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Research Article

COLLECTION, PURIFICATION AND PHYTOCHEMICAL SCREENING OF A NATURAL GUM FOR ORAL CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

Present study highlighted that sustained release matrix tablet of Indomethacin using gum karaya (GK) as matrix former. Various concentrations of KG used to ensure the release model. Preformulation study of Indomethacin was done initially and results directed for the further course of formulation. Based on preformulation studies different batches of tablet have been prepared by wet granulation method by using selected excipients. Granules were evaluated for various tests before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. Dissolution of batch F1 – F6 were carried out in phosphate buffer pH 6.8 media. *In vitro* dissolution test reveal that is dependent upon the nature and concentration of the polymer. It was concluded that F3, F5 and F6 shown best drug release profile after12 hours i.e. 92.39%, 98.54% and 93.525% respectively and the release seem to obey the Higuchi kinetic model and were finally optimized.

Keywords: Higuchi Model, Gum Karaya (GK), Indomethacin, Matrix Tablet, Sustain release (SR)

Introduction:

The term arthritis means "Joint inflammation", but is generally used to describe inflammatory and degenerative conditions of the joints. Contrary to popular misconception, arthritis is not a disease, which is inevitable with old age, it can affect at any age. Also, there are hundred different kinds of arthritis, the most common of which is the osteoarthritis, rheumatoid arthritis and gout [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and Indomethacin is one of them [2]. It is an indole derivative with high gastrointestinal complications. The short biological half-life (about 2-5 hr) and dosing frequency more than one per day make Indomethacin an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of Indomethacin is desirable. Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system. The present study aims to develop sustained release matrix tablets using hydrophilic natural gum [3], such as gum karaya (GK) as polymer with drug in varying proportions by wet granulation method.

Binders are pharmaceutical excipient that are commonly employed in tablet formulation to impact cohesion on the powder mix and hence improves on the flow properties on the granules. Binders act by causing aggregation of powders thereby forming granules through the process of granulation. They modify the cohesive properties of the granules by promoting the formation of strong cohesive bonds between such particles. Gum is a by-product obtained as a result of metabolic mechanisms of plants. Natural gums are either water soluble or absorb water to form a viscous solution. Natural gums are economic, easily available and found useful as tablet binder. Many gums of natural origin have been incorporated in different dosage forms and being studied for their usefulness not only as a binding agent, but also as a release retardant in the formulation of extended release (ER) or sustained release (SR) dosage forms [4,5]. GK also known as *Sterculia* gum, which is used in this study. It is the

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dry exudate of *Sterculia urens*, *S. villosa* and some species of Cochlospermum. However, in India it is mainly collected from *S. urens* and *S. villosa*.

Materials and Methods

Materials

The drug Indomethacin was a gift sample by the Zydus Cadila, Baghekhola, East Sikkim. GK was collected from Sterculia tree in Majhitar, East Sikkim.

Purification of gum

The size reduction and air floatation of loose bark ensure purification to a certain extent. Sand particles are removed by gravity. The gum is then soaked in water for 5-6 hours, boiled for 30 minutes (in case of high concentrations gum will solubilize by cooking under steam pressure) and left to stand for 1 hour to allow complete extraction into the water. The gum was filtered using a multi-layered muslin cloth bag to further remove the dirt and foreign matter from the solution. Acetone (three times the volume of filtrate) was added to precipitate the gum. The gum was separated, dried in an oven at 35^0C, collected, ground, passed through a # 80 sieve and store in desiccators at 30^0C.

FORMULATION DESIGN OF TABLET

Table-1 Formulation of Indomethacin SR tablet with GK (F1-F6).

Sl. No.	Ingredients (mg)	Formulations					
		F1	F2	F3	F4	F5	F6
1.	Indomethacin	150	150	150	150	150	150
2.	Binder (Gum)	7.5	8	8.5	9	9.5	10
3.	Starch	60	60	60	60	60	60
4.	Lactose	275	274.5	274	273.5	273	272.5
5.	Magnesium stearate	5	5	5	5	5	5
6.	Talc	2.5	2.5	2.5	2.5	2.5	2.5

All the batches contained 0.5% w/w talc and 1%w/w magnesium stearate
Total weight of each tablet = 500mg

Preparation of Granules

Wet granulation method was used to prepare granules of drug. The formulations were developed by using Indomethacin as model drug at different ratios of binder : diluent concentrations. All ingredients were dry mixed manually in mortar and water is used as granulating fluid. The wet mass was granulated by passing them manually through a number 12 mesh sieve. Granules were dried at 50°C in hot air oven and again re-sieved through number 16 mesh sieves. Talc and magnesium stearate are then added to the prepared granules.

