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In-Vitro Release Kinetics Study of Loxoprofen Sodium From Natural Polymers Based Sustained Release Matrix System

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ABSTRACT

The aim and objective of the study was to formulate the matrix system of Loxoprofen sodium that has a very short plasma half-life of 1.15 hours. Natural hydrophilic polymers (Xanthan gum and Pectin) were used to formulate matrix system. These polymers were used to sustain the drug in the matrix system that allowed the slow release of the drug. Different concentration of Xanthan gum and Pectin were used, individually as well as polymeric blends. Wet granulation method was selected for the compression of granules into tablets of 350mg each. Both pre-compressional and post-compressional parameters showed good results. Dissolution studies carried out in distilled water and 0.1 N HCl for 12 hours. Matrix system of Xanthan gum showed comparatively good sustained effects in both media with suitable drug released concentration. Kinetics of drug release was studies by different kinetics models and it was observed that Higuchi was the best fit model for F6 that released minimum drug from the matrix. Values of similarity index showed that F5 resembled with the reference formulation (F6). All the tablets showed good swellability upon hydration that was greatly related to polymers concentration.

Keywords: Loxoprofen sodium, Xanthan gum, Pectin, Matrix system.

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INTRODUCTION

Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage. According to World Health Organization (WHO) the pain is one of the most underestimated healthcare problems in the world[1]. Generally classification of the pain depends upon its location, duration, frequency, underlying cause and intensity [2]

Experimental evidence showed that cyclooxygenase enzymes released the prostaglandin E2 (PGE2) that plays a significant part in the introduction of both peripheral and central sensitization. Thus the specificity of certain NSAIDS for the different COX enzymes has significant implications in terms of clinically analgesic potency. NSAIDs modulate pain pathways in multiple ways. NSAIDs reduce inflammatory hyperalgesia and allodynia by reducing prostaglandin synthesis. This can decrease the recruitment of leukocytes and consequently their derived inflammatory mediators and they cross the blood-brain barrier to prevent prostaglandins (i.e. pain-producing neuromodulators) in the spinal cord. In this manner, NSAIDs reduce local inflammation and prevents both peripheral and central sensitization [3].

Loxoprofen sodium is a Non-Steroidal anti-inflammatory drug that has a plasma half-life of 1.15 hours. It has daily dose of 60mg twice a day. It is a pro drug that is converted into its active metabolites after its absorption into system circulation. It is commonly used for the treatment of different pain disorders and inflammation with relatively less potential of being ulcerogennic[4]. It is available in pharmaceutical formulations as Tablets and Transdermal patches [5]. Natural hydrophilic polymers are easily available non-toxic, biodegradable polymers that swell upon exposure to aqueous media and used quite successfully in the preparation of matrix system[6]. Matrix tablets are useful dosage form having potential benefits of better patient compliance, cheap and ease of preparation[7].

The aim of the present study was the preparation of matrix system that would enhance the plasma half-life of Loxoprofen sodium. Matrix system of natural polymers was prepared by wet granulation technique using Isopropyl alcohol as wetting agent. The net weight of each tablet was adjusted to 350mg.

MATERIALS AND METHOD

A gift sample of Loxoprofen sodium was received from Hilton Pharmaceuticals (Pvt) Ltd, Karachi, Pakistan. Polymers (Xanthan gum and Pectin) were gifted pacific NeutroPharma Pvt. Ltd, Lahore, Pakistan. Lactose, Magnesium Stearate, Polyvinylpyrollidon(PVP), Dihydrogen

Potassium Phosphate, Sodium Hydroxide HCl and Distilled Water were taken from the research laboratories of The University of Lahore. All the ingredients were of analytical grades.

