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Formulation and Assessment of Prednisolone Matrix Tablets with a Blend of Natural Polysaccharides: Colon-Specific Drug Delivery Via Wet Granulation Approach

Nandini Ratne[1], Shankar Gavaroji[2], Samriti Vohra[3*], Gireesh Tripathi[4], Amit Chandna[5], Pravin S. Uttekar[6], Zeba Siddiqui[7], Tasneem Mohammed[8]

[1]Department of Pharmacology, Nagpur College of Pharmacy, Wanadongri, Hingna Road, Nagpur, Pin – 441110.
[2]Department of Pharmaceutics, Siddharth College of Pharmacy, Mudhol-587313, Dist. Bagalkot, Karnataka, India.
[3]Department of Pharmacology, Gandhi College of Pharmacy, Karnal, Haryana-132001, India.
[4]Department of Pharmacy, Shri Krishna University Village Chowka Sagar Road Chhatarpur (Madhya Pradesh) India Pin- 471301.
[5]Department of Pharmacy, RP Institute of Pharmacy Bastara, Karnal -132114 Haryana.
[6]Dnyan Kala Krida & Krushi Prathishthan's Late Laxmibai Phadtare College of Pharmacy A/P-Kalamb-Walchandnagar, Tal: Indapur Dist. Pune, Pin Code: 413114.
[7]Institute of Pharmacy, Shri Ramswaroop Memorial University, Tindola, Lucknow-Dewa Road, Uttar Pradesh, India Pin- 225003.
[8]Department of General Sciences, Ibn Sina National College for Medical Studies, Jeddah, KSA
Pin –21418.
*Corresponding Author: Samriti Vohra
Department of Pharmacology, Gandhi College of Pharmacy, Karnal, Haryana-132001, India.
Email: samritichandna20@gmail.com

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ABSTRACT

This study aimed to evaluate the formulation and characterization of matrix tablets using a natural polysaccharide blend of Angelica sinensis polysaccharide and Tamarind Seed Polysaccharide (AT-P). The blend was prepared in a 1:1 ratio and assessed for its potential as a binding agent in controlled-release tablet formulations. Preformulation studies, including pH, viscosity, bulk density, tapped density, and compressibility index, were conducted to ensure compatibility and stability. Five matrix tablet formulations (TF1 to TF5) were developed using wet granulation with Prednisolone as the active pharmaceutical ingredient. The tablets were subjected to various evaluation parameters such as thickness, hardness, friability, and content uniformity, followed by in vitro release studies in both the presence and absence of rat caecal matter to simulate colonic conditions. The kinetic modeling of drug release data revealed that TF3 followed zero-order kinetics, while TF2 and TF5 exhibited strong fits to both zero-order and Higuchi models. In the presence of rat caecal matter, a significant acceleration in drug release was observed, indicating the responsiveness of the formulations to the colonic environment. The study concluded that the natural polysaccharide blend (AT-P) is a promising excipient for controlled drug delivery systems targeting the colon.

Keywords: *Natural polysaccharide, Prednisolone, colon targeting, matrix tablets, microflora.*

1. INTRODUCTION

Colon-targeted drug delivery systems (CDDS) represent a significant advancement in pharmaceutical sciences, aimed at delivering drugs directly to the colon for localized treatment or systemic absorption. This approach offers substantial benefits over conventional drug delivery methods, particularly for treating colonic diseases such as inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, as well as colorectal cancer and irritable bowel syndrome (Azehaf et al., 2023, Bansal et al., 2014, Chourasia and Jain, 2004, Gulbake and Jain, 2012, Jain et al., 2007). Additionally, CDDS is beneficial for the systemic delivery of proteins, peptides, and vaccines, which are often degraded or poorly absorbed in the upper gastrointestinal tract. The colon's distinct environment, characterized by a neutral to slightly alkaline pH, longer transit time, and the presence of a diverse microbial flora capable of enzymatic activity, makes it an ideal site for targeted drug delivery (Patel and Amin, 2011, Patel, 2015, Sinha and Kumria, 2001, Van den Mooter, 2006). The ability to bypass the upper gastrointestinal tract allows for the protection of acid-labile drugs and the reduction of systemic side effects. Furthermore, delivering drugs directly to the colon ensures a higher local concentration, improving therapeutic efficacy while minimizing drug dose and associated side effects (Chadha et al., 2020, Jain and Jain, 2008, Jain and Patil, 2023, Junior et al., 2023, Kotla et al., 2014). The development of effective CDDS requires an understanding of the colon's physiology and the incorporation of polymers and excipients that respond to the unique conditions within the colon, such as pH changes, bacterial enzymes, or pressure differences. Various strategies have been employed to achieve targeted delivery to the colon, including pH-sensitive coatings, time-dependent release systems, and microbially-triggered mechanisms. Among these, natural polysaccharides have garnered attention due to their biocompatibility, biodegradability, and ability to form gel matrices that protect the drug until it reaches the colon. In summary, colon-targeted drug delivery is crucial for treating colonic diseases and for the systemic delivery of certain therapeutics. Its importance lies in improving drug efficacy, reducing systemic exposure, and providing a more patient-friendly treatment option. As research continues to advance, CDDS holds promise for developing more effective therapies with fewer side effects, thereby improving patient outcomes (Chourasia and Jain, 2004, Junior et al., 2023, Naeem et al., 2020, Omar et al., 2007).

Natural polysaccharides have emerged as critical components in the development of colon-targeted drug delivery systems (CDDS) due to their biocompatibility, biodegradability, and ability to interact with the colonic environment. Derived from plant, animal, or microbial sources, these polysaccharides, such as pectin, guar gum, chitosan, and tamarind seed polysaccharide, possess unique properties that make them ideal for targeting drugs to the colon.

One of the key advantages of natural polysaccharides is their susceptibility to enzymatic degradation by the colonic microflora. In the colon, polysaccharides remain largely intact as they pass through the upper gastrointestinal tract, protecting the drug from premature release (Hovgaard and Brondsted, 1996, Van den Mooter and Kinget, 1995). Upon reaching the colon, specific bacterial enzymes break down these polysaccharides, triggering the release of the encapsulated drug. This targeted release mechanism ensures that the drug is delivered directly to the site of action, improving therapeutic efficacy and reducing systemic side effects. The rationale for using natural polysaccharides in CDDS lies in their ability to form hydrogels, which can encapsulate the drug and provide a controlled release environment. Additionally, their natural origin and minimal toxicity make them safe for prolonged use in drug formulations. Overall, natural polysaccharides offer a promising approach to enhancing the effectiveness of colon-targeted therapies, providing a more precise and patient-friendly treatment option for various colonic diseases (Friend and Tozer, 1992, Pinto, 2010, Roldo et al., 2007, Sinha et al., 2007, Yang et al., 2002, Peppercorn and Goldman, 1972).

