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Natural polymers for targeted drug delivery to the colon: A comparative study of tamarind gum and karaya gum

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ABSTRACT

The study aimed to create an effective colon-targeted budesonide delivery system using natural polymers. Various natural gums were assessed for their ability to develop a microbial degradation-based colon-targeted drug delivery system. The sensitivity of polymers to colonic enzymes was tested by evaluating viscosity changes in the presence of a prebiotic culture medium simulating rat cecal content. Tamarind gum and Karaya gum exhibited superior viscometric profiles. Compression coating with these gums, followed by an Eudragit S 100 coat, was employed for successful colon delivery. A 3^2-factorial design optimized the system, using variables like polymer to ethyl cellulose (EC) ratio and Eudragit S 100 weight gain. The design-space stipulated less than 10% drug release in 2 hours (h), less than 15% in 5 h, and over 50% in 7 h for colon targeting. The Tamarind gum batch (TM 9) released 8.91% at 5 h and 50.23% at 7 h, achieving optimal drug delivery to the colon.

Keywords: budesonide, tamarind gum, karaya gum, Eudragit S 100, colon targeting

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INTRODUCTION

Both ulcerative colitis and Crohn's disease are forms of inflammatory bowel disease (IBD). They both possess a prolonged, recurrent inflammation of the digestive tract, yet they are distinct things[1]. The colon and rectum are most affected by the continuous inflammation that describes ulcerative colitis. The most effective therapy for moderate to severe ulcerative colitis is corticosteroids (UC)[1,2]

However, undesirable side effects and a lack of potential for maintenance treatment restrict their long-term use. The therapy of choice for active IBD is a new class of anti-inflammatory glucocorticoids, such as budesonide, with greater topical anti-inflammatory impact and less systemic activity[3, 4].

However, budesonide is poorly absorbed in the colon because of its fast presystemic clearance in hepatocytes and small intestine epithelial cells[5,6].

To treat IBD effectively and reduce the common systemic adverse effects of glucocorticoids, an oral colonic drug delivery (CDD) system for budesonide is desperately needed to boost the drug's local concentration in the colon mucosa[7,8].

For colon-specific drug delivery, several strategies including Prodrug, pH-dependent[9] time-dependent[10], and micro flora-activated systems[11] have been developed. Among several approaches, polymers that are biodegraded by colonic bacterial enzymes show the most potential[9,12].

Numerous reductive and hydrolytic enzymes, such as b-glucuronidase, b-xylosidase, b-galactosidase, a-arabinosidase, nitroreductase, azoreductase, urea hydroxylase, etc., are produced by *Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Lactobacillus, Clostridium,* etc. Di-, tri-, and polysaccharide biodegradation are catalysed by these enzymes[13].

In general, 4% of the rat cecal content is used to imitate the enzymatic environment of the colon in the microbial approach. However, several rats must be killed for this purpose. To prevent this, novel dissolution biorelevant media that function as appropriate media[13,14] were developed using the probiotic culture medium prepared with the bacterial strains of Velgut capsule, and their effectiveness on viscosity of polymeric solution was evaluated and compared to the effectiveness of 4% rat cecal content. On the basis of enzymatic susceptibility, the ideal quantity of probiotic culture medium is determined, and the same amount is used for all dissolution procedures in the research[14].

The colonic drug delivery system was developed utilising novel natural polymers, namely Karaya gum, Khaya gum, Gellan gum, Gum Ghatti, and Tamarind gum[15–17]

Karaya gum is produced by Sterculia urens trees and is one of India's essential forest products. Bacterial enzymes in the colonic region break down Karaya gum, which consists of four galacturonic acid molecules[17,18].

Khaya gum is extracted from the cut stem of the *Khaya grandifoliola* plant, belonging to the Maliaceae family. Khaya gum contains the sugars D-galactose and L-rhamnose as well as the acids D-galacturonic acid and 4-O-methyl-D-glucoronic acid[19].

Gellan gum is an extracellular polymer produced by *Sphingomonas elodea*, formerly known as *Pseudomonas elodea*. Commercial production uses a fermentation process[20].

Gum Ghatti is a non-starch polysaccharide that is indigenous to India and is generated by the Combretaceae plant species *Anogeissus latifolia*[21].

The endosperm of seeds from the tamarind tree (*Tamarindus indica*) may be used to make a gum that has potential health benefits[22]. Tamarind kernel powder is a complex carbohydrate polymer with a high degree of branching, as determined by its chemical composition. Similar to cellulose, its backbone consists of (1-4) b-linked D-glucose units. As an effective excipient in the manufacturing of matrix tablets, Tamarind gum is employed[23].

The 3^2 Full factorial design is a valuable experimental design technique with specific applications in the field of targeted drug delivery. Its advantages include the ability to systematically investigate the effects of multiple variables on drug delivery performance, optimize the formulation parameters for enhanced therapeutic efficacy, reduce side effects, and improve patient compliance[24]. By employing 3^2 Full factorial design, researchers can efficiently explore the design space and identify optimal conditions for targeted drug delivery systems[25].

These systems were meticulously designed and formulated according to predefined selection criteria to achieve colon-targeted drug delivery. The desired drug release profile for the colon-targeted system was defined as the release of no more than 15% of the drug within the initial 5 h, with a minimum of 50% drug release within 7 h.

