



## EVALUATION OF TAMARIND SEED POLYSACCHARIDE AS ABIODEGRADABLE CARRIER FOR COLON SPECIFIC DRUG DELIVERY

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### ABSTRACT

The present study was undertaken to assess the potential of Tamarind seed polysaccharide (TSP) to act as a biodegradable carrier for colon specific drug delivery. Hence an attempt was made to develop matrix tablet based formulation using TSP which protects the drug in upper GIT and release the major amount of drug in colon due to degradation by bacterial enzymes. The matrix tablets were prepared by wet granulation technique containing different concentrations (30% w/w to 70% w/w) of TSP using Ibuprofen as a model drug. The matrix tablets were evaluated for different quality control tests, content uniformity and *in-vitro* drug release study. Drug release profile of prepared tablets was evaluated in simulated gastric fluid (0.1N HCl), simulated intestinal fluid (pH 7.4 Sorensen's phosphate buffer) and simulated colonic fluid (2% w/v rat caecal contents and 4% w/v rat caecal contents) in pH 6.8 Sorensen's phosphate buffer before and after enzyme induction. The *in-vitro* biodegradation studies suggested that TSP is degraded in presence of rat caecal contents (RCC). It was further revealed that enzyme induction leads to better biodegradation of TSP. DSC studies showed the absence of any possible drug excipient interaction. The *in-vitro* drug release studies demonstrated that only 7.24% of drug was released in upper GIT and 81.71% in colon. The 4% w/v RCC after 7 days of enzyme induction degraded TSP remarkably and its presence in dissolution medium provided best conditions for assessing the susceptibility of TSP to colonic bacterial degradation. The results of *in-vitro* drug release study indicate that the matrix tablets prepared by using TSP are able to carry most of the drug to the colon and restrict the release in upper GIT.

**Keywords:** Colon specific drug delivery, Tamarind seed polysaccharide, Matrix tablets, Biodegradable carrier, Enzyme induction.

### INTRODUCTION

The colon specific drug delivery is valuable in the topical treatment of colonic disorders such as irritable bowel syndrome, Crohn's disease, Ulcerative colitis and colon carcinomas. The delivery of drugs to colon is also useful for systemic absorption of drugs especially proteins and peptides which are degraded in upper GIT<sup>1</sup>. Some other examples of usefulness of colonic drug delivery in systemic absorption are antiasthmatics which are targeted to colon for the treatment of nocturnal asthma and antidiabetics like insulin which is degraded by the enzymes present in the upper gastrointestinal tract. The enzymatic activities associated with the microflora of the colon can be used as a tool for colon specific drug delivery. In addition the colon has a longer retention time and appears to be highly responsive to agents that enhance the absorption of poorly absorbed drugs. A colonic drug delivery system could be of absolute value where a delay in systemic absorption is therapeutically desirable, especially in the case of diseases which are affected by Circadian rhythms<sup>2</sup>. Ulcerative colitis is currently treated with anti-inflammatory medications such as sulfasalazine<sup>3</sup>. Enemas and suppositories are not effective for extensive proximal ulcerative colitis. In addition traditional oral dosage forms do not deliver drugs significantly to large intestine. To reduce their adverse effects, these agents should be targeted to the colon for the treatment of inflammatory bowel diseases by modified release oral formulations<sup>4</sup>.

The colon specific drug delivery is required to protect the drug during its transit through upper GIT and allow its release in the colon. The large bacterial population present in the colon is a unique feature that allows the site specific drug delivery using polysaccharides. A number of carriers have been investigated by many coworkers. Guar gum<sup>3,4</sup>, Pectin and its salts<sup>5,6</sup>, amylose, amylose-ethocel films<sup>7</sup>, chitosan<sup>8</sup> and dextrin<sup>9</sup> have been studied for digestion by colonic bacteria for colon specific drug delivery.

