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Original Research Paper

EFFECT OF TAMARIND SEED POLYSACCHARIDE ON DISSOLUTION BEHAVIOUR OF IBUPROFEN TABLETS

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Abstract

Binding property of the polysaccharide extracted from the seeds of *Tamarindus indica* was investigated in tablets using ibuprofen as model drug. The physical properties of granules namely, percentage of fines, particle size, flow properties, and of tablets such as hardness, friability, *in vitro* disintegration time and *in vitro* dissolution profiles were studied as assessment parameters. The tablets exhibited satisfactory properties, which were comparable with corn starch. However, the tablets prepared with tamarind seed polysaccharide exhibited slow dissolution profiles. These properties can be attributed to the viscosity, surface nature and swelling index of the isolated polysaccharide. The dissolution profiles of the tablets were analyzed using Kitazawa plots. The results suggest that the tamarind seed polysaccharide can be used in the formulation of delayed release tablets.

Key Words: Tamarind seed polysaccharide, Ibuprofen, Tablets, Binding agent, Kitazawa plots

Introduction

Excipients, which play a key role in the manufacture of finished dosage forms, are taken very much for granted, and have not been given as much attention as the active drugs. Despite this lack of attention, there have been some notable advances in the field of excipients, both in manufacturing technologies and formulation science.[1]

Plant polysaccharides are important products that are used as stabilizers, thickeners, and binders in various industries such as paper, food, cosmetic, paint, ink and petroleum industries. Pharmaceutical industries also utilize them as binders and disintegrants in tablets, coating materials in microencapsulation, thickening agents in emulsions and suspensions, and sustaining materials in solid dosage forms. The vast applications of plant polysaccharides are because of the low cost, easy availability, and the important properties which they contribute to the products.[2] As a result of this, the demand for natural polysaccharides has greatly increased. To cope up with the demand, it has become necessary to explore newer sources of polysaccharides.

Tamarind seed polysaccharide is a galactoxyloglucan, obtained from the kernels of *Tamarindus indica* (Family: Leguminosae). It possesses properties like high viscosity, broad pH tolerance and adhesivity.[3] Recently, its non-carcinogenicity,[4] mucoadhesivity, biocompatibility,[5] high drug holding capacity[6] and high thermal stability[7] have been reported. Due to these properties, it is being used as stabilizer, thickener, gelling agent and binder in food industry. But, its application in pharmaceutical formulations has not been evaluated so far. In the present study, therefore,

the binding property of polysaccharide from tamarind seed (*Tamarindus indica*) (TSP) in tablets has been explored using Ibuprofen as a model drug and corn starch IP as standard binder for comparison.

Various types of equations have been developed for the analysis of dissolution rate data. Popular ones among them are those of Carstensen, El-Yazigi, Kitazawa, Noyes-Whitney and Wagner.[8] The Kitazawa equation[9] uses ultimate amount of drug released (W_{inf}) in the analysis of dissolution profile. In its simplified form, it can be written as –

$$\ln [W_{inf}/ (W_{inf}-W)] = kt$$

Where, W_{inf} is the amount of drug released at infinite time (i.e., the total amount that could be released), W is amount released at various time intervals t, k is the release rate constant, a first order rate constant that decreases with amount of drug remaining in the dosage form, and 'ln' is the natural logarithm. Usually, the plots of $\ln [W_{inf}/ (W_{inf}-W)]$ versus time generate multiple regression lines intersecting at various times. The times correspond to the phases in which the dosage form changes its physical form from solid through granules to fine particles. The slope of each line gives dissolution rate constant (k) for that particular phase of release. The Kitazawa equation has wide application in the analysis of dissolution profiles of various drug substances. In the present study, therefore, the same equation has been used for the analysis of the suitability of the selected polysaccharide as binding agent in the formulation of ibuprofen tablets.

Materials and methods

Materials

The seeds of the selected plant were collected during January 2001 from places in and around Ootacamund and authenticated by the Medicinal Plants Survey and Collection Unit, Ootacamund.

Acetone (AR grade) was obtained from Ranbaxy Labs (India). Ibuprofen was obtained as a gift sample from Octopus Pharma Pvt Ltd (India). Corn starch (IP grade) and lactose (IP grade) were purchased from Cheminova Remedies Pvt Ltd (India). Talc (AR grade) was obtained from Octopus Pharma Pvt Ltd. Starch-1500 was obtained as gift sample from Colorcon Ltd (India).

