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DESIGN AND CHARACTERIZATION OF PROPRANOLOL HCL TABLET CONTAINING TAMARIND SEED POLYSACCHARIDE AS A RELEASE RETARDANT

Rathi PC*, Bundela MN, Patil KS and Yeole PG

Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha - 442001

Keywords:

Propranolol HCl, hydrophilic matrix, tamarind seed polysaccharide, matrix tablets, treatment of hypertention

For Correspondence:

Rathi PC

Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha - 442001

E-mail:

priyankarathi88@gmail.com

ABSTRACT

Hydrophilic matrices are an interesting option when developing an oral sustained-release formulation. They can be used for controlled release of both water-soluble and water-insoluble drugs. The present work is related with exploitation of tamarind seed polysaccharide (TSP) as an excipient in drug delivery systems. The main aim of proposed work is to focus on the possibilities of using this polysaccharide in industries with particular reference to its physical, chemical properties for the formation of new drug delivery systems. This objective motivates for developing newer synthetic excipient and exploiting the presently own limitation in term of toxicity, compatibility and cost effectiveness. Present study aimed at development and characterization of sustained release matrix tablet of propranolol HCl for treatment of hypertension. The matrix tablets of propranolol HCl prepared by wet granulation method and evaluated for its drug release characteristics. The drug release was decreased with the increase in TSP concentration. Drug release kinetics was explained by Higuchi's equation. The optimized formulation was also subjected for stability testing and was found to have good stability with no appreciable drug degradation. The results suggest that the tamarind seed polysaccharide can be used in the formulation of delayed release tablets.

INTRODUCTION

Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulating authorities[1]. The various polysaccharides used in drug delivery application are cellulose ethers[2], xanthan gum[3], locust bean gum[4] and guar gum. Another natural polysaccharide, Tamarind seed polysaccharide (TSP) obtained from the seed kernel of Tamarindus indica, possesses properties like high viscosity, broad pH tolerance, noncarcinogenicity, mucoadhesive nature, and biocompatibility[5]. It is used as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. The tamarind seed polysaccharide constitutes about 65% of the tamarind seed components[6]. It is a branched polysaccharide with a main chain of -d-(1,4)- linked glucopyranosyl units, and that a side chain consisting of single d-xylopyranosyl unit attached to every second, third, and fourth d-glucopyrnosyl unit through an -d-(1,6) linkage. One d-galatopyranosyl unit is attached to one of the xylopyranosyl units through a - d-(1,2) linkage[7]. The present study was aimed to evaluate the feasibility of using TSP as matrix material for prolonged drug release using a model antihypertensive drug, Propranolol HCl.

MATERIALS AND METHODS

Materials:

The seeds of tamarind were collected from local area of Wardha, Maharashtra, India and authenticated by department of botany, RTM. Nagpur University, Nagpur. Propranolol Hydrochloride was obtained as a gift sample from Quantum Drug and Chemical, Mumbai (India). Lactose Monohydrate (IP grade), Talc (AR grade), Starch and Acetone (AR grade) were obtained from Loba Chemie Pvt. Ltd, Mumbai (India).

Isolation of polysaccharide:

The seeds of *Tamarindus indica* were washed thoroughly with water to remove the adhering materials. Then, the reddish testa of the seeds was removed by heating seeds in sand. The testa was removed. The crushed seeds of *Tamarindus indica* were soaked in water separately for 24 h and then boiled for 1 h and kept aside for 2-3 h for the release of mucilage into water. The soaked seeds were taken and passed through the sieve to remove marc from the filtrate. Then, around three times volume of acetone was added to precipitate the mucilage. The separated

mucilage was dried at 50^{o}C in hot air oven and gave a yield of 35g-40g mucilage/Kg tamarind seed, stored in desiccator for further use.[8]

Chemical Test for Tamarind Seed Polysaccharide: [9, 10, 11]

Extracted mucilages were analyzed for various chemical tests, Molisch's test developed violet green color at the junction of the two layers showed presence of carbohydrate in it. The absence of starch was confirmed by iodine test, showed no color change on addition of iodine solution. The presence of mucilage further substantiated by Ruthenium solution which showed development of pink color.

Physiochemical, Microbiological Properties of Tamarind Seed Polysaccharide: [12, 13, 14]

Separated mucilages was evaluated for various physiochemical properties such as solubility, swelling index, water retention capacity, loss on drying, pH, melting point, microbial load, particle size distribution and rheology as well as for various derived properties such as bulk density, tapped density, compressibility index, Housner ratio and angle of repose.