The study analyzed the impact of the viscosity profile of natural polymers on the release characteristics of formulations, and assessed the ability of the polymer to specifically target drug delivery to the colon[26].

METHODOLOGY

Materials

The budesonide sample was acquired as a gift sample from Zydus Cadila Pharmaceuticals, Ahmadabad. Karaya gum, Khaya gum, Gallan gum and Ghatti gum were purchased from ACS Chemicals, Bombay. The Tamarind gum utilised in this study was acquired as a free sample from H. B. Gum Ltd. Kalol, Gujarat. Eudragit S-100 was obtained as a gift sample from Evonik, Mumbai. The remaining chemicals employed were of analytical quality. The Nutrient Agar media was procured from the Himedia supplier.

Methods

Selection of natural polymers using viscosity measurement

The experiment focused on assessing the viscosity of various natural polymers, namely Khaya Gum, Karaya gum, Gellan gum, Ghatti gum, and Tamarind gum to assess the retardation capacity of gums indirectly. To begin, 1% solutions of each gum were meticulously prepared using a phosphate buffer solution adjusted to a pH of 6.8. These solutions were allowed to rest overnight, enabling the gums to fully soaked within the buffer. The subsequent step involved employing a Brookfield Viscometer, an instrument designed to measure the viscosity of gum solutions. In this case, a standardized approach was adopted, using Spindle No. 63 and a rotation speed of 12 rpm. These adjustment were consistent across all measurements and were chosen to ensure accurate and comparable results[14]. Natural polymers with the significant viscosity were selected.

Core tablet preparation using direct compression technique

The quantified quantity of Budesonide along with all accompanying excipients, underwent sieving through mesh number 60. The dry binding agent employed was polyvinyl chloride (PVP K-30). A suitable measure of Tablettos 100 diluent was incorporated. Talc and magnesium stearate were introduced to the powder formulation to enhance lubrication and augment the flow characteristics of the powder aggregate. The composition of the core tablets containing budesonide is outlined in Table 1. Subsequently, a predetermined mass of the powder aggregate was compacted using an 08/32” flat punch through employment of a double rotating tablet compression machine.

Table 1. Composition of budesonide core tablets

Material	Quantity
Budesonide	9 mg
Tablettos 100	64 mg
PVP K-30	4 mg
Talc	2 mg
Magnesium stearate	1 mg
Total	80 mg

Quantitative determination of drug content in a core tablet of budesonide

A drug content assessment was executed on the budesonide-containing core tablets. Ten tablets were pulverized into a fine powder, and an accurately measured amount of this powder, corresponding to 100 mg of budesonide, was introduced into 100 mL volumetric flasks containing 50 mL of methanol. Following a six-hour period of intermittent sonication to ensure full drug solubility, the solutions underwent sequential dilution and subsequent filtration. The quantification of drug concentration transpired at a wavelength of 245 λ_{max}, employing a UV spectrophotometer, to ascertain the accurate content of the drug within the tablets[27]

Compression coating of the core tablets of budesonide

Using 10/32" D Tooling Concave punches, a compression coating procedure was executed. Approximately one-third of the powder was introduced into the die cavity, followed by precise placement of budesonide core tablets, previously prepared using an 8/32" flat punch, positioned at the center of the cavity. The remaining powder was then added, facilitating the compression process for creating budesonide core tablets with an outer coating. The total mass of the coat formulations employed in the Karaya gum/Tamarind gum (KR/TM) batches was meticulously set at 165 mg. Detailed compositions for compression coating utilizing Tamarind gum and Karaya gum are presented in Table 2.

Table 2. Composition of coating formulation using Karaya gum or Tamarind gum

Ingredients	Coating Composition (mg)
Karaya Gum/ Tamarind Gum and EC	150
PVP K 30	15
Total	165

This study encompassed the comprehensive assessment of various attributes of compression-coated tablets, encompassing aspects such as hardness, friability, weight variation, drug content, and drug release kinetics. Furthermore, the compression-coated tablets underwent a subsequent super-coating step using Eudragit S 100 coating solution containing triethyl citrate (TEC) as plasticizers, accomplished through the pan coating technique[28].

Preparation of different batches using 3^2 full factorial designs

Tablets intended for colonic delivery underwent optimization employing a comprehensive 3^2 full factorial design via Design Expert 11.0 software. This design encompassed a systematic assessment of the main, interaction, and quadratic effects of two independent variables, namely the Proportion of Natural Polymer to EC and the percentage weight gain by Eudragit S100, each at three distinct levels. The selected responses, which represented the dependent variables, were % drug release at 2 h, % drug release at 5 h, and % drug release at 7 h, as precisely detailed in Table 3.

Table 3. Independent and dependent variables and the levels used for factorial design

Factors (Independent variables)	LEVELS			Responses (Dependent variables)
	-1	0	+1	
X1- Proportion of Natural Polymer to EC (mg) (Compression coating)	125:25	100:50	75:75	Y_2= % Cumulative Drug release at 2 h
X2- Coating level of Eudragit S 100 (% Weight Gain) Pan coating	0%	2.5%	5%	Y_5= % Cumulative Drug release at 5 h
				Y_7 % Cumulative Drug release at 7 h

The resultant formulations of Tamarind gum and Karaya gums were succinctly compiled and presented in both Table 4 and Table 5, offering a comprehensive overview of the variables' impact on the colonic delivery performance of the formulated tablets.

