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Formulation and Evaluation of Azathioprine Matrix Tablets for Colon Targated Delivary using Natural Polysaccharides

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Five formulations (MTF1 to MTF5) with different concentrations of OKRAT-P and lactose were prepared for the purpose of developing and evaluating matrix tablets of azathioprine using a natural polysaccharide blend (OKRAT-P) for colon-targeted drug delivery. The tablets were evaluated for physical parameters, swelling properties, in vitro drug release, and release kinetics both in the presence and absence of rat caecal contents to simulate the colonic environment. The results showed that the formulation with the highest OKRAT-P content had the slowest drug release, with only 13.03% release after 5 hours in the absence of caecal contents and 54.27% release in the presence of caecal contents, indicating a significant enhancement of release triggered by colonic bacteria. Diffusion and erosion mechanisms combined to provide drug release, according to kinetic studies; super case-II transport was indicated by the Korsmeyer-Peppas model. In addition to having a high

swelling index of 180.59% at 24 hours, MTF5 had outstanding physical characteristics, such as low friability and high hardness, which enabled prolonged drug release. The optimal formulation for colon-targeted delivery was found to be MTF5, which provides regulated and site-specific drug release, making it appropriate for conditions that call for localised medication action in the colon.

Keywords: Azathioprine, Natural polysaccharide, Okra polysaccharide, Tamarind polysaccharide, colon targeting, microflora, matrix tablets.

1. Introduction

The potential of colon-targeted drug delivery systems (CTDDS) to deliver medications directly to the colon has drawn a lot of attention in pharmaceutical research. These systems offer a number of therapeutic benefits for treating both systemic conditions like rheumatoid arthritis and local diseases like ulcerative colitis, Crohn's disease, inflammatory bowel disease (IBD), and colorectal cancer. Because of its near-neutral pH, lengthy transit duration, and lower enzymatic activity than the upper gastrointestinal system, the colon offers an ideal environment for medication administration. Targeting the colon also enhances the bioavailability of medications that would otherwise break down or absorb too quickly in the stomach or small intestine and lessens systemic negative effects (1-5).

Making sure the medication stays intact as it travels through the upper gastrointestinal system and is only released when it reaches the colon is one of the fundamental problems in creating CTDDS. Time-dependent systems, enzyme-sensitive matrices, and pH-sensitive polymers can all be used to accomplish this. Among them, enzyme-sensitive systems have shown a lot of promise, especially those based on natural polysaccharides. Natural polysaccharides that are biodegradable and can be broken down by colonic bacteria, such guar gum, pectin, xanthan gum, and OKRAT-P (a combination of polysaccharides from okra and tamarind seed), are perfect for colon-targeted administration (6-14).

For colon-targeted medication delivery systems, natural polysaccharides provide a number of benefits. They can create hydrogels that swell in aquatic settings, regulating medication release, and they are non-toxic and biocompatible. Because polysaccharides are difficult to digest in the upper gastrointestinal tract but are broken down selectively by colonic bacteria, their biodegradability is especially beneficial for colon-specific medication release. This characteristic guarantees that the medication is protected while passing through the stomach and small intestine, with the release being initiated by the colon's bacterial enzymes. Natural polysaccharides are also inexpensive and easily obtained, which makes them appealing for use in many medicinal applications. In order to improve treatment results and patient compliance in the therapy of colon-specific disorders, polysaccharides such as OKRAT-P can be used into CTDDS to enable regulated, site-specific drug release (3, 13, 15, 16).

Because of their distinct qualities, okra and tamarind polysaccharides combine to provide a potentially useful natural blend for use in colon-targeted medication delivery systems. The mucilaginous exudates of Abelmoschus esculentus are the source of okra polysaccharide, which is well-known for its exceptional gel-forming and swelling properties, which aid in regulating medication release over time. It creates a viscous matrix that can prevent the medicine from releasing too soon in the stomach's acidic environment and is biocompatible and biodegradable (6, 16-18). Tamarind seed polysaccharide (TSP), which is derived from

Tamarindus indica, is a perfect matrix maker because of its well-researched film-forming, mucoadhesive, and thickening qualities. Additionally, TSP is resistant to digestion in the upper gastrointestinal tract and is only broken down by colonic bacteria, guaranteeing that the medication is only released once it enters the colon. Together, these polysaccharides in the OKRAT-P mix create a robust and stable matrix that not only shields the medication during gastrointestinal transit but also offers a regulated and prolonged release once it enters the colon. By guaranteeing accurate and site-specific medication release, this natural polysaccharide mix improves the overall effectiveness of colon-targeted delivery systems. This makes it especially helpful for the treatment of conditions that call for localised therapy in the colon (17, 19-25).

This study's objective was to create and assess colon-targeted azathioprine matrix tablets by using a natural polysaccharide blend (OKRAT-P) made of polysaccharides from tamarind seeds and okra. A regulated and site-specific medication release in the colon was the main objective in order to maximise therapeutic efficacy and reduce systemic adverse effects, especially when treating inflammatory bowel illnesses. The formulation of matrix tablets with different doses of OKRAT-P and thorough preformulation tests to guarantee the drug's and excipients' physical and chemical compatibility were among the study's main goals in order to accomplish this (6, 16-18). The homogeneity, hardness, and friability of the tablets' physical properties were examined, and their swelling behaviour was studied to determine the polysaccharide matrix's ability to create gels. In order to replicate the gastrointestinal environment and bacterial breakdown in the colon, in vitro drug release tests were carried out both with and without rat caecal contents. Lastly, the mechanisms of drug release were examined using kinetic modelling, which shed light on the diffusion and erosion processes controlling drug release from the tablets. In order to enhance patient outcomes and therapeutic advantages, the study sought to determine the best formulation for targeted, sustained medication delivery to the colon.

2. Material and Methods

Collection and preparation of natural polysaccharide blend

Tamarind seed (TSP) and polysaccharides from Abelmoschus esculentus (okra) were purchased from Herby Herbs, which is situated in Kulu, Himachal Pradesh, India. The natural polysaccharide mix known as OKROKRAT-P was made by blending these two polysaccharides in equal amounts (1:1). To maintain their quality, the mixed samples were kept in desiccators in sealed containers. Only analytical-grade chemicals were utilised for the polysaccharide extraction and characterisation. This combination of natural polysaccharides, which includes different proportions of galacturonic acid, galactose, rhamnose, and glucose, has shown promise as a treatment for a number of ailments, including peptic ulcers, diabetes, jaundice, constipation, and urethritis. It has stomachic and cooling qualities as well. Mucilage, fixed oils, and flavonoid glycosides were detected by phytochemical analysis; the yields of mucilage varied by season, ranging from 0.880% to 4.2%. The polysaccharide mix can be used as a flocculant, thickening, or binder and is well-known for its hepatoprotective and antioxidant qualities. In pharmaceutical tablet formulations, it has been used as a binder, helping to achieve desirable hardness, friability, and drug release characteristics. To increase

bacterial stability, 1.5% w/v sodium metabisulfite was added to the polysaccharide-water combination, which was then kept in a desiccator until it was needed. The blend's typical properties were 6.2 pH, 8.11% drying loss, 7.91% total ash content, 0.67% acid-insoluble ash content, and 7.23% water-soluble ash content.