Isolation of polysaccharide

The isolation of polysaccharide was done by following a reported method[10] with modification. Initially, the brown seed coat of the tamarind seeds was removed and the seeds were crushed to get coarse particles. Then, 250 g of seed powder was soaked in water (7.5 L) for 24 h, heated at 80 °C for 2 h, and kept aside for 2 h for the release of polysaccharide into water. The soaked seeds were taken and squeezed in a muslin bag to separate marc from the filtrate. The filtrate was concentrated to half of its original volume under vacuum at 40 °C and equal quantity of acetone was added to the filtrate to precipitate the polysaccharide. The precipitated polysaccharide was separated by filtration, dried at 40 °C under vacuum, powdered passed through British Standard Sieve no. 80 and stored in airtight container at room temperature until further use.

Identification and purity tests for polysaccharide

The isolated polysaccharide was stained with ruthenium red followed by irrigation with lead acetate and observed for the development of pink color.[11] Tests for reducing sugars[12] and starch[13] were carried out following standard procedures.

Physical characterization of polysaccharide

The viscosity of 1% solution of the polysaccharide was determined using a Brookfield RVDV II+ viscometer (Brookfield Engineering, USA) with a small sample adapter (spindle no: S28, 50 rpm). The pH of the isolated polysaccharide was determined using a digital pH meter. The swelling index was determined using a method, which is described below.[14] Swelling index is the volume (in milliliters) taken up by the swelling of 1 g of polysaccharide under specified conditions. One gram of polysaccharide powder was introduced into a 25 mL glass-stoppered measuring cylinder. Twenty five milliliters water was added and the mixture was shaken thoroughly every 10 min for 1 h. It was then allowed to stand for 3 h at room temperature. Then the volume occupied by the polysaccharide was measured, including the sticky hydrogel portion. The procedure was repeated thrice and the average swelling index was calculated. The surface characters of isolated polysaccharide were studied using scanning electron micrograph (SEM) (Hitachi-S2400, Japan). IR spectrum of the isolated polysaccharide was taken by potassium bromide pellet method using FTIR spectrophotometer (Shimadzu, Japan).

Microbial load

The total bacterial and fungal load per gram of polysaccharide, and specific tests for presence of

Escherichia coli, *Salmonella typhi*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, were carried out according to the procedures described in Indian Pharmacopoeia.[12]

Preparation and evaluation of granules

Wet granulation technique was used for the preparation of granules.[15] The composition of different batches are given in Table 1. Tamarind seed polysaccharide, or corn starch, equivalent to 2.5, 5, 10 and 15% w/w in the final dried granules, was dispersed in distilled water heated to 40 °C. Water was added to correct the weight loss due to evaporation. The wet granules were passed through British Standard Sieve no.10 and dried at 60 °C for 2 h in a tray dryer (Cadmach, India). The dried granules were passed through sieve no 16/22 and the granules, which passed through sieve no 16 and retained on sieve no. 22 were selected and used for further study. The granules that passed through sieve no. 22 were considered as fines. The prepared granules were evaluated for percentage of fines,[16] average particle size by sieve analysis and flow properties.[17]

Table 1. Formula used for the preparation of ibuprofen tablets

Ingredients	Weight per tablet (mg)			
	B1	B2	B3	B4
Ibuprofen	200	200	200	200
Binder (corn starch / polysaccharide)	10	20	40	60
Starch-1500 (disintegrant)	40	40	40	40
Lactose (diluent)	138	128	108	88
Talc (glidant)	12	12	12	12
Weight of each Tablet	400	400	400	400

B1, B2, B3 and B4 represent batches of tablets containing 2.5, 5, 10 and 15% w/w of binder concentration, respectively.

