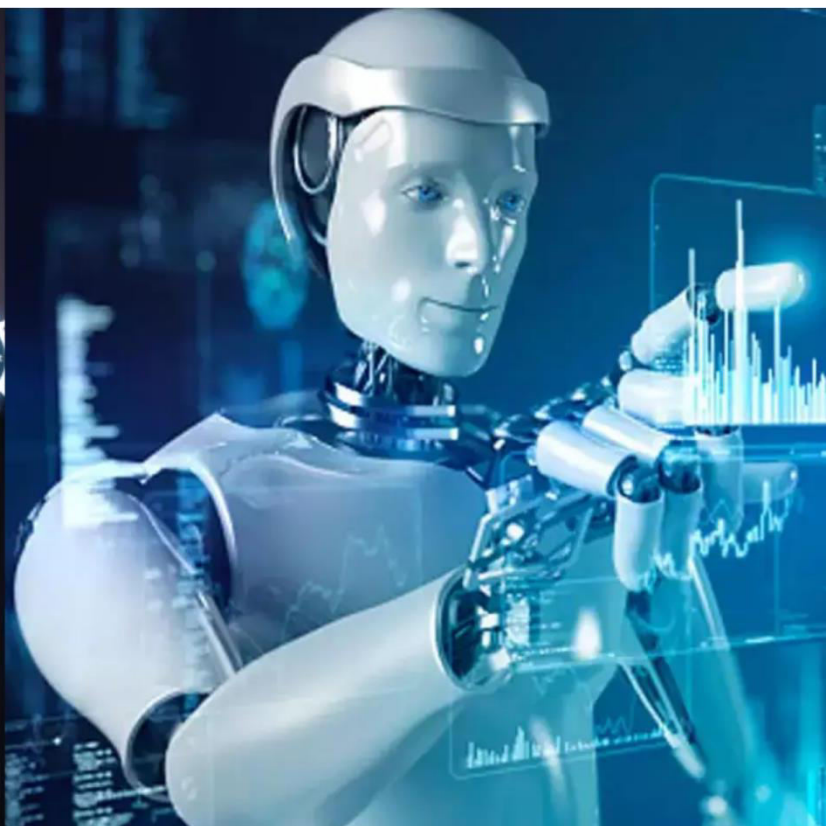




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Formulation and Development of Solid Dispersion Loaded Suppositories for Treatment of Inflammatory Bowel Disease

Prarthana D. Anawade, Aarti L. Gaikwad, Prof. Nilima Chaudhari

JSPM's Rajarshi Shahu College of Pharmacy & Research, Tathawade, Pune, India

JSPM's Rajarshi Shahu College of Pharmacy & Research, Tathawade, Pune, India

Guide, JSPM's Rajarshi Shahu College of Pharmacy & Research, Tathawade, Pune, India

ABSTRACT: The present research work was carried out to formulate and evaluate solid dispersion loaded suppositories of Budesonide for the treatment of inflammatory bowel disease. Budesonide is a glucocorticoid and BCS class II drug possessing low aqueous solubility, which may limit its dissolution and bioavailability. In the present study, solid dispersion of Budesonide was prepared using Soluplus® as a hydrophilic carrier by the spray drying technique. Six solid dispersion batches, SD1 to SD6, were prepared using different drug-to-carrier ratios ranging from 1:1 to 1:11.

The prepared solid dispersions were evaluated for drug content, saturation solubility, in-vitro dissolution and drug-excipient compatibility. FTIR studies indicated compatibility between Budesonide and Soluplus® and suggested molecular dispersion of the drug within the polymeric matrix. Among the prepared batches, SD5 showed enhanced solubility and was selected for further formulation development. The selected solid dispersion was incorporated into rectal suppositories using polyethylene glycol bases by the moulding method. The prepared suppositories were evaluated for appearance, weight variation, drug content, softening time, breaking strength, dissolution and in-vitro drug release.

The formulated solid dispersion loaded suppositories exhibited satisfactory physical and mechanical properties. The detailed dissolution study showed greater Budesonide release from the solid dispersion loaded suppositories compared with plain drug suppositories. The solid dispersion loaded suppositories showed 91.5% drug release at 90 minutes compared with 69% release from plain drug suppositories under the reported experimental conditions. Thus, incorporation of Budesonide solid dispersion into suppositories improved the dissolution performance and may provide a promising approach for localized rectal delivery in inflammatory bowel disease.

