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Formulation And Optimization Of Eco-Friendly Budesonide-Loaded Natural Polymer Nanoparticles Filled Capsule For Colon-Specific Drug Delivery.

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Abstract: Budesonide, a potent corticosteroid used in inflammatory bowel disease (IBD), suffers from poor site-specific delivery and extensive first-pass metabolism. Colon-specific drug delivery can enhance its local effect and minimize systemic exposure. The present study aimed to formulate eco-friendly budesonide-loaded nanoparticles using biodegradable natural polymers (chitosan, pectin, and alginate) via aqueous ionic-gelation and to optimize key formulation parameters using a Box–Behnken design. The nanoparticles were characterized for particle size, polydispersity index (PDI), zeta potential, morphology, encapsulation efficiency (EE), and in-vitro drug release under simulated gastrointestinal conditions. The optimized nanoparticles were filled into pH-sensitive capsules for colon targeting. The approach avoids toxic organic solvents, employs renewable biopolymers, and aligns with sustainable green chemistry. The expected outcome is a nanoparticle-capsule system with <300 nm particle size, >60 % EE, minimal drug release in stomach/small intestine, and enzyme-triggered release in the colon.

Index Terms - IBD, ulcerative colitis, Crohn’s disease, IBD management, Nanoparticles, Nanoparticles loaded Capsule.

I. INTRODUCTION

1. Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis and Crohn’s disease, remains a global health concern with rising incidence [1]. Budesonide, a locally active glucocorticoid, provides effective anti-inflammatory action but has limited bioavailability due to rapid first-pass metabolism and nonspecific release in the upper gastrointestinal tract [2]. Conventional formulations release the drug prematurely, causing suboptimal colonic concentration and systemic side effects [3].

To overcome these limitations, **colon-targeted nanoparticle delivery** systems have emerged as promising alternatives [4]. Natural polymers such as **chitosan, pectin, and alginate** are biodegradable, biocompatible, mucoadhesive, and susceptible to degradation by colonic microflora [5,6]. These properties make them excellent candidates for **enzyme- and pH-triggered drug release** at the colon. Moreover, combining chitosan (cationic) with anionic polysaccharides such as alginate or pectin forms polyelectrolyte complexes that enhance stability and allow controlled release [7].

Recently, attention has shifted toward **eco-friendly formulation strategies**, emphasizing aqueous processing, solvent-free methods, and the use of renewable polymers [8]. The **ionic-gelation technique** is particularly attractive because it uses water as the reaction medium, mild conditions, and non-toxic cross-linkers such as sodium tripolyphosphate (TPP) or calcium chloride [9]. Such methods align with sustainable pharmaceutical manufacturing principles.

Therefore, the present work aims to develop and optimize **budesonide-loaded natural polymer nanoparticles** using a **green ionic-gelation process**, fill the optimized nanoparticles into **enteric capsules**, and evaluate the system for **colon-specific release** and potential therapeutic application in IBD.

2. Objectives

The main objective of this study is:

- To formulate budesonide-loaded nanoparticles using eco-friendly natural polymers for colon-specific drug delivery.
- To determine drug loading, encapsulation efficiency, and production yield.
- To the evaluation of Budesonide nanoparticles.
- To compare the therapeutic potential of the optimized formulation with conventional budesonide delivery systems.
- To ensure the method of preparation is safe, eco-friendly, and suitable for future applications
- To improve patient adherence.

3. Materials

- **Drug:** Budesonide (≥99 %, API grade).
- **Polymers:** Chitosan (85 % deacetylation), pectin (low-methoxyl), sodium alginate (medium viscosity).
- **Crosslinkers:** Sodium tripolyphosphate (TPP) and calcium chloride ($CaCl_2$).
- **Other reagents:** Acetic acid, phosphate buffer, simulated gastrointestinal fluids (SGF, SIF, SCF), all analytical grade.
- **Capsules:** Hydroxypropyl methylcellulose (HPMC) enteric capsules or hard gelatin capsules coated with Eudragit S100.

4. Methods

➢ Characterization of the drug (Budesonide)

Preformulation Studies

These studies are considered a primary tool for determining the physicochemical profile of the drug moiety before integrating it into a formulation. The drug's nature extremely influences the processing parameters, such as preparation technique, loading efficiency, pharmacokinetic response, and the compatibility of the formulation. Preformulation studies are very important protocols for the formulation of efficacious, stable and safe dosage forms.

1 Physical characterisation

The budesonide powder was evaluated for all characteristics such as taste, appearance, colour, and smell. [48].

2 Assessment of melting point

MP of budesonide was evaluated using a capillary method and an MP apparatus. The budesonide powder is placed in a glass capillary whose one end was already sealed by the flame. The capillary containing budesonide powder was immersed in liquid paraffin inside Thiele's tube and gently heated from below using a Bunsen burner until the budesonide powder inside the capillary began to melt. The temperature at which it starts to melt is observed as the melting point. It was determined in triplicate [49].