Preparation and evaluation of tablets

The granules were blended with talc (previously passed through British Standard Sieve no. 80) and compressed using a ten-station rotary tablet machine (Rimek, India) with 10 mm round standard concave punches at a compression speed of 20 rpm. 100 tablets were compressed in each category. The compression force was kept constant for all the batches of tablets. After compression, the tablets were stored for 72 h with silica gel to allow elastic recovery and hardening. The tablets were evaluated for hardness, thickness, friability, disintegration time and *in vitro* dissolution profile. The thickness (n = 6) of the tablets was measured by vernier calipers (Mitutoyo, Japan). The hardness of tablets (n = 6) was determined using a Monsanto hardness tester (Cadmach, India). The friability of 20 tablets was determined using a Roche friabilator (Electrolab, India). The disintegration time was determined using a disintegration test unit (Electrolab, India) at 37 ± 0.5 °C in distilled water.[12] The *in vitro* dissolution studies were carried out using USP-XXIII dissolution apparatus, type II, operated at 50 rpm (Electrolab, India) using phosphate buffer (pH 7.2) maintained at 37 ± 0.5 °C. At specified time intervals, 5 ml of sample was withdrawn and immediately replaced with equal quantity of fresh buffer maintained at the same temperature. The sample was filtered through a membrane of pore size 0.1 µm (Millipore, India), diluted suitably using the same buffer and analyzed at 222 nm using a UV spectrophotometer (Shimadzu-160A, Japan).[12] The study was repeated thrice for each batch with three tablets per study.

Statistical Treatment

The dissolution data was analyzed using repeated measures ANOVA for statistical significance.

Results and discussion

The polysaccharide was isolated from the seeds of *Tamarindus indica* using aqueous extraction followed by precipitation using acetone as non-solvent. The yield of the TSP was calculated with respect to the weight of dried seeds and was found to be 78.07 ± 0.01% w/w. The particles of polysaccharide stained pink with ruthenium red solution, which confirmed that the isolated polysaccharide was mucilage.[13] The tests for reducing sugars and starch were negative, indicating the absence of reducing sugars and starch in the isolated mucilage. The viscosity of 1% w/v solution of the polysaccharide was found to be 74.69 ± 0.31 cP. The pH of the isolated polysaccharide was found to be 6.41 ± 0.25 (Table 2). The swelling index of tamarind seed polysaccharide was found to be 18.70 ± 1.02 mL. In comparison, corn starch had a viscosity of 4.35 ± 0.01 cP, pH 7.01 ± 0.15 and swelling index of 3.1 ± 0.01 mL. Viscosity, pH and swelling index are important physical properties, which can contribute significantly to the understanding of the granule and tablet properties of various substrates. The FTIR spectrum of the isolated polysaccharide is given in Fig. 1. It can be used as standard spectrum for quality control and determination of the purity of TSP.