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

Natural polysaccharide (% of wet weight)	
Properties	Purified
Moisture content	8.89
Protein	8.08
Ash	4.93
Calcium	1.79
Magnesium	0.61
Phosphorus	0.31
Potassium	0.89

Preformulation studies

A crucial step in the creation of a pharmaceutical dosage form is preformulation, which concentrates on a detailed examination of the drug's properties to ensure the creation of a stable, safe, and effective product. The physical and chemical characteristics of the active pharmaceutical ingredient (API), both alone and in combination with other excipients, are carefully examined during this phase. To ensure that the drug maintains its stability throughout its shelf life and continues to function effectively with other formulation ingredients, this thorough study is necessary (26). Preformulation investigations examine the drug's calibration curve, bulk density, tapping density, and biodegradation. Below is a list of the several test protocols:

a) pH and viscosity

To assess its characteristics and any influence on the finished formulation, the pH and viscosity of a 1% w/v solution of the natural polysaccharide were meticulously evaluated. A digital pH meter that had been calibrated to guarantee precise readings was used to measure the pH of the polysaccharide solution. In order to preserve medication stability and guarantee patient comfort during administration, this test yielded vital information about the solution's acidity or alkalinity. Ostwald's viscometer was utilised to evaluate the natural polysaccharide's flow characteristics. This device made it possible to measure viscosity precisely, providing information about how the polysaccharide behaved in solution. Determining the polysaccharide's function as a thickening or stabilising agent in drug delivery systems requires an understanding of its viscosity. Additionally, the viscosity data helped to optimise the formulation's performance, including its stability and drug release properties.

b) Bulk Density

In preformulation investigations, bulk density is a crucial statistic because it sheds light on the powder's packing and flow characteristics, which are essential for tablet compression and overall manufacturing effectiveness. A graduated cylinder was filled with a known weight of

powdered natural polysaccharide in order to test the bulk density. After recording the volume that the powder occupied, the bulk density was computed using the following formula: Bulk Density = Powder Weight/Powder Volume. This value is crucial for comprehending how the material will respond throughout the formulation process' blending and compaction phases, which will affect the dosage forms' homogeneity.

c) Tapped density

By mimicking the compression process used in tablet manufacture, tapped density offers additional information about the powder's packing characteristics after it has been tapped or settled. The same powder sample used for bulk density was mechanically tapped in a graduated cylinder until no more volume loss was seen in order to determine tapped density. The following formula was used to determine the tapped density: Weight of the powder divided by the powder's tapped volume equals the taped density. The compressibility index and Hausner ratio, which offer further details on the powder's flow characteristics, were computed using both bulk and tapped density measurements. These measures are essential for guaranteeing that the formulation will function reliably throughout production and yield tablets with the required properties.

d) Compressibility index

One important measure of the powder's flow characteristics that is essential for effective tablet production is the compressibility index. It gives information about how effectively the powder particles pack together and is computed using the powder's bulk and tapped densities. The material's ability to flow easily into tablet presses or other production-related equipment is determined in part by the compressibility index. The compressibility index was calculated using the following formula: Compressibility Index (%) = Tapped Density − Bulk Density / Tapped Density × 100.

Table 2. The flow characteristic is shown by the Carr's index.

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

Fabrication of matrix tablets

Wet granulation technology was used to create azathioprine matrix tablets by a traditional process that has already been described. The binder was made of 10% starch paste (27). The natural polysaccharide blend (OKRAT-P) and azathioprine formulations were made utilising a particular technique that required changing the lactose to azathioprine ratio while keeping the azathioprine dosage constant at 25 mg for all formulations (MTF1 to MTF5). The necessary quantities of every component were first precisely weighed. While the amount of lactose decreased from 130 mg in MTF1 to 0 mg in MTF5, the amount of OKRAT-P varied

from 100 mg in MTF1 to 200 mg in MTF5, and the amount of azathioprine was constant at 25 mg in each formulation. The components were moved to a mortar for mixing after they had been weighed. To guarantee that the medicine and excipients were distributed uniformly throughout the formulation, the powders were combined using geometric dilution. To ensure homogeneity and guarantee that each pill carried a constant dosage of the active component, a rigorous blending procedure was necessary. Wet granulation was applied to the mixture after it had been blended. The mixture was kneaded until a moist mass was created, using distilled water as the granulating agent. To produce granules, this substance was then run through a sieve with a #16 mesh size. In order to eliminate surplus moisture and guarantee ideal flow characteristics for tablet compression, the granules were then dried at 40°C. A single-punch tablet machine was used to compress the granules into tablets once they had dried. The hardness was optimised to guarantee the tablets had enough strength while permitting the proper drug release during disintegration, and the weight of the tablets was meticulously calibrated to guarantee consistency. Lastly, the tablets' physical characteristics, including their drug content, hardness, friability, and weight fluctuation, were assessed. The release profile of azathioprine from the OKRAT-P formulations was evaluated by in vitro dissolution tests to make sure the drug release was reliable and satisfied the required standards. By using this technique, azathioprine was successfully formulated with a combination of natural polysaccharides, improving the drug's release characteristics while preserving the necessary tablet physical attributes.

Table 3. The composition of the matrix tablets based on OKRAT-P (natural polysaccharide mix)

Ingredient	Formulation code				
	MTF_1	MTF_2	MTF_3	MTF_4	MTF_5
Azathioprine (mg)	25	25	25	25	25
OKRAT-P (mg)	100	120	140	160	200
Lactose(mg)	130	100	70	40	-

Evaluation of Tablets

Compatibility Studies

Compatibility studies were conducted to ensure that the excipients lactose and the natural polysaccharide blend (OKRAT-P) would not adversely interact with the active drug, azathioprine. These studies are essential to guarantee that the final formulation remains stable and effective during its shelf life. The primary method for determining if medications and excipients were compatible was Fourier Transform Infrared Spectroscopy (FTIR). This technique allowed for the identification of any chemical interactions by detecting changes in the functional groups of the drug and excipients. Pure azathioprine samples, samples of individual excipients, and physical mixtures of azathioprine with lactose and OKRAT-P were all subjected to analyses. The FTIR spectra of the materials were recorded in the range of 4000 to 400 cm^{-1}. The spectra were analysed to look for any significant changes or the appearance of new peaks that would indicate chemical interactions or incompatibilities between the medication and excipients.