3 Solubility

The drug was evaluated in a specified amount of 5 to 10 mg of the drug in 10 ml volumetric flasks, and 10 ml of each solvent (distilled water, 0.1 N HCl, ethanol, chloroform, methanol, acetone, DMSO, and phosphate (pH 7.4)) was added distinctly up to the mark. The flask was shaken vigorously and kept aside for some time. If the drug is insoluble, then samples were sonicated by using a bath sonicator for 30 minutes to 1 hour. Noted down the solubility of the drug in different solvents at room temperature, and this study was conducted three times with each solvent [50].

4 Determination of λmax in 0.1 N HCl

The maximum absorption wavelength (λmax) of budesonide in 0.1 N HCl was identified to ensure precise quantification by UV–Visible spectrophotometry. For this purpose, 10 mg of budesonide was accurately weighed and dissolved in 100 mL of 0.1 N HCl using a volumetric flask to obtain the stock solution. From this solution, 1 mL was withdrawn and diluted to 10 mL with 0.1 N HCl to prepare the working solution. The UV–Visible spectrum of the prepared solution was scanned in the 200–400 nm range using a double-beam UV/Vis spectrophotometer, and the wavelength corresponding to the highest absorbance (λmax) was recorded for subsequent analytical studies [51].

5 Determination of λmax in Phosphate Buffer (pH 7.4)

The maximum absorbance wavelength (λmax) of budesonide in phosphate buffer (pH 7.4) was determined using UV–Visible spectrophotometry. A stock solution was prepared by dissolving 10 mg of budesonide in 100 mL of buffer, from which 1 mL was diluted to 10 mL to obtain a working solution. The spectrum was recorded in the 200–400 nm range, and the λmax was noted [52].

- **Calibration Curve of Budesonide**

6 Calibration Plot in Phosphate Buffer (pH 7.4)

Accurately weighed 10 mg of budesonide was dissolved in 5 mL of H_2PO_4 (pH 7.4) in a 10 mL analytical flask, and the volume was brought up to 10 mL with the same buffer to obtain a stock solution of 1000 µg/mL. From this, 1 mL was transferred into a 10 mL flask and diluted with phosphate buffer to obtain a working solution of 100 µg/mL. From this working solution, aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 mL were withdrawn into separate 10 mL volumetric flasks and diluted to volume with phosphate buffer (pH 7.4) to obtain standard solutions of **2, 4, 6, 8, and 10 µg/mL**. The absorbance was measured at 252 nm against phosphate buffer (pH 7.4) as a blank. Plot the graph.

7 Calibration Curve in 0.1 N hydrochloride

Ten mg of budesonide was accurately weighed and dissolved in 5 mL of 0.1 N HCl in a 10 mL volumetric flask, and the volume was made up to 10 mL with 0.1 N HCl to obtain a stock solution of 1000 µg/mL. From this, 1 mL was withdrawn into a 10 mL volumetric flask and diluted with 0.1 N HCl to obtain a working solution of 100 µg/mL. Aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 mL were transferred into 10 mL volumetric flasks and diluted with 0.1 N HCl to yield concentrations of **2, 4, 6, 8, and 10 µg/mL**. Absorbance was recorded at 252 nm against 0.1 N HCl as blank, and a calibration curve was constructed by plotting **concentration vs absorbance**.

8 Calibration Curve in Phosphate Buffer (pH 6.8)

A stock solution of budesonide (1000 µg/mL) was prepared in acetonitrile. From this, a working solution of 100 µg/mL was obtained by suitable dilution with pH 6.8 phosphate buffer. Standard solutions of **2, 4, 6, 8, and 10 µg/mL** were then prepared by serial dilution of the working solution with pH 6.8 phosphate buffer. All solutions were freshly prepared, filtered through a 0.45 µm syringe filter, and analyzed immediately. Absorbance was measured at 252 nm against buffer blank [53, 54].

