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Release characteristics of drugs from cross linked tamarind seed polysaccharide matrix tablets

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ABSTRACT

The study was aimed isolate tamarind seed polysaccharide from tamarind kernel powder, crosslinking of isolated polysaccharide with epichlorohydrin and to assess the release behaviour of drugs, diclofenac sodium and ketoprofen from isolated tamarind seed polysaccharide and cross linked tamarind seed polysaccharide as release retardant. The presence of polysaccharide was confirmed by phytochemical analysis. The drugs and isolated polysaccharide was found to be compatible as confirmed by IR spectral studies. The TSP powder was evaluated for its micromeritic properties viz. Bulk density, tap density, angle of repose, Hausners's ratio, Carr's index and bulkiness and the results indicated good flow properties. The formulations were prepared using TSP powder and crosslinked TSP powder. The prepared granules were free flowing and the compressed tablets showed good friability and hardness. The drug content of all the prepared formulations was ranging from 96.5- 100.0%. The rate of drug release form formulations containing crosslinked TSP was slow when compared to the formulations containing TSP without crosslinking. The release data was incorporated into various mathematical models and the drug release mechanism of formulations was found to be Fickian, non Fickian diffusion and super case II transport. This study confirmed that the crosslinked TSP can be used as an effective release retardant and can be successfully used in commercial products.

Key Words: Tamarind seed polysaccharide, epichlorohydrin, diclofenac sodium, ketoprofen, sustained action.

INTRODUCTION

Polysaccharides and their derivatives have been the choice of polymers as rate controlling carriers in sustains drug delivery system [1]. They possess good mechanical properties for application as fibers, films, adhesives, hydrogels, rheology modifiers, emulsifiers and drug delivery agents [2]. Tamarind seed polysaccharide (TSP) a natural polysaccharide obtained from the seed kernel of Tamarindus indica family Leguminoseae is a branched polysaccharide with a main chain of β-D-(1,4)- linked glucopyranosyl units, and a side chain of single D-xylopyranosyl unit attached to every second, third, and fourth D-glucopyrnosyl unit through an

α-D-(1,6) linkage. One D- xylopyranosyl is attached to xylopyranosyl units through a β-D-(1, 2) linkage with a molecular weight of 52350 daltons [3,4]. It possesses properties like high viscosity, broad pH tolerance, nanocarcinigenic, mucoadhesive, biocompatible, high thermal stability, high drug holding capacity [5], and is stable against acids [6]. It also possess property of forming films which are transparent, non hygroscopic, non sticky, retains its shape even after rough handling and are of high tensile strength and flexibility [7]. Tamarind seed polysaccharide can be crosslinked with epichlorohydrin to sustain release of both water soluble and insoluble drugs for prolonged time period [8]. The model drugs chosen to assess the release behaviour were diclofenac sodium and ketoprofen that are BCS class-II drugs, with low aqueous solubility and high permeability. Diclofenac sodium is an acetic acid non-steroidal anti-inflammatory drug and has analgesic property. It is used in the treatment of pain, ocular inflammation, osteoarthritis dysmenorrhea, ankylosing spondylitis, rheumatoid arthritis and actinic keratosis [9]. Its biological half-life is 1-2 h. It is poorly soluble in water and has acidic pH 1-3 but is rapidly soluble in alkaline pH 5-8 [10]. Ketoprofen is an important analgesic and non-steroidal anti-inflammatory drug, with antipyretic properties, its mechanism of action is the inhibition of prostaglandin synthetase. The drug is also used in treatment of rheumatic disorder and its plasma elimination half-life is 1 to 3 h [11]. The purpose of this study was to study the release behaviour of some water insoluble drugs from crosslinked TSP, in comparison with TSP without crosslinking.

MATERIALS AND METHODS

Materials

Diclofenac sodium and Ketoprofen were purchased from BEC Chemicals Ltd, Mumbai. Dicalcium phosphate, magnesium stearate, and purified talc were purchased from S.D. Fine Chemicals, Mumbai, India. Tamarind kernel powder was purchased from local market, Bangalore. Absolute ethanol and epichlorohydrin were purchased from Central Drug House, Mumbai. All other chemicals used were of A.R grade.

Isolation of TSP

The isolation of TSP was carried out by method reported earlier [12]. To 20 g of tamarind kernel powder, 200 ml of cold distilled water was added to prepare slurry. The slurry was then poured into 800ml boiling distilled water. The solution was boiled for 20 minutes with continuous stirring. The resulting clear solution was kept overnight so that most of the fibers settle down. The solution was then centrifuged at 5000 rpm for 20 min. The supernatant solution was separated and poured into twice the volume of absolute ethanol by continuous stirring to obtain the precipitate. The precipitate was collected and washed twice with absolute ethanol and dried at room temperature for 2 days. The dried product was grounded and passed through BSS # 60 and stored in dessicator till further use.