Angelica sinensis polysaccharide and Tamarind Seed Polysaccharide (TSP) are two natural polysaccharides that have shown significant potential in the development of colon-targeted drug delivery systems (CDDS). Angelica sinensis, commonly known as Dong Quai, is a traditional Chinese medicinal herb rich in bioactive polysaccharides. These polysaccharides possess a range of therapeutic properties, including immunomodulatory, antioxidant, and anti-inflammatory effects. Their ability to form hydrogels makes them suitable for encapsulating drugs, providing a controlled and sustained release specifically within the colon (Wilding et al., 1994, Rubinstein et al., 1992). Tamarind Seed Polysaccharide (TSP) is derived from the seeds of the tamarind tree and is known for its high viscosity, excellent gelling properties, and biocompatibility. TSP has been widely used as a natural

thickener, stabilizer, and gelling agent in various pharmaceutical formulations. In the context of colon-targeted drug delivery, TSP's resistance to digestive enzymes in the stomach and small intestine, coupled with its susceptibility to colonic bacteria, makes it an ideal candidate for ensuring that drugs are released only upon reaching the colon (Omar et al., 2007, Patel and Amin, 2011, Roldo et al., 2007, Yasmin et al., 2022). The combination of Angelica sinensis polysaccharide and TSP leverages the unique properties of both polysaccharides, creating a synergistic effect that enhances the stability and efficiency of CDDS. This blend not only protects the drug during its transit through the gastrointestinal tract but also ensures precise drug release in the colon, maximizing therapeutic efficacy while minimizing systemic side effects (Omar et al., 2007, Patel and Amin, 2011, Roldo et al., 2007, Yasmin et al., 2022).

All these reasons lead to the use of polysaccharides in current research, which break down specifically in the colon and are non-toxic. *Angelica sinensis* polysaccharide and Tamarind Seed Polysaccharide (TSP) were used to prepare the polysaccharide blend. Therefore, the objective of the current study was to synthesise matrix tablets using a blend of natural polysaccharides to be used as a delivery system for the medicine Prednisolone. Next, the study tried to identify the natural polysaccharide blend and assess the matrix tablets as a colon-specific medicine delivery strategy.

2. MATERIAL AND METHODS

Collection and preparation of natural polysaccharide blend

Angelica sinensis polysaccharide and Tamarind Seed Polysaccharide (TSP) were obtained from Angel Herbs, located in Khari Bawri, New Delhi, India. These two polysaccharides were mixed in equal proportions (1:1) to form a natural polysaccharide blend named AT-P. The collected samples of this blend were stored in sealed jars within desiccators to maintain their integrity. For the extraction and characterization of the polysaccharides, analytical reagent grade chemicals were employed. The natural polysaccharide, composed of various ratios of galacturonic acid, galactose, rhamnose, and glucose, has shown potential therapeutic benefits, including treatment for urethritis, diabetes, jaundice, constipation, and peptic ulcers. Additionally, it possesses cooling and stomachic properties. Phytochemical tests revealed the presence of mucilage, fixed oil, and flavonoid glycosides, with seasonal variations in mucilage yield ranging from 0.90% to 3.5%. The polysaccharide exhibits properties such as antioxidant activity, hepatoprotective effects, and functions as a flocculant, thickener, or binder. It has been utilized as a binding agent in pharmaceutical tablet formulations, contributing to desirable drug release profiles, friability, and hardness. The polysaccharide-water mixture was stored in a desiccator until further use, and the addition of 1% w/v sodium metabisulphite was identified as a method to enhance bacterial stability. The standard characteristics of the polysaccharide included a pH of 6.4, a loss on drying percentage of 7.92%, total ash content of 8.01%, acid-insoluble ash content of 0.59%, and water-soluble ash content of 7.001%.

Table 1. Properties of Natural polysaccharide blend (AT-P)

Natural polysaccharide (% of wet weight)	
Properties	**Purified**
Moisture content	9.03
Protein	7.92
Ash	5.03
Calcium	1.88
Magnesium	0.59
Phosphorus	0.22
Potassium	0.91

Preformulation studies

Preformulation is a critical phase in the development of a pharmaceutical dosage form, focusing on the comprehensive study of the drug's properties to ensure the creation of a stable, effective, and safe product. During this stage, the physical and chemical characteristics of the active pharmaceutical ingredient (API) are meticulously examined, both on its own and when combined with various excipients. This thorough examination is vital to

ensure that the drug maintains its stability throughout its shelf life and remains compatible with other components in the formulation (Asian Rockville). One of the key activities in preformulation includes the creation of a calibration curve, which is essential for quantifying the drug's concentration in different formulations and during the development process. This step ensures accurate dosing and effectiveness of the final product. Additionally, assessing the bulk and tapped densities of the drug is crucial. These measurements provide insights into the flow properties and compressibility of the drug, which are important factors in the manufacturing process, particularly in tablet formulation. Proper understanding of these properties helps in optimizing the formulation and preventing potential manufacturing issues such as capping or lamination.

Another important aspect of preformulation is the evaluation of biodegradation. This involves studying how the drug breaks down in the body, which is critical for determining its stability and ensuring it retains its therapeutic efficacy until it reaches its target site.Overall, preformulation studies lay the groundwork for the successful development of a pharmaceutical product. They provide essential data that informs the design of the dosage form, helping to prevent potential stability issues, avoid incompatibilities with excipients, and ultimately ensure the production of a high-quality, stable, and effective medication. Preformulation investigations include the drug's calibration curve, bulk density, tapping density, and biodegradation. Below are the different test procedures:

a) pH and viscosity

The pH and viscosity of a 1% w/v solution of natural polysaccharide were measured using specific instruments. The pH was assessed with a Digital pH meter, ensuring accurate and precise determination of the solution's acidity or alkalinity. To evaluate the viscosity, Ostwald's viscometer was employed, providing insight into the flow characteristics of the polysaccharide solution. This measurement is crucial for understanding the behaviour of the polysaccharide in various formulations, impacting its performance in drug delivery systems.

b) Bulk Density

To determine the bulk density of the powder sample, the material was first passed through sieve number 18 to ensure uniformity. A precise amount of 25 grams of the sieved powder was then weighed and carefully transferred into a 100 ml graduated cylinder. The powder was leveled without applying any pressure, and the unsettled volume (Vo) was recorded. The bulk density of the powder was then calculated in grams per cubic centimeter (g/cm³) using the formula:

$$Bulk\ density\ =\ M/Vo$$

Where, M = mass of powder taken, Vo = apparent unstirred volume.

c) Tapped density

The determination of tapped density began by passing the powder sample through sieve #18 to ensure uniform particle size. A 100 ml graduated cylinder was filled with 25 grams of the sieved powder. The cylinder was then subjected to a tapping process using a tapped density tester, which mechanically tapped the cylinder 500 times at a rate of 300 taps per minute. During this process, the tapped volume (Vo) was recorded. Subsequently, the tapping continued for an additional 750 taps, and the resulting volume (Vb) was observed. This final volume was considered the tapped volume (Vf) since the difference between the volume after 500 taps and the volume after 750 additional taps was less than 2%. The tapped density was then calculated in grams per cubic centimeter (g/cm³) using the following formula:

$$Tapped\ density\ =\ M/Vf$$

Where, M = weight of sample powder taken, Vf = tapped volume.

d) Compressibility index

The compressibility index is a straightforward and effective test used to evaluate the flowability of a powder by comparing its bulk density and tapped density. This test provides insight into how easily a powder can be packed down, which is an important factor in various pharmaceutical processes. Carr's Compressibility Index, a widely used empirical guide, is calculated after determining the bulk density and tapped density of the powder. The formula used to compute the compressibility index is:

$$\text{Carr's index (\%)} = \frac{Tapped\ density - \ bulk\ density}{Tapped\ density}\ \text{X}\ 100$$

Table 2. The Carr's index illustrates the flow characteristic.