The present study aims at utilization of Tamarind seed polysaccharide (TSP)<sup>10</sup> as a carrier for colon specific drug delivery. TSP is an oligosaccharide obtained from the seeds of *Tamarindus indica* family Leguminosae. TSP has been used as a binding agent in tablets<sup>11</sup>, as a suspending agent for insoluble powders and as an

emulsifying agent<sup>12</sup>. Two important useful products namely an absorbable haemostatic dressing and a vehicle for delivery of fallopian tube occluding agents for contraceptive purpose have been prepared out of TSP<sup>13</sup>. It also possesses a unique property of forming films having high tensile strength and flexibility. This film is transparent, non hygroscopic, non sticky and retains its form even on rough handling. This quality can be used in making capsules and catchets<sup>14</sup>. TSP has been studied in Central Drug Research Institute for sustained release tablet dosage form for Verapamil hydrochloride<sup>15</sup>. The release behavior of both water soluble drugs (acetaminophen, Caffeine, Theophylline and Salicylic acid) and water soluble drugs has also been studied in Centre for Biomedical Engineering, Indian Institute of Technology Delhi and All India Institute of Medical Sciences New Delhi, India<sup>16</sup>.

Ibuprofen, a derivative of propionic acid is nonsteroidal anti-inflammatory drug used as a model drug in this study is found to be effective in rheumatic diseases such as osteoarthritis, rheumatoid arthritis, juvenile chronic arthritis and acute arthritis. Ibuprofen is also useful in periarticular and musculoskeletal indications for analgesia in bursitis, tendinitis, fibrosis, tenosynovitis, lumbago, neck pain and myalgia of all types. It is also indicated in infectious diseases for analgesic, antipyretic and anti-inflammatory purpose<sup>17</sup>.

### MATERIALS AND METHODS

#### Materials

Ibuprofen was received as a gift sample from Universal Medicaments Pvt. Ltd, Nagpur, India. Tamarind seed powder (TSP) was procured from Lucid Group, India. All other chemicals and reagents used were of analytical grade.

#### Methods

##### Isolation and standardization of TSP<sup>13,18</sup>

70g tamarind seed powder was boiled with water (1.2 liters) for 45-60 min. During boiling the loss of water was made up by addition of hot water after every 10-15 min. The mixture was then cooled to room temperature and kept overnight preferably in a cold storage to avoid any decomposition due to fermentation or putrefaction. The supernatant mucilaginous solution was carefully decanted off

leaving behind the sediment in the original vessel. The mucilaginous solution (about 1 liter) was treated with an equal volume of 2.5% aqueous solution of sodium hydroxide and the mixture boiled for 10-15 min, cooled to room temperature, acidified with dilute hydrochloric acid (10% w/w) to pH 5.0 and the polyose precipitated by adding sufficient ethanol (95% - 2 liter). The precipitated polyose was separated by straining through a wire gauze (10-20 mesh). The polyose was redissolved by boiling with water (800 ml), pH readjusted to 5.0 by adding dilute hydrochloric acid and polyose reprecipitated with ethanol. After straining through a wire gauze the polyose was macerated with acetone, strained through a wire gauze, dried at 55- 60°C and finally powdered.

#### Biodegradation studies of Tamarind seed polysaccharide (TSP)

The *in-vitro* biodegradation studies of TSP were carried out in presence and absence of 2% w/v and 4% w/v rat caecal contents (RCC) before and after enzyme induction by viscosity measurement by using 1% w/v dispersion of TSP after incubation at 37°C for 24 h. (Table 2)

#### Formulation of matrix tablets:

The matrix tablets were prepared by wet granulation method. Ibuprofen was used as a model drug. Five formulations were prepared using different concentrations of TSP (30% to 70% w/w) as shown in table 1. Accurately weighed pre-sieved ingredients were mixed thoroughly and granulated with 10% w/v paste of TSP. The wet mass was then passed through sieve no 20. Granules thus obtained were air dried for one hour. Dried granules were lubricated with magnesium stearate and compressed using Rimek tableting machine, Mini press - I with 8mm concave faced punches.