Crosslinking of TSP with epichlorohydrin

Partial crosslinking of TSP with epichlorohydrin was done by the method reported earlier with some modifications (vide ref. 8). Briefly 10g of TSP powder was soaked in water. To this 50ml of 1 N sodium hydroxide was added and the temperature was maintained at 54°C and homogenized for 15 minutes. Then 0.5ml epichlorohydrin was slowly added with continuous homogenization for 15 minutes resulting in a gel. The gel was then neutralized with acetic acid and washed 3 times with a solution of water/acetone (60:40 v/v). The resulting solid gel was washed with pure acetone over a filter. The obtained mass was air dried at room temperature for 72 hours, grounded and passed through BSS#85 and stored in airtight container.

Formulation of tablets

The tablets were prepared by wet granulation technique using varying concentrations of TSP and crosslinked TSP as mentioned in Table 1. To the TSP powder diclofenac sodium and dicalcium phosphate (previously passed through sieve no. 80) was added and granulated using 5% polyvinylpyrollidone solution as granulating agent. The wet mass was passed through sieve no 12 and the granules obtained were dried at 45^{o}C for 30mins. The dried granules were subjected to dry screening by passing through mesh no.16 superimposed on mesh no.24 and then the granules were lubricated with the mixture of talc and magnesium stearate. The granules were compressed into tablets using 8mm concave punch in rotary tablet press (Rimek RSB-4 minipress, Cadmach). Ketoprofen tablets with TSP powder were prepared in the same manner. In a similar manner ketoprofen tablets and diclofenac sodium tablets were prepared using the crosslinked TSP as release retarding agent.

Evaluation of isolated TSP powder

1) Phytochemical examination

Ruthenium red test and Molisch's test were performed to confirm the presence of polysaccharide.

2) Micromeritic properties of TSP

Bulk density, tap density, bulkiness, angle of repose, Hausner's ratio and Carr's index were determined.

3) Loss on drying: Loss on drying was carried out as per method mentioned in I.P.2007[13].

4) pH of 1% solution

The pH was measured using a digital pH meter.

5) Drug-excipient interaction studies

The pure drugs sample and the physical mixture of drugs and TSP powder in the ratio 1:1 were subjected to I.R spectral studies using FTIR spectrophotometer (FTIR 8400 S, Shimadzu, Japan) by KBr disc method. The samples were scanned in the range of 4000-400cm^{-1}.

Evaluation of Tablets

1) Granular analysis: Bulk density, tap density, Carr's index and Hausner's ratio of the prepared granules were determined using Electrolab Tap Density tester, USP, ETD-1020.

2) Post compression analysis: The prepared tablets were evaluated for weight variation test, hardness, disintegration time and friability.

3) Drug content determination: Ten tablets of each formulation were powdered. Powder equivalent to 400mg of diclofenac sodium and ketoprofen was weighed accurately and transferred to two 100ml volumetric flasks separately. To the flask 50ml of phosphate buffer solution pH 6.8 was added and shaken thoroughly. Then the volume was made up to 100 ml with phosphate buffer pH 6.8 solution. The resulting solution was filtered, diluted and the drug content was estimated at 276 nm for diclofenac sodium and 260 nm for ketoprofen using UV spectrophotometer using phosphate buffer as blank.

4) *In-vitro* drug release: Drug release studies were carried out using USP dissolution test apparatus-II (Electro lab, Mumbai, India). The study was conducted at 37^{o}C and 50 rpm. The dissolution medium used was 900ml of phosphate buffer pH 6.8 and study was carried up to 9hours. 3ml of sample was withdrawn at different time intervals and replaced with fresh medium in order to maintain sink condition. The withdrawn samples were diluted suitably and drug content was estimated spectrophotometrically at 276 nm for Diclofenac sodium and 260 nm for ketoprofen.