10. Formulation of Budesonide-loaded Nanoparticles:

Budesonide-loaded nanoparticles were prepared using a natural polymer such as chitosan by the nanoprecipitation technique. Briefly, accurately 10mg of budesonide was dissolved in a suitable organic solvent like ethanol to form the organic phase. The selected natural polymer was dissolved in deionized water containing a stabilizer such as poloxamer 188 to prevent aggregation. Under continuous magnetic stirring, the organic phase was added dropwise into the aqueous phase, resulting in the spontaneous formation of nanoparticles due to solvent diffusion and polymer precipitation. The suspension was stirred for 2–3 hours to ensure complete solvent evaporation. Nanoparticles were collected by centrifugation, washed repeatedly to remove unentrapped drug and residual solvent, and finally lyophilized to obtain a dry, free-flowing powder suitable for further characterization or encapsulation into colon-targeted capsules. This method produces biodegradable, biocompatible nanoparticles with controlled size and drug-loading properties **(Zhou & Qian, 2018; Michailidou et al., 2020).**

Table 1.1: Drug Design for Nanoparticles

Batch	Budesonide	Chitosan	Poloxamer
F1	10mg	0.5	0.5
F2	10mg	1.0	1.0
F3	10mg	1.5	1.5
F4	10mg	0.5	1.0
F5	10mg	0.5	1.5
F6	10mg	1.0	0.5
F7	10mg	1.0	1.5
F8	10mg	1.5	0.5
F9	10mg	1.5	1.0

10 Evaluation Parameter:

Percentage Yield

After collecting them, the nanoparticles were accurately weighed. After that, the yield was determined as a percentage (percent) using the formula below [55].

$$\frac{\text{Mass of nanoparticles obtained} \times 100}{\text{Total weight of drug and polymer}} \quad \ldots.(1)$$

Encapsulation Efficiency (EE) of Nanoparticles

For 90 minutes, a 10 ml nanoparticle formulation was centrifuged at 10,000 rpm and 10 °C. The amount of bilberry was determined using a UV set to a maximum wavelength of 517 nm after the clear supernatant obtained from the centrifuge solution was diluted ten times with double-distilled water **(56)**.

$$\textbf{Encapsulation efficiency} = \frac{\text{Total amount of drug} - \text{Amount of free drug} \times 100}{\text{Total amount of drug}} \quad \ldots(2)$$

In-Vitro Drug Release of Nanoparticles:

Out of the 9 batches of nanoparticles (F1 through F9), the dialysis bag method was employed. To a dissolving test apparatus with a basket-style stirring element, 30 mg of drug-loaded nanoparticles were added. The basket contained the dialysis bag. The dissolving medium, a phosphate buffer solution (pH 7.4), was maintained at 37 °C. The basket was turning 100 revolutions per minute. At intervals of ½, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours, 5.0 mL of medium was extracted using a 5.0 mL syringe and replaced with 5.0 mL of phosphate buffer solution (pH 7.4). With a UV spectrophotometer set at 517 nm, the drug content was determined **(56)**.

11 Formulation of Nanoparticle Capsules

Prepared NPs were filled in size 3 hard gelatin capsules. Lactose was selected as a diluent and mixed with NPs. The geometric dilution process was adopted for proper mixing. Lastly, manual filling of the capsules was done, taking care to load 5 mg of formulated NPs into every unit.

Table 1.2: Design to Formulate Nanoparticle Capsule

Batch	NP weight per capsule (mg)	Diluent (mg)	Capsule size
1	5 mg	45 mg lactose	Size 3
2	10 mg	40 mg lactose	Size 3
3	15 mg	35 mg lactose	Size 3

12 Evaluation Parameter of Nanoparticle Capsule:

Encapsulation Efficiency and Drug Content:
Encapsulation efficiency was assessed by centrifuging the nanoparticle suspension and analyzing the free drug in the supernatant using UV–Vis spectrophotometry. Drug content was determined by dissolving nanoparticles in a suitable solvent and measuring absorbance.

Disintegration Test:
Disintegration studies were performed in simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) to confirm capsule stability in upper GIT conditions.

In Vitro Drug Release:
Drug release studies were performed using the dialysis bag method in sequential media of pH 1.2 (stomach), 6.8 (small intestine), and 7.4 (colon). Samples were withdrawn at specific time intervals and analyzed spectrophotometrically to establish colon-targeted release behavior.

CHAPTER 3: RESULT

3.1 Characterization of the drug (Budesonide)

Characterization of Budesonide was performed. They include physical and analytical characterization.

Pre-formulation Studies

Preformulation studies of drugs were performed. They include physical characterization, melting point, and solubility.

3.1.1 Physical characterization

Physical character of the drug was characterized, the Color of the drug powder was checked by visual observation with the naked eyes, and the results obtained are shown below:

Table 3.1: Physical characterization of the drug

Physical properties	Standard	Observation
Color	White	White
Dour	Odorless	Odorless
Taste	Bitter	Bitter

This characteristic of the drug was compared with the standard characteristic and were found to be similar.

3.1.2 Melting point determination

For Budesonide it was recorded by capillary method. The temperature at which drug goes in the liquid state was consider as the melting point of Budesonide. Practically it was found that drug get melts at 226ºC - 234ºC. Documented melting point of the drug Budesonide is 224ºC - 232 ºC. The melting point of budesonide matched the standard hence the drug identified as Budesonide and the drug is in the pure form.