Evaluation of Granules

Angle of repose [6]**:** The static angle of repose (θ), was measured according to the fixed funnel and free standing cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation:

tan θ= h/r

Where, h = height of pile,
θ = angle of repose,
r = radius of base pile

Table: 2 Specification of Angle of Repose

Angle of repose (degrees)	Type of flow
<20	Excellent
20 – 30	Good
30 - 34	Passable
>40	Very poor

Bulk and tap densities: 2 g quantity each of the powder sample was placed in a 10 ml measuring cylinder and the volume, V_0, occupied by each of the samples without tapping was noted. After 100 taps on the table, the occupied volume V_t was read. The bulk and tap densities were calculated as the ratio of weight to volume (V_0 and V_t respectively).

Bulk density (D_b) = M/V_0

Where M = mass of powder

This was done thrice, from that average bulk density and standard deviation was calculated.

Tapped density (D_t) = M/V_t

This was done thrice, from that average tap density and standard deviation was calculated.

Hausner's index: This was calculated as the ratio of tapped density to bulk density of the samples.

Hausner's ratio = D_t/D_b

Compressibility index (C %): This was calculated using the equation:

%Compressibility (Carr's index) = $D_t - D_b / D_t$ x 100

Evaluation of tablet formulations

Determination of hardness of tablets [7]:

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Monsanto hardness tester.

Determination of friability [7]:

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed

and the percentage loss in tablet weight was determined.

% loss = Initial wt. of tablets - Final wt. of tablets x 100

Initial wt. of tablets

Determination of thickness of the tablets [7]:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauze on 3 randomly selected samples.

Weight variation [8]:

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the (Table 7) and none deviates by more than twice that percentage.

Determination of drug content in tablets:

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder equivalent to 10 mg drug was dissolved in 10 ml of 0.1N NaOH and the volume was made upto 100 ml with pH 6.8 phosphate buffer. The solution was shaken for 1 h and kept for 24 h. From the stock solution, 1 ml solution was taken in 10 ml volumetric flask and the volume was made with pH 6.8 phosphate buffers. Solution was filtered and absorbance was measured spectrophotometrically at 320 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Determination of disintegration time of tablets:

Disintegration is defined as the state in which no residue of the tablet or capsule remains on the screen of the apparatus, or if a residue remains, it consist of a fragment of insoluble coating of the tablet or capsule shells or is a soft mass with no palpable core. *In vitro* disintegration time of 6 tablets from each of the formulation was determined by using a digital tablet disintegration apparatus. *In vitro* disintegration was carried out at 37 ± 2°C in 900 ml phosphate buffer pH 6.8.

***In-vitro* drug release study**

In vitro drug release was studied using Electrolab Dissolution Apparatus (Electrolab TDT-08L, USP), in 900 ml phosphate buffer pH 6.8, maintained at 37±1°C for 12 hours, at 100 rpm. 5ml of sample was withdrawn after specified time interval, and was replaced by an equal volume of fresh dissolution medium. Collected samples were analyzed spectrophotometrically at measured wavelength of 320 nm, and cumulative percent drug release was calculated. The test was performed in triplicate to assure significance of results. Drug release profile was studied using percentage drug release vs time (hours) plot.

Kinetic studies

The dissolution data were subjected to release kinetic study. Drug dissolution from solid dosage form has been described by kinetic models in which the dissolved amount of drug (Q) is compared to the function of the test time (t). Some analytical definitions of the Q versus t are commonly used, such as Zero order, First order, Weibull, Higuchi and Korsmeyer-peppas kinetic models.

Zero order release kinetics [9]:

It defines a linear relationship between the fractions of drug release versus time,

$Q = K_0 t$..... (1)

Where Q is the fraction of drug release at time t and K_0 is the zero order release rate constant. A plot of fraction of drug release against time will be linear, if the release obeys Zero order release kinetics.