5) *In*-vitro release mechanism: *In vitro* Release mechanism was determined by using PCP DISSO V3 software. To analyze the in vitro release data various kinetic models such as zero order, first order, Hixson-Crowell cube root law, Peppas model and Higuchi model were used to describe the release kinetics. Based on this the following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (Higuchi model) log cumulative % drug release vs. log time (Korsmeyer model) and cube root of drug % remaining in matrix vs. time (Hixson-Crowell cube root law). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$Mt / M\infty = Kt^{n}$$

Where Mt / M∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms

RESULTS AND DISCUSSION

Table 1: Composition of TSP and cross linked TSP matrix tablets

S.No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Diclofenac sodium	100	100	100	100	---	---	---	---
2	Ketoprofen	---	---	---	---	100	100	100	100
3	TSP	100	200	---	---	100	200	---	---
4	C TSP	---	---	100	200	---	---	100	200
5	Dicalcium phosphate	185	85	180	80	80	5	180	80
6	Polyvinyl pyrollidone (5%)	qs	qs	qs	qs	qs	qs	qs	qs
7	Talc	10	10	12	12	12	12	12	12
8	Magnesium stearate	5	5	8	8	8	8	8	8
Total weight of tablet (mg)		400	400	400	400	400	400	400	400

Table 2: Characterization of isolated TSP powder

S.No.	Parameters	Values observed*
1	Bulk density (g/cc)	0.741
2	Tap density (g/cc)	0.833
3	Angle of repose (θ)	15.83
4	Carr's index (%)	14.33
5	Hausner's ratio	1.166
6	Bulkiness	1.400
7	Average particle size (µm)	6.4
8	Loss on drying (%)	20.0
9	pH of 1 % solution	7.0

** - Average of three determinations*

The yield of TSP was 76%. The identification of the polysaccharide was confirmed by ruthenium red test as it stained red in colour, and the presence of carbohydrates was confirmed by Molisch's test as there was formation of violet ring at the junction of the liquids. The results of

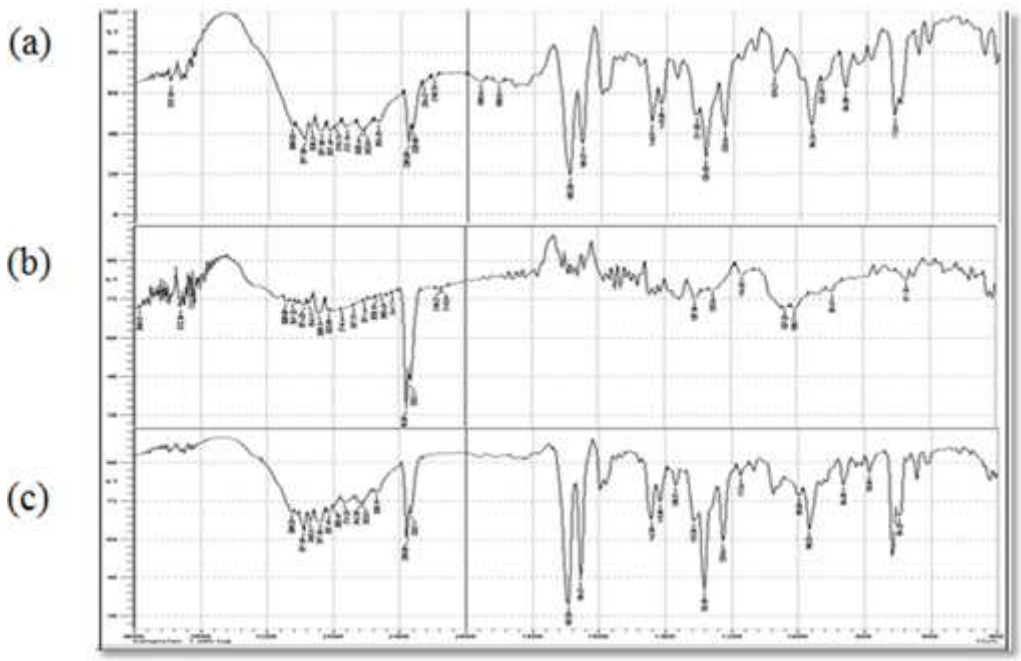
micromeritic properties of isolated TSP powder were shown in table 2. The values of bulk density, tap density, Hausner's ratio and bulkiness of TSP powder were 0.741 g/cc, 0.833 g/cc, 1.166, 1.400. The values of angle of repose and compressibility index of TSP powder were found to be 15.83^0 and 14.33% indicating excellent flow properties. An angle of repose of less than 30 degrees indicates good flow properties. This was further supported by the lower compressibility index. Granules with Carr's index values around 21% and below are considered to have fair and excellent flow properties.

