Research Article

Available online through
www.ijrap.net

IJRAP
ISSN 2229-3566

FORMULATION OF ACECLOFENAC SUSTAINED RELEASE MATRIX TABLET USING HYDROPHILIC NATURAL GUM

Parasuram Rajam Radhika*, Pankaj R. Kharkate, Thangavel Sivakumar
Department of Pharmaceutics, Nandha College of Pharmacy, Erode- 638052, India

Received on: 08/04/2011 Revised on: 17/05/2011 Accepted on: 11/06/2011

ABSTRACT
In order to reduce production costs, a simple, direct compression sustained release formulation consisting of drug Aceclofenac and by using hydrophilic polymer guar gum and tamarind gum as the release modifier was investigated. No interaction between drug and polymer was confirmed by FTIR, which shows the suitability of all excipients with the drug to formulate the sustained release matrix tablets. Five batches of sustained release matrix tablets of Aceclofenac with both guar gum and tamarind gum were prepared by using different drug: polymer ratio i.e. 1; 2, 1:2.5, 1:3, 1:3.5, and 1:4 by direct compression method. The tablets were analyzed for their various parameters such as hardness, friability, weight variation. *In- vitro* release was performed with the phosphate buffer of pH 7.4 for 24 hrs. Swelling index study was carried out to study the dispersibility of gums at different concentration. The results of *in vitro* drug release shows that as the concentration of gum increases, swelling index also increases proportionately. Batch **F2** and **F7** shows maximum drug release with sustained release rate and when compared **F7** was more sustained. It is clear through the dissolution study and the kinetic release study of the Aceclofenac matrix tablets prepared using tamarind gum, retarded up to 24 hrs and tamarind gum is best suitable for sustained release formulation by direct compression method.
KEY WORDS: Sustained release, Matrix Tablets, Hydrophilic Polymers, Guar Gum, and Tamarind Gum.

***Address for Correspondence**
Parasuram Rajam Radhika, Nandha College of Pharmacy, Koorapalayam Pirivu, Erode-638052 TamilNadu India
Email: radhi_kannan2005@yahoo.co.in

INTRODUCTION

Over the past 30 years, as the expense and complication involved in marketing new drug entities have increased. With concomitment recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release system. The goal of sustained or controlled delivery system is to reduce the frequency of dose or increase the effect of the drug at the site of action. Hydrophilic matrices are commonly used for oral drug delivery system and are sustained for their good compatibility[1]. Drug release from hydrophilic matrix tablets are sustained by formation of hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water in to the tablet and also the movement of dissolved solute out of matrix tablet[2].

Hydrophilic polymers have attracted considerable attention in recent years as sustained controlled release devices for the delivery of water soluble and water insoluble agents. Their characteristics and their ability to hydrate and form a gel layer are well known and essential to sustain and control drug release from matrices[3]. The hydrated gel layer thickness determines the diffusion path of the drug molecules through the polymer mass in to dissolution medium[4]. A number of natural and number of polysaccharides, such as xanthan gum, guar gum, Karaya gum, alginate and carragenan, have been showed to be useful for controlled release due to their hydrophilic properties[5].

Aceclofenac, a non steroidal anti-inflammatory drug (NSAID) with analgesic property used to treat pain, dysmenorrheal, ocular inflammation, osteoarthritis, rheumatoid arthritis, etc. Due to short half life and multiple dosing regimens, Aceclofenac requires sustained release formulation for patient compliance. Hydrophilic matrices are an interesting option when developed in an oral sustained-release formulation. The release behavior of drugs varies with the nature of matrix, its swelling, diffusion, and erosion process. The

present investigation is aimed to formulate the matrix tablet with the natural hydrophilic polymers like tamarind gum and guar gum by varying parameters prepared using Aceclofenac as a model drug. *In- vitro* drug release and their release mechanism from the matrix tablets were also evaluated.

MATERIAL AND METHODS

Aceclofenac was obtained as a gift sample from Micro Labs, Bangalore. Guar Gum and Ethanol was obtained from Loba Chem Pvt. Ltd., Mumbai. All other chemicals used were of analytical grade.