First order release kinetics [10]:

Assuming that the exposed surface area of a tablet decreases exponentially with time during dissolution process; suggest that drug release from most of the slow release tablets could be described adequately by apparent first order kinetics. The equation that describes first order kinetic is

$\ln (1-Q) = -K_1 t$..... (2)

Where Q is the fraction of drug released at time t. and K_1 is the first order release rate constant. A plot of the logarithm of the fraction of the drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi kinetic model [11]:

It defines a linear dependence of the active fraction released per unit of square root of time.

$Q = K_2 t^{1/2}$..... (3)

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law square root time dependent.

Power law (Korsmeyer and Peppas equation) [12]:

In order to define a model, which would represent a better value for the dissolution data was further analyzed by Korsmeyer Peppas and equation.

$\text{Log } M_t / M_\infty = n \text{ Log } t + \log k$..... (4)

Where Mt is the amount of drug released at time t and $M\alpha$ is the amount released at timeα, thus the M_t/M_∞ is the fraction of drug released at time t, K is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvents penetration and drug release can be used as abstracted. A plot between log of M_t/M_∞ against log of time will be linear if the release obeys and Korsmeyer-peppas equation and the slope of this plot represent n value. This enables the interpretation of diffusion exponent and solute release mechanism for cylindrical shape release mechanism from polymeric film.

Result and discussion

Standard curve of Indomethacin

Standard curve of Indomethacin was prepared using Phosphate buffer pH 6.8 as a medium.

Table: 3 Standard curve readings for Indomethacin.

Sl. No.	Concentration (µg/ml)	Absorbance (nm)
1.	0.0000	0.0000
2.	1.0000	0.0220
3.	2.0000	0.0420
4.	3.0000	0.0630
5.	4.0000	0.0840
6.	5.0000	0.1050

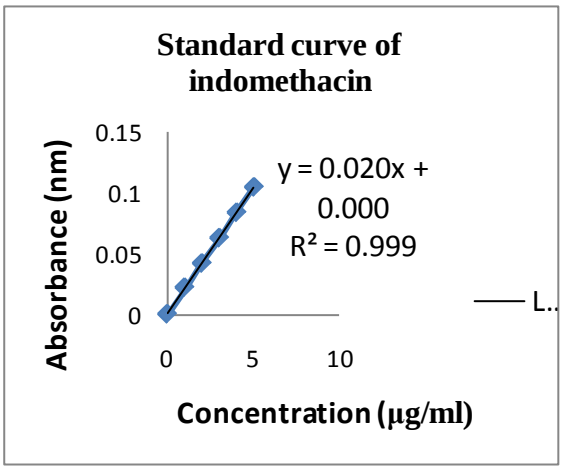

Figure 1: Standard curve of Indomethacin.

Drug polymer interaction study

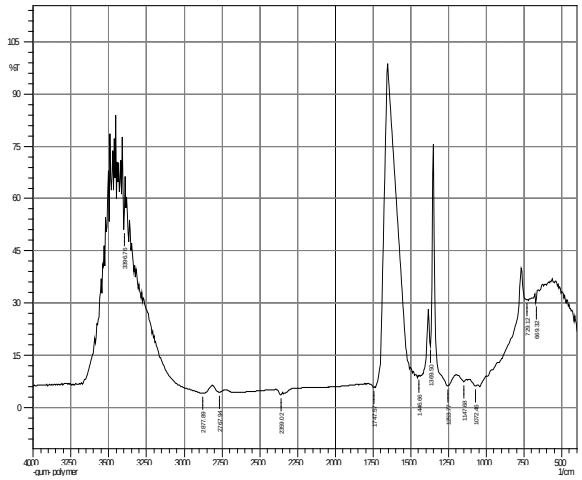

Figure 2: FTIR spectra of polymer (GK).

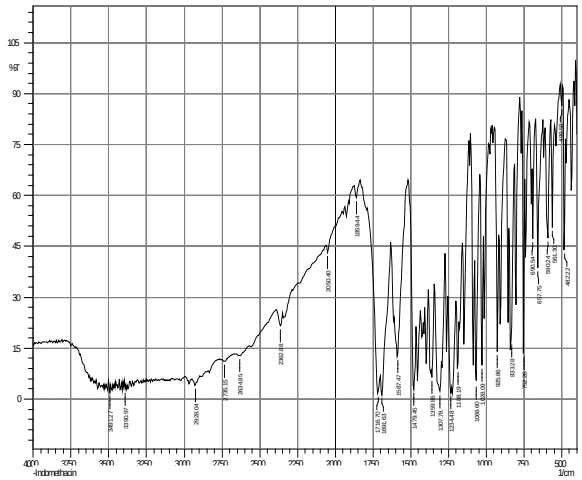

Figure 3: FTIR spectra of pure drug (Indomethacin).