Table 3.2. Melting point of Budesonide

Drug	Melting point		
	Practical	Average	Standard
Budesonide	2260C	228.330C	224 0C-2320C
	2310C		
	2280C		

3.1.3 Solubility

The solubility of drug Budesonide was tested in the following solvents and the obtained results are as listed in the table 9.3.

Table 3.3. Solubility of the drug

Sr. No.	Solvents	Budesonide
1	D.W.	Practically insoluble
2	0.1 N Hydrochloric acid	Soluble
3	Ethanol	Sparingly soluble
4	Methanol	Sparingly soluble
5	Chloroform	Slightly soluble
6	Acetone	Soluble
7	DMSO	Soluble
8	Phosphate buffer pH 7.4	Sparingly soluble

Analytical characterization of drug

Analytical characterization of the performed to check the absorption maxima of drug, calibration curve in pH 7.4 buffer of and 0.1 N HCl, respective analytical instrument.

3.1.4 Determination of λ max in 0.1 N HCl

Overlain spectra of Budesonide in 0.1N HCl exhibit λ max of 252.00 nm. This wavelength was selected for the separate estimation of Budesonide because it is noticeable to that wavelength and it is expected to be a wavelength which is sensitive. Standard calibration curves for Budesonide were linear with range correlation coefficients ®.

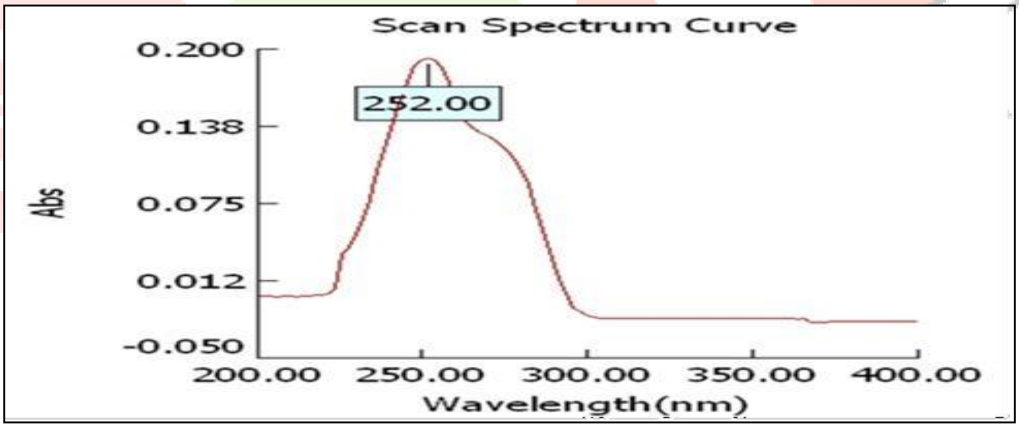

Figure 3.1. λ max of drug in 0.1N HCL

3.1.5 Determination of λ max in phosphate buffer 7.4

The overlain spectra of Budesonide in phosphate buffer exhibit λmax of 252.56 nm. This wavelength was selected for the simultaneous estimation of Budesonide and it is assumed to be sensitive wavelength. Standard calibration curves for Budesonide were linear with range correlation coefficients (r).

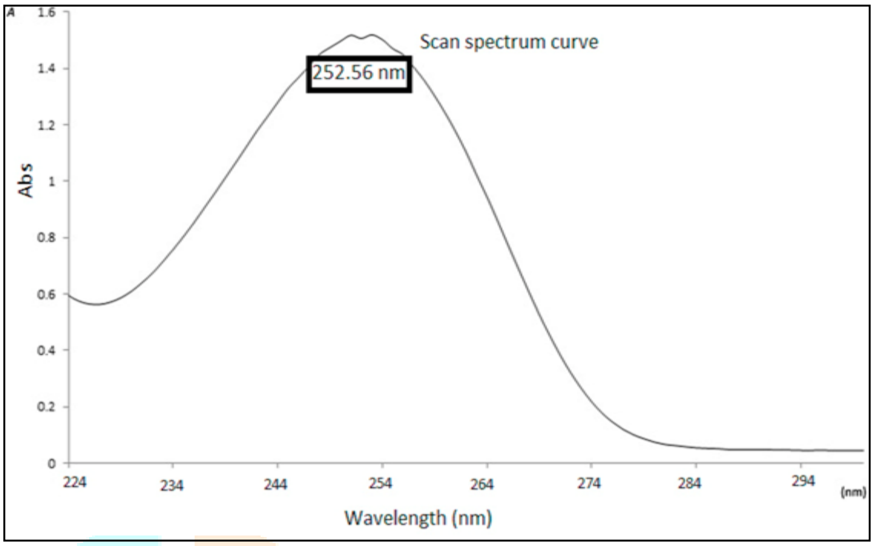

Figure 3.2. λ max of drug in phosphate buffer 7.4

Preparation of calibration curve of budesonide

Budesonide calibration curve was determined in both the pH 7.4 buffer of phosphate and the 0.1 N HCl and the graphs along with the correlation coefficient are discussed below:

3.1.6 Calibration curve in phosphate buffer pH 7.4

The calibration curve of the drug in phosphate buffer pH 7.4 is determined in the graph below with a 0.9948 correlation coefficient.