Carr's index (as %)	Flow Type
5 -15	Excellent
12 -16	Good
18 - 21	Fair to passable
23 - 35	poor
33 - 38	Very poor
> 40	Extremely poor

Formulation of matrix tablets

Prednisolone matrix tablets were made by wet granulation technology using a previously described standard process. The binder utilised was 10% starch paste (Krishnaiah et al., 2002). Matrix tablets containing Prednisolone were formulated using the wet granulation technique, following a standardized procedure previously described in the literature. The formulation process involved the use of a 10% starch paste as a binder. Lactose served as the diluent, while a combination of magnesium stearate in a 2:1 ratio acted as the lubricant. The carriers used in this study were natural biocompatible polysaccharide blend derived from *Angelica sinensis* and Tamarind. Five different matrix tablet formulations were created, labelled as TF1, TF2, TF3, TF4, and TF5, each containing varying concentrations of the natural polysaccharide blend (AT-P). Each formulation was standardized to contain 10 mg of Prednisolone. The composition of these formulations is detailed in Table 3. To ensure uniformity, all ingredients were passed through sieve number 100. The powders, excluding talc and magnesium stearate, were thoroughly mixed with the 10% starch paste to form a wet mass. This mass was then passed through sieve number 16 to produce wet granules, which were subsequently dried at 50°C for two hours. The dried granules were further passed through sieve number 18 and then lubricated with a mixture of talc and magnesium stearate (in a 2:1 ratio). The lubricated granules were compressed into tablets using an 8mm round, slightly concave punch on a rotary tablet press, applying a compression force of 4000–5000 kg. The resulting tablets were then evaluated for various parameters, including drug content, percent friability, hardness, thickness, and weight variation, to ensure they met the desired quality standards.

Table 3. Formulation composition of Prednisolone-Natural Polysaccharide Blend (AT-P) formula

Ingredient	Formulation code				
	TF_1	TF_2	TF_3	TF_4	TF_5
Prednisolone (mg)	10	10	10	10	10
AT-P (mg)	100	120	140	160	200
Lactose(mg)	125	95	65	35	-

Evaluation of Tablets

Compatibility Studies

To investigate potential chemical interactions between the drug and the polymer, infrared (IR) spectroscopy was employed by comparing the infrared spectra. In this study, 400 mg of potassium bromide (KBr) was mixed with 10 mg each of the drug, the polymer, and a physical mixture of both. This mixture was then subjected to a hydraulic press at 10 tonnes of pressure to form a clear pellet, weighing approximately 100 mg. The IR pellets were scanned using a Fourier-transform infrared (FTIR) spectrophotometer, with the spectral range extending from 4000 cm^{-1} to 400 cm^{-1}. The infrared spectra of the formulation were then compared to those of the pure drug and the pure polymer to detect any new peak appearances or the disappearance of existing peaks, which could indicate chemical interactions between the components.

Content uniformity

To determine a tablet's potential for efficacy, the dosage per tablet has to be tracked batch to batch and tablet to tablet (Mishra and Kumari, 2019). To ensure the efficacy of a tablet, it is crucial to monitor the drug content both from batch to batch and within individual tablets. The content uniformity test begins by weighing ten tablets to

determine their average weight. Subsequently, all the tablets are crushed, and a sample containing 0.1 g of Prednisolone is accurately weighed. This sample is then transferred into a 100 ml volumetric flask, where the drug is dissolved in a small amount of ethanol. The solution is then diluted to volume with 0.1N NaOH. To ensure complete dissolution, the mixture is placed on a mechanical stirrer. After achieving full solubilization, 1 ml of this solution is withdrawn and further diluted with 0.1 ml of NaOH in another 100 ml volumetric flask. The concentration of Prednisolone in the final solution is determined by measuring its absorbance using a UV double beam spectrophotometer at a wavelength of 221 nm. This method ensures that the drug is uniformly distributed within the tablets, providing consistent dosage and effectiveness.

Thickness, Hardness and Friability

The tablets' thickness determined the consistency of their size. If the thickness varies throughout tablets, so does the medication release. In the current experiment, the thickness of the manufactured tablets was evaluated using a tablet tester. After averaging ten tablets, the standard deviation was calculated (Lieberman et al., 2020). The hardness of a tablet is a key factor that determines its resistance to breakage during handling, storage, and transportation. To assess the hardness of each tablet formulation, a Monsanto hardness tester was employed. This test ensures that the tablets are robust enough to withstand the mechanical shocks encountered during production, packaging, and distribution. In addition to hardness, the strength of a tablet is also evaluated by measuring its friability, which indicates its ability to resist crumbling under mechanical stress. To assess friability, the following procedure was conducted using a Roche friabilator. Ten pre-weighed tablets were placed in the friabilator, which was then rotated at 25 revolutions per minute for four minutes, totaling 100 revolutions. During each revolution, the tablets were dropped from a height of six inches, simulating the conditions they might experience during handling. After the test, the tablets were re-weighed, and the percentage of friability was calculated using the formula:

$$\% \text{ Friability} = \frac{Initial\ weight\ of\ tablets - Final\ weight\ of\ tablets}{Initial\ weight\ of\ tablets} \text{ X } 100$$

Weight variation

To ensure consistency in drug content and in vitro behavior, the weight variation of the tablets was assessed. This evaluation was performed using an electronic balance with a least count of 0.1 mg. A total of 20 tablets from each batch were individually weighed, and the average weight of the batch was calculated. Since the tablets weighed more than 100 mg, their individual weights were compared to the average weight. According to the Indian Pharmacopoeia (IP) standards, the tablets pass the weight variation test if no more than two of the individual tablet weights deviate by more than 5% from the average weight. Following the individual weight measurements, the average weight and standard deviation for each batch were calculated and recorded. The results, including the percentage deviation allowed under the IP weight variation test, were summarized and presented in Table 4. This test ensures that the tablets maintain uniformity in weight, which is crucial for consistent drug dosing and overall product quality.