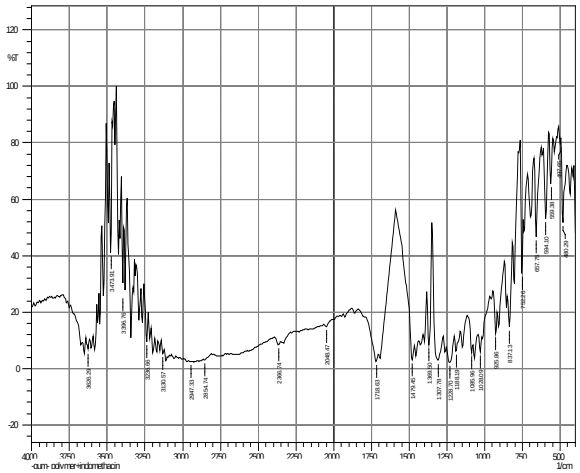

Figure 4: FTIR spectra of (Indomethacin + GK)

Table: 4 Functional groups of Indomethacin.

Functional groups	Band cm^{-1}
C=O Stretching	1600 - 1750
-OH Stretching	2400
-CH of alkane	2850
-Cl	600 - 700

Evaluation of granules

Table: 5 Evaluation of granules prepared from GK (F1-F6).

Sl No.	Parameters	Formulation					
		F1	F2	F3	F4	F5	F6
1.	Bulk density (gm/cc)	0.336	0.316	0.353	0.329	0.368	0.666
2.	Tapped density (gm/cc)	0.386	0.364	0.424	0.371	0.396	0.741
3.	Angle of repose (θ)	28.572	29.744	27.6257	26.26	25.9637	25.873
4.	Compressibility index (C%)	12.9534	13.157	16.666	11.111	7.142	10.00
5.	Hausner's ratio	1.148	1.151	1.2	1.125	1.076	1.111

Table: 6 Evaluation of tablets

Formulations	% Friability	Drug content (%)	Hardness (kg/cm²)	Thickness (mm)	Disintegration time (hrs)
F1	1.566 ± 0.04	98.87 ± 0.12	4.1 ± 0.01	4.1 ± 0.012	02:45
F2	1.882 ± 0.03	99.4 ± 0.40	4.0 ± 0.23	4.1 ± 0.025	03:30
F3	1.464 ± 0.02	99.53 ± 0.30	4.47 ± 0.35	4.2 ± 0.03	04:14
F4	3.292 ± 0.02	99.67 ± 0.16	4.45 ± 0.13	4.3 ± 0.02	04:49
F5	1.437 ± 0.06	100 ± 0.02	4.90 ± 0.21	4.12 ± 0.01	05:28
F6	0.808 ± 0.10	99.8 ± 0.11	5.45 ± 0.16	4.2 ± 0.021	06:30

In-vitro release kinetic studies

Table 7: Zero order kinetic model F1 to F6.

Time (hrs)	Percentage cumulative drug release (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	19.01408	6.94165	29.23644	25.88629	19.2	17.1
2	25.75956	16.33635	39.34528	35.66221	35.20667	33.095
3	34.85077	23.9336	56.88212	43.54181	37.995	36.48333
4	38.82461	31.21898	78.68051	44.48829	38.31	41.30167
5	41.56271	40.61536	76.69123	52.3194	57.81167	55.42833
6	46.40677	43.98726	82.10482	52.66388	63.92	63.60667
7	56.39336	55.1727	82.43637	59.28763	71.75333	69.05167
8	61.57948	60.06372	84.3704	72.26756	86.79667	79.88167
9	66.73877	65.52314	87.50469	77.45652	90.78	89.54167
10	70.99262	70.6841	88.11654	84.70903	96.20167	90.795
11	75.24145	73.73072	90.71132	86.25418	97.73167	92.00167
12	74.96311	76.46378	92.39384	87.76756	98.54	93.525