Preparation of matrix system containing loxoprofen sodium

Loxoprofen sodium, polymers and other ingredients were accurately weighed. Drug was initially mixed with PVP and polymers with lactose than both these mixture mixed together using pestle and mortar for 15-30 minutes to achieve uniform mixing. Sufficient amount of isopropyl alcohol was added drop wise to form a wet mass. Formed wet mass was passed through sieve no 10 to obtained granules. Granules were air dried for an hour and again passed through sieve no 16 to achieve uniform sized granules. Mg stearate was mixed in the granules that were compressed into 350mg matrix table of Loxoprofen sodium using single punch machine (AR-400 Erweka, Germany)

Table 1: Composition of matrix tablets of Loxoprofen sodium

Formulations code	Loxoprofen sodium(mg)	Xanthan gum(mg)	Pectin (mg)	Lactose (mg)	PVP (mg)	Mg.stearate (mg)
F1	60	35	-	227.5	24.5	3.5
F2	60	70	-	192.5	24.5	3.5
F3	60	105	-	157.5	24.5	3.5
F4	60	140	-	122.5	24.5	3.5
F5	60	175	-	87.5	24.5	3.5
F6	60	-	35	227.5	24.5	3.5
F7	60	-	70	192.5	24.5	3.5
F8	60	-	105	157.5	24.5	3.5
F9	60	-	140	122.5	24.5	3.5
F10	60	-	175	87.5	24.5	3.5
F11	60	10	30	122.5	24.5	3.5
F12	60	20	20	122.5	24.5	3.5
F13	60	30	10	122.5	24.5	3.5

In-vitro characterizations of granules

Granules were assessed by Carr's index, Hausner's ratio and angle of repose to evaluate the compressibility and flow properties of the granules

In-vitro characterization of compressed matrix tablets

Appearance of the tablets was observed by necked eye to check for tablets defects like picking, chipping or cracking. Thickness and diameter of 10 tablets from each formulation was measured using vernier caliper. Weight variations of 20 tablets selected randomly from each formulation to observe the weight variations that was calculated using digital electrical weighing balance. For the evaluation of the hardness 20 tablets were selected from each formulation and hardness tester (TB-24 Erweka, Germany) was used to evaluate the crushing strength of the tablets. Friability test was performed by selecting 20 tablets randomly from each batch. Tablets were placed in the

friabilator (Pharma test PTFE) that was adjusted at 25 rpm and run for 100 revolutions. % weight loss was calculated by finding the difference between the weight taken before and after the test [8]

Contents uniformity test

20 tablets were crushed to form powder mass. The powder containing loxoprofen sodium equivalent to 60mg was taken and added to the volumetric flask containing 100ml of dissolution media (distilled water). Drug containing powder was dissolved in the media and finally volume was make up to 900ml. Sample was taken and filtered through 10um sintered filter paper. Finally filtered sample was diluted and observance was calculated by UV-Visible spectrophotometer (Pharma Test Type PT-DTT) at 220nm [7].

In-vitro dissolution studies and kinetics modeling

900ml of dissolution media (distilled water and 0.1 N HCl) was taken in the vesicles at 50 rpm and 37±5 ^{0}C. Dissolution studies were carried out for 12 hours. Aliquots were taken at different time intervals and absorbance of the samples was taken at 220nm using UV-Visible spectrophotometer.% Drug release was calculated as [7].

% Drug release= (absorbance of the sample/ absorbance of the standard) × 100

Swellability index

It is the measurement of swelling characteristics of the tablets upon hydration. It was calculated by placing the tablets in distilled water taken in the Petri dish for 10 hours

Similarity index

On the basis of drug release, F6 was selected as reference formulation and all other formulations were compared with it to find out the similarity and difference amongst the formulations.

RESULTS AND DISCUSSION

In-vitro characterizations of granules

Granules of all the formulation were tested for different physical parameters. They showed good results of bulk and tap density, values of Carr's index and Hausner's ratio indicated the good compressibility properties of the granules formulated with natural gums values of angle of repose were also below 30 which is the indication of good flow properties according to B.P. Bulk density was 0.39±0.01 to 0.42±0.01, tap density was 0.43±0.00 to 0.46±0.02, Carr's index 8.69±1.31 to 11.11±1.01, Hausner's ratio was 1.09±0.01 to 1.12±0.01 and angle of repose was 26.98±0.35 to 29.69±0.51.