Microbial Load: [15, 16, 17]

The test is designed for the estimation of the number of viable aerobic micro-organisms present in pharmaceuticals. Total viable aerobic microbial count was determine by plate count method.

Particle Size Distribution:

Few particles of Tamarind seed mucilage powder were taken on a glass slide, uniformly spreaded by a brush, such that individual particle can be seen and particle size distribution was measured by Microscope Image Analyzing System (Vision plus-5000).[12]

Rheology Study of Tamarind seed polysaccharide: [18, 19]

Rheological measurements were carried out using a rotational viscometer (Brookfield R/S plus rheometer) equipped with C25 measuring spindles and for each test, approximately 0.2-0.5 ml sample was transferred to sample compartment (cone and plate).

Drug-Excipient Interactions:

It is important to check any kind of interaction between drug and mucilage. It was done by using Fourier transformed infrared spectroscopy and Differential Scanning Calorimetry**.**

1. Fourier Transform Infrared Spectroscopy:

IR spectra of pure Propranolol HCl and mucilage were taken separately and physical mixture of drug and mucilage were kept for a month at room temperature and then their FTIR were taken to know any possible interaction between drug and mucilage.

2. Differential Scanning Calorimetry:

A differential scanning calorimeter was used for thermal analysis of drug, excipient and their physical mixture. The drug and excipients were passed through sieve no. 60 Drug alone and its mixture with excipient was weighed directly in the pierced DSC aluminium pan (Aluminium Standard 40µl) and scanned from temperature range of 100^0 to 200°C and at heating rate of 10°C/min in nitrogen atmosphere at flow rate 50 ml/min. the thermogram obtained were observed for any interaction.

Preparation of Granules and Tablet:

Drug and excipient were weighed accurately as per composition given in **Table No 3** and powdered to obtained uniform particle size using mortar and pestle. The powder was thoroughly mixed to obtain uniform mixing of dug and excipient. To the above mixture required amount of starch paste was added to form damp mass. Then prepared damp mass was passed through sieve no # 16/22 and the granules, which passed through sieve no #16 and retained on sieve no. #22 to prepare uniform sized granules. The prepared granules were kept for drying in hot air oven at 50-60^o. Then dried granules were collected, separated from fines by sieving. Separated granules were weighed and analyzed for true density, angle repose, bulk density and Carr's index.[20] Weighed amount of prepared granules were taken, to it lubricants and fines were added and uniformly mixed. The prepared mixture was taken for compression.

Evaluation of Tablets:

Prepared tablet was evaluated for weight variation, hardness, friability, thickness and diameter, drug content.[20]

Determination of Swelling and Erosion Behavior of Sustained Release Matrix Tablet: [21- 23]

$$\% \text{ Swelling} = (W_t - W_0) / W_0 \times 100$$

$$\% \text{ Erosion} = (W_0 - W_r) / W_0 \times 100$$

Where,

W_t = the weight of the matrix after swelling

W_0 = the initial weight of the matrix

W_r = the weight of the eroded matrix

Dissolution Studies:

The *in vitro* release of Propranolol HCl from formulated tablets was carried out in acid buffer pH 1.2 for 2 h and then phosphate buffer pH 6.8 for remaining 10 h. The studies were performed in

USP dissolution apparatus II, (Dissolution Test Apparatus**,** Model. DA-3**,** Veego Scientific Devices, Mumbai) at 37 ± 0.5° C and 50 rpm speed. Samples were taken at 1 hour interval and analyzed for Propranolol HCl content at 319 nm by using UV–visible spectrophotometer, (Model. UV 2401 PC, Shimadzu Corporation, Singapore). [24]

Stability Study:

The optimized batches FT_4 was kept for stability study, results shows insignificant difference for drug release and other evaluation parameter for the period of 3 months at 40^0C/75% RH.

Table No 1: Characterization of Tamarind seed Polysaccharide:

Property of mucilage	Result
Bulk density (g/cc)	0.511 ± 0.03
Tapped density (g/cc)	0.683 ± 0.02
Compressibility Index (%)	25.18 ± 0.04
Housner Ratio	1.33 ± 0.08
Angle of repose (^{0})	$23^0$40'± 0.14
Swelling Index (%)	1500 ± 0.58
Water Retention (%)	14.00 ± 1.21
Loss on drying (%)	7.4 ± 0.28
pH	6.85 ± 0.23
Melting point (^{0}C)	240^0 - 260^0
Practical yield (g/Kg)	35g-40g

*Each value represent the mean ± standard deviation (n=3)

Table No. 2 Effect of Concentration on Viscosity of Tamarind seed mucilage.