Table No. 3.4: Concentration v/s Abs. data phosphate buffer 7.4

S.no	Concentration	Absorbance
1.	0	0
2.	2	0.019
3.	4	0.034
4.	6	0.045
5.	8	0.063
6.	10	0.075

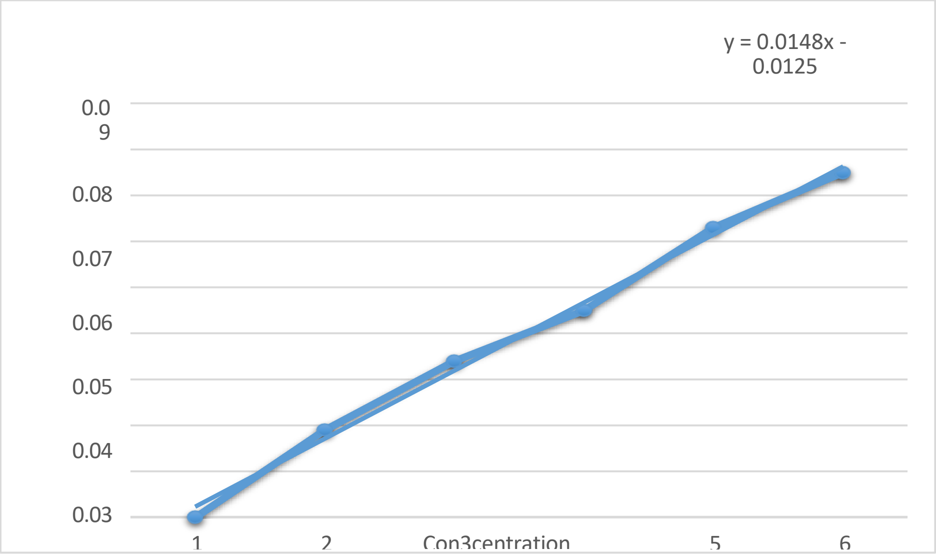

Fig.No.3.3 : Calibration curve of phosphate buffer 7.4

3.1.7 Calibration curve in 0.1 N HCl

Budesonide calibration curve in 0.1 N HCl is as revealed in the graph; it has a correlation coefficient of 0.997.

Table No. 3.5: Concentration v/s Abs. data of 0.1N HCL

S.no	Concentration	Absorbance
1	0	0
2	2	0.014
3	4	0.029
4	6	0.041
5	8	0.059
6	10	0.07

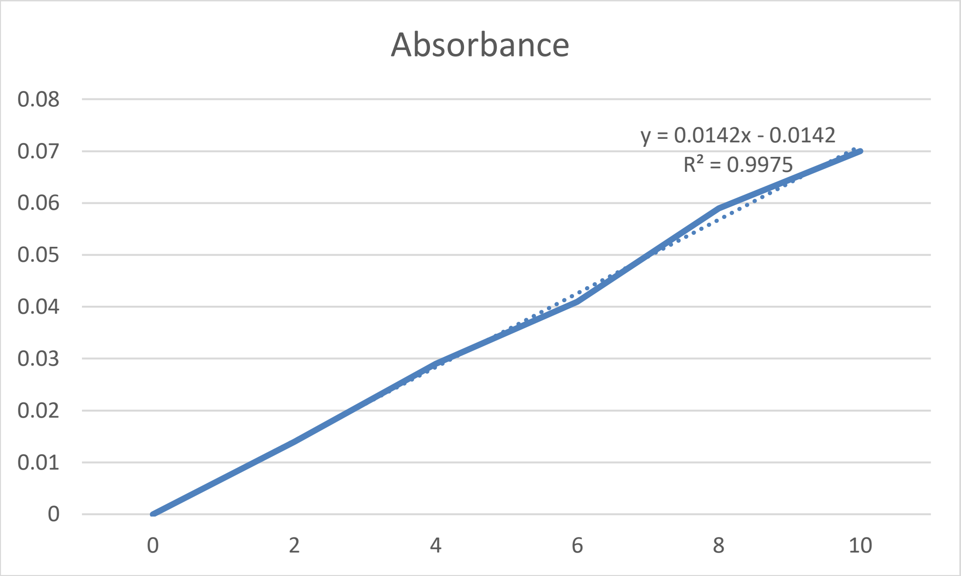

Fig. 3.4: Conc. Vs Absorb. Of 0.1N HCL

3.1.8 Calibration curve in 6.8 buffer:

Budesonide calibration curve in 6.8 buffer is as revealed in the graph; it has a correlation coefficient of 0.9959.