Table 2: In-vitro characterizations of granules

Formulations	Bulk density Mean± SD, n=5	Tap density Mean± SD, n=5	Carr's index Mean± SD, n=5	Hausner's ratio Mean± SD, n=5	Angle of repose Mean± SD, n=5
F1	0.40±0.00	0.45±0.01	11.11±1.01	1.12±0.00	28.91±0.51
F2	0.41±0.01	0.46±0.02	10.86±1.12	1.12±0.01	28.92±0.37
F3	0.39±0.01	0.43±0.01	9.30±1.21	1.10±0.02	27.58±0.47
F4	0.40±0.02	0.44±0.01	9.09±1.24	1.1±0.02	27.89±0.41
F5	0.41±0.02	0.45±0.00	8.88±1.01	1.09±0.02	26.98±0.35
F6	0.41±0.01	0.45±0.01	8.88±1.22	1.09±0.03	28.51±0.39
F7	0.40±0.01	0.44±0.02	9.09±1.26	1.1±0.02	28.48±0.41
F8	0.42±0.01	0.46±0.00	8.69±1.31	1.09±0.01	27.97±0.29
F9	0.39±0.02	0.43±0.01	9.30±1.29	1.10±0.00	28.59±0.44
F10	0.39±0.01	0.43±0.00	9.30±1.31	1.10±0.01	28.26±0.61
F11	0.40±0.00	0.44±0.02	9.09±1.33	1.1±0.03	29.69±0.51
F12	0.41±0.01	0.45±0.02	8.88±1.18	1.09±0.02	28.41±0.33
F13	0.40±0.01	0.44±0.01	9.09±1.11	1.1±0.02	28.43±0.38

In-vitro characterization of compressed matrix tablets

Prepared matrix tablets of Loxoprofen sodium were subjected to different tests. Selected tablets from all the formulations showed reliable thickness and diameters values with very minor variations. Weight variation was within the acceptable limits according to the pharmacopoeia. Hardness and % friability results also met the compendia requirements. Good percentage of drug contents per tablets showed that natural polymers have the potential of loading sufficient amount drug.

Table 3: In-vitro characterizations of tablets compressed tablets

Formul.	Thickness (mm) Mean±SD, n=5	Diameter (mm) Mean±SD, n=5	Hardness kg/cm^3 Mean±SD, n=20	Friability (%) Mean±SD, n=20	Weight variations (mg) Mean±SD, n=20	Drug contents (%) Mean±SD, n=20
F1	4.02±0.01	10.01±0.010	7.98±0.19	0.15±0.07	351.15±1.2	97.38±0.3
F2	4.01±0.01	10.01±0.01	8.44±0.27	0.18±0.04	352.11±2.0	97.59±0.2
F3	4.03±0.01	10.00±0.01	8.51±0.34	0.16±0.04	351.39±1.3	98.17±0.1
F4	4.02±0.01	10.00±0.01	8.59±0.31	0.19±0.06	350.67±2.1	100.7±0.2
F5	4.01±0.01	10.01±0.01	9.02±0.29	0.15±0.07	351.75±2.1	101.4±0.1
F6	4.01±0.01	10.00±0.01	8.15±0.15	0.23±0.09	349.3±2.12	98.8±0.25
F7	4.03±0.01	10.01±0.01	8.32±0.24	0.21±0.08	352.25±2.4	99.9±0.19
F8	4.03±0.01	10.00±0.01	8.39±0.23	0.18±0.04	350.15±2.1	100.1±0.2
F9	4.02±0.01	10.00±0.01	8.45±0.18	0.16±0.06	351.55±1.4	100.3±0.4
F10	4.03±0.00	10.00±0.01	8.55±0.27	0.17±0.05	352.35±1.3	101.2±0.1
F11	4.02±0.01	10.00±0.01	8.35±0.25	0.19±0.04	351.85±2.2	96.8±0.26
F12	4.03±0.01	10.01±0.01	8.23±0.13	0.18±0.04	350.5±1.13	98.6±0.22
F13	4.01±0.00	10.01±0.01	8.42±0.21	0.22±0.05	352.5±1.11	99.9±0.23