Table 4. The percentage Variations are allowed.

Average wt. of tablet	% deviation permitted
Less than 80 mg	±10
80 to 250 mg	±7.5
Greater than 250 mg	±5

Swelling index

The swelling index of the tablets was measured to evaluate their capacity to absorb fluid and swell over time. Each tablet was initially weighed individually (recorded as W1) and then placed in a separate petri dish containing 10 milliliters of pH 7.4 phosphate buffer. At predetermined time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours), the tablets were carefully removed from the petri dishes. Excess buffer solution was gently blotted off using filter paper to remove any surface moisture. The swollen tablets were then reweighed, and the new weight was recorded as W2. The percentage swelling index for each tablet was calculated using the following formula (Rao and Patil, 2007):

$$\% \text{ Swelling Index } = \frac{W2 - W1}{W1} \text{ X } 100$$

***In vitro* release studies**

For the in vitro assessment of colon-specific drug delivery systems, the ideal dissolution testing should have pH and enzyme types that are substantially similar to those seen in vivo. The conventional basket method of dissolving colon delivery systems has generally been evaluated in different buffers for different durations of time to simulate the GI tract pH and the transit time that the colon-specific delivery system may encounter in vivo (Prasad et al., 1998). The in vitro release studies for colon-specific drug delivery systems aim to mimic the in vivo conditions, particularly with respect to pH and the presence of enzymes. The goal is to simulate the gastrointestinal (GI) environment and predict how the delivery system will perform in the human body. In this study, the traditional basket method was used to evaluate the drug release, reflecting the varying pH levels and transit times that a colon-specific delivery system would encounter in vivo. The dissolution experiments were conducted using a USP basket-type dissolution apparatus, set at 37±1°C and 100 rpm.

The in vitro drug release was assessed in three stages:

1. **Simulated Colonic Fluid**: The tablets were first placed in 100 ml of simulated colonic fluid for two hours to replicate the conditions of the colon.
2. **Gastric Conditions (pH 1.2)**: The tablets were then transferred to 900 ml of hydrochloric acid (HCl) buffer at pH 1.2 for three hours to simulate the acidic environment of the stomach.
3. **Intestinal Conditions (pH 7.4)**: Finally, the tablets were placed in 900 ml of phosphate buffer at pH 7.4 for five hours to simulate the environment of the small intestine.

At the end of each time interval, a 1 ml sample was withdrawn and diluted to 10 ml with the appropriate dissolution medium. The absorbance of these samples was measured using a double beam UV spectrophotometer at 221 nm to determine the amount of Prednisolone released from the tablets. Additionally, the efficacy of the colon-specific delivery system was tested using rat feces as an alternative dissolution medium. This approach leverages the similarity between the human and rodent colonic microbiota, which predominantly consists of *Bifidobacteria*, *Bacteroides*, and *Lactobacillus*, to more accurately assess how the drug would be released in the colon. This comprehensive testing approach helps ensure that the drug release profile aligns with the desired colon-specific delivery, providing valuable insights into the potential in vivo performance of the formulation.

Preparation of Simulated Colonic Fluid (SCF)

To evaluate the sensitivity of the natural polysaccharide blend to colonic bacteria, drug release assays were conducted using Phosphate Buffered Saline (PBS) at pH 6.8, both in the presence and absence of rat caecal contents. This approach leverages the similarity between rat caecal contents and human intestinal microbiota. To prepare the simulated colonic fluid, four male albino rats weighing between 150 and 200 grams were selected and maintained on a regular diet. To induce the production of enzymes that specifically act on the natural polysaccharide in the caecum, each rat was intubated with Teflon tubing and administered 1 ml of a 2% w/v dispersion of natural polysaccharide in water directly into the stomach. This procedure was repeated daily for seven days. Thirty minutes before the drug release trials began, the rats were euthanized using spinal traction. The abdominal cavity was then opened, and the caecal bags were carefully removed. These caecal bags were immediately placed into a pH 6.8 phosphate buffer that had been pre-bubbled with CO2 to maintain an anaerobic environment. To prepare the simulated colonic fluid, the caecal bags were opened, and their contents were extracted, weighed individually, and pooled. The pooled caecal contents were then suspended in the phosphate buffer to achieve a final concentration of 4% w/v. Throughout this process, CO2 was used to maintain the anaerobic conditions necessary for the caecum. This preparation of simulated colonic fluid was then used in the drug release assays to better mimic the conditions within the colon and to assess how the natural polysaccharide blend interacts with colonic bacteria.

Drug release studies in the presence and absence of rat caecal contents

The drug release studies were conducted using a slightly modified USP Dissolution Test apparatus, operating at 100 rpm and maintained at 37°C. The experiments were designed to simulate colonic conditions by comparing drug release in the presence and absence of rat caecal contents. For the studies, a 150 ml beaker filled with water was placed within the water bath of the dissolution apparatus. The actual dissolution medium consisted of 100 ml

of pH 6.8 phosphate buffer, which contained 4% rat caecal contents. The tablets were placed into the baskets of the apparatus, which were then submerged in the dissolution medium containing rat caecal matter. To maintain the anaerobic environment necessary for the caecal contents, a continuous supply of CO2 was provided throughout the experiment. The experiment was carried out over a period of five hours. At predetermined time intervals, 1 ml samples were withdrawn from the dissolution medium and immediately replaced with 1 ml of fresh phosphate buffer solution that had been pre-bubbled with CO2. Each withdrawn sample was then diluted to 10 ml with phosphate buffer solution, filtered, and analyzed. The concentration of Prednisolone in the filtrate was measured using a Double Beam UV Spectrophotometer at a wavelength of 221 nm. This method allowed for the assessment of drug release under conditions that closely mimic the colonic environment, providing insights into how the presence of colonic bacteria, represented by the rat caecal contents, affects the release of the drug from the tablet formulation.

Analysis of release data

The release data from the dissolution experiments were analyzed to determine the mechanism of drug release from the natural polysaccharide-based matrix tablets. The analysis was conducted using PCP Dissolving Software version 3, which enabled the fitting of the drug release data to various kinetic models. The dissolution experiments were performed in two different media: 0.1N HCl and phosphate buffer at pH 7.4. The release data were then evaluated to identify which of the following models best described the drug release behaviour:

1. **Zero-Order Kinetics**: This model suggests that the drug is released at a constant rate over time, independent of its concentration.
2. **First-Order Kinetics**: In this model, the rate of drug release is proportional to the remaining concentration of the drug, leading to a gradual decrease in the release rate over time.
3. **Hixson-Crowell Model**: This model accounts for changes in the surface area and diameter of the drug particles as they dissolve, reflecting a release mechanism that depends on the dissolution of the drug's surface.
4. **Korsmeyer-Peppas Model**: This model is used to describe drug release from polymeric systems and is particularly useful for identifying the type of release mechanism (e.g., Fickian diffusion, non-Fickian transport) based on the value of the release exponent (n).