Table No. 3.6: Concentration v/s Abs. data phosphate buffer 6.8

S.NO	Concentration	Absorbance
1	0	0
2	2	0.015
3	4	0.032
4	6	0.043
5	8	0.055
6	10	0.071

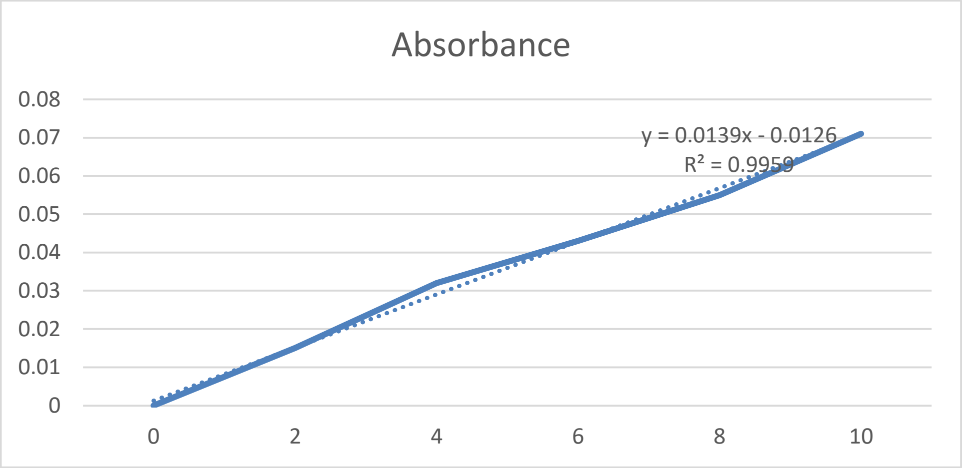

Fig. 3.5: Conc. Vs Absorb. Of buffer 6.8

3.2 Evaluation of Nanoparticles

3.2.1 Percentage yield of drug-loaded nanoparticles

Table No. 3.7: Percentage Yield

Batch of Nanoparticles	% of yield
F1	54.83±0.22
F2	79.35±0.23
F3	58.53±0.45
F4	63.41±0.35
F5	52.5±0.2
F6	67.17±0.11
F7	72.90±0.78
F8	65.36±0.25
F9	63.91±0.78

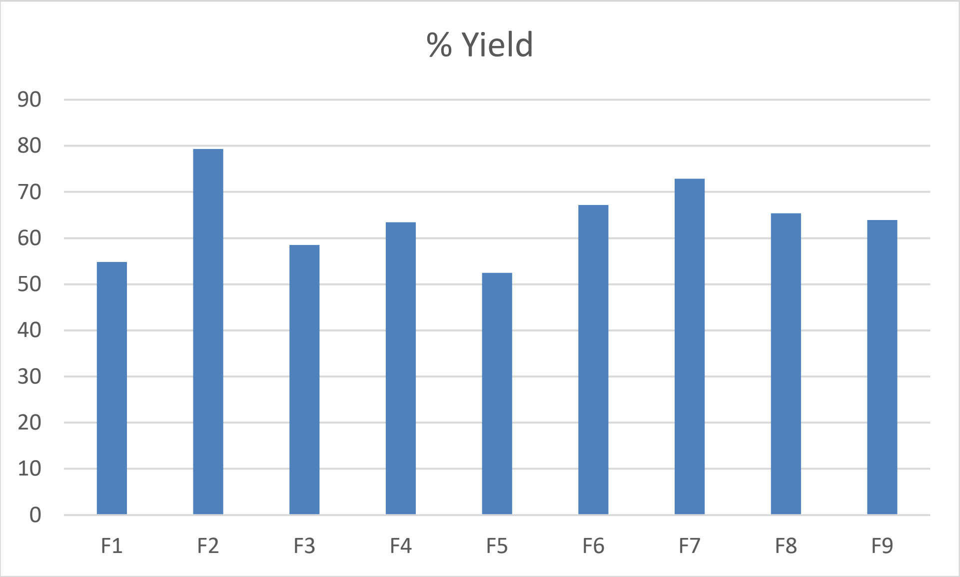

Fig. 3.6: Percentage yield of Nanoparticle

3.2.2 Encapsulation Efficiency %: A UV spectrophotometer set at 252 nm was used to measure the amount of active ingredient in the supernatant. The absorbance values were then used to compute the amount of free drug, which in turn calculated the EE%.