Sr. No.	Concentration (%)	Viscosity (Pa.s)
1	1	9.69
2	2	14.26
3	3	17.44

Table No 3: Composition of Propranolol HCl Tablets:

Ingredients (mg)	FT_1	FT_2	FT_3	FT_4	FT_5
Propranolol HCl	40	40	40	40	40
Lactose monohydrate	203	178	153	128	103
Tamarind seed mucilage	100	125	150	175	200
Magnesium stearate	07	07	07	07	07

Table No 4: Post Compression Parameter of Propranolol HCl Tablets.

Formulations	Hardness*(kg/cm^2)	Friability*(%w/w)	Thickness*(mm)	Diameter*(mm)	%Drug Content*
FT_1	3.11±0.07	0.24±0.05	5.07±0.058	10.03±0.14	98.32 ± 0. 20
FT_2	4.38±0.06	0.48±0.02	4.98±0.052	10.06±0.12	96.65 ± 0. 19
FT_3	4.74±0.05	0.45±0.03	5.10±0.056	10.17±0.10	95.57±0.59
FT_4	4.69±0.08	0.39±0.04	5.03±0.059	10.08±0.18	98.90±0.09
FT_5	4.93±0.09	0.29±0.04	4.97±0.043	10.04±0.13	96.00±0.27

* Each value represents mean (n=3) ± SD

Table No 5: Percentage Swelling Indices of Formulations FT_1 – FT_5

Time (min)	% Swelling Index				
	FT_1	**FT_2**	**FT_3**	**FT_4**	**FT_5**
0	0±0	0±0	0±0	0±0	0±0
30	21.04±1.10	22.36±1.65	25.76±1.38	26.34±1.07	30.29±1.78
60	31.42±1.23	32.68±1.08	34.48±1.62	36.64±1.98	39.64±1.36
90	38.76±1.39	40.12±1.78	42.72±1.56	43.6±1.42	45.87±1.87
120	44.99±1.81	45.72±1.88	48.24±1.97	50.37±2.01	53.24±1.75
180	50.22±1.06	51.77±1.87	55.21±1.35	60.18±1.78	63.18±2.04
240	56.18±2.03	58.44±1.97	60.76±2.07	67.84±1.89	69.34±1.93
300	62.49±1.98	65.14±1.04	69.73±1.98	74.92±1.62	78.64±1.57
360	49.73±1.75	48.36±1.61	75.19±1.37	84.06±1.50	91.13±1.44
420	40.85±1.03	39.1±1.35	52.18±1.59	60.93±1.67	61.62±1.79
480	32.96±1.26	33.76±1.49	40.27±1.61	43.39±1.42	42.04±1.87

*Each value represent the mean ± standard deviation (n=3)

Table No 6: Percentage Erosion of Formulations FT_1-FT_5

Time (h)	% Erosion*				
	FT_1	**FT_2**	**FT_3**	**FT_4**	**FT_5**
0	0±0	0±0	0±0	0±0	0±0
1	10.36±1.06	8.6±1.12	6.3±1.32	5.25±1.19	4.46±1.24
2	19.43±1.26	15.31±1.25	10.83±1.36	8.39±1.84	6.79±1.34
3	27.64±1.45	21.48±1.72	16.45±1.74	12.18±1.58	9.16±1.52
4	36.28±1.09	28.18±1.64	20.13±1.85	16.42±1.62	13.25±1.67
5	45.81±1.28	33.35±1.34	24.33±1.74	21.51±1.54	17.56±1.48
6	57.38±1.67	39.59±1.66	28.53±1.82	25.28±1.85	21.83±1.97
7	-	44.41±1.45	33.48±1.53	30.67±1.59	26.93±1.87
8	-	50.87±1.63	37.28±1.48	36.43±1.33	30.82±1.69
9	-	-	42.38±1.29	41.61±1.93	35.38±1.95
10	-	-	47.63±1.08	46.46±1.42	41.79±1.55
11	-	-	-	51.29±1.33	46.79±1.97
12	-	-	-	56.32±1.74	52.56±1.59

*Each value represent the mean ± standard deviation (n=3)

Table No 7: *In vitro* Dissolution Profiles of Propranolol HCl Tablets (FT_1-FT_5).