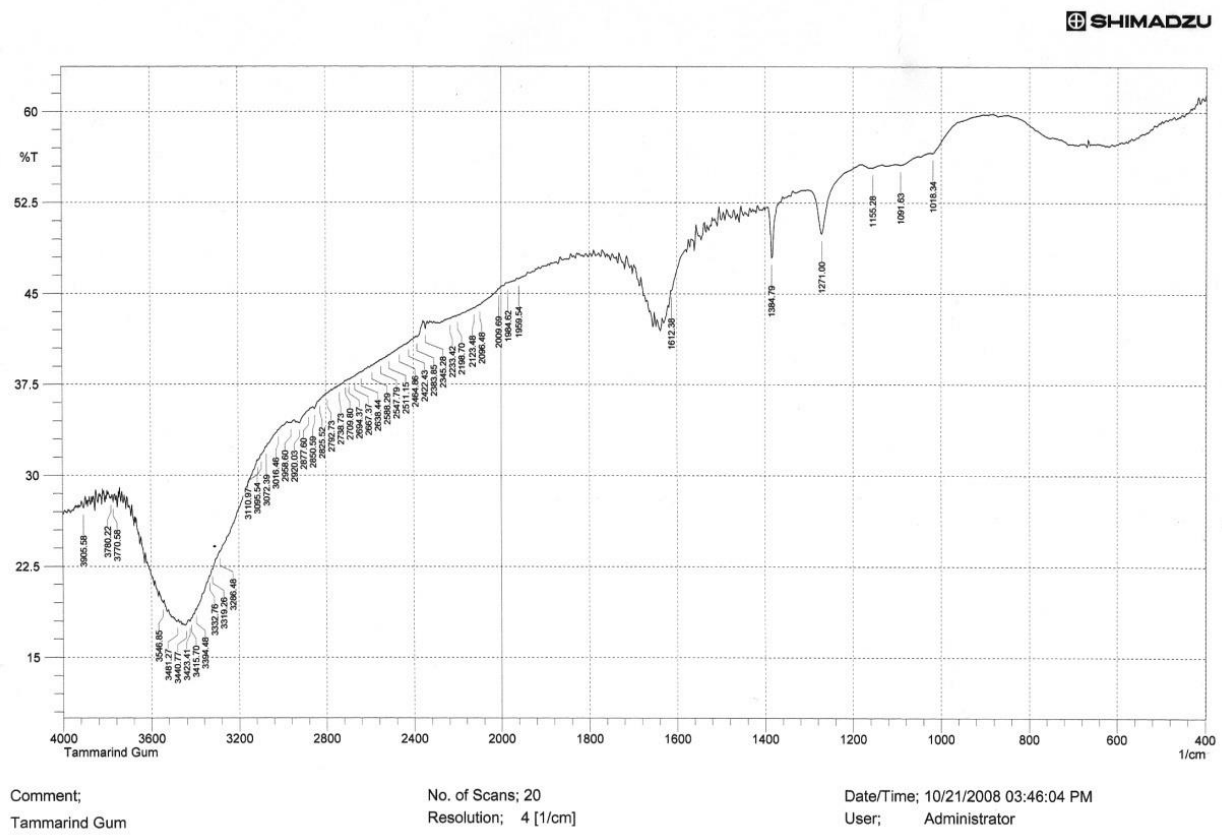

Fig. 1. FTIR spectrum of tamarind seed polysaccharide

Table 2. Physical characteristics of tamarind seed polysaccharide and corn starch

Parameter	Tamarind seed polysaccharide	Corn starch
Yield (% w/w)	78.07 ± 0.01	---
Viscosity of 1% solution (cP)	74.69 ± 0.31	4.35 ± 0.01
pH	6.41 ± 0.25	7.01 ± 0.15
Swelling index (mL)	18.7 ± 1.02	3.1 ± 0.01
Values represent mean ± SEM; n = 3.		

In the microbial load testing, the polysaccharide showed 150.33 ± 0.33 colony forming units of bacteria per gram and did not show any fungal colonies. The specific tests for presence of *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, were found to be negative. Hence, the microbial load of the polysaccharide was within acceptable limits for natural products.[18] The above results indicated that the selected polysaccharide can be used as an excipient in dosage forms.

The results of evaluation of granules are shown in Table 3. With an increase in binder concentration, one can expect an increase in particle size, and a decrease in the percentage of fines.[19,20] In the present study also, similar results were observed. The particle size of granules was found to increase and the percentage of fines was found to decrease with increase in the binder concentration. This may be because of the better cohesion of the solid mass at high concentration of binder. The flow properties of the granules were found to increase with increase in binder concentration, which is evident from the decrease in angle of repose (Table 3). This can be attributed to increase in the average particle size at higher concentration, which might have led to the formation of better granules that could flow easily. In comparison, there was no significant difference in percentage of fines between 10% w/w and 15% w/w concentration of starch. This might be due to the fact that as the concentration of the starch is increased, there might be a change in binding mechanism, because of which the granule size might have not changed.[19]

Table 4 shows the evaluation parameters for the tablets. At minimum concentration of tamarind seed

polysaccharide (2.5% w/w), the hardness of the tablets was very low, whereas, the friability was very high, which indicated poor physical quality of the tablets. The corn starch tablets also exhibited poor physical quality at 2.5% concentration. This might be due to insufficient binder concentration. The tablets prepared with 5, 10 and 15% w/w concentration of tamarind seed polysaccharide exhibited hardness and friability values that were comparable with the tablets prepared with corn starch as binder. The disintegration time was found to be more in tamarind seed polysaccharide tablets. However, the disintegration time was well within the requirements of Indian pharmacopoeia for uncoated tablets.[12] This can be attributed to the formation of a gel layer around the tablet that inhibits disintegration. Fig. 2 depicts the SEM of the isolated polysaccharide. The particles exhibited rough surface with pores and crevices. From the SEM, it is also evident that the particle size distribution was not in a narrow range. A major portion of the powder consisted of fine particles, which might fill the voids between the larger ones and lead to compact packing. Decrease in porosity has been reported to increase the disintegration time.[20] The disintegration time of corn starch tables was less. This might be due to increase in the mean pore diameters and porosity of tablets by corn starch. As the porosity or pore diameter increases, disintegration time decreases.[20]