#### Evaluation of tablets

The prepared matrix tablets were evaluated for weight variation, thickness, friability, drug content and *in-vitro* drug release studies. Hardness of tablets was tested using Monsanto hardness tester. Friability was determined in a Roche Friabilator (Labline, Mumbai). The thickness of the tablets was measured by Vernier callipers. Weight variation was performed according to official method. Drug content for Ibuprofen was analyzed as per IP.

#### Preparation of Rat caecal content medium<sup>3</sup>

Albino rats weighing 150-200g maintained on normal animal feed, (Gold mohar rat feed, Hindustan Lever Ltd.) were used for the preparation of rat caecal content medium, without enzyme induction. Thirty minutes before commencement of studies, 3 rats were killed, abdomen opened, the caecai isolated, ligated at both ends, cut loose and immediately transferred to pH 6.8 Sorensen's phosphate buffer previously bubbled with CO<sub>2</sub>. The caecal bags were opened, their contents were individually weighed, mixed and then suspended in pH 6.8 Sorensen's phosphate buffer to give required caecal dilution of 2% w/v. As the caecum is naturally

anaerobic, all these operations were carried out under supply of CO<sub>2</sub>. Similarly 6 rats were used for preparing a caecal dilution of 4% w/v.

#### *In-vitro* drug release studies<sup>3</sup>

The method suggested by Satyanarayan *et.al* was employed in this study. The *in-vitro* drug release studies were carried out under conditions mimicking mouth to colon transit in presence of RCC using USP XVIII dissolution test apparatus (Basket type Method I) at 100 rpm. In absence of RCC dissolution test was carried out for a total period of 21 h using HCl (pH1.2) solution (900ml) as dissolution medium at 37°C± 0.5°C for first 2 h, pH Sorensen's phosphate buffer solution (900ml) for next 3 h and pH 6.8 Sorensen's phosphate buffer solution (150ml) for rest of the period. 1ml of sample was withdrawn at the end of 2 h and 3 h and replaced with the same volume of pre-warmed (37°C±0.5°C) fresh dissolution medium respectively. To the samples of 0.1M HCl, 1ml of ethanol was added to dissolve finely suspended drug particles. The volumes were then made upto 10 ml with respective dissolution fluids and filtered. The drug content was analyzed by measuring absorbance at 220nm and 223 nm respectively using UV/VIS spectrophotometer. Then the dissolution medium was replaced with 150ml of pH 6.8 Sorensen's phosphate buffer containing 2% w/v RCC which is kept in water maintained in the jar which in turn is in the water bath of the apparatus. 1ml of sample was withdrawn at regular intervals and replaced with the same volume of pre-warmed (37°C±0.5°C) fresh dissolution medium. The volume of samples were finally made upto 10ml with pH 6.8 Sorensen's phosphate buffer, filtered and absorbance measured at 223nm. The actual content in samples was read from calibration curve prepared with standard Ibuprofen. The above procedure was repeated in presence of 4% w/v RCC. Dissolution test was also carried out in presence of RCC after 3 days and 7 days of enzyme induction by above mentioned procedure. The experiments were carried out initially in the same manner in 0.1M HCl and pH 7.4 Sorensen's phosphate buffer. After this testing the dissolution medium was replaced with a beaker containing 150ml of 2% w/v RCC obtained after enzyme induction and continued upto 21h. The rest of the procedure for determination of drug content was same as mentioned earlier. All the dissolution studies were carried out with continuous CO<sub>2</sub> supply into the beakers.

#### Differential Scanning calorimetry

The DSC curve of mixture of ibuprofen and TSP were generated by a Differential scanning calorimeter (Perkin Elmer Norwalk) at heating rate of 5°C/min over a range of 40°C to 100°C.