KEYWORDS: Budesonide, Solid dispersion, Soluplus®, Spray drying, Suppositories, Inflammatory bowel disease, Ulcerative colitis, Drug dissolution.

I. INTRODUCTION

1.1 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) represents a group of chronic disorders involving persistent inflammation of the gastrointestinal tract. The major forms of IBD are Crohn's disease and ulcerative colitis. These conditions develop through abnormal inflammatory responses within the gastrointestinal system and may produce recurrent symptoms that affect the quality of life of affected individuals.

Ulcerative colitis primarily involves the mucosal lining of the colon and usually begins in the rectal region before extending toward the proximal portions of the colon. Common clinical manifestations include diarrhoea, rectal urgency and the presence of blood in stools. The severity and anatomical extent of inflammation influence the selection of an appropriate therapeutic approach.

1.2 Ulcerative Colitis and Its Treatment

Ulcerative colitis is a relapsing inflammatory disorder in which the colonic mucosa undergoes repeated episodes of inflammation. Pharmacological management may involve aminosalicylates, corticosteroids, immunomodulators and biological therapies depending on the severity and extent of disease.

Topical drug delivery can be particularly useful when inflammation is localized in the distal portion of the gastrointestinal tract. Rectal formulations can provide drug directly to the affected region and may reduce unnecessary systemic exposure compared with therapies administered through systemic routes.

Corticosteroids are commonly used for controlling inflammatory episodes. However, prolonged systemic corticosteroid therapy may be associated with undesirable effects. Therefore, development of a suitable localized delivery system capable of providing the drug at the site of inflammation is of pharmaceutical interest.

1.3 Budesonide

Budesonide is a potent synthetic corticosteroid possessing anti-inflammatory activity and is used in the management of inflammatory bowel conditions. The drug has been investigated for both oral and rectal administration in ulcerative colitis.

Budesonide belongs to Biopharmaceutics Classification System (BCS) Class II, characterized by high permeability and comparatively low aqueous solubility. Its poor aqueous solubility can limit the rate at which the drug dissolves and becomes available for absorption or therapeutic action.

Therefore, improving the dissolution characteristics of Budesonide is an important consideration in the development of an effective pharmaceutical formulation. The thesis work selected a solid dispersion approach to improve the solubility and dissolution behaviour of Budesonide.

1.4 Solid Dispersion

Solid dispersion is a formulation technique used to improve the dissolution characteristics of poorly water-soluble drugs. In this approach, the drug is incorporated into a suitable hydrophilic carrier, which can improve wetting, dispersion and apparent solubility of the drug.

Soluplus® was selected as the carrier for Budesonide in the present study because of its suitability for improving the solubilization of poorly water-soluble substances. Different drug-to-polymer ratios were investigated to identify a formulation providing improved dissolution performance.

The thesis describes six Budesonide-Soluplus® ratios: 1:1, 1:3, 1:5, 1:7, 1:9 and 1:11, designated as SD1, SD2, SD3, SD4, SD5 and SD6, respectively. The prepared solid dispersions were subsequently characterized using drug-content, saturation-solubility, dissolution and instrumental studies.

1.5 Spray Drying Technique

Spray drying is a useful pharmaceutical processing technique for preparing solid dispersions and other particulate drug-delivery systems. The technique converts a liquid feed containing the drug and carrier into dried particles through rapid removal of the solvent.

In the present work, spray drying was employed for the preparation of Budesonide-Soluplus® solid dispersions. Water and acetonitrile were used as the solvent system, and the prepared feed solution was subjected to spray drying under controlled processing conditions.

The thesis reports the use of different Budesonide-to-Soluplus® ratios for preparation of the solid dispersion batches. Spray drying was selected to obtain a finely dispersed drug-carrier system with improved dissolution characteristics.

1.6 Rectal Drug Delivery

Rectal administration provides an alternative route for delivering drugs intended to act in the lower gastrointestinal region. Local administration can produce a relatively high drug concentration near the affected tissue while potentially limiting systemic exposure.

For inflammatory conditions involving the rectum and distal colon, topical rectal dosage forms can provide advantages over conventional systemic administration. Suppositories are one of the dosage forms that can be used for rectal drug delivery.

The thesis emphasizes that topical therapy may provide a quicker response and lower systemic absorption in suitable cases. Suppositories can therefore be considered a useful dosage form for delivering anti-inflammatory drugs directly to the site of inflammation.

1.7 Suppositories as a Drug Delivery System

Suppositories are solid dosage forms intended for administration through the rectal route. After administration, the dosage form undergoes melting, softening or dissolution, allowing the incorporated drug to become available at the site of administration.