Table 3. Evaluation of ibuprofen granules prepared using the tamarind seed polysaccharide or corn starch as binder

Polymer	Concentration (%)	Percentage of fines	Average particle size (μm)	Angle of repose (deg)
Tamarind seed polysaccharide	2.5	35.00 ± 0.18	375.30 ± 2.56	32.44 ± 0.45
	5	27.62 ± 0.01	551.10 ± 2.80	30.21 ± 0.11
	10	24.93 ± 0.18	775.20 ± 3.43	24.50 ± 0.17
	15	20.03 ± 0.00	976.60 ± 1.18	20.30 ± 0.36
Corn starch	2.5	31.25 ± 0.03	382.20 ± 2.55	36.18 ± 0.31
	5	30.17 ± 0.58	584.60 ± 2.23	35.13 ± 0.24
	10	25.68 ± 0.01	849.20 ± 3.31	24.40 ± 0.31
	15	25.30 ± 0.12	995.60 ± 2.81	18.82 ± 0.35

Values represent mean ± SEM; n = 3.

Table 4. Properties of tablets prepared using tamarind seed polysaccharide and corn starch as binders

Polymer	Conc. (%)	Thickness[a] (mm)	Hardness[a] (kg/cm^2)	Friability[a] (%)	Disintegration time[b] (D_t, min)	H/FD[c]	$T_{80\%}$[d] (min)	T[e] (min)
TSP	2.5	5.44 ± 0.07	2.50 ± 0.09	5.21 ± 0.52	8.70 ± 0.90	0.06	--	--
	5	5.51 ± 0.06	5.51 ± 0.08	0.40 ± 0.07	12.60 ± 0.01	1.09	135	36
	10	5.51 ± 0.59	5.74 ± 0.08	0.32 ± 0.08	12.60 ± 0.09	1.51	143	37
	15	5.51 ± 0.33	6.02 ± 0.13	0.31 ± 0.05	12.80 ± 0.05	1.56	153	39
Corn starch	2.5	5.52 ± 0.20	3.00 ± 0.40	2.81 ± 0.53	0.25 ± 0.08	4.29	--	--
	5	5.47 ± 0.24	5.50 ± 0.40	0.31 ± 0.09	0.50 ± 0.01	36.6	27	10
	10	5.62 ± 0.48	5.51 ± 0.40	0.20 ± 0.05	1.00 ± 0.05	27.5	28	12
	15	5.61 ± 0.29	5.70 ± 0.53	0.20 ± 0.40	1.00 ± 0.05	28.5	30	15

Values represent mean ± SEM; [a] n = 3; [b] n = 6; [c] H/FD is the ratio of the tablet hardness divided by the product of its friability and disintegration time; [d] $T_{80\%}$ is the time required for the release of 80% of the drug from the tablet during dissolution testing; [e] T is the time taken by the tablet to disintegrate during dissolution process.

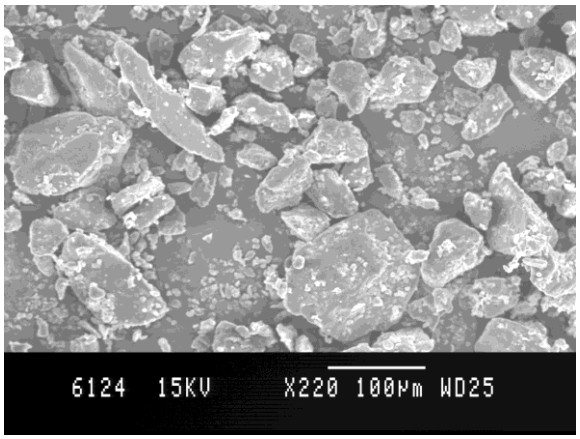

Fig. 2. Scanning electron micrograph of *Tamarindus indica* polysaccharide (TSP) powder (220x magnification)

The hardness-friability-disintegration time ratio (H/FD) ratio has been identified as better index of tablet quality than the traditional hardness-friability ratio.[21,22] This index assesses tablet strength (hardness), weakness (friability) and simultaneously evaluates the negative effects of these parameters on disintegration. H/FD ratio, was, therefore, calculated to assess the overall quality of tablets. This ratio was found to be very low in case of tablets prepared with tamarind seed polysaccharide, which indicated a delayed release. This can be attributed to the high viscosity and high swelling index of tamarind seed polysaccharide, which led to the formation of gel layer around the tablet, which in turn, would not allow the tablet to disintegrate.