Table 4. Composition of experimental formulations of Karaya gum

Batch	Amount of Karaya Gum in Compression Coating (mg)	Amount of Ethyl cellulose in Compression Coating (mg)	Coating level of Eudragit S 100 (% Weight gain)
KR 1	125	25	0
KR 2	100	50	0
KR 3	75	75	0
KR 4	125	25	2.5
KR 5	100	50	2.5
KR 6	75	75	2.5
KR 7	125	25	5
KR 8	100	50	5
KR 9	75	75	5

Table 5. Composition of experimental formulations of Tamarind gum

Batch	Amount of Tamarind gum in Compression Coating (mg)	Amount of Ethyl cellulose in Compression Coating (mg)	Coating level of Eudragit S 100 (% Weight gain)
TM 1	125	25	0
TM 2	100	50	0
TM 3	75	75	0
TM 4	125	25	2.5
TM 5	100	50	2.5
TM 6	75	75	2.5
TM 7	125	25	5
TM 8	100	50	5
TM 9	75	75	5

Preparation of probiotic culture medium

In the context of probiotic culture media preparation, the utilisation of the velgut prebiotic and probiotic capsule (manufactured by Eris Life Science Ltd.) is recommended. The velgut probiotics comprise a diverse range of 5 billion bacterial species, namely *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, and Saccharomyces boulardi*[14].

Fluid Thioglycollate Medium (FTM) was used for the incubation and activation of anaerobic bacteria in the probiotic capsule. 8.94 grammes of FTM were mixed with 300 mL of deionized water. The mixture was autoclaved for fifteen minutes at 121 °C and 15 pounds of pressure. Subsequently, the medium was subjected to an inoculation process involving 325 mg of a probiotic combination taken out of a capsule. The medium was then incubated for 48 h at a temperature of 35 °C while being maintained under anaerobic conditions[13,14].

In vitro dissolution testing

In vitro drug release of colon-specific budesonide tablets was conducted in a United State Pharmacopeia (USP) Type II (Paddle) apparatus at a rotation speed of 50 rpm and at 37±0.5 °C. Initially, the test was done in 0.1 N HCl for 2 h to mimic the environment of stomach[29]. The test was then conducted for three hours in phosphate buffer pH 7.4, which mimics the milieu of the small intestine[29]. In reality, the small intestine can be categorized into three distinct segments: the duodenum, which exhibits a pH range of 5 to 6; the jejunum, with a pH of approximately 6.63±0.53; and the ileum, which maintains a pH level of around 7.49±0.46. The ileum is the longest section of the small intestine, and as a result, its mean pH is 7.3±0.34[30,31]. The remaining investigation was conducted in biorelevant medium with a pH of 6.8, which is comparable to the mean pH of the large intestine (6.63±0.04)[30,31], and CO_2 aeration to create a favorable environment for anaerobic bacteria[13]. Samples were extracted at regular intervals and analyzed spectrophotometrically at a wavelength of 243 nm.

Statistical analysis

The assessment of the data pertaining to the percentage of drug released at the completion of each dissolution test was a pivotal step in understanding the drug delivery behavior of the formulated dosage forms. To elucidate the relationship between the independent variables X1 and X2 and the dependent variables Y2, Y5, and Y7, a comprehensive statistical model was constructed. This model was predicated on a second-order polynomial equation, embody-

ing both main and interaction effects of the variables:

Dependent Variable = b0 + b1X1 + b2X2 + b11X1^2 + b22X2^2 + b12X1X2

Here, b0 represents the intercept, b1 and b2 denote the coefficients for X1 and X2 respectively, while b11, b22, and b12 represent the quadratic and interaction coefficients.

To individually capture the relationship between the response variables (Y2, Y5, and Y7) and the independent variables, the Design Expert 11.0 software facilitated the fitting of a second-order polynomial model for each response variable.

In order to assess whether the response variables exhibited statistically significant differences, the Dunnett test was performed. A P-value of less than 0.05 was established as the criterion for declaring a result as statistically significant. This threshold was chosen to indicate a high level of confidence in the observed differences.

RESULTS and DISCUSSION

The literature has documented the utilisation of guar gum as a carrier for targeted drug release in the colon, either through a matrix tablet or a compression coat enveloping a central drug core tablet[32]. On account of that knowledge, the capacity of different polysaccharides to deliver the drug to the colonic environment was evaluated[12].

The viscosity profile was used to screen natural gums for their ability to delay drug release in the upper gastrointestinal tract, since this lag time is assessed by the viscosity profile.

Figure 1 depicts the viscosity of 1% solutions of various natural polymers produced in a 6.8 pH phosphate buffer.

