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Sustained release matrix tablets of indomethacin using *Hibiscus rosa-sinensis* as release retardant

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ABSTRACT

In the present investigation an attempt has been made to study the formulation and evaluation of matrix tablets of indomethacin using mucilage ofHibiscus rosa-sinensis as a release retardant. The mucilage was extracted from the leaves of Hibiscus rosa-sinensis using acetone. The matrix tablets were formulated using different concentrations (0.15, 0.3 and 0.45) of Hibiscus mucilage. The developed formulations of tablets were evaluated for pre-compression and post-compression parameters. The results of pre-compression parameters likebulk density, tapped density, Carr's index and Hausner's ratio were found to be within the limits indicating good flow properties of the granules.Swelling index reveals that with increasing mucilage concentration there is increased swelling showing 68% for F3 at the end of 5 hwhere as for F1 and F2 it was around 58.3 % and 66.66 % respectively. In-vitro drug release for F3 formulation was found to be 62.86 % at the end of 8 h. With increase in mucilage concentration the drug release from the matrix tablets got retarded. In-vitro drug release data obtained were fitted to various release models access the possible mechanism of drug release.All the formulations showed matrix (Higuchi Matrix) as a best fit model and the release mechanism was found to be Fickian Difussion. Thus, Matrix tablets of indomethacin formulated by using Hibiscus mucilage as a release retardant could be employed for retardant drug release.

Key words: Indomethacin, *Hibiscus rosa-sinensis*, Mucilage, matrix tablets.

INTRODUCTION

The oral route of administration has received maximum attention with respect to research on physiological and drug constraints as well asdesign and testing of products. This is because there is more flexibility in dosage form design for the route than for other routes. Patient compliance of the oral route is quite high and it is relatively safe route of administration [1].Introduction of

matrix tablets as sustained release has given a new break through for novel drug delivery in field of pharmaceutical technology [2].Sustained release (SR) drug delivery systems are developed to modulate the release of drug, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance [3].

Indomethacin is non-steroidal anti-inflammatory agent with antipyretic and analgesic properties. It is a nonselective inhibitor of cyclooxygenase (COX) 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. It has been used in the symptomatic management of painful and inflammatory conditions. Usual initial dose by mouth in musculoskeletal and joint disorder is 25 mg two or three times daily with food. To alleviate night pain and morning stiffness, 100 mg may be administered by mouth. The half-life of the drug is 4.5h. Therefore,Indomethacin was selected as a model drug for this study [4].

Presently the use of natural gums and mucilages is gaining importance in pharmaceutical formulations as valuable excipient. Natural plant based materials are economical, devoid of side effects, biocompatible, biodegradable, renewable source, environmental-friendly Processing and better patient compliance [5].*Hibiscus rosa-sinensis*, (Malvaceae family) commonly known as China rose is a popular landscape shrub, creates a bold effect with its medium-textured, glossy dark green leaves with 4-6 inch wide and up to 8 inch long, showy flowers, produced throughout the year and grows upto 7-12 feet [6].Mucilages are polysaccharide complexes formed from sugarand uronic acid units. Mucilages form slimy masses in water, are typically heterogeneous in composition[7]. Hence, the present study was planned to formulate sustained release matrix tablets using *Hibiscus rosa-sinensis* mucilage as a release rate retardant.

MATERIALS AND METHODS

Indomethacin YarrowChemicals(Mumbai). *Hibiscusrosa-sinensis*(Bangalore). Microcrystalline cellulose (Avicel) and Magnesium stearate (Central drug house Pvt. Ltd). All other chemicals were of AR (analytical reagent) grade.

Extraction of mucilage

The fresh leaves of *Hibiscus rosa-sinensis* were collected and washed repeatedly with water. The leaves were then crushed and then kept for soaking for 5-6 h. The leaves were boiled for 30 min and left to stand for 1 h for complete release of the mucilage. The mucilage was extracted using a muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of the filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 35°C, collected, grounded, passed throughsieve no #80 and stored in a dessicator at 35°C and 45% relative humidity till use[8].