Table No. 3.8: EE% of Nanoparticles

Batch of Nanoparticles	**Encapsulation Efficiency (EE %)**
F1	81.44±0.23
F2	89.33±0.45
F3	85.13±0.36
F4	81.54±0.52
F5	85.13±0.10
F6	80.64±0.52
F7	73.94±0.84
F8	69.44±0.35
F9	73.97±0.85

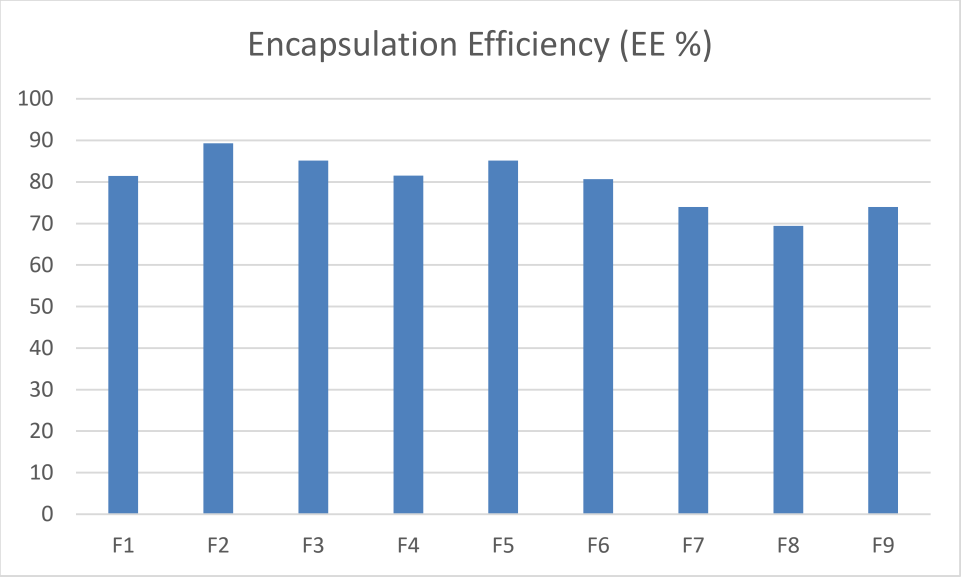

Fig. 3.7: EE% of Nanoparticles

3.2.3 In-Vitro Release: All batches of drug-loaded nanoparticles were tested for dissolving profiles in phosphate buffer at a pH of 7.4. For twelve hours, the in-vitro dissolving test was conducted. The range of the bilberry-loaded nanoparticles' in vitro drug release tests.

Table No. 3.9: In-Vitro Release of Drug

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
30 min.	0.25	0.62	0.24	0.28	0.32	0.76	0.84	0.22	0.65
1 hr	3.55	3.75	3.45	3.4	3.6	3.22	4.36	2.99	4.12
2hr	9.51	9.66	9.86	9.73	9.63	8.73	12.23	9.52	9.43
4hr	18.53	19.56	18.44	18.34	17.2	16.8	21.54	18.24	16.71
6hr	29.72	34.26	28.65	29.71	26.8	27.52	30.3	27.88	25.71
8hr	45.79	53.5	43.38	46.45	39.71	40.57	47.22	41.88	37.31
10hr	64.45	67.5	59.59	63.52	57.38	56.76	67.34	59.23	55.76
12 hrs	72.24	83.45	80.27	79.45	76.77	73.44	72.11	70.32	76.78