Table 3: Drug release parameters along with best fit model for drug release from matrix tablets prepared with TSP and crosslinked TSP

Parameters	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation[a] (%)	400±2	401±5	404±8	401±4	402±2	400±1	402±1	399±2
Hardness[a] (kg/cm^2)	4±0.5	5±0.4	4.5±0.6	6.5±0.5	4.4±0.3	4.8±0.2	4.6±0.4	4.6±0.5
Friability[a] (%)	0.12±0.01	0.15±0.03	0.25±0.04	0.24±0.05	0.25±0.04	0.6±0.03	0.4±0.04	0.5±0.03
Drug content[a] (%)	96.5±0.5	98.3±0.4	99.6±0.8	100.0±.6	99.0±0.7	97.0±0.4	98.90±0.5	99.45±0.4
Disintegration time[a] (min)	5±0.2	7±0.5	6±0.3	4±0.6	5±0.4	6±0.3	5±0.5	4±0.6
Best Fit Model	Korsmeyer - Peppas	Korsmeyer - Peppas	Korsmeyer - Peppas	Korsmeyer - Peppas	Korsmeyer - Peppas	Korsmeyer - Peppas	Hixson-Crowell	Zero order
r	0.9993	0.9985	0.9920	0.9899	0.9989	0.9953	0.9942	0.9964
K*	9.6753	8.2984	24.8565	19.6737	63.0412	10.6783	10.4144	7.7009
n*	1.1282	1.2598	0.6336	0.7117	0.3475	0.8972	0.8550	0.9448
Drug Release at 8th hour[a] (%)	99.3±1.2	79.4±2.3	80.4±0.98	74.6±1.01	99.4±2.1	76.4±1.4	84.6±1.1	75.4±0.99
$T_{50\%}$ (hrs)	3.9	4.4	5.1	4.8	4.3	4.9	5.2	5.1
$t_{90\%}$ (hrs)	7.1	10.1	10.5	10.6	7.2	10.3	10.4	11.1

** The value of K and n are shown according to Korsmeyer - Peppas equation.; a: n=6*

Fig 1: IR Spectra of (a) Ketoprofen, (b) TSP, (c) Physical mixture of Ketoprofen and TSP



The compatibility between the drug and isolated mucilage powder was found to be good as confirmed by the I.R spectral studies. The infra-red spectra of pure ketoprofen showed peaks at 2827.5 cm$^{-1,}$ 1683.83 cm$^{-1,}$ 1415.66 cm$^{-1,}$ and 2977.29 cm^{-1} confirming presence of OH, C=O, CH_3 and CH. The spectra of TSP showed peaks at 1045.35cm^{-1}, 1643.24 cm^{-1} 1728.10 cm^{-1} ,

2939.31 cm^{-1} , and 3406.20 cm^{-1} showing C-O-C and ether group absorbance, C=O and aldehyde absorption, C-H stretching, presence of primary OH and secondary OH, which indicates that isolated product was polysaccharide. Similar peaks were observed at respective wave numbers in the physical mixtures TSP powder with ketoprofen (Fig.1-a, b, c). The infra-red spectra of pure diclofenac sodium showed amino peak at 3338.55 cm^{-1}, C-Cl stretching at 769.54 cm^{-1}, N-H bending at 1554.52 cm^{-1} and OH bending at 1384.79 cm^{-1}. The spectra of the physical mixtures TSP with diclofenac sodium showed similar characteristic peaks at their respective wave numbers (Fig. 2- a, b, c). This part of the study confirmed that there was no interaction between the drug and TSP.

Fig 2: IR Spectra of (a) Diclofenac sodium, (b) TSP, (c) Physical mixture of Diclofenac sodium and TSP