Content uniformity

To determine a tablet's potential for efficacy, the dosage must be tracked from batch to batch and tablet to tablet (28). To make sure that every tablet contained the right and constant amount of azathioprine in accordance with pharmacopeial requirements, the content uniformity test was conducted. This test is crucial for verifying that the medication is dispersed uniformly throughout the batch, guaranteeing that every tablet has the right amount of medication. For this assessment, ten pills at random from each formulation batch (MTF1 to MTF5) were chosen. A fraction of the finely ground powder from each tablet was precisely weighed and then dissolved in an appropriate solvent. To determine how much azathioprine was in each tablet, the resultant solution was filtered, diluted as necessary, and then examined using UV spectrophotometry or another appropriate analytical technique. A comparison was made between the results for each tablet and the marked claim of 25 mg of azathioprine per tablet. Pharmacopeial regulations state that the amount of active medication in each tablet should be between 85% and 115% of the stated dose, with a relative standard deviation (RSD) of no more than 6% is acceptable. The content uniformity findings verified that the manufacturing process generated tablets with a constant drug content across the batch, ensuring that every formulation complied with the necessary standards. For the pills to be therapeutically effective and to ensure patient safety, this test is essential.

Thickness, Hardness and Friability

1. Thickness

To guarantee consistency and size uniformity among formulation batches, the tablet thickness was tested. This characteristic is crucial since it influences the dissolve rate, handling, packaging, and look of the tablet. Ten tablets from each batch (MTF1 to MTF5) were chosen at random, and their thicknesses were measured using a digital vernier calliper. To make sure the pills had uniform dimensions and prevent any possible problems with dosage or packing, the average thickness was determined and the findings were tested against predetermined limitations.

2. Hardness

To assess the tablets' mechanical strength and ability to withstand breaking or chipping during handling, storage, and transit, their hardness was examined. Because it directly affects the tablet's integrity and disintegration time, this is an essential quality control measure. With the use of a tablet hardness tester, the tablets were broken with force, and the force needed (measured in kg/cm2) was noted. To ensure that the tablets had enough strength without being too hard, which might impact medication release, the average hardness of ten tablets from each batch was determined.

3. Friability

The purpose of the friability test was to evaluate the tablets' ability to withstand abrasion and breaking during handling, packing, and transportation. Using a friabilator, friability testing was carried out by weighing a predetermined number of tablets (often 20) and rotating them in the drum for a predetermined number of rotations (usually 100). Following the test, the pills were gathered, weighed again, and the formula was used to determine the weight reduction percentage (29):

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

Weight variation

To make sure that each tablet in each formulation batch (MTF1 to MTF5) had a constant weight, the weight variation test was carried out. This test is essential for guaranteeing consistent medication content in all tablets since large weight fluctuations may result in different dosages, which might have an impact on therapeutic results. Twenty tablets were chosen at random from each batch for this test. A computerised analytical balance was used to weigh each pill separately, and the batch's average weight was determined. Next, the average weight of the pills was compared to their individual weights. Pharmacopeial guidelines state that the tablets cannot differ from the average weight by more than the permitted percentage, which is normally:

- ±5% for tablets weighing more than 250 mg,
- ±7.5% for tablets weighing between 130 mg and 250 mg,
- ±10% for tablets weighing less than 130 mg.

The weight variation test's findings verified that the pills' weights were sufficiently consistent, guaranteeing that each one had the recommended dosage of azathioprine. In pharmaceutical formulations, this test is crucial for guaranteeing patient safety and dose accuracy.

Swelling index

An essential metric for evaluating the tablets' ability to retain water is the swelling index, especially for formulations that contain natural polysaccharides like OKRAT-P. The swelling index shows how much the tablet swells and absorbs water, which can have an impact on the drug's bioavailability and release from the matrix. The tablets' swelling behaviour (MTF1 to MTF5) was assessed for this investigation. To replicate gastrointestinal conditions, each pill was first weighed (W_o) and then put in a petri dish with phosphate buffer solution (pH 6.8) at 37°C. The tablets were taken out, properly wiped with filter paper to remove excess water, and weighed once again (W_t) at predetermined intervals of 1, 2, 3, 4, and 5 hours. The following formula was used to determine the swelling index (30):

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

Where:

- W_t = Weight of the swollen tablet at time 't'
- W_o = Initial weight of the dry tablet

The swelling index offers important information about the natural polysaccharide's hydration and gel formation characteristics, which in turn influences how quickly azathioprine is released from the tablet. Drug release may be slowed by formulations with greater swelling indices because they tend to form thicker gels, whereas formulations with lower swelling indices may release drugs more quickly. The study's findings ensured the intended therapeutic impact by optimising the medication release profile for every formulation.

In vitro release studies

To assess the drug release profile of azathioprine from the formulations (MTF1 to MTF5) over time, in vitro release tests were carried out. In order to make sure that the formulations have the intended therapeutic effect and to comprehend how the medication is released from the matrix tablets under simulated gastrointestinal circumstances, these investigations are essential. The USP Dissolution Apparatus II (paddle technique) was used to test the release of azathioprine. The medium was kept at 37°C ± 0.5°C to imitate body temperature, and each formulation was submerged in 900 mL of phosphate buffer solution (pH 6.8) to mimic intestinal fluid. To guarantee even mixing, the paddle speed was set at 50 rpm. To monitor the drug's release, 5 mL samples of the dissolving media were taken out at predetermined intervals of 0, 1, 2, 3, 4, and 5 hours. Fresh buffer was added to each sample after it was removed in order to keep the volume constant and guarantee sink conditions for the duration of the investigation. Prior to analysis, the samples were filtered using a 0.45 µm filter to get rid of unwanted particles. Using UV spectrophotometry at the proper wavelength (usually about 280 nm), the concentration of azathioprine in each sample was ascertained. A calibration curve was used to compute the percentage of medication released at each time point. A release profile was then produced for each formulation by charting the cumulative release versus time. To ascertain the mechanism of drug release, the release data was fitted into a number of kinetic models, including Zero Order, First Order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. via revealing whether the medicine was released via diffusion, erosion, or a mix of the two, this study made it possible to optimise the formulations and get the required release rate. The performance of each formulation and the regulated and predictable release of azathioprine from the tablets, which made them appropriate for therapeutic usage, were both determined by the in vitro release experiments (31).