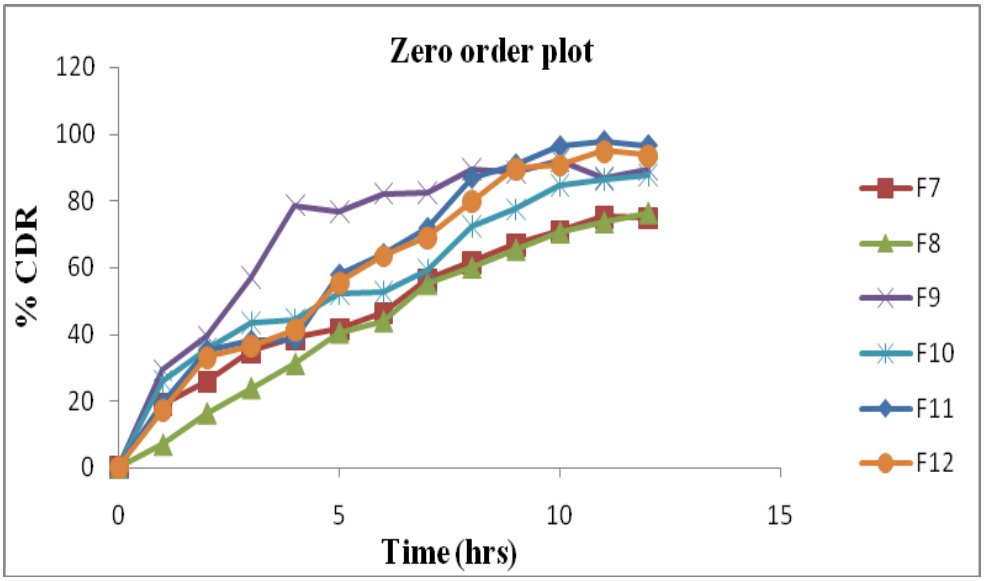

Figure 6: Zero order release kinetic for formulation F1 to F6.

Table 8: First order release kinetic model of F1 to F6.

Time (hrs)	Log of %Amount remaining to be absorbed					
	F1	F2	F3	F4	F5	F6
1	1.908409	1.968755	1.84981	1.869899	1.907411	1.918555
2	1.870641	1.922537	1.782865	1.808466	1.81153	1.825459
3	1.813909	1.881193	1.634657	1.751727	1.792427	1.802888
4	1.786577	1.837469	1.328777	1.744385	1.790215	1.768626
5	1.76669	1.773674	1.367519	1.678342	1.625192	1.649059
6	1.72911	1.748287	1.252736	1.675193	1.557267	1.561022
7	1.639553	1.651543	1.244614	1.609726	1.450967	1.490637
8	1.584563	1.601368	1.026517	1.442988	1.120684	1.303592
9	1.521938	1.537528	1.060521	1.353021	0.964731	1.019462
10	1.462508	1.467103	0.896717	1.184435	0.579593	0.964024
11	1.393725	1.419448	1.123482	1.138171	0.355707	0.698825
12	1.39858	1.371737	1.025558	1.087513	0.539076	0.81124