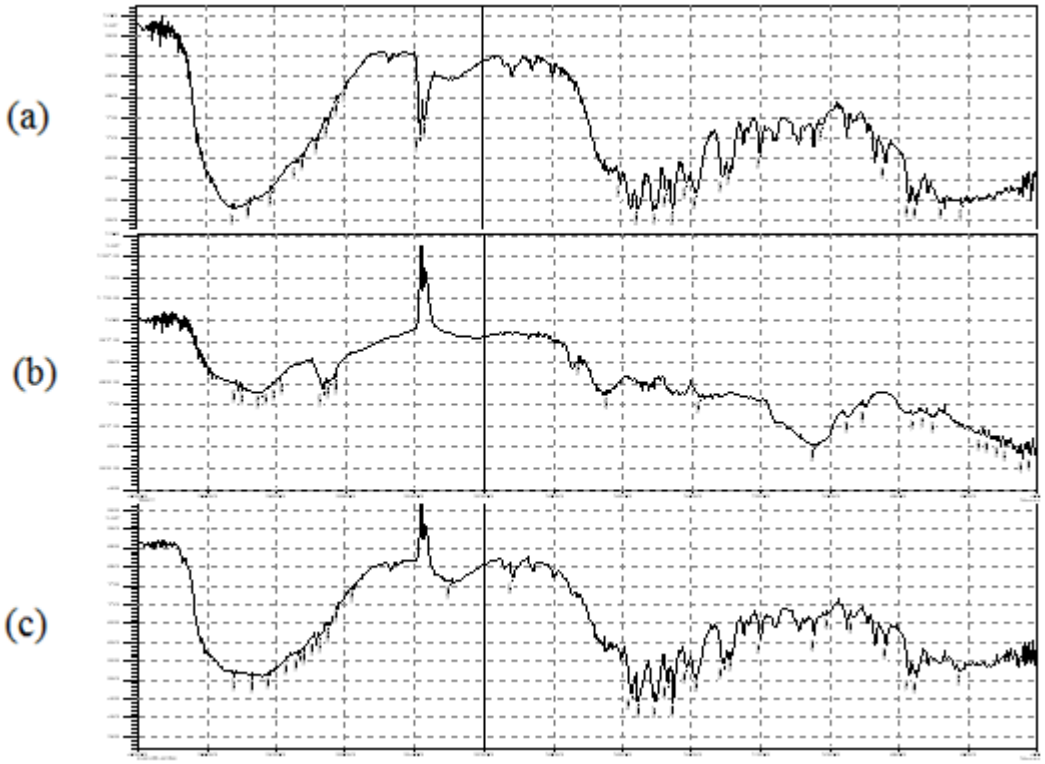


Fig 3: Cumulative % drug release of prepared tablet formulations

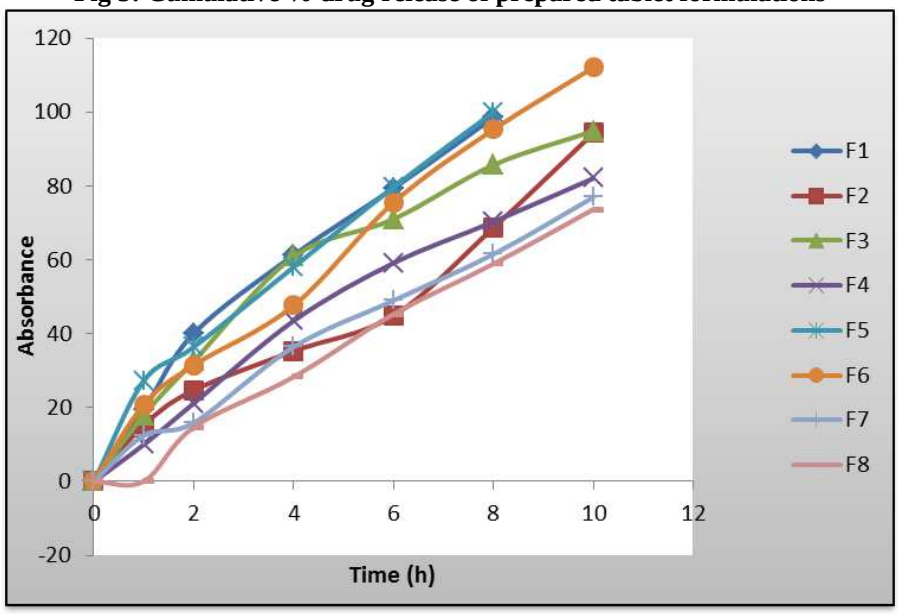


Fig 4: Prediction of drug release mechanism for formulation F1

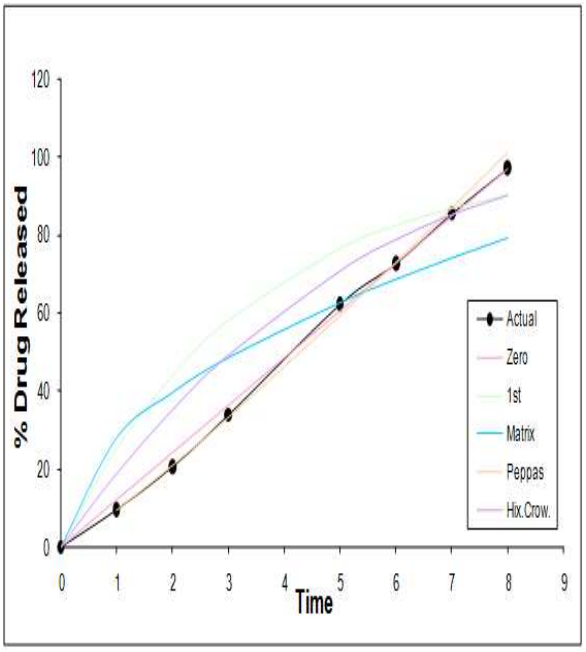