#### Stability studies

The optimized formulation was subjected to stability testing at 27°C ± 2°C 65% RH, 40°C± 2°C, 75% RH and in the refrigerator at 05-08°C for 60 days. The tablets were analyzed for drug content.

Table 1: Formulation of Ibuprofen matrix tablets (410mg)

S.no.	Ingredients	Formulations				
		T-1	T-2	T-3	T-4	T-5
1.	Ibuprofen	200	200	200	200	200
2.	TSP	60	80	100	120	140
3.	Lactose	146	126	106	86	66
4.	Magnesium stearate	04	04	04	04	04
<b>Total weight</b>		<b>410</b>	<b>410</b>	<b>410</b>	<b>410</b>	<b>410</b>

\*All the quantities are in mg; TSP-Tamarind seed polysaccharide.

#### RESULTS AND DISCUSSION

The results of evaluation tests of extracted polysaccharide were found to be within the limits. The degradation of TSP in 4% w/v RCC was more than 2% w/v RCC as the viscosity decrease was proportionately more in 4%w/v RCC. The viscosity measurements revealed that there is more reduction in viscosity with enzyme induction as compared to without enzyme induction, as enzyme induction increased the amount of enzymes produced by bacterial flora.

The decrease in viscosity was more with 4% w/v RCC than 2% w/v RCC due to increase in microbial population. The results of table.2 indicate that 7 days of enzyme induction increase enzyme level markedly as was evident from decrease in viscosity which was due to more complete digestion of TSP. The viscosity decrease was much more than that after 3 days of enzyme induction with 2% w/v RCC and 4% w/v RCC and without enzyme induction. The results of enzyme induction after 7 days indicate excellent bacterial degradation in the colon.

Table 2: Biodegradation studies of Tamarind seed Polysaccharide by \*viscosity measurement

1% w/v dispersion of TSP	Viscosity (cp) without RCC	Viscosity(cp) with 2% w/v RCC	Viscosity(cp) with 4%w/v RCC
Without EI			
Initial hydration	46.0	--	--
After 24 h incubation	42.5	--	--
With 3 days of EI			
Initial hydration	42.5	42.0	42.5
After 24 h incubation	29.0	19.0	14.0
With 7 days of EI			
Initial hydration	45.0	44.0	46.0
After 24 h incubation	23.5	15.0	11.0

TSP- Tamarind seed polysaccharide, EI- Enzyme induction; \*Viscosity measurements are carried out at 25°C

The compressed tablets were tested for weight variation, hardness, friability and drug content. All the weights were within 5% deviation range and passed the weight variation according to IP. The hardness of the tablets was found to be more than 3.5% kg<sup>2</sup>/cm. The friability of the tablets was found within the desirable range 0.5-1% and hence the tablets passed the friability tests. The tablets were assayed and the drug content was found to be in the range 95% - 105%. Hence the tablets complied with IP standards. DSC studies showed the absence of any interaction between the drug and carrier. Stability study of formulation T-7 confirms that tablets were stable and there was no significant change in Hardness, Friability, Drug content and Dissolution.

In absence of RCC, results of the drug release studies in 0.1M HCl for 2 h and pH 7.4 Sorensen's phosphate buffer indicate that TSP is capable of protecting the drug at higher concentrations (60% and 70% w/w). The cumulative drug release after 5h was 9.95% and 7.06% respectively. The drug release was relatively higher at lower concentrations of TSP. With the increase in carrier concentration there was progressive decrease in drug release. The percent drug released in 0.1M HCl was more than in pH 7.4 Sorensen's phosphate buffer as the initial drug release was probably due to the dissolution of the drug from the surface of tablets and the lag time required for complete hydration of the carrier. A viscous gel layer formed around the tablets lowered the drug release by slowing down further seeping in of the dissolution fluids towards the tablet core and hence lesser drug release was observed in pH 7.4 Sorensen's phosphate buffer as compared to 0.1M HCl from the matrix.