The software facilitated the comparison of the experimental release data with these models, helping to determine the most accurate description of the drug release mechanism. By understanding which model the release data adhere to, insights can be gained into the underlying processes controlling the drug release, such as diffusion, erosion, or a combination of both. This information is critical for optimizing the formulation and ensuring consistent, predictable drug delivery (Vandamme et al., 2002).

Statistical Analysis

As the mean with standard deviation (SD) of multiple independent determinations, the release data of the natural blend of polysaccharide-based matrix tablets and the experimental data in the presence and absence of rat faeces have been provided. The unpaired "t" test was utilised with the statistical software GraphPad Prism tm to ascertain the significance of the differences. A significance level of $p < 0.05$ was applied.

4. RESULTS AND DISCUSSION

Compatibility Studies

The compatibility of Prednisolone with a natural polysaccharide mix was assessed using the Fourier Transform Infrared (FTIR) spectral matching method. The relevant spectra are presented in Figure 1. By comparing the FTIR spectra of Prednisolone, the natural polysaccharide mix, and their physical mixtures, it was determined that there was no significant alteration in the spectral patterns of the drug-polymer mixtures. The major peaks observed in the IR spectra of the mixtures closely matched those of the pure drug, indicating that there were no interactions between Prednisolone and the polymers. This confirmed the compatibility of Prednisolone with the natural polysaccharide mix, suggesting that the drug and polymers can be used together in formulation without risk of chemical interaction.

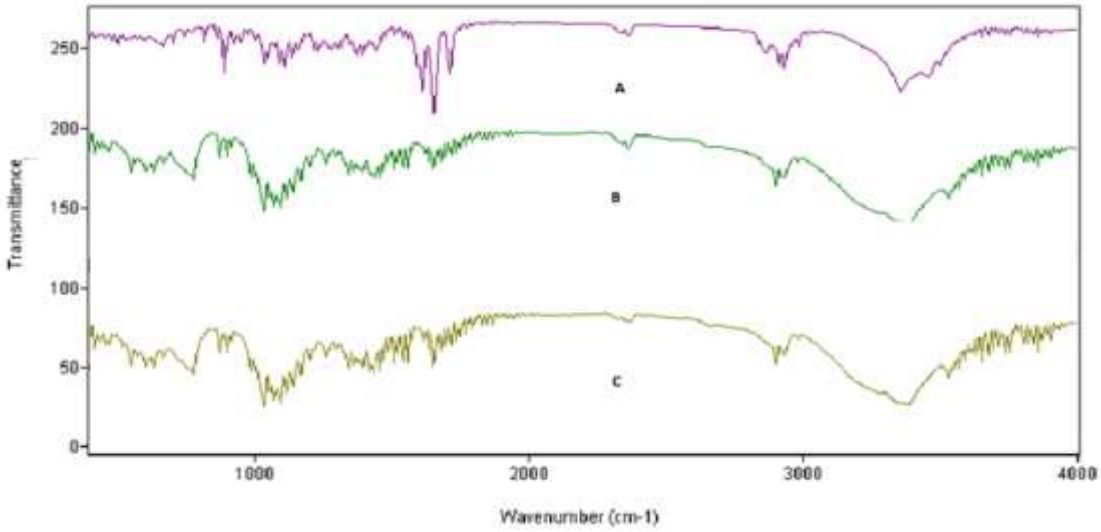

Figure 1. FTIR spectra of Prednisolone, AT-P and TF_3

Evaluation of physical Parameters

pH and Viscosity

The pH of the 1% w/v AT-P solution was measured at 6.4, indicating a slightly acidic environment. The viscosity of the AT-P solution at this concentration was determined to be 204.72 centipoise (cp). Viscosity is a crucial parameter in determining the drug release rate from polymer-based matrices. Higher viscosity values generally indicate that the polymer matrix is more resistant to erosion and dissolution, which can slow down the drug release. Therefore, the viscosity of a polymer gel plays a significant role in controlling the dissolution rate of the drug, making it a key factor in the design and optimization of sustained or controlled release formulations.

Compressibility Indices and Hausner ratio

The provided data reveals distinct differences in the flow properties of AT-P and Prednisolone. AT-P exhibits a bulk density of 0.479 g/cm³ and a tapped density of 0.690 g/cm³, resulting in a relatively high compressibility index of 30.58% and a Hausner ratio of 1.440. These values indicate that AT-P has poor flow properties and tends to compress significantly when subjected to tapping, which suggests that it may be prone to clumping or poor flow during the manufacturing process. This could potentially impact the uniformity and consistency of the final formulation, necessitating additional measures such as the use of flow aids or careful control of process parameters to mitigate these issues. On the other hand, Prednisolone demonstrates a bulk density of 0.448 g/cm³ and a tapped density of 0.507 g/cm³, leading to a lower compressibility index of 11.64% and a Hausner ratio of 1.13. These values suggest that Prednisolone possesses good flow properties and minimal compressibility upon tapping, indicating that it is less likely to cause flow-related issues during manufacturing. Consequently, Prednisolone is expected to be easier to handle, leading to more consistent and uniform tablet production. The significant contrast in the compressibility index and Hausner ratio between AT-P and Prednisolone underscores the need for careful consideration of AT-P's flow characteristics during formulation development, while Prednisolone presents fewer challenges in this regard. Results from Hausner ratios and compressibility indices showed that the AT-P under investigation had low flow characteristics. Prednisolone tablets were produced by a wet granulation process with starch paste as a binder since they had poor flow characteristics and required a high incorporation rate in the matrix tablets. Table 5 presents the findings.

Table 5. Assessment of physical parameters

S. No	Ingredient	Bulk density (g/ cm^3)	Tapped density (g/ cm^3)	Compressibility index (%)	Hausner Ratio
1.	AT-P	0.479	0.690	30.58%	1.440
3.	Prednisolone	0.448	0.507	11.64%	1.13

Tablet Thickness, Hardness of Tablet, Friability, Weight Variation and Content Uniformity

The data for the physical-chemical evaluation of several batches of natural polysaccharide-based (AT-P) matrix tablet formulations, codenamed TF1 to TF5, reveals some variability across different parameters, which are essential for assessing the quality and consistency of the tablets. The thickness of the tablets varies slightly, with TF1 and TF3 showing similar thicknesses around 6.04 mm and 6.06 mm, respectively, while TF2, TF4, and TF5 are slightly thinner, ranging from 5.75 mm to 5.80 mm. This variation is within an acceptable range but could potentially impact handling and packaging processes. The weight variation among the formulations is minimal, with average weights close to 300 mg for all batches. TF4 has the highest average weight at 302.6 mg, and TF5 the lowest at 299.6 mg, indicating good uniformity and ensuring consistent dosage in each tablet.

