherical pellets | White spherical pellets |
| Water content (%w/w) | 1.75 | 1.75 | 1.76 |
| Assay (%) | 99.9 | 100 | 100 |

**Table 5.1: stability studies data regarding pH at 40ºC +/- 2ºC /75 +/- 5% RH**

| pH | Time (minutes) | % drug released | | |
|---|---|---|---|---|
| | | initially | First month | Third month |
| 1.2 | 120 | 0 | 0 | 0 |
| 7.5 | 240 | 37 | 37.1 | 36 |
| | 360 | 46.9 | 47 | 46.9 |
| | 480 | 65 | 66 | 65 |
| | 600 | 78 | 78 | 78 |
| | 720 | 87 | 87.1 | 87.2 |

At 30°C +/- 2°C /65 +/- 5% RH

**Table 5.2: Stability study data at 30ºC +/- 2ºC /65 +/- 5% RH**

| Parameter | Initially | First month | Third month |
|---|---|---|---|
| Description | White spherical pellets | White spherical pellets | White spherical pellets |
| Water content (%w/w) | 1.75 | 1.75 | 1.76 |
| Assay (%) | 99.9 | 100 | 100 |

**Table 5.3: stability study data regarding pH at 30ºC +/- 2ºC /65 +/- 5% RH**

| pH | Time (minutes) | % drug released | | |
|---|---|---|---|---|
| | | Initially | First month | Third month |
| 1.2 | 120 | 0 | 0 | 0 |
| 7.5 | 240 | 37 | 37.1 | 36 |
| | 360 | 46.9 | 47 | 46.9 |
| | 480 | 65 | 66 | 65 |
| | 600 | 78 | 78 | 78 |
| | 720 | 87 | 87.1 | 87.2 |

The present investigation was undertaken to formulate budesonide controlled release pellets 1% w/w in capsules for treatment of Crohn's disease. Drug excipient compatibility studies were conducted and found all the inactive ingredients were compatible with the drug and shown no interference due to diluents and excipients. As per above solubility data, BUDESONIDE API was more soluble n pH 3.0 (USP) when compared to other buffers. The ninth trial batch was found to be the optimized batch. All the evaluation tests were passed and were within the limits. The optimized trial batch i.e. ninth one was subjected to "ACCELERATED STABILITY TESTING" at 40 +/- 2°C / 75 +/- 5% RH , 30 +/- 2°C / 65 +/- 5% RH and 25 +/- 2°C / 60 +/- 5% RH for 3 months in HDPE containers.

## 4. SUMMARY AND CONCLUSION

1. The active pharmaceutical ingredient budesonide was subjected to Pre-formulation studies which encompass particle size distribution, pH solubility at different pH and the accelerated drug excipient compatibility study and the results obtained with selected excipients showed good compatibility with budesonide.
2. The budesonide controlled release pellets were prepared by using different concentration of ethyl cellulose. But the optimized formula contains the matrix which was coated onto highly water soluble substrate, then applied a barrier /sub coating with 2.0% followed by enteric coating.
3. Then the formulated pellets were filled in size 1 capsule .it showed good results in formulation of stable dosage form of enteric coated pellets.
4. The dissolution studies were performed for all trial batches and the 9th trail batch results were within the limits and it matched with the innovative product (entocortec )
5. The stability of the pellets was determined by conducting "accelerated stability testing" in 40+ /- 2°C/75+/- 5% RH, 30 +/- 2°C/65+/-5% RH for three months.
6. So the release was found similar to that of innovator product, so the prepared product was said to be equivalent with Entocort EC.
7. The method of formulating the pellets with matrix containing 1.8% EC coated on sugar spheres, then sub coating with HPMC E5 2.0% followed by enteric coating with HPMC P 55S (10%) showed the release of drug in a similar manner as that of innovator.

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