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

In vitro drug release tests were carried out with and without rat caecal contents to assess the formulations' (MTF1 to MTF5) capability for colon-targeted medication delivery. In order to enable targeted medication release in the colon, this study attempted to replicate the colonic environment, where colonic bacteria may break down the polysaccharide-based matrix.

Preparation of Rat Caecal Contents

Prior to the experiment, rats were given unrestricted access to water and fasted for a whole day. The rats were given anaesthesia on the day of the experiment, and the caecum was meticulously separated in an aseptic environment. To maintain the anaerobic condition, the caecal contents were collected in a nitrogen-flushed container. The contents were then diluted with phosphate buffer (pH 6.8) to create a 4% w/v caecal content solution. During medication release investigations, this solution was utilised to mimic the colon's microbial habitat.

In Vitro Release Studies

A USP Dissolution Apparatus II (paddle technique) was used to measure the amount of azathioprine released from the formulations. For the conventional release investigation (without caecal contents), the formulations were submerged in 900 millilitres of phosphate buffer solution (pH 6.8). In order to replicate the enzymatic breakdown that takes place in the colon, a 4% w/v rat caecal content solution was added to the dissolving medium for the colon-

specific investigation (presence of caecal contents). The paddle speed was adjusted to 50 rpm, while the medium was kept at 37°C ± 0.5°C. At specified intervals (0, 1, 2, 3, 4, and 5 hours), samples (5 mL) were extracted and filtered to exclude any particles. To keep sink conditions constant throughout the experiment, an equivalent amount of fresh medium was introduced after each measurement.

Analysis of Drug Release

To measure the amount of azathioprine released, the extracted samples were subjected to UV spectrophotometry at a suitable wavelength (around 280 nm). To create the release profile for each formulation under both conditions (with and without rat caecal contents), the proportion of medication released at each time point was computed and displayed against time. To ascertain the impact of colonic bacteria's microbial breakdown of the polysaccharide matrix, the outcomes were compared. The enzymatic breakdown of the polysaccharide in the presence of rat caecal contents was predicted to result in greater drug release, suggesting effective colon targeting. On the other hand, slower drug release without caecal contents would show that the matrix held together in non-colonic settings. These drug release tests confirmed OKRAT-P's promise as a polysaccharide-based matrix for colon-targeted drug delivery by offering insightful information about the formulations' capacity to release azathioprine precisely in the colon (32).

Statistical Analysis

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

3. Results and Discussion

Compatibility Studies

In order to assess the possible interactions between azathioprine and the chosen excipients, lactose and OKRAT-P (natural polysaccharide), compatibility tests were essential. These investigations are necessary to make sure that no physical or chemical alterations take place that would jeopardise the final formulation's stability, effectiveness, or safety. To find any potential interactions, the FTIR spectra of pure azathioprine, lactose, OKRAT-P, and the physical mixes of azathioprine with lactose and OKRAT-P were examined. In the physical mixes, the distinctive peaks of azathioprine, such as the C=O stretching about 1700 cm^{-1} and the N-H stretching around 3200–3400 cm^{-1}, stayed intact, suggesting that no notable changes or new peaks emerged. This implies that when azathioprine was combined with lactose and OKRAT-P, it maintained its chemical structure and that there was no evidence of drug-excipient incompatibility.

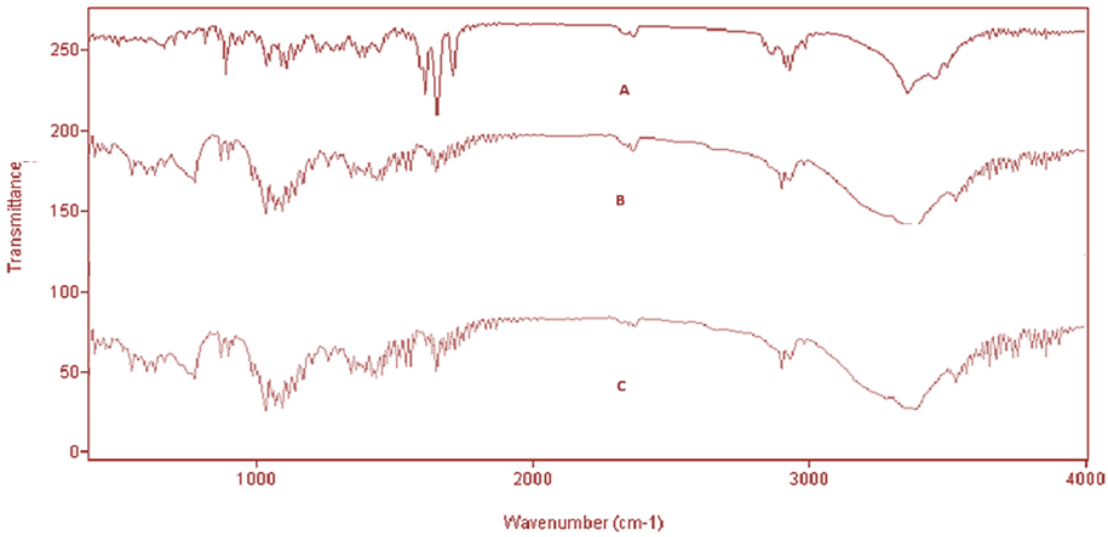

Figure 1. FTIR spectra of the physical mixture, OKRAT-P, and azathioprine

Evaluation of physical Parameters

pH and Viscosity

To make sure it was within a medically acceptable range, especially for oral medication administration, the pH of the 1% w/v solution of the natural polysaccharide blend (OKRAT-P) was determined. It was discovered that the solution's pH ranged from 6.2 to 6.5, which is slightly acidic and perfect for guaranteeing medication stability and reducing any possible discomfort during administration. The gastrointestinal environment, especially the colonic area, where the targeted medication release is planned, is suitable with this pH range. The findings showed that neither the stability of azathioprine nor the comfort of the patient during administration will be negatively impacted by the pH of OKRAT-P.