The results of drug release studies in pH 6.8 Sorensen's phosphate buffer after 21h of testing in absence of RCC are shown in fig. 1. The results indicate that the cumulative mean percent drug released after 21h decreases with increase in carrier concentration.

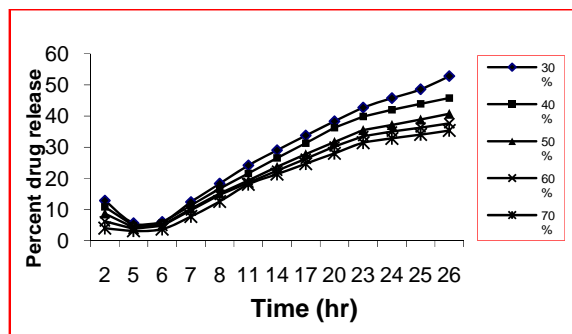


Fig.1: In-vitro dissolution profile of different formulations containing ibuprofen in absence of rat caecal contents

From fig.1 It can be clearly observed that after a short fall in drug release from 6 h to 8 h in pH 6.8 Sorensen's phosphate buffer, after 8h drug was released at a slow rate upto 21h. Tablet retained its shape at the end of 21h, indicating the drug release by matrix diffusion and not by erosion of the carrier.

Considering the drug release in pH 6.8 Sorensen's phosphate buffer and protection provided by the carrier in simulated upper GI fluids, one tablet combination having 70% w/w carrier concentration was selected for further studies in RCC as at this concentration the drug release was less, indicating higher resistance to the drug release.

The presence of rat caecal contents improved the drug release as evident from the fig.2 when compared with control i.e pH 6.8 Sorensen's phosphate buffer without rat caecal contents. The percent drug released from matrix tablets after 21h in pH 6.8 Sorensen's phosphate buffer was increased to 44% with 2% w/v RCC and 56.67% with 4% w/v RCC. This indicates that polysaccharidases are present in caecal matter that metabolizes TSP. In pH 6.8 Sorensen's phosphate buffer with RCC, during the first two to three hours the drug release was faster due to faster erosion of the matrix and diffusion of the drug through it. In next 15 h, drug release was less due to slower bacterial degradation. The drug release after 23 h increased significantly with 4% w/v RCC due to increased enzymatic activity, whereas with 2% w/v RCC the drug was released at a comparatively slower rate after 23 h. (fig.2.)

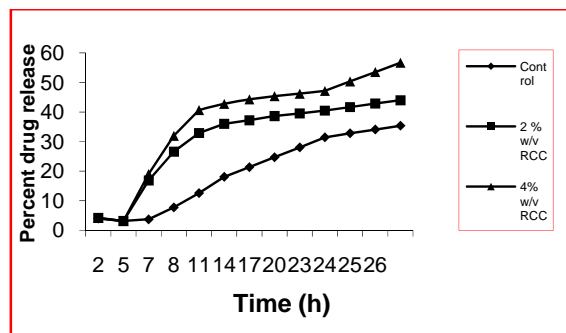


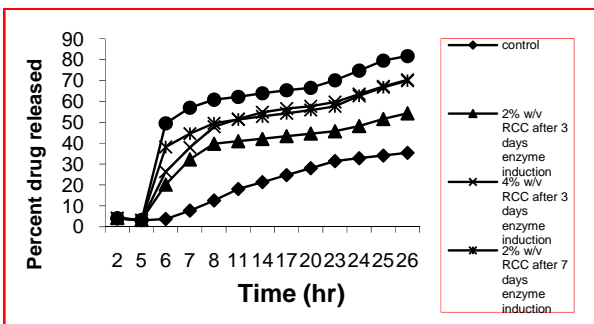
Fig. 2: In-vitro dissolution profile of the formulation of ibuprofen containing 70% w/w of carrier (Tamarind seed polysaccharide) concentration in presence of 2%w/v and 4% w/v rat caecal contents.