Time (h)	Cumulative % Drug Release*				
	FT_1	FT_2	FT_3	FT_4	FT_5
0	0	0	0	0	0
1	19.61±0.91	18.64±0.88	15.11±0.83	14.79±0.98	9.64±1.03
2	27.11±0.72	23.25±0.32	19.37±0.71	20.33±0.51	15.16±0.65
3	66.11±0.68	58.50±0.79	44.12±0.52	45.83±0.73	35.79±0.71
4	77.95±0.81	67.32±0.41	52.51±0.64	49.35±0.82	40.40±0.93
5	86.86±0.57	73.56±0.63	60.94±1.30	61.13±64	51.04±0.82
6	93.94±0.65	79.46±0.84	64.54±0.98	63.98±0.44	56.11±0.54
7	-	84.65±1.13	70.04±1.03	68.92±0.51	62.71±0.32
8	-	92.11±0.92	75.57±1.01	71.61±0.89	65.60±0.47
9	-	-	84.13±0.89	77.52±102	70.75±0.91
10	-	-	91.60±0.72	82.70±0.99	72.93±0.79
11	-	-	-	84.92±1.31	76.24±0.98
12	-	-	-	88.14±0.57	79.94±1.15

*Each value represent the mean ± standard deviation (n=3)

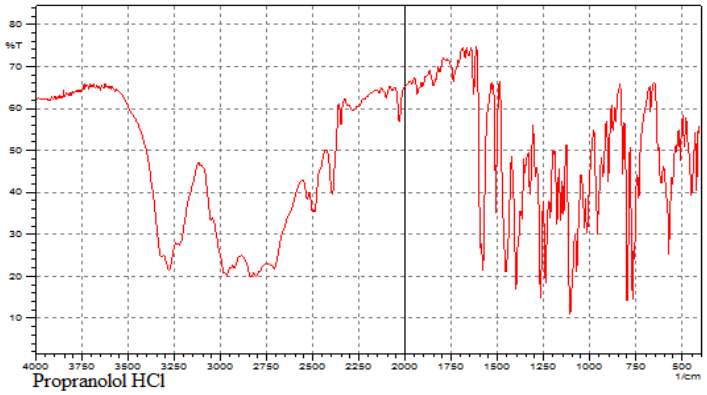

Figure No 1: FTIR Spectra of Propranolol HCl

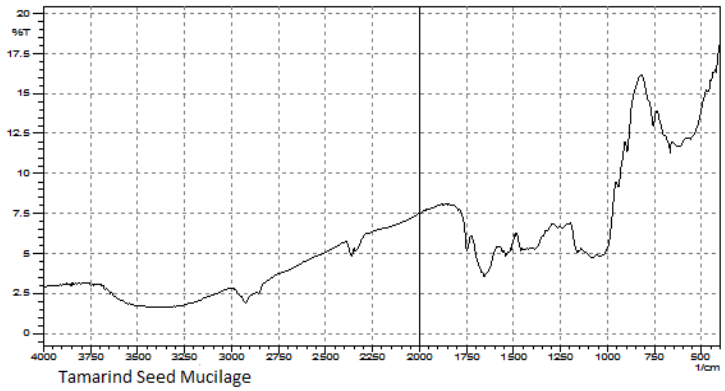

Figure No 2: FTIR Spectra of Tamarind seed mucilage.

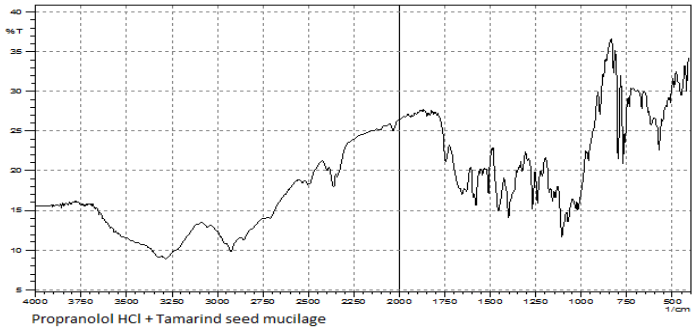

Figure No 3: FTIR Spectra of Physical Mixture of Propranolol HCl and Tamarind seed mucilage