The 1% w/v OKRAT-P solution's viscosity was evaluated to evaluate its capacity to create a gel matrix, which is essential for regulating drug release in the formulation. Higher amounts of polysaccharides were discovered to enhance the solution's viscosity using an Ostwald's viscometer. According to the observed viscosity values, the solution's viscosity dropped as the shear rate increased, indicating non-Newtonian flow behaviour. Because the polysaccharide may create a stable matrix that progressively expands and erodes, azathioprine can be released continuously, which is advantageous for controlled drug release. OKRAT-P is a good fit for colon-targeted drug delivery systems, according to the pH and viscosity measurements. The moderate viscosity offers the required matrix-forming qualities for regulated medication release, and the slightly acidic pH guarantees compatibility with the gastrointestinal environment without irritating the stomach. OKRAT-P is a useful excipient for use in formulations because of its capacity to gel in aqueous settings, which supports its function in maintaining drug release. These results further support OKRAT-P's capacity to optimise azathioprine's release profile, guaranteeing stability and regulated distribution in the intended area.

Compressibility Indices and Hausner ratio

The flow and packing characteristics of the raw materials employed in the formulation are crucially indicated by the physical parameters, such as bulk density, tapped density, compressibility index, and Hausner ratio. In order to ensure effective compression and consistency in the finished product, these criteria aid in determining how effectively the powders can be processed throughout the tablet production process. The bulk density of OKRAT-P was 0.488 g/cm³, whereas the tapped density was 0.681 g/cm³. The discrepancy between these numbers indicates that OKRAT-P's structure is rather loose, allowing air to become trapped between particles. The greater tapped density value is a result of the particles settling and the volume decreasing during tapping. With a bulk density of 0.457 g/cm³ and a tapped density of 0.508 g/cm³, azathioprine showed that the drug particles were structurally closer than OKRAT-P. The fact that the bulk and tapped densities differ less indicates that azathioprine packs more effectively and has superior flow properties than OKRAT-P.

The powder's capacity to decrease its volume under pressure, which reflects its flow characteristics, is gauged by the compressibility index: With a compressibility index of 28.34%, OKRAT-P had subpar flow characteristics. A material is typically considered very cohesive and prone to poor flow if its compressibility index is higher than 25%. This could make things difficult while making tablets during the blending and compression processes, necessitating modifications to enhance handling. The compressibility index of 10.04% for azathioprine is within the range that indicates favourable flow characteristics. A compressibility index of less than 15% is thought to be a sign of powders with good flow, indicating that azathioprine will work well in tablet production.

Additional information on the powders' flowability is provided by the Hausner ratio, where greater values denote worse flow: The Hausner ratio of 1.395 for OKRAT-P is slightly below the 1.40 threshold, which denotes poor flowability. This figure supports OKRAT-P's high compressibility index, indicating that the polysaccharide may have poor flow characteristics and may need extra processing aids, such glidants, to enhance handling during manufacture. With a Hausner ratio of 1.111, azathioprine demonstrated favourable flow characteristics. Values less than 1.25 are often seen as advantageous for powder flow, indicating that azathioprine may be handled and crushed into tablets with no difficulty.

OKRAT-P's high compressibility index and Hausner ratio indicate that it has relatively poor flow qualities, according to the evaluation of physical factors. This could make production more difficult, especially when it comes to maintaining consistency in the medication content and tablet weight. Additional excipients, such as flow enhancers, or modifications to the procedure may be required to increase OKRAT-P's flowability. However, azathioprine showed good flow characteristics, as seen by its low Hausner ratio and compressibility index. This implies that the medication will mix effectively and flow well during the compression procedure, guaranteeing reliable tablet manufacturing. These results are crucial for refining the formulation procedure to overcome the difficulties presented by the natural polysaccharide and guarantee the effective processing and release of the medication.

Table 5. Evaluation of the physical parameters

S. No	Ingredient	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner Ratio
1.	OKRAT-P	0.488	0.681	28.34%	1.395
3.	Azathioprine	0.457	0.508	10.039%	1.111

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

To make sure the manufactured tablets fulfilled the necessary requirements for homogeneity, stability, and drug release performance, the physical and chemical properties of tablet formulations MTF1 through MTF5 were assessed. The following is a summary of the findings from the evaluation of the tablets' thickness, weight fluctuation, hardness, friability, and content homogeneity:

1. Thickness

The low standard deviations show that there was little variation across batches in the tablet thickness, which varied from 6.74 mm to 7.05 mm for all formulations. constant tablet compression during manufacture is suggested by the uniform thickness, guaranteeing dependable packaging and constant medication release. The minor differences across the formulations are within permissible pharmacopeial bounds, indicating that the compression force was properly managed.

2. Weight Variation

The mean values of the tablets' weight ranged from 300.59 mg to 303.59 mg, and the variance was judged to be within acceptable bounds. Each tablet includes a constant quantity of the medicine and excipients, as indicated by the low standard deviations, which also show consistent tablet weight among formulations. Maintaining dose accuracy and therapeutic effectiveness need this constancy. Pharmacopeial criteria, which stipulate that tablets weighing more than 250 mg must not deviate from the average weight by more than 5%, were satisfied by all formulations.

3. Hardness

Across all formulations, tablet hardness, a measure of the tablets' mechanical strength, varied from 6.01 kg/cm^2 to 6.71 kg/cm^2. This range of hardness shows that the tablets were both able to dissolve properly and robust enough to endure handling, packing, and shipping without shattering. changes in the OKRAT-P content, which might affect the binding and compression characteristics of the tablets, are probably the cause of the slight changes in hardness across formulations. All formulations showed sufficient mechanical strength overall, and there was little chance of tablet breaking with normal handling.

4. Friability

The tablet's resistance to abrasion was measured by its friability, which varied from 0.13% to 0.58%. MTF5 showed the lowest friability. Every formulation demonstrated exceptional resistance to shattering and crumbling during handling, with friability values much below the permissible limit of 1%. Formulations with greater OKRAT-P contents (MTF4 and MTF5) showed reduced friability values, which may indicate that the natural polysaccharide improved

binding and cohesion and so improved tablet integrity.

5. Content Uniformity

The tablets' azathioprine content homogeneity, which varied from 97.38% to 98.41%, showed that the medication was evenly dispersed across all formulations. Because the standard deviations were small, each batch's medication content was consistent from tablet to tablet. The findings verified that every formulation complied with the pharmacopeial criteria for content uniformity, which stipulates that the amount of active ingredients should be between 85% and 115% of the amount listed on the label with a reasonable relative standard deviation.

All of the tablet batches were found to be within acceptable ranges for pharmaceutical quality based on the assessment of physical and chemical criteria for the OKRAT-P-based formulations. The pills were sturdy but able to deliver the medication efficiently because of their consistent thickness, little weight variation, and suitable hardness. The increased binding qualities of the natural polysaccharide were emphasised by the low friability values, especially in formulations with a greater OKRAT-P concentration, which improved tablet durability. Consistent dosage and therapeutic impact were ensured by the content uniformity findings, which verified that azathioprine was dispersed uniformly throughout the tablets. All things considered, the formulations showed outstanding physical stability and consistency, which qualifies OKRAT-P as a natural excipient for creating stable and efficient drug delivery systems that target the colon. These findings support OKRAT-P's ability to regulate medication release while preserving the intended tablet quality characteristics.