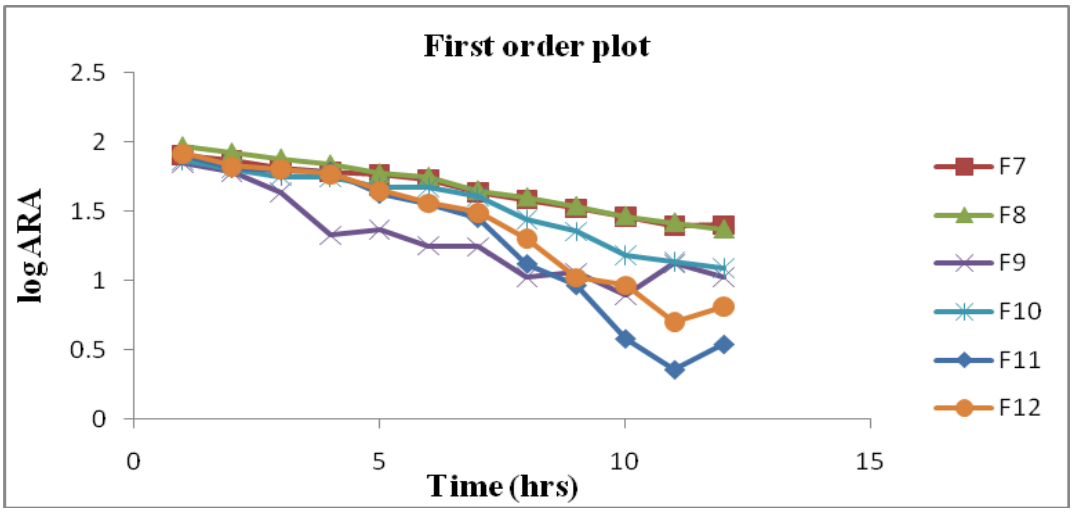

Figure 7: First order release kinetic for formulations F1 to F6.

Table 9: Higuchi's release kinetic model of F1 to F6.

√Time	Percentage cumulative drug release (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	19.01408	6.94165	29.23644	25.88629	19.2	17.1
1.414214	25.75956	16.33635	39.34528	35.66221	35.20667	33.095
1.732051	34.85077	23.9336	56.88212	43.54181	37.995	36.48333
2	38.82461	31.21898	78.68051	44.48829	38.31	41.30167
2.236068	41.56271	40.61536	76.69123	52.3194	57.81167	55.42833
2.44949	46.40677	43.98726	82.10482	52.66388	63.92	63.60667
2.645751	56.39336	55.1727	82.43637	59.28763	71.75333	69.05167
2.828427	61.57948	60.06372	89.3704	72.26756	86.79667	79.88167
3	66.73877	65.52314	88.50469	77.45652	90.78	89.54167
3.162278	70.99262	70.6841	92.11654	84.70903	96.20167	90.795
3.316625	75.24145	73.73072	86.71132	86.25418	97.73167	95.00167
3.464102	74.96311	76.46378	89.39384	87.76756	96.54	93.525

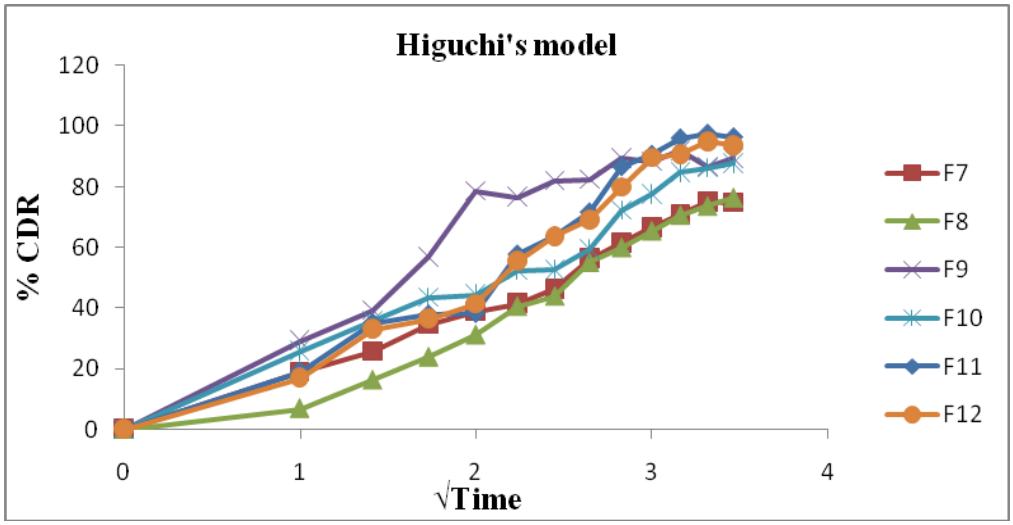

Figure 8: Higuchi's release kinetic for formulation F1 to F6.

Table: 10: Korsmeyer-peppa's kinetic model of F1 to F6.