The hardness of the tablets ranges from 5.02 kg/cm² in TF5 to 5.72 kg/cm² in TF3. While all formulations maintain adequate hardness to withstand normal handling and transportation, TF5 appears to be the least hard, which might make it more susceptible to breaking under pressure. The friability values show more significant variation, with TF1 and TF2 having higher friability (0.59% and 0.56%, respectively), indicating a greater tendency to crumble compared to TF4 and TF5, which have much lower friability values (0.29% and 0.14%, respectively). TF3 also demonstrates good resistance to friability at 0.305%, suggesting a robust formulation.

Content uniformity across all formulations is relatively consistent, with values ranging from 96.39% in TF3 to 97.42% in TF2, indicating uniform drug distribution within the tablets, which ensures consistent therapeutic efficacy. Overall, while there is some variability, all formulations generally meet the acceptable standards for thickness, weight variation, hardness, friability, and content uniformity. TF3, in particular, exhibits a good balance between hardness and low friability, indicating a strong formulation, while TF5, despite its slightly lower hardness, shows excellent resistance to crumbling. However, TF1 and TF2 might require attention due to their higher friability, which could pose challenges during handling and transport. In conclusion, these formulations are consistent and well-formulated, with specific strengths and minor areas for potential optimization to enhance performance further.

Table 6. Assessing the physical and chemical properties of the natural tablet formulations fabricated based on polysaccharides (AT-P)

S. No	Parameters	Formulations (Codenamed)#				
		TF_1	TF_2	TF_3	TF_4	TF_5
1.	Thickness (mm)	6.04± 0.06	5.80±0.08	6.06±0.08	5.75±0.04	5.78±0.06
2.	Weight Variation (mg)	301.6± 2.88	300.4±2.82	300.5±2.74	302.6±2.88	299.6±2.22
3.	Hardness (kg/cm^2)	5.43± 0.98	5.68±0.89	5.72±0.87	5.36±0.92	5.02±0.94
4.	Friability (%)	0.59±0.03	0.56±0.03	0.305±0.02	0.29±0.02	0.14±0.04
5.	Content Uniformity (%)	96.69±1.34	97.42±1.33	96.39±1.45	96.72±2.09	96.91±1.08

 # Result are presented as mean ± SD, n=6

Swelling Index

The data presented in Table 7 illustrates the swelling properties of natural polysaccharide-based (AT-P) matrix tablets across five different formulations (TF1 to TF5), observed over a 24-hour period. The percentage swelling index indicates the extent to which each formulation swells when exposed to a medium, which is a key factor influencing the drug release rate. Initially, at the 1-hour mark, TF3 shows the highest swelling index at 80.09%, indicating rapid swelling compared to the other formulations. TF2 and TF5 also exhibit relatively high swelling rates, while TF1 has the lowest swelling index at 39.35%. As the time progresses, by the 2-hour mark, all formulations show significant increases in their swelling index, with TF3 continuing to lead at 94.11%. By the 6-hour point, TF3 reaches 160.08%, maintaining its position as the formulation with the highest swelling capacity,

while TF1 remains the least swollen at 118.58%. At the 12-hour mark, the swelling indices of all formulations further increase, with TF3 reaching 184.21%, still the highest among the group. TF2 and TF5 also show substantial swelling, while TF1 continues to swell the least, though it still shows a considerable increase. By the 24-hour mark, TF3 achieves the highest swelling index overall at 201.20%, indicating a strong and sustained swelling capacity that suggests it may provide the slowest and most controlled drug release, making it suitable for sustained-release applications. In contrast, TF1, which consistently shows the lowest swelling index, may result in a faster drug release, potentially making it more appropriate for immediate-release formulations. TF4 and TF5 exhibit moderate swelling properties, positioning them between TF1 and TF3, which could make them suitable for applications requiring a balanced drug release profile. Overall, the swelling properties of these formulations suggest that they could be tailored for various drug delivery profiles, depending on the desired release rate and duration. TF3 would be ideal for a longer, more sustained release, while TF1 would be better suited for quicker release, with TF4 and TF5 offering intermediate options

Table 7. Swelling properties for the matrix tablets prepared based on Natural polysaccharide blend (AT-P)

S. No	Time (h)	% Swelling Index				
		TF1	TF2	TF3	TF4	TF5
1	0	0	0	0	0	0
2	1	39.35	45.63	80.09	73.90	77.34
3	2	63.45	68.25	94.11	83.24	90.28
4	4	89.27	102.59	140.81	132.47	127.19
5	6	118.58	126.17	160.08	145.21	138.45
6	12	149.28	159.33	184.21	160.51	157.54
7	24	162.63	166.52	201.20	183.31	178.22

In vitro release study

The in vitro release characteristics of matrix tablets made with AT-P were analyzed over a 5-hour period for five different formulations, codenamed TF1 to TF5. Initially, at 0 hours, none of the formulations released any drug. As time progressed, differences in the release profiles became evident. At 1 hour, TF1 exhibited the highest release at 9.78% ± 1.33%, while TF2 and TF3 followed with 6.59% ± 0.72% and 6.71% ± 2.17%, respectively. TF4 and TF5 displayed lower releases of 4.48% ± 0.71% and 4.08% ± 0.84%. By 2 hours, TF2 surpassed TF1 in drug release, with 10.79% ± 0.85% compared to TF1's 10.06% ± 0.76%, while the other formulations showed relatively lower releases. At the midpoint of the study, specifically at 3 hours, TF1 significantly increased its drug release to 20.55% ± 2.59%, the highest among all formulations, with TF2 close behind at 17.01% ± 0.57%. TF5 continued to show the lowest release at this time point, with 6.44% ± 0.67%. By 4 hours, TF1 and TF2 maintained their leading positions in drug release, with TF1 reaching 24.20% ± 2.16% and TF2 at 20.69% ± 0.63%. Meanwhile, TF3 and TF4 showed moderate releases, and TF5 remained the lowest with 8.35% ± 0.85%. At the final time point of 5 hours, TF1 maintained the highest cumulative release of 25.43% ± 1.56%, followed by TF2 at 21.76% ± 0.57%. TF5 consistently demonstrated the slowest and most controlled release, with a cumulative release of 11.22% ± 1.26%. Overall, TF1 consistently showed the highest drug release across all time points, suggesting it may have the least polymer or excipients controlling the release, whereas TF5 exhibited the slowest and most controlled release, indicating a potential formulation strategy aimed at sustained release. The variability in TF3's release profile, as indicated by its larger standard deviations at certain points, suggests some inconsistency in its formulation or release mechanism. These findings suggest that the different formulations offer varying release profiles, which could be tailored to meet specific therapeutic requirements based on the desired release rate from the matrix tablets