Preparation of matrix tablets

Sustained release matrix tablets of indomethacin with *Hibiscus rosa-sinensis* leaves mucilage were prepared using different drug: mucilage ratios viz.,1:0.15, 1:0.3 and 1:0.45. (Table1)*Hibiscus rosa-sinensis* leaves mucilage was used as matrix forming material while

microcrystalline cellulose as a diluent and Magnesium stearate as a lubricant. All ingredients were passed through sieve #100, weighed and blended. The granules were prepared by wet granulation technique and compressed by using 6mm flat faced punches in a rotatory tablet punching machine[9].

Table 1:Formula for matrix tablets of Indomethacin using mucilage of *Hibiscus rosa-sinensis*leaves

Formula	Formulations		
	F1(mg)	F2 (mg)	F3(mg)
Indomethacin	100	100	100
Mucilage	15	30	45
Avicel	130	115	100
Magnesium stearate	5	5	5
Total tablet weight	250	250	250

Evaluation of tablet blend

Bulk density: Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is.

Tapped density: Tapped density was determined by USP method II using tapped density tester (Electrolab tap density tester, USP,ETP-1020)

Angle of Repose:The flow property of the powder blend was determined by fixed funnel method.

Carr's index and Hausner ratio: This was measured for the flow property of a powder to be compressed; as such they are measured for relative importance of inter-particulate interactions [10].

Evaluation of matrix tablet

Weight variation:Twenty tablets were randomly selected from each batch individually for the average weight and standard deviation of 20 tabletswas calculated as per IP specification for weight variation.

Thickness: The thickness of the tablet was measured by using screw gauge, Twenty tablet from each batch were randomly selected and thickness were measured.

Hardness: Hardness was measured using Pfizer hardness tester, tablet from each batch and measured in kg/cm^2.

Friability: Ten tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighedto check that the variation is less than less than 1% [11].

Drug content uniformity

This test is performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equal to 250 mg of indomethacin was dissolved in phosphate buffer pH 7.2 in

100ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 265.5 nm using phosphate buffer pH 7.2 as blank and the % drug content was estimated [12].

Swelling index

The swelling index of the formulation was carried out by taking one tablet from each batch and placed in a petridish containing phosphate buffer pH 7.2 At the end of 1h, the tablet was withdrawn, kept on a tissue paper and weighed. The weighing carried out for a period of 5h [13].

***In-Vitro* dissolution Study**

The study was carried out in 900 ml of phosphate buffer pH 7.2 at 75 Rpm, which was maintained at 37^{o}C ±0.5^{o}C using the USP apparatus type II (Electrolab Disso 8000).5 ml samples were withdrawn at regular intervals of 1 hr and the absorbance was measured at 265.5nm using Shimadzu UV spectrophotometer 1700. Sink condition was maintained by replacing with fresh buffer medium. Thedissolution study was carried out for 8 hrs followed by mathematical treatment of the solved dissolution data [14].

RESULTS AND DISCUSSION

The extracted mucilage of *Hibiscus rosa-sinensis* was studied for the desired physical properties and results are shown in **Table 2**. Matrix tablet each containing 100 mg of Indomethacin were prepared using dried mucilage of *Hibiscus rosa-sinensis* leaves in various ratio of 1:0.15, 1:0.3, 1:0.45 (drug: mucilage).

Table 2: Flow properties of dried *Hibiscus rosa-sinensis* leave mucilage

PARAMETERS	VALUE
Bulk density(g/ml)	0.42
Tapped density(g/ml)	0.44
Carr's index (%)	4.54%
Hausner's ratio	1.047
Angle of repose (□)	23°14'

The pre-compression parameters of granules analysis likebulk density, tapped density, Carr's index, Hausner's ratio and results are shown in **Table 3**. The bulk density and tapped density ranged from 0.92 to 0.45 g/ml and 1.3 to 1.05 g/ml. Carr's index and Hausner's ratio ranges from0.58 to 0.33 and 2.4 to 1.5 respectively indicating good flowability of granules. Post compression parameters like thickness, hardness, friability and drug content are shown in **Table 4**. Hardness and friability ranged from 5.8 to 6.8 kg/cm^2 and 0.8 to 0.4%.