Tablets of all the formulations were found defects free. Thickness of the tablets was 4.01±0.008 to 4.03±0.012, diameter was 10.00±0.010 to 10.01±0.012, hardness was 7.98±0.19 to 9.02±0.29, % friability was 0.15±0.07 to 0.23±0.09, weight variations were 349.3±2.12 to 352.5±1.11 and drug contents were 96.8±0.26 to 101.4±0.19

In-vitro dissolution studies and kinetics modeling

All formulation showed sustained effects in both distilled water and 0.1N HCl used as dissolution media. Release of the drug was found to be greatly related with the concentration of the polymers (Figure 1 and Figure 2). F5 formulated with 50% concentration of Xanthan gum released 84% and 86% of the drug in distilled water and 0.1 N HCl respectively. Natural polymers (Xanthan gum and Pectin) are of hydrophilic nature and have the ability to become swelled upon hydration. They form a gel layer which is the primary barrier in the release of the drug. It was observed that as the polymer got hydrated they begin to swell and formation of gel layer also begun. With the passage of time, more dissolution media entered in the matrix of the polymer hydrate them that cause increase in the swelling as well as in the thickness of the gel layer which further slower down the erosion process and hence release of the drug[(7)].It was studied that when there is incorporation of hydrophilic drugs (Loxoprofen sodium) in the polymer matrix of hydrophilic polymers, the dissolution media enter into the matrix and established an osmotic gradient. The development of osmotic gradient cause more penetration of the media in the matrix which further hydrate the polymer that increase the swelling and gel layer thickness and hence retardation in the drug release from the matrix system.

In 0.1 N HCl F1, F2, F3, F4, F9 and F10 released more than 90% drug in 12 hours of dissolution studies, F6 and F7 released 100% drug in 10 hours and F5 released 86% drug in 12 hours (Figure 1). In distilled water F1, F2, F3, F4, F9 and F10 released more than 90% drug in 12 hours, F6, F7 and F8 released 100% drug in 12 hours while F5 released only 84% of the drug in 12 hours of dissolution studies. When combination of xanthan gum and pectin was used in different concentrations they released 90% to 96% of the drug from compressed matrix tablets during 12 hours.

Release of the drug from matrix of hydrophilic and swellable natural polymers (Xanthan gum and Pectin) usually followed the diffusion process of drug release. Higuchi and Korsmeyer Peppas models were found to be applicable. Higher correlation values of zero order (0.945-0.992) also indicated that release of the drug was slow and well controlled. Formulation F5 was considered as the best as it followed zero order kinetics and release only 84% of the drug in 12 hours of the dissolution studies

In distilled water F1, F4, F6, F7, F12 and F13 followed Higuchi model, F2, F3, F8, F9, F10 and F11 followed Korsmeyer Peppas model and F5 followed zero order kinetics models. The value of n in Korsmeyer Peppas model showed that the release of the drug from formulation F1, F2, F3, F11, F12 and F13 followed Fick's diffusion (case-1 transport) and F4 and F5followed the non-Fickian diffusion (anomalous transport) [9](Table 4). In 0.1 N HCl for F1to F9 and F11 and F12the best fitted model was Korsmeyer Peppas while F10 and F13 followed Higuchi model, Formulations F1 toF8, F11 and F12 as the value of n<0.49 followed Fick's diffusion (case-1 transport) mechanism and F9, F10 and F13 as the value of n>0.49 followed non-Fickian diffusion (anomalous transport) (Table 5 and 6).