Log time	Log M_t/M_∞					
	F1	F2	F3	F4	F5	F6
0	-0.72092	-1.15854	-0.53408	-0.58693	-0.71525	-0.76555
0.30103	-0.58906	-0.78684	-0.40511	-0.44779	-0.45193	-0.47879
0.477121	-0.45779	-0.62099	-0.24502	-0.36109	-0.41882	-0.43646
0.60206	-0.41089	-0.50558	-0.10413	-0.35175	-0.41524	-0.38258
0.69897	-0.3813	-0.39131	-0.11525	-0.28134	-0.23653	-0.25482
0.778151	-0.33342	-0.35667	-0.08563	-0.27849	-0.19291	-0.19505
0.845098	-0.24877	-0.25828	-0.08388	-0.22704	-0.14271	-0.15938
0.90309	-0.21056	-0.22139	-0.04881	-0.14106	-0.06005	-0.0961
0.954243	-0.17562	-0.18361	-0.05303	-0.11094	-0.04056	-0.04652
1	-0.14879	-0.15068	-0.03566	-0.07207	-0.01537	-0.04049
1.041393	-0.12354	-0.13235	-0.06192	-0.06422	-0.00851	-0.02082
1.079181	-0.12515	-0.11654	-0.04869	-0.05667	-0.01384	-0.02762

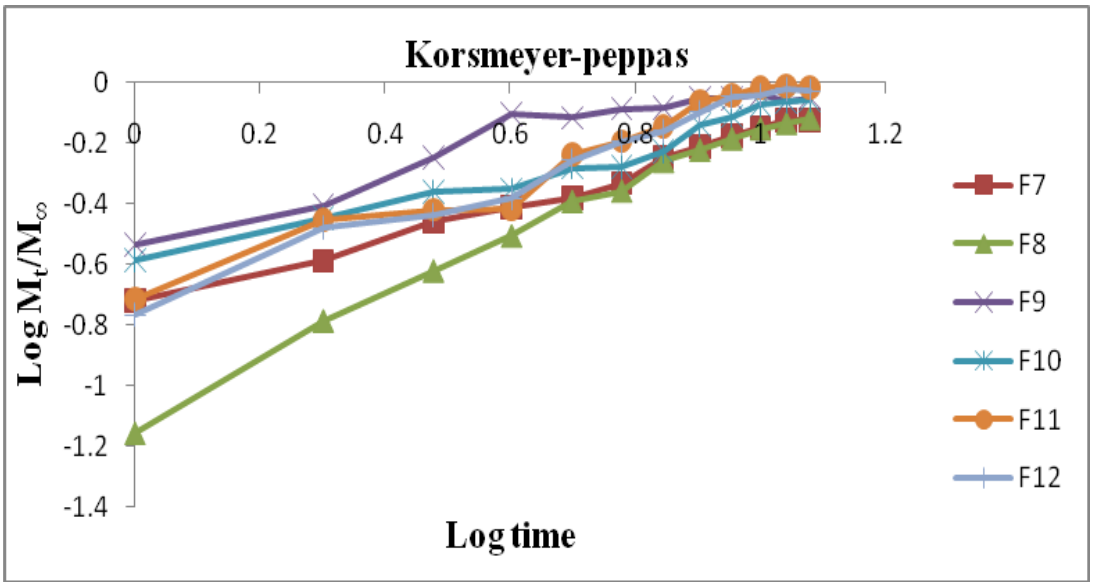

Figure 9: Korsmeyer-peppas release kinetic for formulations F1 to F6.

Table 11: Results obtained for zero order and first order release kinetic (F1-F6)

Gum %	Zero order model			First order model		
	Slope (n)	Rate constant K_0 = slope	R^2	Slope (n)	K_1	R^2
F1	5.867	5.867	0.959	-0.050	0.115	0.981
F2	6.467	6.467	0.980	-0.056	0.1289	0.993
F3	6.356	6.356	0.740	-0.078	0.1796	0.838
F4	6.532	6.532	0.941	-0.074	0.1704	0.941
F5	8.160	8.160	0.953	-0.148	0.3408	0.912
F6	7.864	7.864	0.959	-0.115	0.264	0.941

Table 12: Higuchi and Korsmeyer-peppas kinetic model for all formulations

Gum %	Higuchi's		Korsmeyer-peppas	
	Slope (n)	R^2	Slope (n)	R^2
F1	0.042	0.982	0.582	0.986
F2	25.21	0.951	0.958	0.989
F3	27.27	0.913	0.464	0.899
F4	0.038	0.975	0.504	0.965
F5	0.030	0.957	0.681	0.965
F6	0.031	0.968	0.700	0.982

Table 13: n-values obtained according to Korsmeyer-peppas kinetic model

Formulations	'n' values	Type of Transport
F1	0.582	Non-Fickian
F2	0.958	Non- Fickian anomalous
F3	0.464	Fickian diffusion
F4	0.504	Fickian diffusion
F5	0.681	Non-Fickian
F6	0.700	Non-Fickian

Summary

Calibration curve was done in a single medium i.e. phosphate buffer pH 6.8. The R^2 value was found to be 0.999.