In the present formulation, polyethylene glycol bases, specifically PEG 4000 and PEG 6000, were used for preparing Budesonide suppositories. The solid dispersion was incorporated into the molten suppository base and the formulations were prepared using the moulding technique.

The prepared formulations were evaluated for pharmaceutical characteristics including appearance, weight variation, drug content, softening time, breaking strength, dissolution and in-vitro drug release.

1.8 Rationale of the Study

Budesonide has useful anti-inflammatory activity for inflammatory bowel conditions, but its low aqueous solubility presents a formulation challenge. Improving the dissolution behaviour of the drug can contribute to better availability of the drug from the dosage form.

The combination of solid dispersion technology with rectal suppository delivery provides a formulation approach intended to address both aspects. Soluplus® was used as a hydrophilic carrier to improve the dissolution properties of Budesonide, while the suppository system was designed to provide localized rectal delivery.

Therefore, the present study was undertaken to formulate and evaluate Budesonide solid dispersion loaded suppositories as a potential dosage form for the treatment of inflammatory bowel disease.

II. MATERIALS AND METHODS

2.1 Materials Used

Drug

- Budesonide

Polymer/Carrier

- Soluplus®

Suppository Bases

- Polyethylene glycol 4000 (PEG 4000)
- Polyethylene glycol 6000 (PEG 6000)

Other Materials

- Acetonitrile
- Distilled water
- Methanol
- Phosphate buffer pH 7.4
- 0.1 N Hydrochloric acid
- Glycerin
- Whatman filter paper

2.2 Instruments and Analytical Equipment

The experimental work involved the following equipment and analytical techniques:

- UV-Visible spectrophotometer
- FT-IR spectrophotometer
- Spray dryer
- Magnetic stirrer
- Orbital shaker
- USP Type II dissolution apparatus
- Digital weighing balance
- Suppository mould
- Hot plate/heating arrangement

- Glass mortar and pestle
- Oven
- Volumetric flasks
- Whatman filter paper

2.3 Preformulation Study of Budesonide

Preformulation studies were performed to establish the basic characteristics of Budesonide before formulation development. Organoleptic properties, melting point, ultraviolet absorption maximum, calibration behaviour and FT-IR characteristics were evaluated.

The drug was observed as a **white crystalline powder without characteristic odour**. Its reported melting point was **223–232°C**.

2.4 Determination of λ_{max} of Budesonide

A stock solution of Budesonide was prepared by dissolving **100 mg of drug in 100 mL methanol**. One millilitre of this solution was further diluted to 100 mL with phosphate buffer pH 7.4.

The prepared solution was scanned over the wavelength range of **200–400 nm** using a UV-Visible spectrophotometer. The maximum absorbance of Budesonide was obtained at **247 nm**.

2.5 Preparation of Calibration Curve of Budesonide

Different concentrations of Budesonide ranging from **5–25 $\mu\text{g/mL}$** were prepared using phosphate buffer pH 7.4. The absorbance of each solution was measured at **247 nm** against the corresponding blank.

The concentrations used were:

5, 10, 15, 20 and 25 $\mu\text{g/mL}$.

The calibration curve was prepared by plotting absorbance against concentration. The thesis reports the regression equation:

$$y = 0.0385x + 0.0011$$

with:

$$R^2 = 0.9987$$

2.6 Preparation of Budesonide Solid Dispersion

Solid dispersions of Budesonide were prepared using **Soluplus®** as the hydrophilic carrier by the **spray-drying technique**.

Six drug-to-polymer ratios were investigated:

Batch	Budesonide : Soluplus®
SD1	1:1
SD2	1:3
SD3	1:5
SD4	1:7
SD5	1:9
SD6	1:11

Table 1. Composition of Budesonide Solid Dispersion Batches

Ingredients	SD1	SD2	SD3	SD4	SD5	SD6
Budesonide	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
Soluplus®	4 mg	12 mg	20 mg	28 mg	36 mg	44 mg

Water:ACN	1:5	1:5	1:5	1:5	1:5	1:5
Solvent volume	250 mL	250 mL	250 mL	250 mL	250 mL	250 mL

The drug and polymer were dissolved in the solvent system and continuously stirred using a magnetic stirrer to maintain uniformity during spray drying. The reported spray-drying conditions were an **inlet temperature of 90°C**, **feed rate of 6 mL/min**, and **aspirator setting of 25%**. The dried particles were collected and stored for subsequent evaluation

2.7 Preparation of Physical Mixture

Physical mixtures of Budesonide and Soluplus® were prepared separately for comparison with the solid dispersions. The required quantities of drug and polymer were mixed in a glass mortar for approximately **5–15 minutes**. The prepared mixtures were passed through **sieve No. 60** and stored in a desiccator until further evaluation.