Fig. 3 shows the dissolution profiles of corn starch and tamarind seed polysaccharide tablets. The corn starch tablets were found to possess faster dissolution profiles than tamarind seed polysaccharide tablets. The tablets formulated with tamarind seed polysaccharide failed to comply with the official *in vitro* dissolution test of Indian Pharmacopoeia for uncoated tablets.[12] This can be attributed again to the formation of gel layer around the tablet, which would not allow the tablet to disintegrate, and the drug release through such layer would be diffusion-controlled. Also, it has been reported that if the binder concentration is sufficiently large, delayed release can be obtained.[20] The tamarind seed polysaccharide tablets took 3 h time for maximum release of the drug, whereas, the corn starch tablets released the drug within 1 h. The time required to release 80% of the drug ($T_{80\%}$) was determined using the cumulative percent release vs time graphs (Table 4). The corn starch tablets had $T_{80\%}$ values in the range of 27-30 min, whereas the tamarind seed polysaccharide tablets took 135-153.5 min time to release 80% of the drug. The *in vitro* dissolution data was analyzed using one way repeated measures ANOVA to establish the significance within the batches of tamarind seed tablets and also between tamarind and corn starch tablets. The results showed that the dissolution profile was significant between 5 and 15% of tamarind concentration ($p<0.01$). In case of corn starch tablets, the results were not significant within different batches ($p>0.05$). But between the batches of tamarind and starch tablets, the results were highly significant ($p<0.001$). An attempt was also made to correlate $T_{80\%}$ of dissolution with H/FD ratio. The $T_{80\%}$ was found to increase with H/FD ratio, but this increase was not linear.

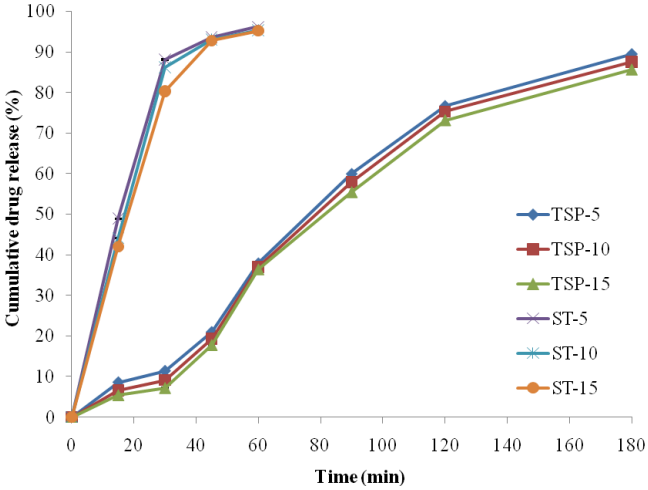

Fig. 3. Dissolution profiles of ibuprofen tablets containing different concentrations of tamarind seed polysaccharide (TSP) and corn starch (ST) as binders

The dissolution data were analyzed using Kitazawa plots (Fig. 4, Table 5), which produced linear graphs with two segments corresponding to the phases of drug dissolution from the tablet surface and granules, and from disaggregated (i.e., fine) particles. The observation was in correlation with that made by Kitazawa *et al*.[9] The time T in Table 4 represents the time when the tablet disintegrated during the dissolution process (Fig. 4). There was a difference between the disintegration time estimated in disintegration test (D_t) and in the dissolution profile (T). This might be because of the milder conditions prevalent in the dissolution apparatus. The correlation between T and $T_{80\%}$ ($r = 0.9937$) was found to be better than that between D_t and $T_{80\%}$ ($r = 0.9022$), as has been reported in the literature.[23,24] In

case of corn starch, the correlation coefficient between T and $T_{80\%}$ was found to be 0.8874, and that for D_t and $T_{80\%}$ was found to be 0.9972. This poor correlation between disintegration time and $T_{80\%}$ may be a result of difference in the hydrodynamic effect of the test apparatus. The tablets prepared using corn starch as binder did not exhibit typical 'two phases' in the release pattern. This can probably attributed to the difference in the tablet break up process. Hence, the Kitazawa parameters could not be calculated for starch tablets.