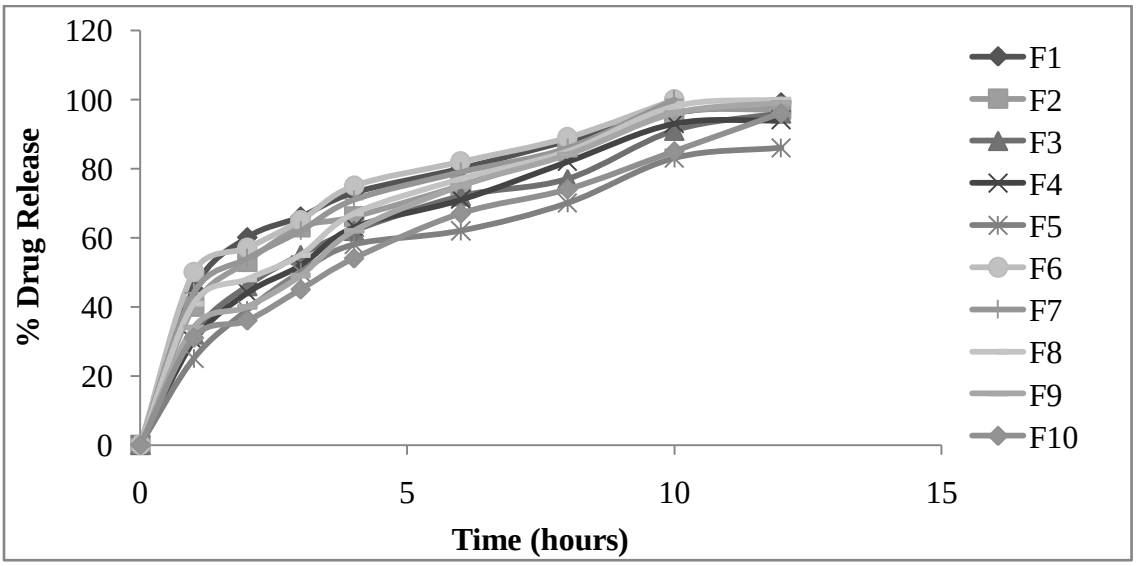

Figure. 1: % Drug release from matrix tablets of Loxoprofen sodium (0.1 N HCl)