During preformulation study FTIR (Fourier Transform Infrared) study of the pure drug (Indomethacin) alone and in combination with polymers (GK) study carried and shown in figure 2-4. Major frequencies of functional groups (Shown in table-3) of pure drug remained unchanged in presence of polymers. Hence there is no major interaction between the drug and the polymers used in the study.

The granules of different formulations were evaluated for Angle of repose, Bulk density, Tapped density and Compressibility index and Hausner's ratio were calculated. The granule indicated good flowability with an angle of repose values ranging from 25 - 29^0. Result shown in table 4.

The bulk and tapped density of the granules of all the formulations (F1 to F6) were within the range from 0.316 g/cm^3 to 0.666 g/cm^3 and 0.364 g/cm^3 to 0.741 g/cm^3 respectively and shown in table-5. The compressibility index (Carr's index) for all the formulations was found to be below 17%, indicating desirable properties.

All the tablets were subjected to various evaluation parameters and the result shown in the table no-6. The weight variation test indicated that all the tablets were uniform with low standard deviation values. The tablets' mean thickness

values ranged from 4.1±0.012 to 4.3 ± 0.02 mm. The hardness of all the tablets was within a range of 4.0±0.23 to 5.45±0.16 kg/cm^2. The loss in total weight in friability test was in a range of 0.808±0.10 to 3.292±0.02%. The percentage drug content for different tablet formulations varied from 98.87±0.12 to 100±0.02 % was found to be within the limit which indicated uniform distribution of drug in all formulations and disintegration time ranges from 2 hrs 45 min to 6 hrs 30 min (Table-5).

All batches of formulations were subjected to dissolution study at pH 6.8 phosphate buffer. The release profile of all formulations was shown to graph (Figure 6-9) for Zero order, First order, Higuchi and Korsmeyer-peppas model respectively. Simple visual observation of the percent cumulative drug release versus time plot shows an initial burst effect. From all the formulation near about 20-30% of the loaded drug was released within the first 1 hour of the dissolution study. This initial amount of drug release can be attributed to the immediate release layer of the formulation. Further release of the drug was studied for 12 hours.

Three formulations F3, F5 and F6 were found to have the best drug release towards the end of 12 hours i.e. 92.39%, 98.54% and 93.525% respectively. At an overall consideration it was observed that all the formulations seem to follow Higuchi kinetics as the values were more nearer to unity. In order to verify the release pattern, the Korsmeyer-peppas had been employed. While highlighting these three formulations (F3, F5 and F6) the regression coefficients according to zero order, first order kinetic and Higuchi models were found to be 0.740, 0.838, 0.913 and 0.953, 0.912, 0.957 and 0.959, 0.941, 0.968 respectively. Therefore, the release seem to obey the Higuchi kinetic model (Table-12.). The Korsmeyer-peppas release exponent (n) for the formulation F3, F5 and F6 was 0.464, 0.681 and 0.700 respectively, indicating release governed by the Fickian diffusion for F3 and Non-Fickian diffusion for F5 and F6 (Table 13).

Conclusion

Indomethacin is a non-steroidal anti-inflammatory drug with analgesic property which is used for the better treatment of arthritis. Moreover, the site of absorption of Indomethacin is in the intestine and has a short half life of 2 to 5 h. Therefore, the present investigation was concerned with the development of the sustained release matrix tablets, which after oral administration were designed to prolong the duration of action. Various formulations were

developed by using release rate controlling and gel forming polymer like GK by wet granulation method. Different proportion of GK was associated with decrease in the overall cumulative drug release rate. The higher viscosity polymer had been seen to inhibit the initial

burst release of Indomethacin. Thus, we conclude that from among all the developed formulations, F3, F5 and F6 formulations sustained the drug release for longer period of time over 12 h when compare to other formulations. So, F3, F5 and F6 were selected as the best formulation. From the result, it is evident that GK by forming a matrix retards the release rate of drug from the tablet be used as sustained release dosage form. Thus, the objective of the present work was formulating a sustained release dosage form of Indomethacin by using different proportions of release rate controlling and gel forming natural polymer has been achieved with success. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product.

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