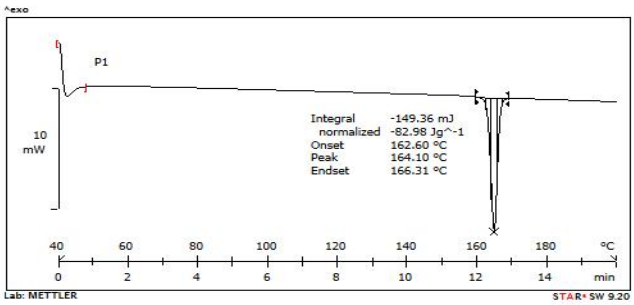

Figure No 4: DSC Thermograph of Propranolol HCl

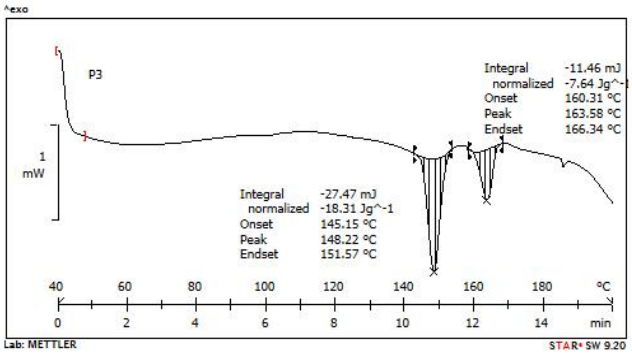

Figure No 5: DSC Thermograph of Propranolol HCl and Tamarind seed mucilage

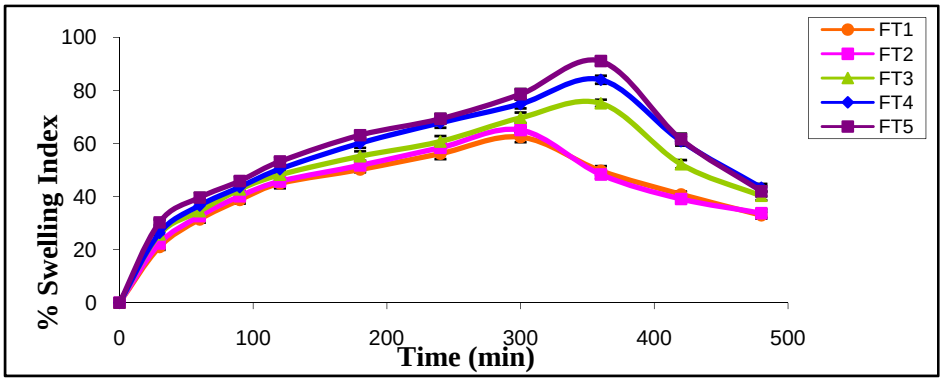

Figure No 6: Percentage Swelling Indices of Formulations FT_1 – FT_5.

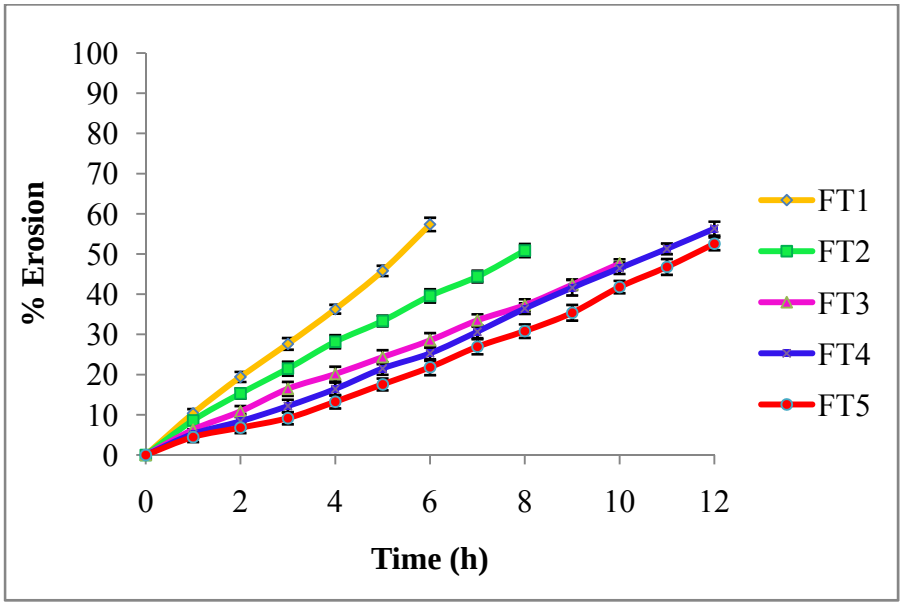

Figure No 7: Percentage Erosion of Formulations FT_1-FT_5.