In vitro release studies in the presence and absence of rat caecal contents

The in vitro release profiles of formulations TF4 and TF5 were examined under two different conditions: in the absence of rat caecal matter and in its presence, which simulates the colonic environment. In the absence of rat caecal matter, both TF4 and TF5 exhibited a controlled release pattern, with TF4 releasing the drug more rapidly

than TF5 across all time points. For instance, at 1 hour, TF4 released 9.65% ± 2.35% of the drug, while TF5 released 5.11% ± 0.85%. By 5 hours, TF4 reached a cumulative release of 22.99% ± 0.34%, compared to 17.46% ± 0.99% for TF5, indicating that TF5 has a more sustained release profile without the influence of the colonic environment. In contrast, when rat caecal matter was present, both formulations experienced a significant acceleration in drug release. TF4 released 41.09% ± 1.92% of the drug at 1 hour, while TF5 released 37.67% ± 1.05%. By 5 hours, TF4 achieved a cumulative release of 55.37% ± 1.18%, and TF5 reached 52.19% ± 1.11%. This marked increase in drug release in the presence of caecal matter suggests that both formulations are designed to respond to the colonic environment, likely due to the enzymatic activity in the caecal matter that triggers or enhances drug release. Overall, TF5 is the better choice if a more sustained release is desired, even in the presence of colonic enzymes, while TF4 may be preferred for a quicker onset of action in the colon. Both formulations effectively demonstrate responsiveness to the colonic environment, making them suitable candidates for targeted drug delivery to the colon.

Kinetics of release data

The kinetic modeling of the release data for formulations TF1 to TF5 reveals important insights into the mechanisms governing drug release from these matrix tablets. TF3 shows the highest correlation with zero-order kinetics (R = 0.9910), suggesting that it follows a constant release rate independent of concentration. TF2 and TF5 also exhibit strong fits to zero-order kinetics, indicating a significant zero-order release component in these formulations. When examining first-order kinetics, TF5 demonstrates the highest R value (0.9864), implying a concentration-dependent release, with TF3 and TF2 also showing good fits to this model. The Higuchi model, which suggests diffusion-driven release, is best exemplified by TF2 (R = 0.9753), with TF4 and TF3 also displaying strong correlations, indicating the role of diffusion in drug release from these formulations. The Hixson-Crowell model, which accounts for dissolution and surface area changes, fits best with TF3 (R = 0.9867) and TF5 (R = 0.9787), highlighting the contribution of these factors to drug release.

The Korsmeyer-Peppas model, often used to characterize complex release mechanisms, shows the best fit for TF2 (R = 0.9826) with an 'n' value of 0.82, suggesting a combination of diffusion and erosion mechanisms. TF3 and TF4 also fit well with the Peppas model, indicating a similar combined mechanism. TF5, with a lower 'n' value (0.5552), leans toward Fickian diffusion, though it still maintains a reasonable fit to the Peppas model. Overall, the data suggest that drug release from these formulations involves a combination of diffusion, erosion, and matrix dissolution, with the Peppas model providing the most comprehensive fit, particularly for TF2, TF3, and TF4. This indicates that these formulations are well-suited for controlled-release applications, where both the polymer matrix structure and interactions with the surrounding medium play crucial roles in the release process.

Table 8. Understanding release mechanisms

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5<n<1.0	Anomalous transport
1.0	Case II transport
Higher than 1.0	Super case II transport

Statistical analysis

Analysis of the release data using statistical methods showed that the release data obtained with and without rat faeces differed significantly ($p<0.001$). A statistical study revealed that there was no significant difference ($p<0.001$) in the release data obtained when using matrix tablets based on natural polysaccharides in the presence or absence of a colon environment. This demonstrated that the natural matrix tablets based on polysaccharides were exhibiting good dissolving characteristics.

Table 9. *In vitro* release characteristics of matrix tablets made with AT-P

Serial No.	Time (h)	Formulations (Codenamed)#				
		TF_1	TF_2	TF_3	TF_4	TF_5

1	0	0	0	0	0	0
2	1	9.78 ± 1.33	6.59 ± 0.72	6.71 ± 2.17	4.48 ± 0.71	4.08 ± 0.84
3	2	10.06 ± 0.76	10.79 ± 0.85	8.28 ± 1.85	10.41 ± 0.47	4.65 ± 0.37
4	3	20.55 ± 2.59	17.01 ± 0.57	11.63 ± 2.83	17.11 ± 0.30	6.44 ± 0.67
5	4	24.20 ± 2.16	20.69 ± 0.63	13.68 ± 1.85	18.54 ± 0.74	8.35 ± 0.85
6	5	25.43 ± 1.56	21.76 ± 0.57	16.15 ± 2.74	20.68 ± 0.36	11.22 ± 1.26

#Results are presented as mean ± SD, n=3

Table 10. *In vitro* release profile in the absence of rat caecal matter

S. No	Time (h)	Formulation Code	
		TF_4	TF_5
1	0	0	0
2	1	9.65 ± 2.35	5.11 ± 0.85
3	2	15.63 ± 1.44	6.22 ± 0.98
4	3	18.99 ± 1.06	9.15 ± 1.08
5	4	22.01 ± 0.40	12.71 ± 0.95
6	5	22.99 ± 0.34	17.46 ± 0.99

Table 11. *In vitro* release profile in presence of rat caecal matter

S. No	Time (h)	Formulation Code	
		TF_4	TF_5
1	0	0	0
2	1	41.09 ± 1.92	37.67 ± 1.05
3	2	43.26 ± 1.98	39.57 ± 1.14
4	3	46.08 ± 1.11	41.98 ± 1.12
5	4	48.57 ± 1.26	47.17 ± 1.24
6	5	55.37 ± 1.18	52.19 ± 1.11