Fig 5: Prediction of drug release mechanism for formulation F2

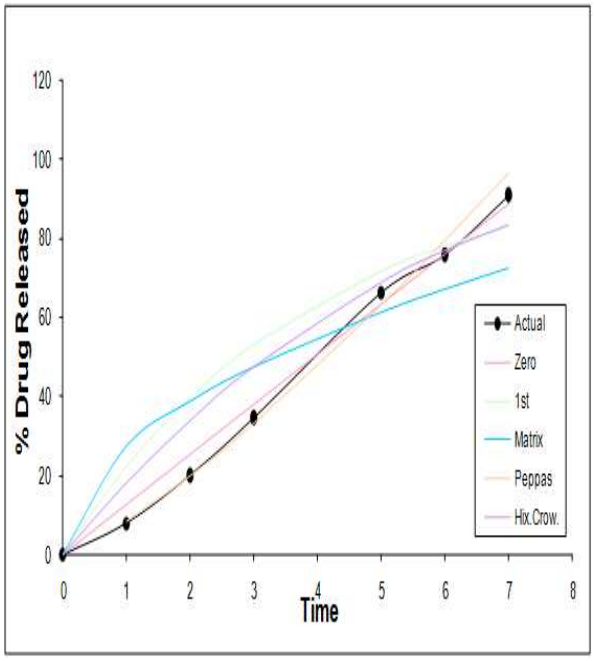


Fig 6: Prediction of drug release mechanism for formulation F3

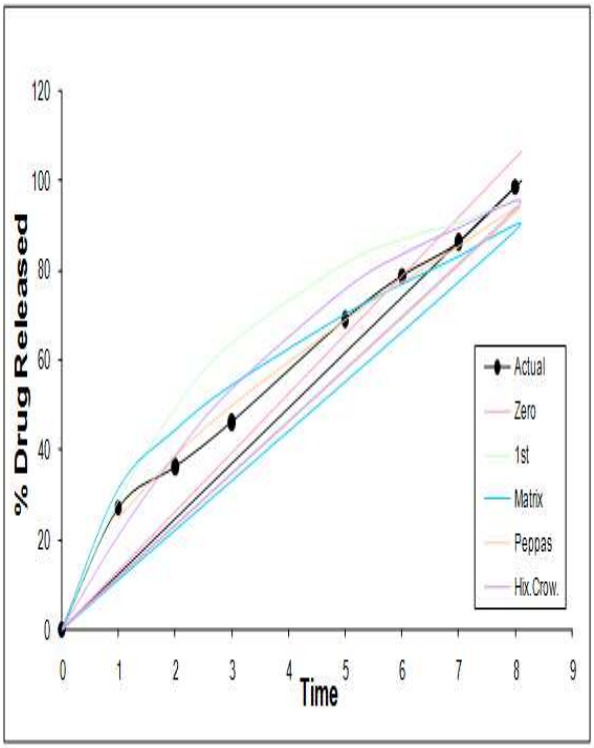
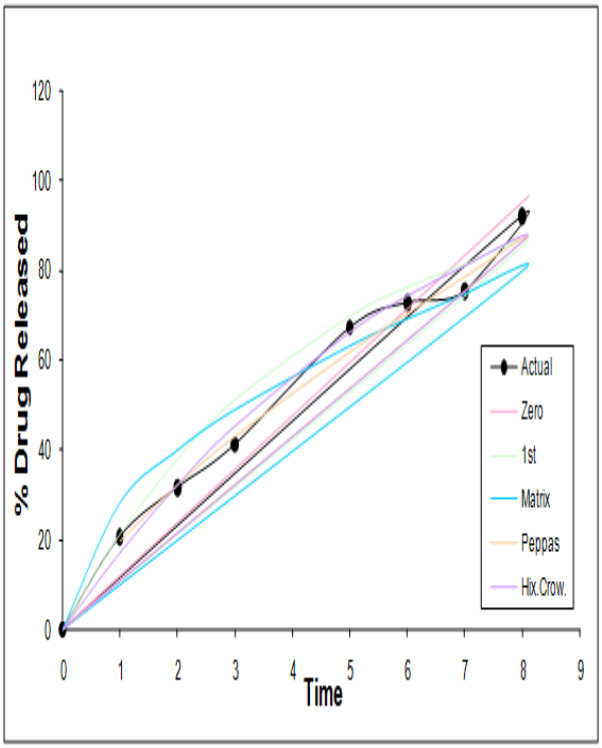