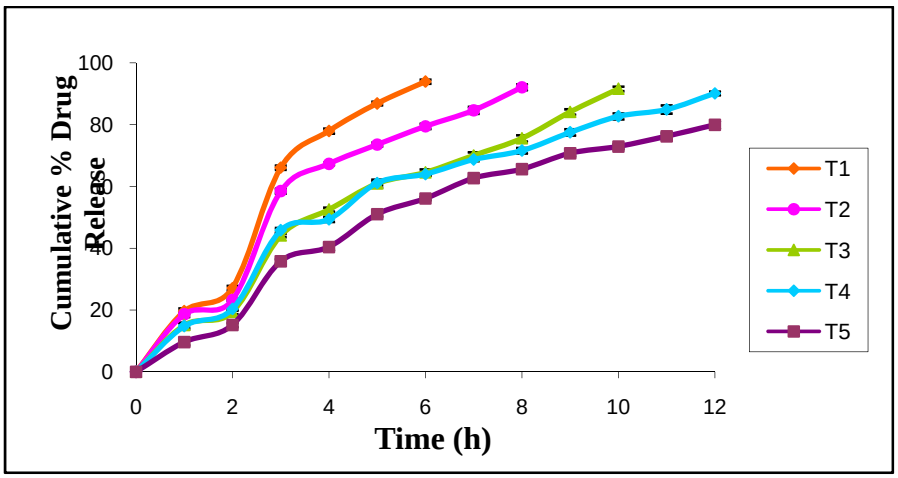

Figure No 8: *In vitro* Dissolution Profiles of Propranolol HCl Tablets (FT_1-FT_5).

DISCUSSION AND CONCLUSION

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 35g-40g. Extracted mucilages were analyzed for various chemical tests, Molisch's test developed violet green color at the junction of the two layers showed presence of carbohydrate in it. The absence of starch was confirmed by iodine test, showed no color change on addition of iodine solution. The presence of mucilage further substantiated by Ruthenium solution which showed development of pink color. The

viscosity of 1% w/v solution of the polysaccharide was found to be 9.69 Pa.s. The pH of the isolated polysaccharide was found to be 6.85 ± 0.23. Viscosity and pH 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. 2. It can be used as standard spectrum for quality control and determination of the purity of TSP. In the microbial load testing, the polysaccharide showed 8000colony forming unit per gram of bacteria which was in acceptable limits for the natural products. The above results indicated that the selected polysaccharide can be used as an excipient in dosage forms. The compatibility between the drug and the isolated polysaccharide (TSP) was found to be good by the FTIR and DSC studies (Fig.1, 2, 3, 4 and 5). The matrix tablets of Propranolol HCl using the TSP were prepared by wet granulation method. Table 4 shows the data obtained from the evaluation of tablets. The hardness of the tablets was found to be in the range of 3.1 – 4.9 kg/cm$^{2.}$ The tablets showed 95.57- 98.90% of the labeled amount of drug, indicating uniformity in drug content. The individual weight variation was found to be within ±7.5% of the average tablet weight and the friability values were found to be in the range of 0.24-0.48% for all the formulations. The swelling index increased with the increase in concentration of TSP. The matrices underwent both water uptake and erosion simultaneously immediately after placement in the dissolution medium. The drug release decreased as the concentration of TSP in the matrix increased. The in-vitro drug release profile of Propranolol HCl from all the formulations is shown in Fig.8.The results indicated retardant release of drug from all the formulations with increase in the polymer concentration. The Formulation FT_4 showed a slow and complete drug release of 88.14±0.57 over a period of 12 hr. The 'n' value of formulation FT_4 from korsmeyer-peppas equation was found to be 0.738 indicating that the release mechanism was non-Fickian or anamolous release ($0.5 < n < 1$). It showed that the release was dependent on both drug diffusion and polymer erosion. R^2 value (i.e., 0.984) was maximum for Higuchi plot. Therefore release kinetics fits Higuchi plot**.**

CONCLUSION

The result of the present study demonstrated the isolated TSP can be used as a drug release retardant, which was evident, from the results. The drug release was extended over a period of 12 hours and the mechanism of drug release was observed to be following release. Thus the polymer could serve as a new effective drug release retardant with better patient compliance.

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