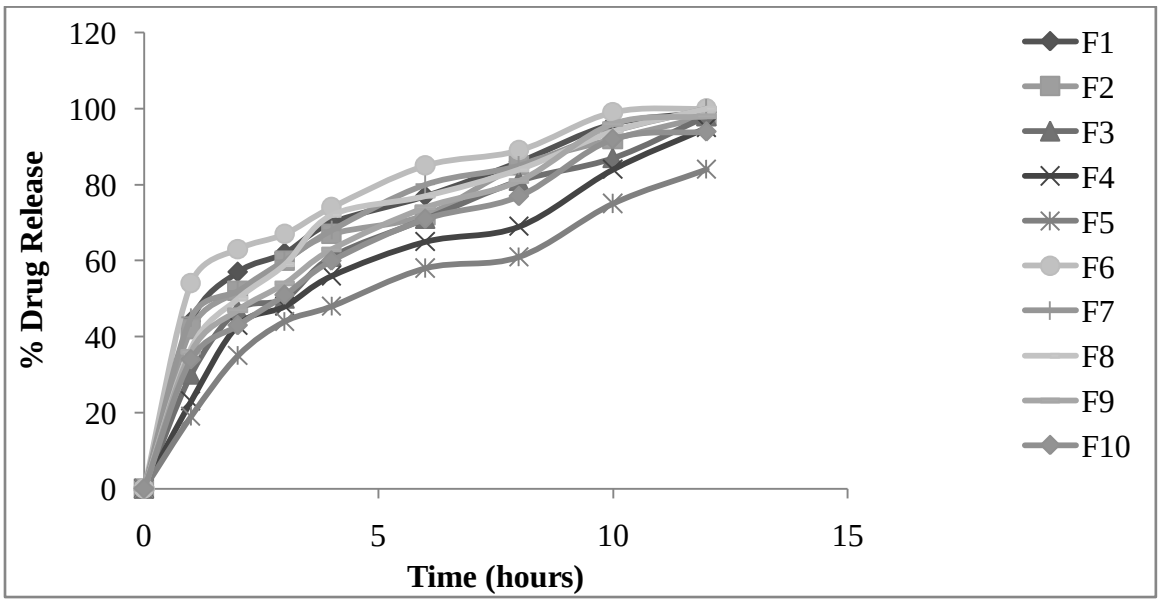

Figure. 2: % Drug release from matrix tablets of Loxoprofen sodium (Distilled water)

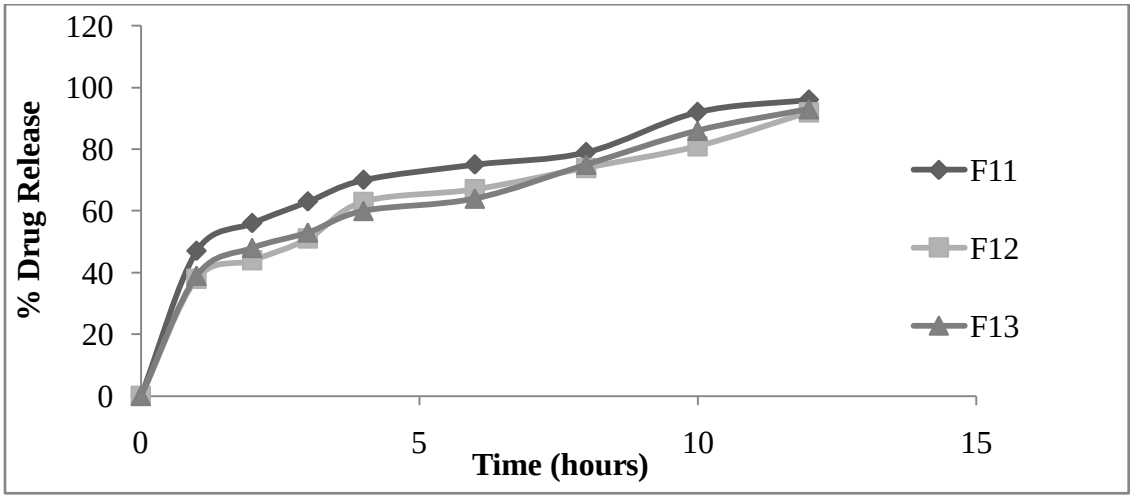

Figure. 3: % Drug release from matrix tablets of Loxoprofen sodium (0.1 N HCl)