As the large amount of drug remained to be released from the dosage form, enzymes were induced in the animals. The results in fig.3. indicate that after 3 days of enzyme induction, the total percent drug released at 2% and 4% w/v RCC were 54.32% and 70.37% respectively. This also indicates that enzyme induction improved drug release at various time intervals. In the first two to three hours in pH 6.8 Sorensen's phosphate buffer with RCC, the drug release was faster which may be due to combined effect of enzyme activity and drug release by diffusion through matrix. The amount of drug released during next 15 h was due to slow erosion of hydrated TSP by enzymatic action. A further rise in the amount of drug released after 23 h was observed which may be due to considerable amount of erosion of hydrated TSP, thereby exposing fresh surface containing drug particles to the dissolution fluids and hence the tablets were distorted. Since the level of enzymes in 2% w/v RCC is low, the erosion was not complete and hence biphasic curve was not observed with 2% w/v RCC whereas it was observed

with 4% w/v RCC. The drug release after 21h was more with 4% w/v RCC than 2% w/v RCC.

Even though improvement in drug release was noted, but still a considerable amount of drug remained to be released from the tablet. Hence enzyme induction for 7 days was carried out and the above experiment was repeated with tablets having carrier concentration 70% w/w of tablets in presence of RCC obtained after 7 days of enzyme induction.

A marked improvement in total percent drug released as shown in fig.3. was observed with caecal matter obtained after 7 days of enzyme induction. The drug released after 21h for 2% w/v RCC and 4% w/v RCC was 69.90% and 81.71% respectively. A significant rise in percent drug release was observed from the beginning, whereas a steep rise was observed with 4% w/v caecal matter form the beginning due to faster erosion of the carrier.



**Fig. 3: In-vitro dissolution profile of the formulation of ibuprofen containing 70% w/w of carrier (Tamarind seed polysaccharide) concentration in presence of 2% w/v and 4% w/v rat caecal contents after 3 days and 7 days of enzyme induction.**

The results clearly demonstrate that TSP is susceptible to enzymatic degradation in presence of rat caecal contents and the percent drug released in presence of different concentrations of caecal matter is better than without caecal matter. The results with caecal matter obtained after 3 days of enzyme induction indicate that enzymes metabolizing TSP can be used and thereby drug release can be improved. Pretreatment with TSP for 7 days further improved the drug release at 4% w/v concentration of caecal matter. Hence it appears that the presence of 4% w/v RCC in dissolution medium obtained after 7 days of enzyme induction is ideal for *in-vitro* evaluation of TSP tablets meant for colon targeting.

#### CONCLUSION

It has now been established that colon can be an important site for the absorption and delivery of drugs. Although colonic surface area is low as compared to the small intestine, suggesting relatively poor drug absorption, the slower transit rate of dosage forms through the colon compensates it.

The exploitation of properties of colonic bacteria has been successful in the development of prodrugs of 5-amino salicylic acid. Polysaccharide based dosage forms of synthetic polymer coatings are also under development using above property. Polysaccharides used as matrices and coating agents are however the most reliable and successful approach of drug delivery to colon as compared to pH and or time dependent mechanisms which are less reliable.

Tamarind seed polysaccharide in the form of matrix tablets (prepared by wet granulation) is capable of protecting the drug from being released completely in the physiological environment of the upper GIT and releasing it into the colon.

*In-vitro* biodegradability studies suggested that TSP is degraded in the presence of rat caecal contents under conditions mimicking colon. *In-vitro* drug release studies under conditions mimicking mouth to colon transit, demonstrated the ability of TSP to release

the drug in pH 6.8 Sorenson's phosphate buffer with RCC. The RCC 4% w/v level after 7 days of enzyme induction degraded tamarind seed polysaccharide remarkably and its presence in dissolution medium provided best conditions for assessing the susceptibility of tamarind seed polysaccharide to colonic bacterial degradation.

Thus from the above studies, it can be concluded that tamarind seed polysaccharide can be used as a biodegradable carrier for colon specific drug delivery.

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