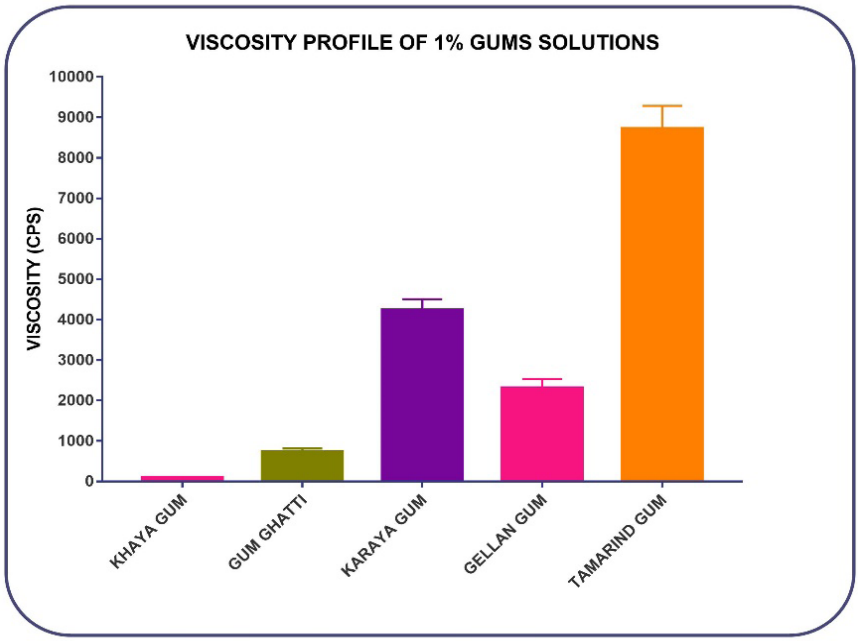


Figure 1. Viscosity profile of 1% solutions of various natural polymers

The viscosity profiles of Tamarind gum and Karaya gum were found to be statistically significant in achieving the desired lag time. On the basis of viscosity profiling, formulations including Tamarind gum and Karaya gum were designed to evaluate the efficacy of a polymer in delivering the drug to the colon. Tamarind gum is also used as a matrix-former in the formulation of matrix tablets and as controlled drug release carriers for a number of different pharmaceuticals[22,33]. In addition, it is employed in the development of oral[34], buccal[35], colon[36], nasal[37], and ocular[38] drug delivery systems. Karaya gum was effectively tested for its appropriateness in the development of colon-specific drug carriers[18], gastro-retentive drug delivery systems[17], sustained release matrices[17], etc.

The study indicates that the core tablet formulations that were prepared have successfully passed the Indian Pharmacopiea (IP)-96 test for weight variation and friability. 3^2 full factorial designs were used to evaluate the impact of independent factors, Proportion of Natural Polymers relative to EC and % weight growth, on dependent variables, % drug release at 5 h and % drug release at 12 h. Table 6 displays the dependent variables of the compression-coated tablets that were produced in accordance with the experimental design.

Table 6. Experimental runs obtained from 3^2 Factorial design and their responses for Tamarind and Karaya formulations

Batch No.	Amount of Tamarind gum	% Weight Gain	% CDR at 2 h	% CDR at 5 h	% CDR at 7 h	Batch No.	Amount of Karaya gum	% Weight Gain	% CDR at 2 h	% CDR at 5 h	% CDR at 7 h
1	-1	-1	34.43	99.05	99.01	1	-1	-1	47.38	99.05	99.95
2	0	-1	30.66	74.2	100.01	2	0	-1	28.86	100.45	100.01
3	1	-1	22.73	60.55	89.8	3	1	-1	21.5	72.52	100.67
4	-1	0	11.18	49.32	83.82	4	-1	0	17.32	99.25	99.92
5	0	0	7.36	38.41	73.19	5	0	0	15.35	72.72	99.67
6	1	0	5.08	33.66	69.65	6	1	0	14.13	61.94	92.81
7	-1	1	3.38	26.65	62.71	7	-1	1	3.43	42.64	74.41
8	0	1	2.98	16.89	51.23	8	0	1	2.59	32.91	59.57
9	1	1	2.93	8.91	50.23	9	1	1	2.28	22.87	47.03

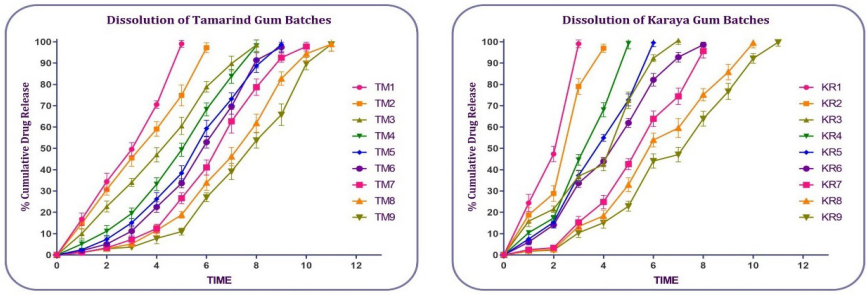
The post compression parameters for the core tablets and coated tablets are summarized in Table 7 demonstrating that all batches satisfy the required standards of all parameters.