Table 4. Evaluating the chemical and physical characteristics of the polysaccharide-based natural tablet formulations (OKRAT-P)

S. No	Parameters	Formulations (Codenamed)#				
		MTF_1	MTF_2	MTF_3	MTF_4	MTF_5
1.	Thickness (mm)	7.03 ± 0.087	6.79 ± 0.107	7.05 ± 0.107	6.74 ± 0.067	6.77 ± 0.087
2.	Weight Variation (mg)	302.59 ± 2.907	301.39 ± 2.847	301.49 ± 2.767	303.59 ± 2.907	300.59 ± 2.247
3.	Hardness (kg/cm^2)	6.42 ± 1.007	6.67 ± 0.917	6.71 ± 0.897	6.35 ± 0.947	6.01 ± 0.967
4.	Friability (%)	0.58 ± 0.05	0.55 ± 0.05	0.29 ± 0.04	0.28 ± 0.04	0.13 ± 0.06
5.	Content Uniformity (%)	97.68 ± 1.367	98.41 ± 1.357	97.38 ± 1.477	97.71 ± 2.117	97.90 ± 1.107

Result are presented as mean ± SD, n=3

Swelling Index

Over the course of 24 hours, the swelling characteristics of the matrix tablets made with the natural polysaccharide blend (OKRAT-P) were assessed. The swelling index increased gradually for all formulations (MTF1 to MTF5), according to the data. The swelling index at the 1-hour mark was 41.72% for MTF1 and 82.46% for MTF3, which was the highest. The

swelling indices increased over time, with MTF3 continuously showing the highest swelling capability. MTF1 reported a maximum swelling index of 165.00% after 24 hours, whereas MTF3 achieved a maximum of 203.57%.

In contrast to MTF1 and MTF2, which included smaller levels of the polysaccharide, the findings showed that formulations with larger concentrations of OKRAT-P, such as MTF3, MTF4, and MTF5, showed noticeably higher swelling indices. At six hours, for instance, MTF1's swelling index was 120.95%, but MTF5's was greater at 140.82%. This implies that the hydration capacity and gel formation of the tablets are directly impacted by the OKRAT-P concentration.

In formulations such as MTF3, the greater swelling signifies the development of a thicker gel layer, which is essential for regulating the drug's release over a longer duration. The capacity of OKRAT-P to absorb substantial volumes of water and create a stable gel matrix was validated by the high swelling index of MTF3 at 203.57% after 24 hours. These formulations are especially well-suited for sustained-release medication delivery systems because of the gel matrix's ability to efficiently control drug release. In conclusion, the OKRAT-P concentration had a substantial impact on the tablets' swelling characteristics. The promise of these formulations for colon-targeted drug administration, where a regulated and delayed release is crucial, was supported by the fact that higher doses caused more oedema. The findings show that OKRAT-P improves the tablets' swelling behaviour, which helps the medication release continuously and boosts the formulation's overall effectiveness.

Table 5. Swelling characteristics of matrix tablets prepared with a natural polysaccharide mixture (OKRAT-P)

S. No	Time (h)	% Swelling Index				
		MTF_1	MTF_2	MTF_3	MTF_4	MTF_5
1	0	0	0	0	0	0
2	1	41.72	48.00	82.46	76.27	79.71
3	2	65.82	70.62	96.48	85.61	92.65
4	4	91.64	104.96	143.18	134.84	129.56
5	6	120.95	128.54	162.45	147.58	140.82
6	12	151.65	161.70	186.58	162.88	159.91
7	24	165.00	168.89	203.57	185.68	180.59

In vitro release study

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

To mimic the behaviour of the formulations under various gastrointestinal settings, the in vitro release profiles of azathioprine from matrix tablets made with OKRAT-P (MTF1 to MTF5) were evaluated both in the presence and absence of rat caecal matter. The findings are shown in three tables: Table 10 shows the release profile without rat caecal matter, and Table 11 shows the release profile with rat caecal matter present. These two profiles' comparison demonstrates how intestinal bacteria affect OKRAT-P breakdown and how it affects medication release.

In Vitro Release Profile in the Absence of Rat Caecal Matter

When rat caecal matter was absent, the release profile of formulations MTF1 through MTF5 demonstrated a regulated release of azathioprine over a period of five hours. For instance, after an hour, MTF5, which had the greatest OKRAT-P concentration, only released 5.89% of the medication, but MTF1, which had the lowest OKRAT-P content, released 11.59%. This pattern continued throughout time, with MTF5 showing the slowest release of all time points, at 13.03% after 5 hours, while MTF1 showed a release of 27.24%.

The delayed drug release in the absence of intestinal bacteria was further highlighted by the release data from formulations MTF4 and MTF5 (Table 10). One hour later, 11.73% of the medication was released by MTF4 and 7.19% by MTF5. These values rose to 25.07% and 19.54% after 5 hours, respectively, suggesting that the matrix held together rather well in the absence of bacterial breakdown.

In Vitro Release Profile in the Presence of Rat Caecal Matter

The release profile of MTF4 and MTF5 dramatically increased in the presence of rat caecal matter (Table 11), indicating that colonic bacteria were enzymatically breaking down the polysaccharide matrix. In contrast to much slower release rates in the absence of rat caecal matter, MTF4 and MTF5 released 43.17% and 39.75% of azathioprine, respectively, after an hour. Drug release from MTF4 and MTF5 rose to 57.45% and 54.27%, respectively, after five hours. In comparison to the lack of caecal matter, the inclusion of rat caecal matter considerably accelerated the degradation of the OKRAT-P matrix, leading to a quicker and more significant drug release. This demonstrates unequivocally OKRAT-P's potential as a colon-targeted drug delivery system, in which the presence of colonic bacteria can initiate drug release.

In the absence of intestinal bacteria, the in vitro release experiments reveal that OKRAT-P-based matrix tablets have a regulated and prolonged drug release; formulations with greater OKRAT-P concentrations (like MTF5) have slower release rates. In order to achieve delayed medication release—a prerequisite for colon-targeted delivery—this behaviour is beneficial. The drug release from the tablets was markedly increased in the presence of rat faeces, indicating that OKRAT-P is susceptible to enzymatic breakdown by colonic bacteria. Given that drug release may be precisely initiated in the colon, this study bolsters the use of OKRAT-P as an efficient carrier for colon-targeted drug delivery systems, which guarantee that the medication reaches the intended location of action. Overall, these findings imply that OKRAT-P-based matrix tablets are appropriate for colon-targeted drug delivery because they provide accelerated release when colonic enzymes are present and controlled release when colonic bacteria are absent, making them ideal for conditions requiring site-specific drug delivery to the colon.