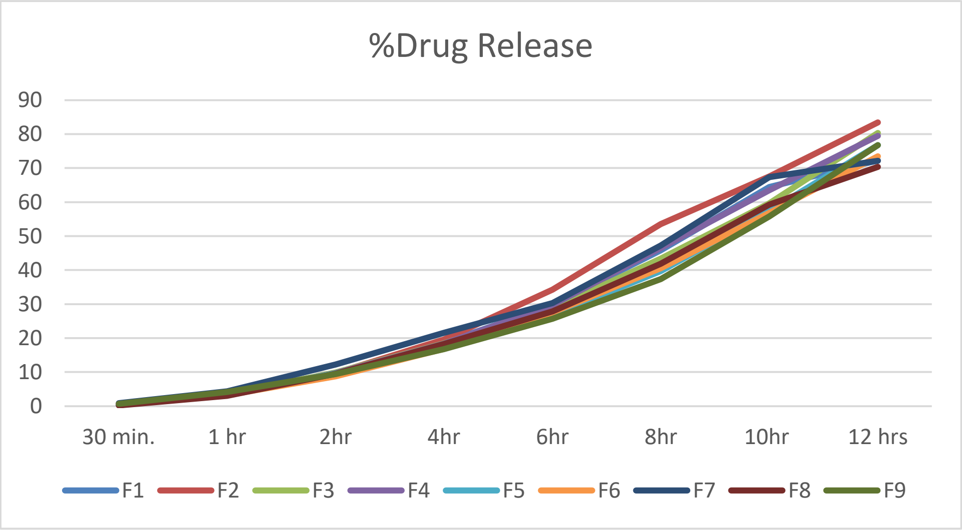

Fig. 3.8: In-vitro Release of Nanoparticles

3.3 Evaluation of Nanoparticle Capsule:

Table No. 3.10: EE%, Drug Content, % Drug release of Nanoparticle Capsule

Batch	NP per capsule (mg)	% Yield	EE (%)	Drug content (%)	Capsule weight (mg)	Disintegration time (min) pH 1.2 / 6.8	% Drug released at pH 7.4 (colon)	Result
1	5	90	55	96	50 ± 2.0	>120 / >120	70	Low NP load, faster release
2	10	85	75	92	50 ± 2.5	>120 / >120		Balanced NP load, moderate release
3	15	83	85	90	50 ± 3.0	>120 / >120	65	High NP load, slowest, sustained release

3.4 RESULT:

Budesonide was observed as a white, odorless, and bitter-tasting drug, consistent with its standard description. The melting point was determined to be 228.33 °C, confirming its purity and thermal stability. Solubility studies showed that the drug was freely soluble in dimethyl sulfoxide and acetone, moderately soluble in 0.1 N HCl, and sparingly soluble in aqueous buffers, highlighting the need for a suitable delivery system to enhance its therapeutic performance. The λmax in 0.1 N HCl was found at 252 nm, while in phosphate buffer (pH 7.4) it was 252.56 nm, indicating stability of its absorbance peak across different media. Calibration curves prepared in 0.1 N HCl, phosphate buffer pH 6.8, and phosphate buffer pH 7.4 exhibited excellent linearity, with correlation coefficients of 0.997, 0.9959, and 0.9948 respectively, confirming reliable quantification for further analysis. Budesonide nanoparticles were successfully formulated using the nanoprecipitation method with chitosan as a natural polymer and poloxamer as stabilizer. Nine trial batches showed percentage yields ranging between 52.5% and 79.35%. The highest yield was obtained in formulation F2, while the lowest was observed in F5. Encapsulation efficiency values ranged from 69.44% to 89.33%, with maximum entrapment in F2, suggesting that an optimized drug-to-polymer ratio significantly influences nanoparticle performance. In vitro release studies revealed a sustained release pattern, with cumulative release values between 70.32% and 83.45%. Formulations with higher polymer concentrations showed comparatively slower release due to denser matrix formation, while those with lower polymer content released the drug more rapidly.

Optimized nanoparticles were then filled into hard gelatin capsules containing 5 mg, 10 mg, and 15 mg drug equivalents. The percentage yields of the three capsule batches were 90%, 85%, and 83%. Encapsulation efficiency was recorded as 55%, 75%, and 85%, while drug content was found to be 96%, 92%, and 90% respectively, all within pharmacopeial limits. Weight variation analysis demonstrated uniformity, with all batches showing deviations within ±5%. Disintegration studies confirmed capsule stability in gastric and intestinal conditions, as the formulations remained intact for more than two hours, which is essential for colon-targeted delivery. Drug release from the nanoparticle-loaded capsules in simulated gastrointestinal conditions showed minimal release at acidic and intestinal pH, followed by significant drug release at colonic pH (7.4). At this stage, cumulative drug release was approximately 70% for the 5 mg capsules, 68% for the 10 mg capsules, and 65% for the 15 mg capsules. The slightly lower release at higher doses may be attributed to increased polymer density, which limited drug diffusion.

Overall, the results demonstrate that Budesonide nanoparticles can be effectively formulated and encapsulated to achieve high drug entrapment, reproducible capsule filling, and sustained drug release at colonic pH. Among the tested formulations, the 10 mg NP-loaded capsules provided the best balance between encapsulation efficiency, drug content, and controlled release, making them a promising candidate for colon-specific drug delivery.

3.5 CONCLUSION:

The study successfully formulated Budesonide-loaded chitosan–poloxamer nanoparticles and further developed colon-targeted capsule formulations. Drug characterization confirmed compliance with standard properties, and calibration curves indicated reliable spectrophotometric quantification. Nanoparticles showed good yields, high encapsulation efficiency, and sustained release, while capsule formulations-maintained drug integrity, ensured dosage uniformity, and released Budesonide in a controlled manner at colonic pH. Among the tested batches, the 10 mg NP-loaded capsule demonstrated an optimal balance of encapsulation efficiency, drug content, and sustained release. Overall, the developed nanoparticle-based capsules hold strong potential as an eco-friendly and effective colon-specific drug delivery system for Budesonide.

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