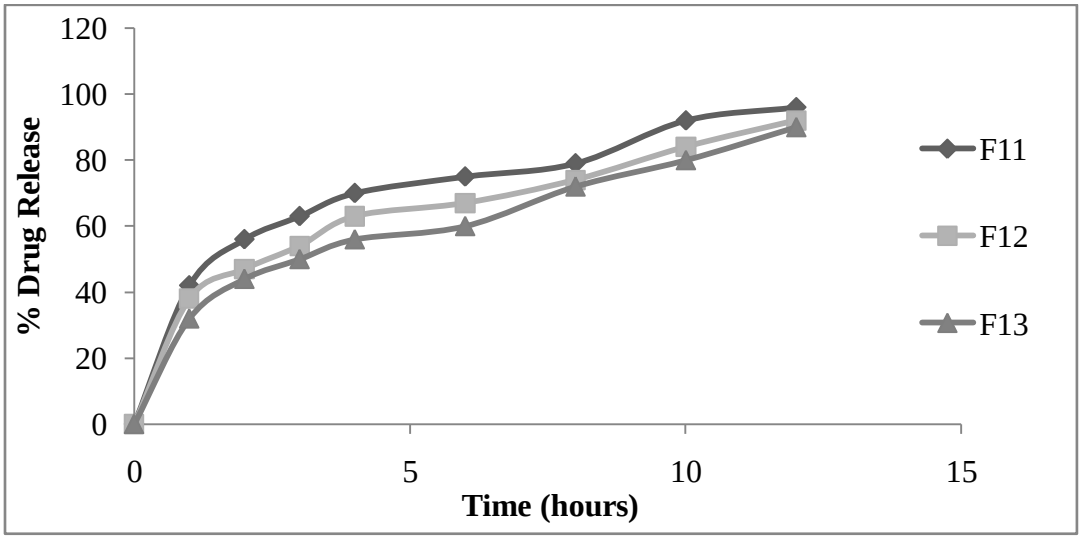

Figure. 4: % Drug release from matrix tablets of Loxoprofen sodium (Distilled water)

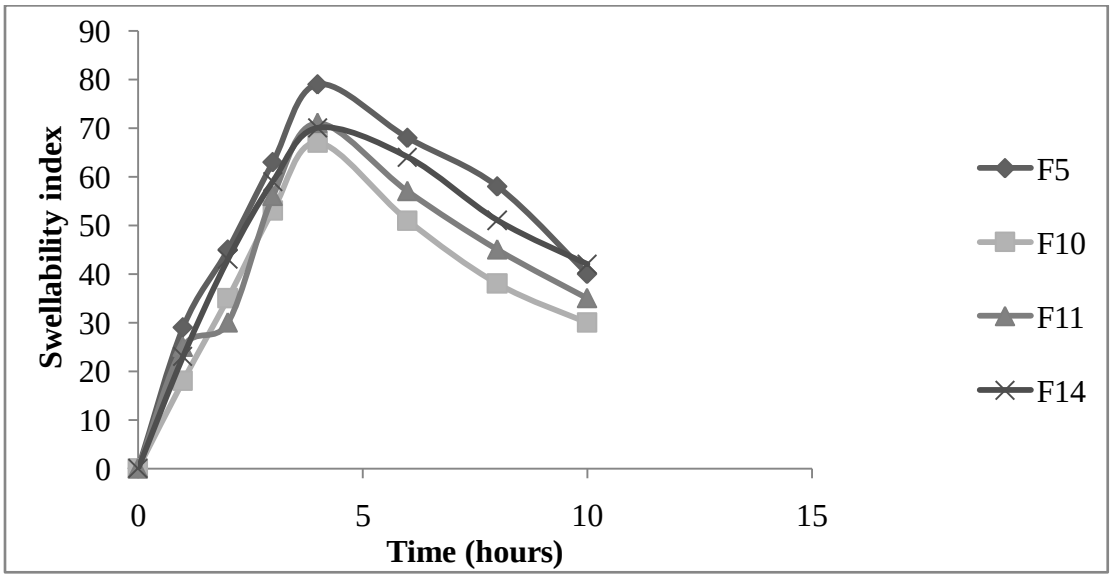

Figure. 5: Swellability index of matrix tablets of Loxoprofen sodium

Table 4: Kinetics modeling of drug release from matrix tablets in distilled water

Kinetics Models		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Zero Order	R^2	0.945	0.96	0.972	0.977	0.992	0.956	0.967	0.931	0.967	0.972	0.96	0.965	0.986
	K_0	4.500	4.808	5.091	5.100	5.383	4.207	4.958	5.308	5.618	5.486	4.187	4.625	4.707
First Order	R^2	0.937	0.937	0.935	0.954	0.949	0.898	0.893	0.89	0.921	0.949	0.928	0.931	0.936
	K_I	0.331	0.286	0.257	0.211	0.170	0.374	0.332	0.326	0.308	0.221	0.217	0.164	0.181
HixonCrowel Cube Route	R^2	0.936	0.926	0.938	0.949	0.982	0.935	0.94	0.879	0.933	0.941	0.934	0.937	0.968
	K_S	0.113	0.093	0.102	0.116	0.119	0.076	0.095	0.106	0.114	0.115	0.081	0.097	0.097
Higuchi Model	R^2	0.996	0.994	0.994	0.99	0.972	0.989	0.995	0.98	0.992	0.99	0.983	0.981	0.983
	K_H	20.98	22.29	23.47	23.40	24.28	19.50	22.91	24.82	25.93	25.23	19.31	21.26	21.41
KorsmeyerPeppas Model	R^2	0.994	0.996	0.995	0.989	0.956	0.987	0.989	0.987	0.994	0.991	0.985	0.977	0.977
	kKp	44.06	40.81	32.11	27.42	22.72	52.02	42.31	39.19	34.92	32.46	45.87	35.46	36.053
	n	0.327	0.349	0.444	0.486	0.523	0.266	0.344	0.379	0.420	0.433	0.289	0.368	0.367