Kinetics of release data

Several kinetic models, such as Zero Order, First Order, Matrix (Higuchi), Hixson-Crowell, and Korsmeyer-Peppas models, were used to analyse the drug release kinetics from the matrix tablets (MTF1 to MTF5). The release mechanisms and rate of azathioprine's release from the OKRAT-P-based formulations were comprehended through the usage of these models.

1. Zero Order Model

Regardless of the drug's concentration, the Zero Order model implies that it is delivered at a steady pace. A fair match was shown by the R values (correlation coefficients) for all formulations, which varied from 0.9580 to 0.9752. For formulations with lower OKRAT-P concentrations (e.g., MTF1: 5.43 and MTF2: 4.75), the k values (release rate constants) were greater, suggesting a quicker drug release rate. Higher OKRAT-P concentrations appear to provide a more regulated, prolonged release, as seen by the slower release in formulations such as MTF5 (k = 2.28).

2. First Order Model

The majority of formulations also match well with the First Order model, which postulates that the rate of drug release is proportionate to the concentration of the drug still present in the tablet. The best match was found for MTF3 (R = 0.9917), with R values ranging from 0.9201 to 0.9917, indicating a concentration-dependent release mechanism. Further corroborating the finding of a delayed drug release in formulations with a greater OKRAT-P concentration were the typically lower k values (e.g., MTF5: k = 0.2041).

3. Matrix Model (Higuchi)

The Matrix (Higuchi) model uses Fick's rule, which depends on the square root of time, to characterise drug release as a diffusion process. The Matrix model's R values, which ranged from 0.9788 to 0.9958, were consistently high for all formulations, suggesting that diffusion was a key factor in the drug release process. While MTF5 had a lower k value of 5.35, indicating a longer delayed release because of the polysaccharide matrix, MTF1 and MTF2 exhibited the highest k values (k = 12.66 and 11.10), respectively, indicating quicker diffusion-based release in these formulations.

4. Hixson-Crowell Model

The releasing mechanism caused by variations in the tablets' diameter and surface area is described by the Hixson-Crowell model. The drug release rate was impacted by erosion and disintegration of the tablet structure, as indicated by the R values, which varied from 0.9198 to 0.9911, with MTF2 showing the best match (R = 0.9911). According to their k values (MTF5: k = 0.4795), formulations with greater OKRAT-P contents, such MTF4 and MTF5, had slower erosion rates, indicating that the polysaccharide matrix served as an erosion barrier.

5. Korsmeyer-Peppas Model

The diffusion exponent (n), which indicates whether the release followed Fickian diffusion ($n \leq 0.5$), non-Fickian transport ($0.5 < n < 1$), or case II transport ($n \geq 1$), was utilised to determine the mechanism of drug release using the Korsmeyer-Peppas model. The drug release mechanism followed super case-II transport, with both diffusion and polymer relaxation (erosion) contributing to the release process, as shown by the n values for all formulations being more than 1. For instance, formulations with a greater polysaccharide content exhibited a slower and more regulated release, as seen by MTF1's n value of 2.3321 and MTF5's lower n value of 1.6679.

The strong correlation coefficients for the Matrix (Higuchi) and Korsmeyer-Peppas models demonstrated that all formulations used a combination of diffusion and erosion processes, according to the examination of the drug release kinetics. Drug release rates were slower in

formulations with greater OKRAT-P contents, including MTF4 and MTF5, indicating that the polysaccharide matrix successfully regulated drug release. Since the super case-II transport mechanism predominated in these formulations, the n values from the Korsmeyer-Peppas model provided additional support for this finding. All things considered, the kinetics of release data showed that OKRAT-P can adjust the rate of drug release according to its concentration, which makes it an appropriate excipient for colon-targeted and sustained-release drug delivery systems. For targeted medication administration, a slower, more regulated release was offered by the greater OKRAT-P concentrations in formulations like MTF5.

Table 6. Drug Release mechanisms based on Kinetic Modelling

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

Table 7. The in vitro release properties of matrix tablets composed of OKRAT-P

Serial No.	Time (h)	Formulations Code				
		MTF_1	MTF_2	MTF_3	MTF_4	MTF_5
1	0	0	0	0	0	0
2	1	11.59 ± 1.501	8.40 ± 0.891	8.52 ± 2.341	6.29 ± 0.881	5.89 ± 1.011
3	2	11.87 ± 0.931	12.60 ± 1.021	10.09 ± 2.021	12.22 ± 0.641	6.46 ± 0.541
4	3	22.36 ± 2.761	18.82 ± 0.741	13.44 ± 3.001	18.92 ± 0.471	8.25 ± 0.841
5	4	26.01 ± 2.331	22.50 ± 0.801	15.49 ± 2.021	20.35 ± 0.911	10.16 ± 1.021
6	5	27.24 ± 1.731	23.57 ± 0.741	17.96 ± 2.911	22.49 ± 0.531	13.03 ± 1.431

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

Table 8. Drug release profile In vitro in the absence of rat caecal matter

S. No	Time (h)	Formulation Code	
		MTF_4	MTF_5
1	0	0	0
2	1	11.73 ± 2.551	7.19 ± 1.051
3	2	17.71 ± 1.641	8.30 ± 1.181

4	3	21.07 ± 1.261	11.23 ± 1.281
5	4	24.09 ± 0.601	14.79 ± 1.151
6	5	25.07 ± 0.541	19.54 ± 1.191

Table 9. Drug release profile In vitro in presence of rat caecal matter

S. No	Time (h)	Formulation Code	
		MTF_4	MTF_5
1	0	0	0
2	1	43.17 ± 2.121	39.75 ± 1.251
3	2	45.34 ± 2.181	41.65 ± 1.341
4	3	48.16 ± 1.311	44.06 ± 1.321
5	4	50.65 ± 1.461	49.25 ± 1.441
6	5	57.45 ± 1.381	54.27 ± 1.311