Table 7. Post-compression parameters for Tamarind and Karaya formulations

Batch No.	Tamarind Gum based formulation					Karaya Gum based formulation				
	V	F	D	H (kg/ cm^2)	C	V	F	D	H (kg/ cm^2)	C
1	Pass	0.92	4	4.5	98.45	Pass	0.91	3	4.1	98.52
2	Pass	0.76	5	4.3	99.25	Pass	0.82	6	4.5	99.45
3	Pass	0.67	4.5	4.2	98.23	Pass	0.65	4	4.1	99.67
4	Pass	0.89	6	4.5	98.19	Pass	0.96	3	4.2	98.15
5	Pass	0.78	5.5	4.1	99.36	Pass	0.82	4	4.3	99.43
6	Pass	0.69	5	4.2	98.45	Pass	0.62	5	4.2	99.72
7	Pass	0.91	6	4.6	98.45	Pass	0.94	3.5	4.5	98.45
8	Pass	0.71	4	4.2	100.08	Pass	0.76	6	4.6	99.15
9	Pass	0.65	5	4.3	98.16	Pass	0.62	5	4.2	99.45

V: weight variation, F: friability, D: Disintegration (core tablet) in min,
H: hardness, C: Drug content (core tablet)

Figures 2 (a and b) show the results of the dissolution test of coated budesonide tablet prepared from Karaya gum and Tamarind gum respectively. The predetermined *in vitro* release profile for colon-specific targeting requires restricting drug release to no more than 5% within the first 2 h, no more than 10% by the end of the small intestine (5 h) and achieving a release of over 50% within 7 h. Actually, gastro-intestinal (GI) tract transit time is 15–30 h yet a third dependent variable determined that more than 50% of the drug should be released within 7 h because the main function of the colon is absorption of water. The reduction of water content in the colon has the potential to hinder the release of drugs from the dosage form over time. Therefore, a time duration of 7 h was deemed appropriate for achieving drug release of over 50% from the colon-targeted drug delivery system.



(a) (b)

Figure 2. Mean (±S.D.) Percent of budesonide released from compression-coated tablets (n=3) containing different amount of Karaya gum (a) and Tamarind gum (b)

Upon exposure to dissolution fluids, the Eudragit S 100 super-coating would impede the release of the drug in the upper gastrointestinal tract. Subsequently, the Eudragit S 100 coat would dissolve in the lower section of the small intestine, and the Karaya gum or Tamarind gum would undergo hydration, forming a dense gel layer. This layer, in the form of a compression coat, would serve the dual purpose of safeguarding the drug from release in the small intestine's physiological environment and facilitating its release in the colon with the aid of colonic bacteria. Consequently, experiments were conducted to investigate drug release using *in vitro* methods. The pH of the phosphate-buffered solution was adjusted to 6.8, and 4.5 mL of probiotic culture medium was added to the solution to mimic colonic environment.

As per the findings of the dissolution studies (Figure 2), it has been observed that all batches of Tamarind gum-based formulation (TM1-TM8) and Karaya gum-based formulation (KR1-KR8) exhibit a drug release rate of over 10%

within a period of 5 h. Karaya gum with KR 9 batch exhibited a drug release of 22.87 % in 5 h, while Tamarind gum having TM 9 batch exhibited a drug release of 8.91 %. This indicates that Tamarind gum with batch TM 9 has a greater capacity to protect the drug release in the upper portion of the GI tract and to transport the drug in intact form to the colonic milieu.

Regression analysis of formulations by 3^2 factorial designs

The result of ANOVA analysis (Table 8) yielded helpful findings regarding the significance and predictive power of the model. The Model F-value of 249.53 highlighted the model's significance for Y2 (% cumulative drug release at 2 h)[24], with P-values below 0.05 of tamarind formulation indicating the statistical significance of the model terms.

Table 8. Analysis of variance (ANOVA) for three dependent variables for Tamarind and Karaya formulation batches

Source	Dependent Variable (For TM Formulations)			Dependent Variable (For KR Formulations)		
Source	Y2- % CDR at 2 h	Y5- % CDR at 5 h	Y7- % CDR at 7 h	Y2- % CDR at 2 h	Y5- % CDR at 5 h	Y7- % CDR at 7 h
Sum of Squares	1253.432	6575.982	2862.32	1638.35	6187.93	3364.281
df	5	5	3	3	2	5
Mean Square	250.6863	1315.196	954.11	546.12	3093.97	672.8563
F-value	249.5313	66.69654	101.37	41.99	23.5	99.1675
p-value	0.000398	0.002835	< 0.0001	0.0006	0.0015	0.001575
R^2	0.9976	0.9911	0.9838	0.9618	0.8868	0.9940
Adjusted R^2	0.9936	0.9762	0.9741	0.9389	0.8491	0.9840
Predicted R^2	0.9757	0.8913	0.9309	0.7932	0.7280	0.9368
Adeq Precision	39.4191	23.2825	26.4859	17.5431	12.9431	26.0538

The quadratic models representing Y2 exhibited an adjusted R^2 of 0.9976, indicating a strong representation of variance. The predicted R^2 of 0.9757 indicated the model's accuracy in predicting future data, with the minimal difference between adjusted R^2 and predicted R^2 supporting the model's predictive capability[39].