2.8 Evaluation of Solid Dispersion

2.8.1 Drug Content

An accurately weighed **40 mg** quantity of solid dispersion or physical mixture was dissolved in phosphate buffer pH 7.4 and filtered. The filtrate was suitably diluted and analysed using a UV spectrophotometer at **247 nm** to determine the drug content.

2.8.2 Saturation Solubility Study

Saturation solubility studies were conducted in:

- Distilled water
- 0.1 N HCl
- Phosphate buffer pH 7.4

Excess drug, physical mixture or solid dispersion was added to **20 mL** of each medium. The samples were equilibrated in an orbital shaker at **30.5°C for 24 hours**.

After equilibration, the suspensions were filtered through Whatman filter paper and analysed by UV spectrophotometry at **247 nm**. The study was performed in triplicate.

2.8.3 In-vitro Dissolution Study of Solid Dispersion

The dissolution behaviour of SD1–SD6 was evaluated using a **USP Type II dissolution apparatus**.

The experimental conditions were:

- Dissolution medium: Phosphate buffer pH 7.4
- Medium volume: 900 mL
- Temperature: 37°C
- Stirring speed: 50 rpm
- Sampling intervals: 30, 45, 60, 75 and 90 minutes
- Analytical wavelength: 247 nm

At each sampling point, an aliquot was withdrawn and replaced with an equivalent quantity of fresh dissolution medium to maintain sink conditions. Cumulative percentage drug release was subsequently calculated.

2.8.4 Drug–Excipient Compatibility Study

Compatibility between Budesonide and formulation excipients was investigated using drug-excipient mixtures prepared at different ratios of **1:1, 1:3, 1:5 and 1:9**.

The mixtures were maintained at **37°C for 30 days**. FT-IR spectra and drug content were subsequently evaluated to identify any significant interaction between the drug and excipients.

2.8.5 FT-IR Spectroscopy

FT-IR analysis was performed on Budesonide, Soluplus®, physical mixture and the prepared solid-dispersion batches. The samples were examined over the spectral range of **400–4000 cm⁻¹** to evaluate characteristic functional groups and possible changes associated with drug-polymer interaction

2.9 Preparation of Solid Dispersion Loaded Suppositories

Before formulation, the suppository mould was calibrated using the base material. The average weight of the prepared suppositories was determined, and the melted base volume was recorded.

The suppositories were prepared using **PEG 4000 and PEG 6000** as water-soluble bases. The thesis reports a PEG 4000:PEG 6000 base composition of **33:47** for the selected formulation.

The bases were heated until melting, after which the required drug or solid dispersion was incorporated with continuous stirring to obtain a homogeneous mixture. The suppository mould was lubricated with glycerin, and the molten formulation was transferred into the mould. The moulds were then maintained at room temperature to allow the suppositories to form.

2.10 Determination of Displacement Value

The displacement value was determined by measuring the quantity of suppository base required and the quantity displaced by the drug or solid dispersion.

The theoretical and practical weights were compared and the displacement produced by the incorporated material was calculated according to the method described in the thesis.

2.11 Evaluation of Suppositories

The prepared suppositories were evaluated for:

1. Drug content
2. Weight variation
3. Appearance
4. Softening time
5. Breaking strength
6. Dissolution time
7. In-vitro drug release

The drug content was determined by melting the suppository, dissolving it in phosphate buffer pH 7.4 and analysing suitable dilutions at **247 nm**.

Softening time was determined using phosphate buffer pH 7.4 maintained at **37°C**. Breaking strength was assessed by progressively increasing the applied weight until the suppository fractured.

For dissolution testing, the suppository was placed in phosphate buffer pH 7.4 maintained at **37 ± 0.5°C**, and the time required for complete melting or dispersion was recorded.

The in-vitro release study was performed using a **USP Type II dissolution apparatus** containing phosphate buffer pH 7.4 at **37°C** and a stirring speed of **50 rpm**. Samples were withdrawn at **30, 45, 60, 75 and 90 minutes**, replacing each withdrawn sample with fresh medium. The samples were analysed at **247 nm** using a UV spectrophotometer.