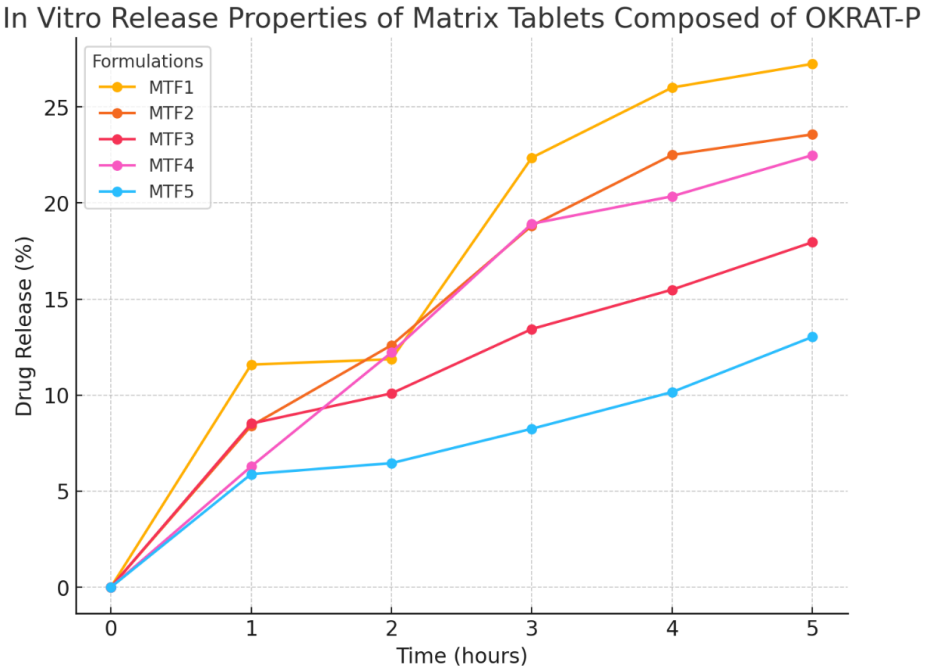

Figure 2. Properties of matrix tablets prepared with OKRAT-P in vitro release

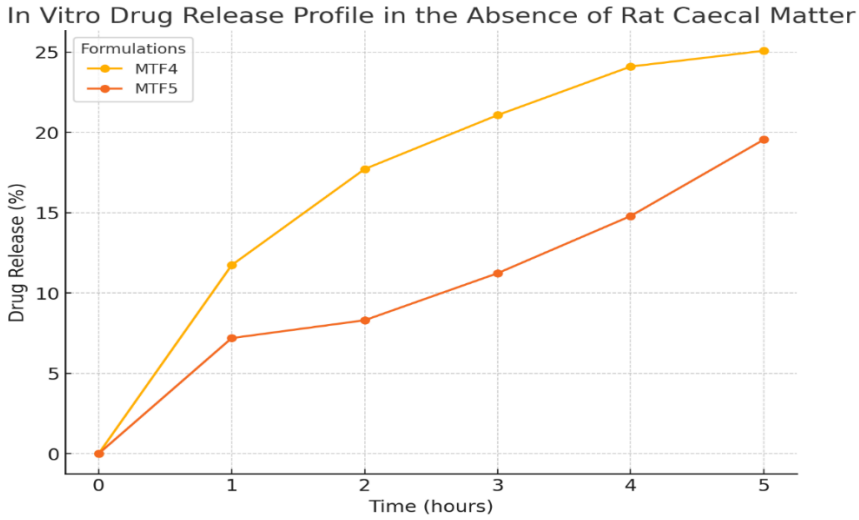

Figure 3. The release profile in vitro without rat faeces

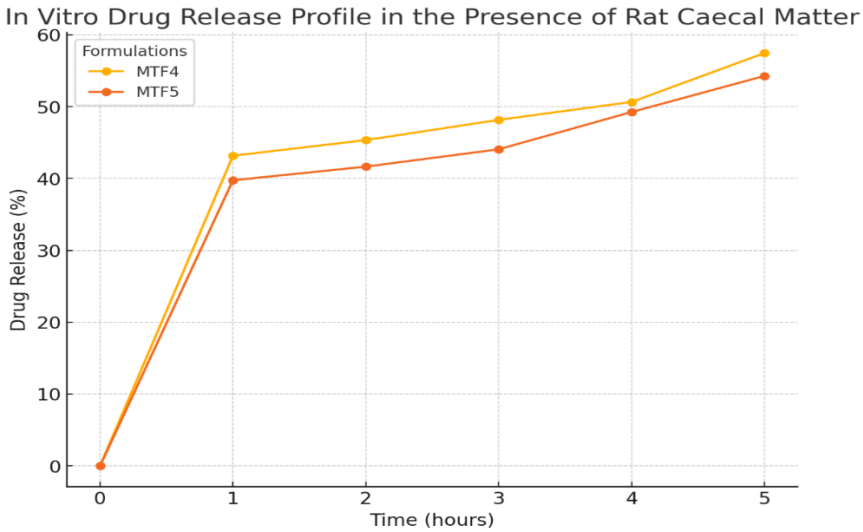

Figure 4. Drug release profile In vitro in presence of rat caecal matter

Table 10. 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
MTF1	0.9612	5.43	0.9310	0.2494	0.9718	12.66	0.9198	0.6129	2.3321	0.9612
MTF2	0.9752	4.75	0.9557	0.2643	0.9877	11.10	0.9911	0.6820	2.1211	0.9752
MTF3	0.9580	3.26	0.9917	0.1920	0.9958	7.81	0.9793	0.4718	2.0844	0.9580
MTF4	0.9728	4.61	0.9201	0.3058	0.9788	10.70	0.9835	0.8133	1.9029	0.9728

MTF5	0.9634	2.28	0.9909	0.2041	0.9804	5.35	0.9356	0.4795	1.6679	0.9634

4. Conclusion

This study effectively illustrated the potential of the natural polysaccharide mix OKRAT-P for use in medication delivery systems that target the colon. Azathioprine matrix tablets demonstrated regulated drug release patterns, favourable physical attributes, and swelling characteristics. The formulation with the greatest concentration of OKRAT-P, MTF5, was shown to be the most promising option for distribution to the colon. MTF5 released only 13.03% of the medicine when colonic bacteria were absent and 54.27% when rat faeces were present, demonstrating its exceptional mechanical strength, low friability, and prolonged release profile. According to kinetic modelling, diffusion and erosion processes regulated the drug release, with super case-II transport playing a role in the controlled release behaviour. According to the findings, OKRAT-P is a viable excipient for colon-targeted and sustained-release drug delivery systems since it can efficiently control drug release. Particularly, MTF5 may be used to treat diseases like inflammatory bowel disease, where effective treatment depends on localised medication release in the colon.

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