Fig 7: Prediction of drug release mechanism for formulation F4



Based on these results the isolated TSP was crosslinked with epichlorohydrin and on crosslinking, the TSP powder turned into light brown in colour. Using this crosslinked TSP, ketoprofen and diclofenac sodium tablets were prepared and their release behaviour was assessed. Four formulations of diclofenac sodium (F1 to F4) were prepared of which formulations F1 and F2 were made using TSP and formulations F3 and F4 with crosslinked TSP. Similarly formulations F5 and F6 containing ketoprofen were prepared using TSP and formulations F7 and F8 were prepared with crosslinked TSP. The prepared tablets complied with

the pharmacopoeial specifications for weight variation test, hardness and friability of less than 1%, thereby substantiating the mechanical resistance of the tablets during transit. All the tablets disintegrated within seven minutes and the drug content in all the formulations was found to be in the range of 96.5-100%. Table 3 gives the physical parameters (hardness, and thickness, friability), weight uniformity and drug content of all the fabricated tablets.

Fig 8: Prediction of drug release mechanism for formulation F5

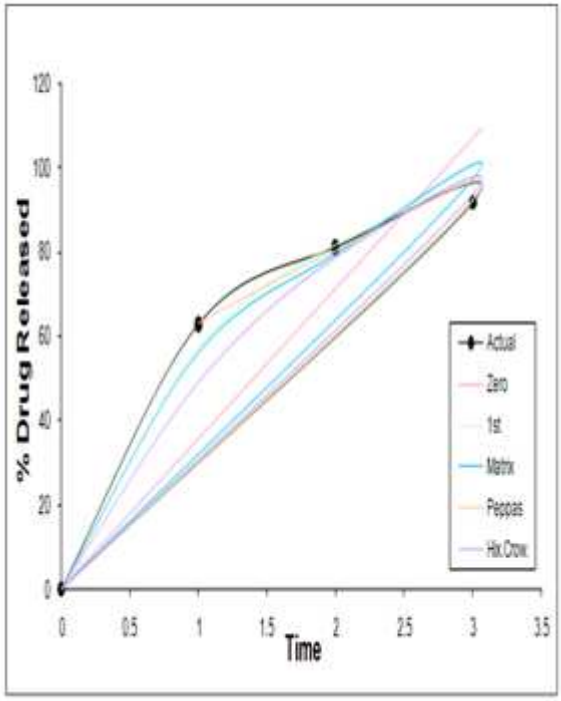


Fig 9: Prediction of drug release mechanism for formulation F6

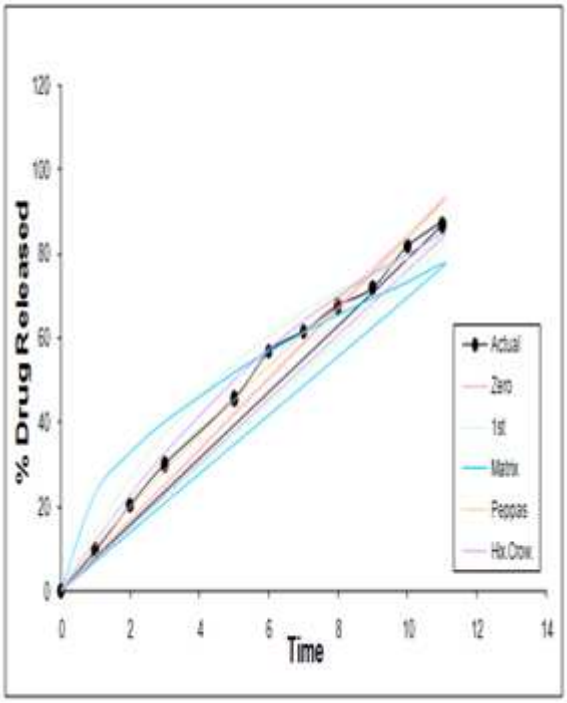


Fig 10: Prediction of drug release mechanism for formulation F7

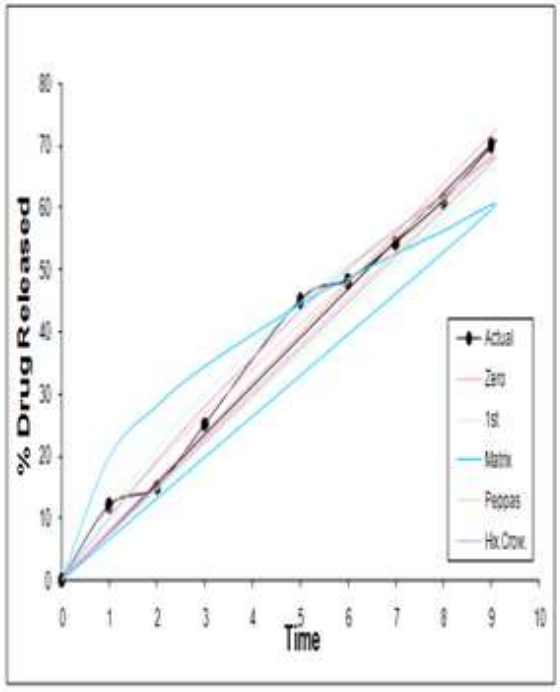
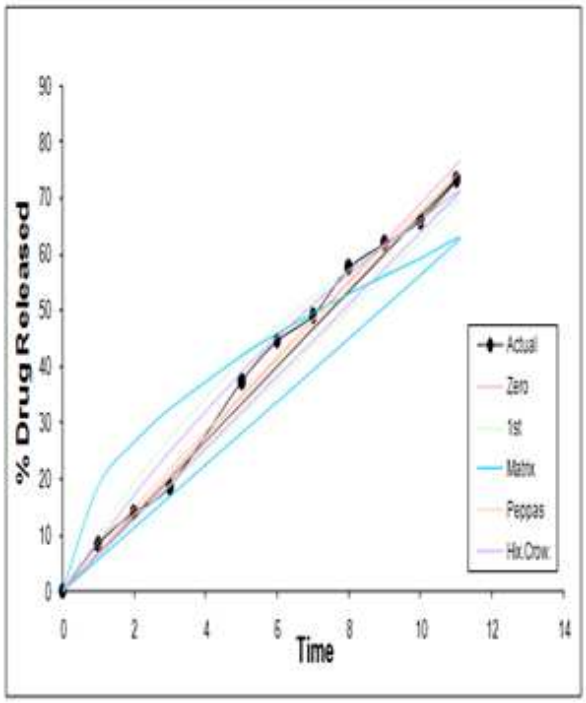


Fig 11: Prediction of drug release mechanism for formulation F8



Formulations F1 and F5 released the entire drug content within 8 hours. Formulations F2, F3, and F4 showed 94.3, 86.54 and 90.06% at the end of 10 hours, whereas formulations F6, F7 & F8 showed at the end of 10 hours 90.04, 76.92 and 70.66% respectively (Fig.3). The results of drug release studies revealed that the crosslinked TSP retards the drug release for longer time period as compared with the TSP powder without crosslinking. This part of the study correlated with the earlier research findings[8]. The dissolution data (from the values of 1 to 8 hours drug release) of all batches were fitted to first-order, Higuchi, zero-order and Korsemeyer-Peppas models. The model that best fitted the release data was evaluated by correlation coefficient (r^2); the values for all formulations in various models are given in Table 3.