For TM formulation (% CDR at 2 h) = 8.12556 – 3.04167X1 – 13.0883X2 + 2.812X1X2 – 0.37833X1^2 + 8.31167*X2^2

Analysis of the polynomial equation, the 3D response curve (Figure 3a), and the contour plot (Figure 3b) revealed that the percentage weight gain due to Eudragit S 100 coating (X2) significantly influenced Y2. As coating level (X2) increased, Y2 (drug release at 2 h) decreased substantially. Tamarind gum amount (X1) had a similar negative impact on Y2, but it less pronounced than that of X2.

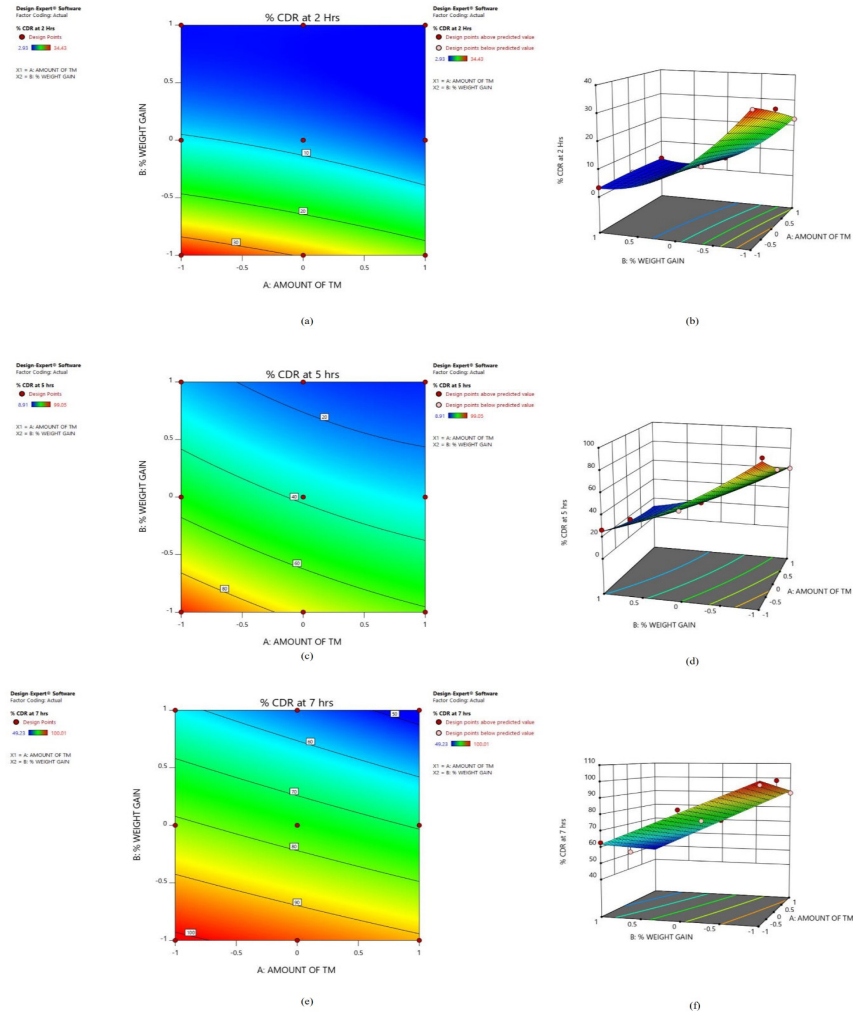


Figure 3. Contour Plot and 3D Response Plot for Tamarind formulation for Y2 (% CDR at 2 h – (a and b)), Y5 (% CDR at 5 h – (c and d)), Y7 (% CDR at 7 h – (e and f))

A comparable trend was observed in the formulation containing Karaya gum. The model F-value of 41.99 highlighted the statistical significance of the model. This conclusion is further substantiated by considering the adjusted R^2 (0.9389) and predicted R^2 (0.7932) values, which demonstrate the model's

robust predictive power.

For KR formulation (% CDR at 2 h) = 16.9822 – 5.03667*X1* – *14.9067*X2 + 6.1825*X1X2

Analysing the polynomial equation for Y2, in conjunction with the 3D response curve (Figure 4a) and contour plot (Figure 4b), it becomes evident that the effect observed in the Karaya gum formulation is even more pronounced than what was noted in the Tamarind formulation. The greater impact on Y2, as demonstrated by these graphical representations, signifies that the variables exert a stronger influence in the case of Karaya gum-containing formulations compared to those with Tamarind gum.