III. RESULTS AND DISCUSSION

3.1 Preformulation Study

Budesonide was obtained as a white crystalline powder. The melting point was found to be **223–232°C**. UV spectroscopic analysis showed the maximum absorption of Budesonide at **247 nm**, which was subsequently used for quantitative estimation of the drug.

The calibration curve was prepared in phosphate buffer pH 7.4 over a concentration range of **5–25 µg/mL**. A linear relationship was observed between concentration and absorbance, with regression equation $y = 0.0385x + 0.0011$ and $R^2 = 0.9987$.

3.2 Drug Content of Solid Dispersions

The drug content of the prepared solid dispersions ranged from **92% to 98%**, indicating satisfactory drug incorporation during the spray-drying process. SD5 and SD6 showed the highest drug content of **98 ± 0.28%** and **98 ± 0.43%**, respectively.

Batch	Drug Content (%)
SD1	92 ± 0.55
SD2	94 ± 0.73
SD3	93 ± 0.57

SD4	96 ± 0.35
SD5	98 ± 0.28
SD6	98 ± 0.43

3.3 Saturation Solubility

Formation of solid dispersion substantially improved the aqueous solubility of Budesonide. SD5 exhibited approximately **7-fold, 6-fold and 9.3-fold enhancement** in water, 0.1 N HCl and phosphate buffer pH 7.4, respectively, compared with plain Budesonide. SD6 showed a slightly higher solubility than SD5, but the additional improvement was not considered significant.

In phosphate buffer pH 7.4, the solubility increased from **15 ± 0.34 µg/mL for plain drug to 140.04 ± 0.50 µg/mL for SD5.**

3.4 In-vitro Dissolution of Solid Dispersions

All solid-dispersion batches showed improved dissolution compared with plain Budesonide. At 90 minutes, plain Budesonide showed **45.61 ± 1.77%** drug release, whereas SD5 and SD6 showed **96.39 ± 1.29%** and **96.36 ± 1.42%**, respectively.

The enhanced release may be associated with improved wetting and molecular dispersion of Budesonide within the Soluplus® matrix following spray drying.

Based on the overall formulation findings, **SD5 was selected for further development of the suppository formulation.**

3.5 FT-IR Study

FT-IR evaluation indicated no major incompatibility between Budesonide and Soluplus®. The SD5 spectrum showed changes in some characteristic bands and broadening of peaks, while other functional-group peaks remained identifiable. These findings supported the molecular dispersion of Budesonide within the polymer matrix without significant alteration of the drug structure.

3.6 Evaluation of Suppositories

The plain drug suppository was coded **F1**, while the SD5-loaded suppository was coded **F2**. Both formulations exhibited uniform size, bullet-shaped geometry, white colour and smooth texture. Drug content was within **97–100%**, and weight variation was below **5%**

Both formulations showed adequate mechanical properties. F2 exhibited a shorter softening time than F1, indicating comparatively faster softening of the solid-dispersion formulation.

Parameter	F1	F2
Drug content	97–100%	97–100%
Weight variation	<5%	<5%
Softening time	10–12 min	8–10 min
Breaking strength	65.23 ± 1.56	58.61 ± 2.56

3.7 In-vitro Release from Suppositories

The release profile demonstrated a clear improvement following incorporation of SD5 into the suppository base.

Time (min)	F1 (%)	F2 (%)
30	25.22 ± 1.56	45.67 ± 1.45
45	32.00 ± 1.45	61.49 ± 1.25
60	50.00 ± 2.31	81.00 ± 0.98
75	60.00 ± 1.27	89.00 ± 1.54
90	69.00 ± 1.45	91.50 1.51

IV. CONCLUSION

The present study successfully developed Budesonide solid-dispersion-loaded suppositories using Soluplus® and PEG-based suppository bases. The spray-dried solid dispersion improved the solubility and dissolution behaviour of

Budesonide. Among the prepared batches, SD5 demonstrated satisfactory drug content, enhanced solubility and improved dissolution characteristics and was therefore selected for suppository development.

The SD5-loaded suppository showed acceptable physical and mechanical properties and demonstrated **91.5 ± 1.51% drug release at 90 minutes**, compared with **69 ± 1.45%** from the plain drug suppository.

Therefore, the developed solid-dispersion-loaded suppository represents a promising formulation approach for localized delivery of Budesonide in inflammatory bowel disease. Further in-vivo and pharmacokinetic investigations would be required to establish its therapeutic performance.

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