Table 5: Kinetics modeling of drug release from matrix tablets in 0.1 N HCl

Kinetics Models		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Zero Order	R^2	0.944	0.956	0.965	0.954	0.952	0.946	0.933	0.957	0.962	0.987	0.949	0.941	0.969
	K_0	4.449	4.906	5.292	5.527	5.159	4.653	5.086	5.559	5.089	5.753	4.413	4.872	6.684
First Order	R^2	0.922	0.943	0.937	0.949	0.934	0.928	0.929	0.919	0.918	0.897	0.878	0.931	0.944
	K_I	0.328	0.275	0.235	0.225	0.162	0.383	0.389	0.374	0.337	0.189	0.308	0.217	0.232
HixonCrowel	R^2	0.906	0.906	0.864	0.937	0.913	0.922	0.905	0.924	0.928	0.959	0.918	0.894	0.901
Cube Route	K_S	0.128	0.119	0.134	0.151	0.114	0.111	0.097	0.109	0.129	0.129	0.083	0.099	0.157
Higuchi Model	R^2	0.997	0.989	0.992	0.99	0.976	0.987	0.98	0.989	0.987	0.99	0.987	0.988	0.996
	K_H	20.76	22.74	24.45	25.65	23.80	32.792	31.938	30.945	29.723	27.013	20.50	22.74	30.87
Korsmeyer	R^2	0.996	0.993	0.995	0.993	0.983	0.993	0.989	0.991	0.992	0.981	0.991	0.994	0.992
Peppas Model	kKp	48.126	40.362	34.851	30.157	27.838	47.906	43.022	37.698	31.009	26.799	47.713	38.752	21.288
	n	0.295	0.345	0.406	0.427	0.439	0.304	0.346	0.399	0.478	0.504	0.293	0.361	0.607

Swellability index

Swellability was also good and found to be related to the concentration of the polymer and time (Figure 5). Up to 4 hours the swellability increased greatly and after that it went on decreasing as the outer layer of the polymer was begun to dissolve in the media. Tablets formulated with the combinations of the polymers (F11, F12 and F13) also showed good release characteristics but it was observed that release controlling effect of xanthan gum was comparatively better than the pectin.

Swellability of the selected tables was measured and it was observed that tablets with greater polymers concentration showed greater swelling upon hydration. Comparison of different formulation is given in figure 5.

Similarity index

F5 showed comparable results when it was subjected to similarity index calculations. All formulations were compared with F5. F4 showed good comparable results with f_1 15.5 and f_2 55.8. F13 showed f_1 and f_2 19.3 and 50.78 respectively. Other formulations showed greater dissimilarities with the reference formulation.

CONCLUSION

Findings of current study suggested that sustained release matrix tablets of Loxoprofen sodium can be successfully prepared by natural polymers. These polymers can effectively increase the plasma half-life of the Loxoprofen that has very short half-life of 75 mins. Both these polymers and especially xanthan gum has the potential of retarding the release of the drug alone as well as in the combination with pectin. Combination of xanthan gum and pectin in the concentration range 30:10 can effectively prolong the release of the drug. Tablets of Loxoprofen sodium used to treat different pain disorder so sustained release tablets of Loxoprofen sodium can be used to treat the different chronic condition of the pain with better patient compliance.

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