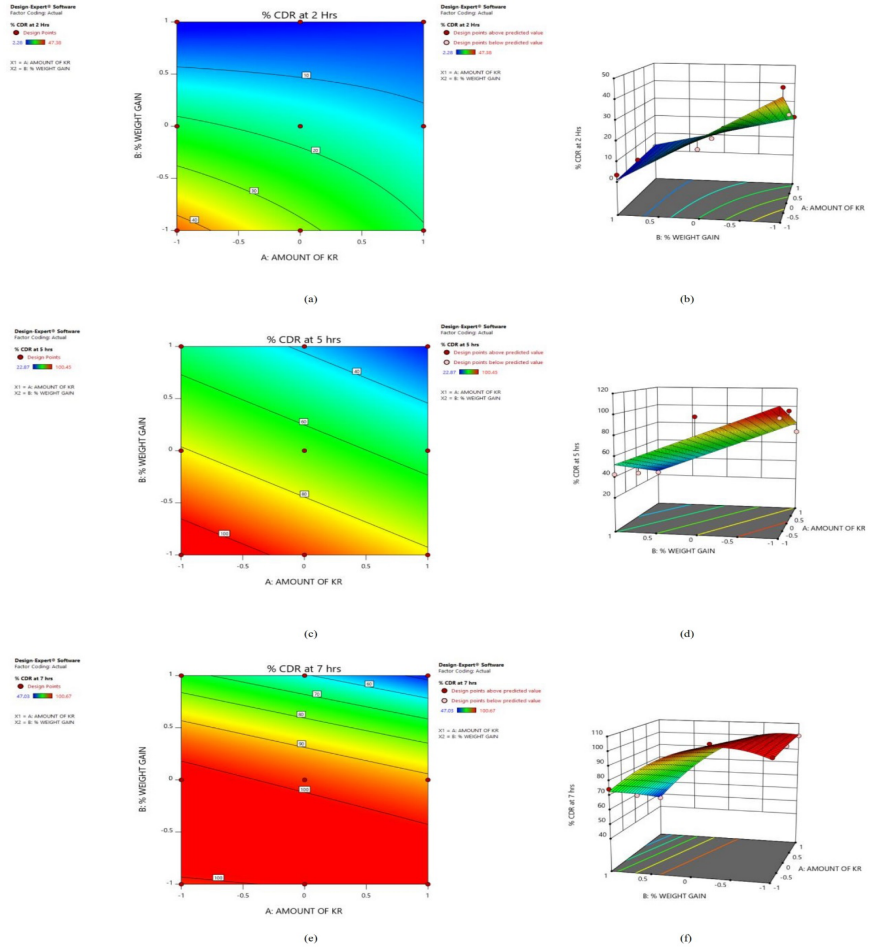


Figure 4. Contour Plot and 3D Response Plot for Karaya Formulations for Y2 (% CDR at 2 h – (a and b)), Y5 (% CDR at 5 h – (c and d)), Y7 (% CDR at 7 h – (e and f))

The Model F-value of 66.69 indicate the model's notable significance for Y5, which represents the percentage cumulative drug release at 5 h. The presence of P-values below 0.05 for the Tamarind formulation emphasized the statistical significance of the model terms in this context. The quadratic models used to depict Y5 produced an adjusted R^2 value of 0.9762, suggesting a strong and reliable representation of the observed variance. The theoretical analysis demonstrated the model's proficiency in describing variations in the response, as shown by the predicated R^2 value of 0.8913. The small differences observed between the adjusted and predicted R^2 values provides additional evidence to support the claim that the model displays an adequate capacity for prediction.

For the TM formulation: % CDR at 5 h = 38.3367 – 11.9833*X1* – *30.225*X2 + 5.19*X1X2* + *3.19*X1^2 + 7.245*X2^2

Analysing the polynomial equation, the 3D response curve (Figure 3c), and the contour plot (Figure 3d) revealed that the percentage weight gains due to Eudragit S 100 coating (X2) exerted a significant influence on Y5. As the coating level (X2) increased, Y5 (drug release at 5 h) exhibited a considerable decrease. Similarly, the amount of tamarind gum (X1) also negatively impacted Y5, although to a lesser extent compared to X2.

This comparable trend extended to the Karaya gum-containing formulation. A model F-value of 23.5 improved the statistical significance of the model, confirming its importance. The small difference between adjusted R^2 (0.8491) and predicted R^2 (0.7280) values further showed to the model's reliable predictive capacity.

For the KR formulation: % CDR at 5 h = 67.15 – 13.935X1 – 28.9333X2

Analysing the polynomial equation for Y5 within the context of the 3D response curve (Figure 4c) and contour plot (Figure 4d) indicate that more pronounced effect in the karaya gum formulation compared to the tamarind formulation. The sharp impact on Y5, as demonstrated by these graphical representations, underlined the increased influence of variables within Karaya gum-containing formulations.

The Model F-value of 101.37 served as a prominent indicator of the model's significance in relation to Y7 (% cumulative drug release at 7 h) for the tamarind formulation. The presence of P-values below 0.05 highlighted the statistical significance of the model terms, solidifying their relevance. The quadratic models representing Y7 displayed an adjusted R^2 of 0.9741, signifying a robust representation of variance. Meanwhile, the predicted R^2 of 0.9309 testified to the model's precision in forecasting future data. This alignment between ad-

justed R^2 and predicted R^2 confirmed the model's exceptional predictive capability.

For the Tamarind formulation: % CDR at 7 h = 75.4056 – 6.14333 * X1-20.9417*X2 -1.0675*X1X2

Evaluation of the polynomial equation, coupled with scrutiny of the 3D response curve (Figure 3e) and contour plot (Figure 3f), showed the substantial impact of quantity of tamarind gum (X1) on Y7. Additionally, the percentage of Eudragit S 100 (X2) yielded a comparable, yet less pronounced, negative effect on Y7 as compared to X1.