The release mechanism of formulations F1, F2, F3, F4 containing diclofenac sodium was found to be by Peppas model with r^2 values of 0.9993, 0.9985, 0.9920 and 0.9899 respectively. The predicted that the possible drugs release mechanism would be diffusion process. Formulations F5 and F6 containing ketoprofen showed peppas model of release, with correlation coefficient (r) values 0.9989 and 0.9953. Formulation F7 showed Hixson-Crowell release with correlation coefficient value 0.9942 and formulation F8 showed zero order release mechanism with correlation coefficient value 0.9964. The plot for prediction of drug release mechanisms for all the fabricated tablet formulations were depicted in figures 4 to 11. Drug release kinetics indicated that drug release was best explained by peppas plot, as these plots showed the highest linearity (r2 but a close relationship was also observed for some formulations with zero-order kinetics and Hixson-Crowell release. By incorporating the release data, mechanism of release was indicated according to Korsmeyer where n is the release exponent, formulations F1, F2 showed super case II transport F3, F4 showed non Fickian diffusion and F5, F6, F7, F8 showed Fickian diffusion. The diffusion mechanism of drug release was further confirmed by Korsmeyer-Peppas plots that showed fair linearity with less slope values, indicating that drug release mechanism from the formulated tablets was diffusion controlled. Also Korsmeyer's plots indicated an n value of above 0.57, which confirmed an anomalous diffusion mechanism or diffusion coupled with erosion; hence, the drug release was controlled by more than one process. Hixson-Crowell plots indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time. This study thus confirmed that the release of both the poorly water soluble drugs was prolonged by the use of crosslinked TSP as compared with TSP powder.

CONCLUSION

This study provided an insight into the release mechanism of diclofenac sodium and ketoprofen from both TSP and crosslinked TSP matrix tablets. Based on these findings it can be thus concluded that crosslinked TSP is more effective in retarding the drug release when compared to the TSP without crosslinking. Thus, the isolated tamarind seed polysaccharide and crosslinked TSP can be used for retarding the drug release for prolonged period of time.

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