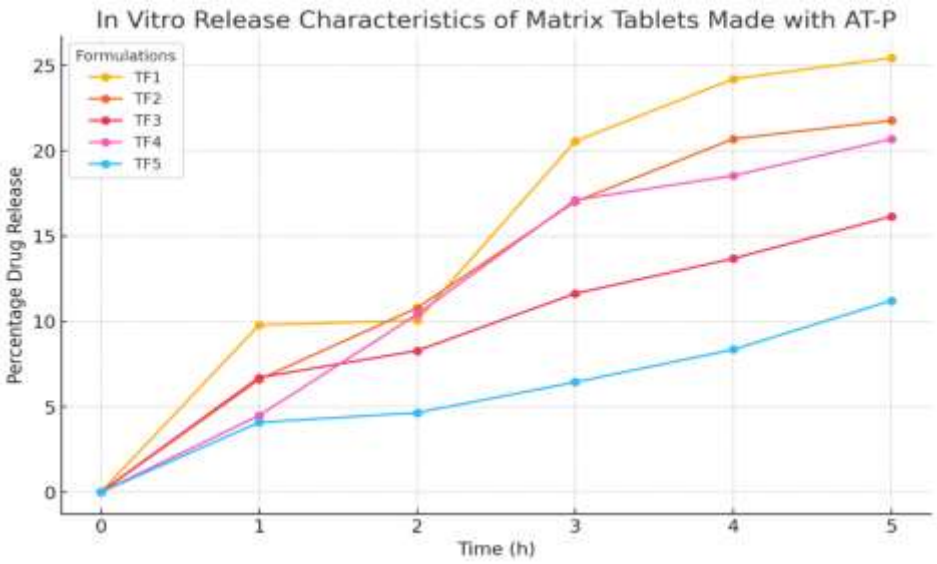

Figure 2. *In vitro* release characteristics of matrix tablets made with AT-P

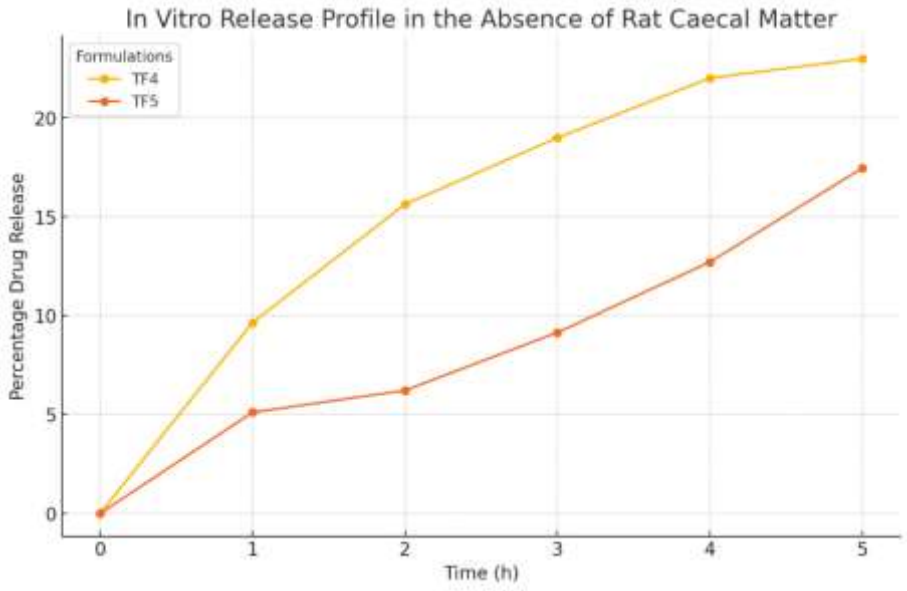

Figure 3. ***In vitro*** **release profile in absence of rat caecal matter**

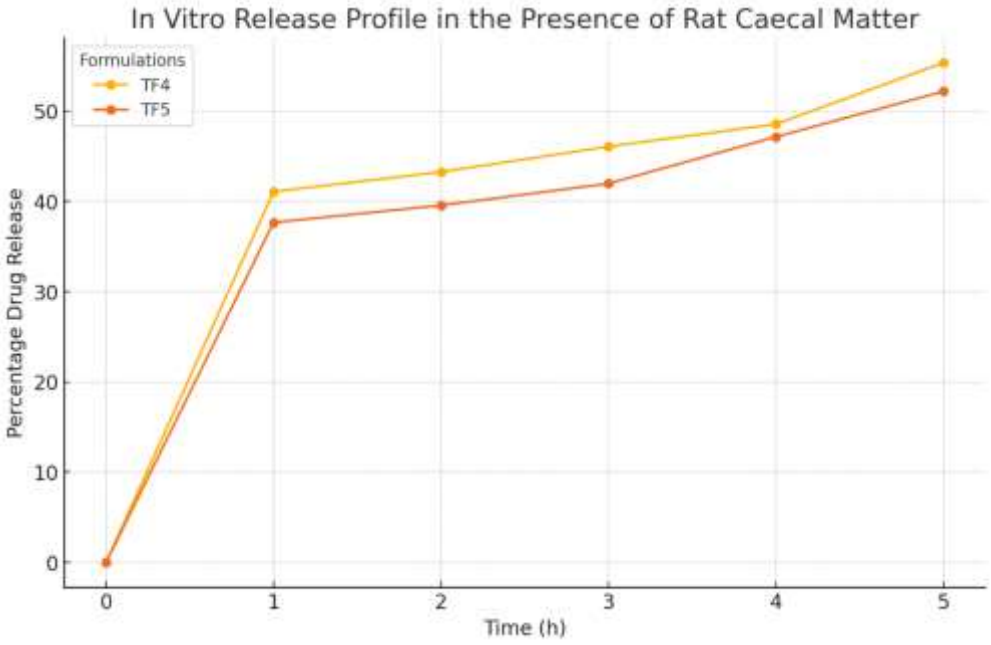

Figure 4. ***In vitro*** **release profile in presence of rat caecal matter**

Table 12. Kinetics of Release Data

Formulations	Parameters									
	Zero order		First order		Matrix model		Hix. Crow		Peppas	
	R	k	R	k	R	k	R	k	n	R
TF1	0.8947	4.54	0.8639	0.1211	0.8900	14.72	0.8743	0.2338	0.9335	0.8453
TF2	0.9531	4.02	0.9055	0.1320	0.9753	13.22	0.9253	0.2369	0.82	0.9826
TF3	0.9910	2.43	0.9807	0.10	0.9716	7.811	0.9867	0.1651	0.7992	0.9640
TF4	0.9221	4.05	0.8296	0.1579	0.97	13.47	0.8658	0.2655	0.6923	0.9602
TF5	0.9513	1.80	0.9864	0.1132	0.8921	5.6568	0.9787	0.1641	0.5552	0.89093

Table 13. Mechanism of drug transport

Formulation Code	Drug transport mechanism
TF_1	Anomalous
TF_2	Super case II transport
TF_3	Anomalous
TF_4	Super case II transport
TF_5	Super case II transport

5. CONCLUSION

The comprehensive evaluation of matrix tablets formulated with a natural polysaccharide blend of Angelica sinensis polysaccharide and Tamarind Seed Polysaccharide (AT-P) demonstrated its potential as a viable excipient for controlled drug delivery, particularly for colon-targeted therapies. The preformulation studies confirmed the blend's compatibility with Prednisolone, and the subsequent formulation of five matrix tablets (TF1 to TF5) showcased varying release profiles. TF3 emerged as the most consistent formulation following zero-order kinetics, suggesting a constant release rate, while TF2 and TF5 showed strong diffusion-controlled release patterns, fitting the Higuchi model. In vitro release studies conducted with and without rat caecal matter revealed that the presence of colonic enzymes significantly enhanced drug release, with TF4 and TF5 demonstrating marked responsiveness to the colonic environment. Statistical analysis confirmed the significance of these findings, highlighting the blend's effectiveness in controlled-release applications. Overall, AT-P as an excipient offers a promising approach for developing matrix tablets that can effectively deliver drugs to the colon, providing a targeted and sustained release profile suitable for various therapeutic needs.

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