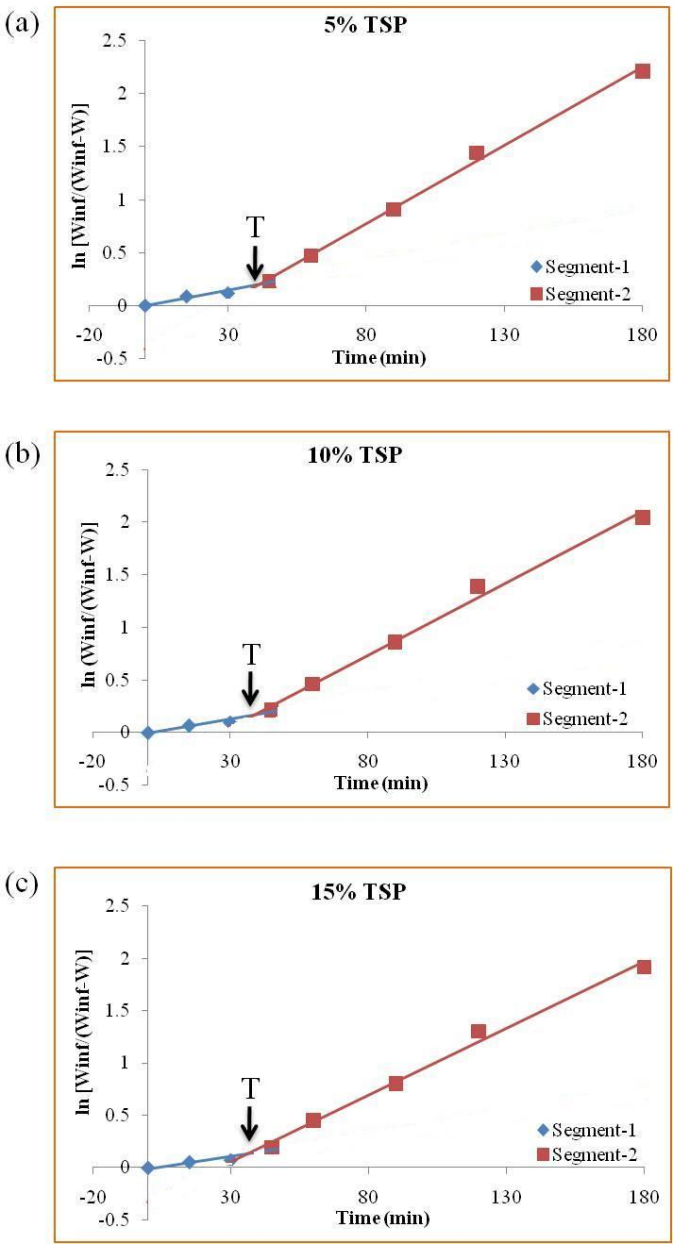

Fig. 4. Kitazawa plots for the kinetics of dissolution of ibuprofen from tablets containing tamarind seed polysaccharide (TSP) as binder

Table 5. Parameters for Kitazawa plots of ibuprofen dissolution from tablets containing tamarind seed polysaccharide as binder

Conc. of TSP (%)	Kitazawa plot parameters			
	k_1 (min^{-1})	k_2 (min^{-1})	r_1	r_2
5	0.0048	0.0145	0.9782	0.9984
10	0.0048	0.0132	0.9674	0.9963
15	0.0046	0.0122	0.9483	0.9957

r_1, r_2 represent correlation coefficients of the two segments of the Kitazawa plots shown in Fig. 4

Conclusion

The polysaccharide from *Tamarindus indica* seeds was found to be suitable excipient for the preparation of tablets. Tablets formulated with 5% w/w and above concentrations of tamarind seed polysaccharide exhibited satisfactory physicochemical properties comparable with those of corn starch binders. However, slow dissolution rates were observed with tamarind seed polysaccharide, which did not comply with the official pharmacopoeial requirements for uncoated tablets. It can be concluded that tamarind seed polysaccharide can be used as a functional excipient for obtaining delayed release profiles.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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