A similar trend was observed in the formulation containing Karaya gum. The model F-value of 99.16 underscored the statistical significance of the model, emphasizing its relevance. This conclusion is buttressed by the adjusted R^2 (0.9840) and predicted R^2 (0.9368) values, both of which highlighted the model's robust predictive capability.

For the Karaya formulation: % CDR at 7 h = 97.8789 – 5.62833*X1-19.9367*X2-7.025*X1X2-0.618333*$X1^2$-17.1933*$X2^2$

A comprehensive analysis of the polynomial equation for Y5, coupled with the insights gained from examining the 3D response curve (Figure 4e) and contour plot (Figure 4f), affirmed that the effect witnessed in the Karaya gum-containing formulation exhibited even more pronounced characteristics than those observed in the tamarind formulation. This heightened impact on Y5 signified that the variables exerted a more substantial influence within the context of Karaya gum-containing formulations, setting them apart from those formulated with Tamarind gum.

The figures shown in this study, namely Figure 5a for Tamarind gum and Figure 5b for Karaya gum formulations, clearly demonstrate that tamarind gum has the potential to create a design space that is favorable for developing optimized formulations. In contrast, it might be stated that Karaya gum does not provide a comparable range of design options that are ideal for this particular objective.

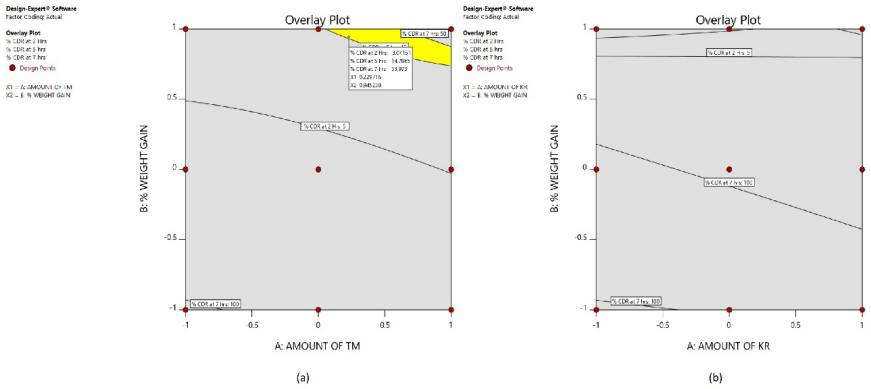


Figure 5. Design space generated by 3^2 factorial design (a) Tamarind formulations (b) Karaya formulations

Graphs in Figure 6a and 6b illustrate the correlation between the observed values in the actual world and the expected values produced by the model.

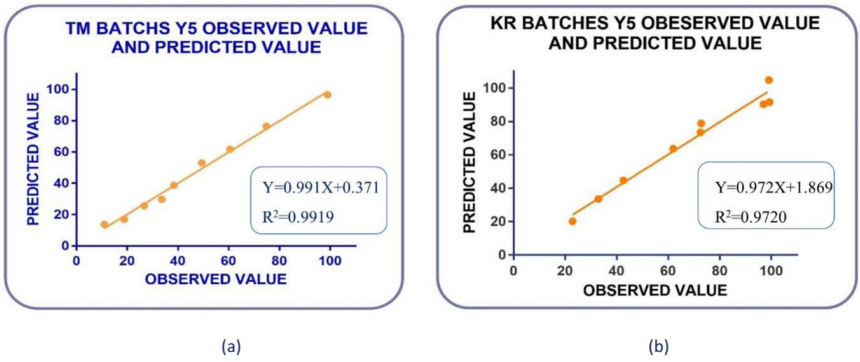


Figure 6. The predicted and actual values of Y5 responses for Tamarind gum (a) and Karaya gum (b) containing formulations

These predictions are based on the independent variables within the TM and KR formulations, respectively. The strong correlation between the observed and projected results provides evidence of the model's significant predictive capability. The alignment seen between the observed and anticipated values provides empirical evidence supporting the model's dependability in properly predicting future outcomes.

Based on the results, Tamarind gum was found to be superior to Karaya gum in delivering the drug to the colon, with TM 9 batch showing the highest concentration of intact drug released in the colon among all the batches. The op-

timized Tamarind-based formulation was able to meet the necessary selection criteria, ensuring not more than 15% of the substance is released in five hours and not less than 50% in seven hours.

Moreover, the results obtained from the Dunnett test revealed a statistically significant disparity in the in vitro release data of the optimized sample when compared to the other batches. The P-value associated with this difference was found to be less than 0.001. The notable discrepancy in the patterns of release shows the efficacy of the optimization procedure, providing further validation for the practicality of the developed model in predicting actual effects.

In conclusion, the study provides insights into the use of natural polymers in the development of colon-targeted drug delivery systems. Further research could explore the potential of other natural polymers and super-coating agents to improve the efficiency of colon-specific drug delivery systems. With the continuous advancements in technology, it is hoped that natural polymer-based colon-targeted drug delivery systems could be developed and used to treat various colon-related diseases effectively.

STATEMENT OF ETHICS

Not applicable as no human or animal subjects were involved in the study.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Jaymin Patel contributed to the article's conception/design and data analysis/interpretation. Kaushika Patel wrote/edited the article with major intellectual input. Dr. Shreeraj Shah provided substantial support for the argument/analysis and finalized for publication.

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