Table 3: Pre-compression parameters of the granules

Formulation Code	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)	
					Without glidant	With glidant
F1	0.92	1.375	0.33	1.5	15 θ 26'	14 θ 37'
F2	0.45	1.08	0.58	2.4	17 θ 28'	15 θ 36'
F3	0.515	1.05	0.559	2.03	18 θ 17'	17 θ 25'

Table 4: Post-compression parameters of tablets

SI. NO	Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	F1	3.75	5.8	0.4	82
2	F2	3.70	6.2	0.8	90
3	F3	3.64	5.7	0.4	96

Drug content was ranging from 82% to 96%.Swelling index for the formulations F1, F2 and F3 were found to be 58.3 %, 66.66 % and 68% respectively (**Figure 1)**. *In-vitro* release profile of indomethacin matrix tablets showed sustained release pattern with the maximum release of 78.74 % for formulation-1 for 8 h and considerable decline in drug with increase in mucilage concentration (**Figure 2**). Thus, with increased concentration of mucilage, drug release also decreased.

Figure 1: Swelling index of formulations F1, F2 and F3

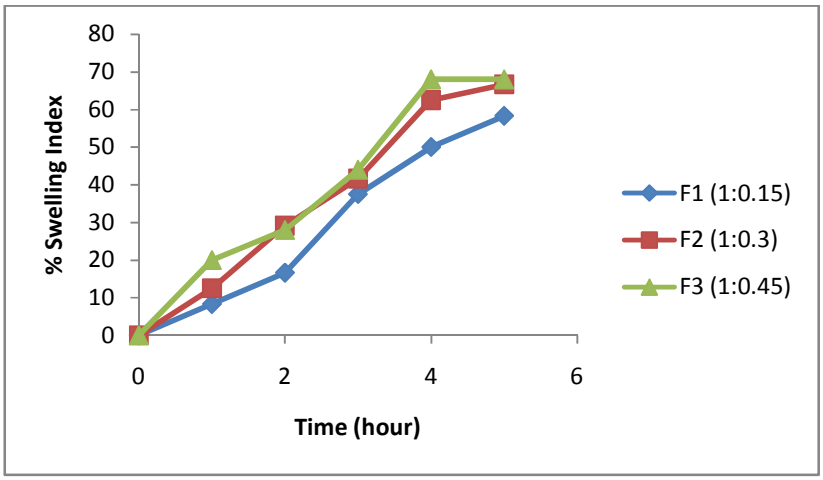
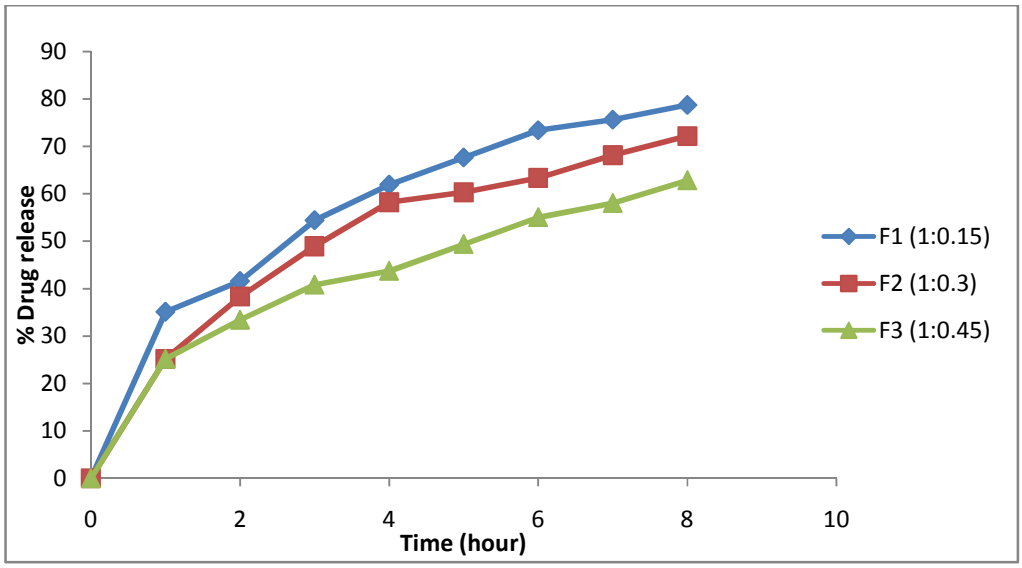


Figure 2: *In-vitro* drug release studies of formulations F1, F2 and F3

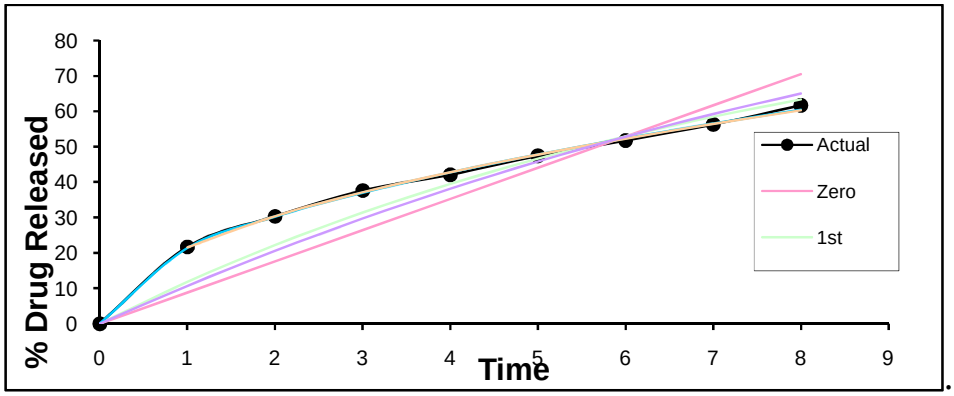


The *In- vitro* drug release data were fitted to release kinetics. The predicted drug release mechanism by PCP Disso V3 software indicated that all the formulations showed R^2 value between 0.9931-0.9995. Formulation F3 showed R^2 value of 0.9995 and k value of 21.3978.The regression coefficient values for formulations F1, F2 and F3 were shown in **Table 5**.This predicted that the drug release mechanism was by Matrix model where the drug release could be by diffusion process. The release kinetics of formulation F3 was shown in **Figure 3**.

Table 5: Release kinetics of formulations F1, F2 and F3

Form. Code	Release kinetics									
	Zero order		First order		Matrix		Peppas		Hix.crow	
	R^2	K	R^2	K	R^2	k	R^2	K	R^2	k
F1	0.8187	11.7	0.9659	-0.2	0.9934	28.6	0.9925	31.8	0.9316	-0.05
F2	0.8591	10.4	0.9630	-0.1	0.9945	25.5	0.9890	24.6	0.9368	-0.04
F3	0.8892	8.81	0.9698	-0.1	0.9995	21.3	0.9993	21.6	0.9498	-0.03

Figure 3: Release kinetics graph of formulation F3



CONCLUSION

The study deals with the investigation of release retardant effect of *Hibiscus rosa-sinensis* mucilage when formulated as a matrix tablet. The mucilage exhibited an appreciable physicochemical properties and suited best for the development of sustained release tablets as indicated by the drug release studies. This can be used as a potential natural source over the synthetic release retardant. Hence, *Hibiscus rosa sinensis* could be employed as a release rate retardant for sustaining the drug release from the formulation.

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