Isolation of gum from tamarind seed

The crushed seeds of *Tamarindus indica* were soaked in water for 24 hrs, boiled for 1 hrs, and kept aside for 2 hrs for the release of gum into water. [6-8] The soaked seeds were taken and squeezed in a muslin bag to remove marc from filtrate. Then, to the filtrate, equal quantity of absolute ethyl alcohol was added to precipitate the gum. The gum was separated by filtration. The marc was not discarded but it was sent for multiple extraction with decreasing quantity of extracting solvent, i.e. water with the increase of number of extractions. The isolation was continued until the material was free of gum. The separated gum was continued until the material was free of gum. The separated gum was dried in hot air oven at temperature 40^{o}C. The dried gum was powdered and stored in airtight containers at room temperature.

Preparation of sustained release matrix tablet

Sustained Release matrix tablet of Aceclofenac were prepared by using different drug: polymer ratios as 1:2, 1:2.25, 1:3, 1:3.5, 1:4 for various batches F1 to F5 using Guar Gum as the polymer **(Table 1)** and the batches F6 to F10 were formulated by using Tamarind gum as the matrix forming polymer[9-10]**.** Microcrystalline cellulose was used as the fillers to maintain the tablet weight. All ingredients were passed through sieve no. 20 weighed and blended.

Evaluation of blends

The ideal characteristics of a tablet that make it a popular and acceptable dosage form are compactness, physical stability, rapid production capability, chemical stability and efficacy[11]. In general, the characteristics of tablet are dictated by the quality of the blend from which it is made. Therefore, various methods to evaluate certain blend characteristics have been developed to monitor blending suitability for tabletting. Physical mixture of drug with different excipients were prepared by mixing in a dried mortar for 5 min. Angle of repose (θ), Compressibility index (C.I.), Bulk density, Tapped density were evaluated. The blends were then compressed by direct compression method using 8 mm shallow concave punch. The formulated tablets were evaluated with different parameters.

Evaluation of tablets

All prepared SR matrix tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation. Friability was determined by subjecting a sample of twenty pre weighed matrix tablets to abrasion in automated USP Friabilator (Roche Friability test apparatus, model EF-2, Electro lab, Mumbai). It was operated at 25 rpm for 4 min. The percentage friability was calculated by using formula

$$F = 100 (1- W_0/W_1)$$

Where, F = percentage friability

W_o = Initial weights of 20 tablets

W_1 = weight after friability testing

Hardness of ten tablets of each formulation was determined by using Pfizer hardness tester in triplicate for all formulation as per USP XXIV monograph. Thicknesses of the formulated tablets were measured by using vernier caliper as per USP XXIV monograph. The readings were carried out in triplicate and average value was noted. The tablets were powdered, and 50 mg equivalent weight of Aceclofenac was accurately weighed and transferred in to a 100 ml volumetric flask[12]. Initially, 10 ml of phosphate buffer pH 7.4 was added and shaken for 10 minutes, and then the volume was made up to 100 ml with phosphate buffer pH 7.4. Subsequently, the solution in volumetric flask was filtered, and 1 ml of filtrate was diluted and the drug content was analyzed by using UV-visible spectrophotometer at 276 nm.

In-vitro drug release study

Drug release study was determined in USP II (Rotating Paddles). In this study the 900 ml of phosphate buffer of pH 7.4 was used. The temperature of the bath maintained at 37^{0}C and the paddle was rotated at 100 rpm [13-14]. 5 ml sample of the dissolution medium were taken at a regular interval and the same quantity of the medium was replaced. The amounts of the drug released were determined using an UV spectrophotometer at the wavelength of 275 nm. Drug dissolved at specified time period was plotted as percent release versus time.

Drug release kinetics

In order to propose the possible release mechanism, the release pattern was evaluated to check the goodness of fit for zero order release kinetic, first order, Higuchi and Korsmayer-peppas equation[15]. The goodness of it was evaluated by 'r' values.

Swelling behavior of sustained release matrix tablet

Measurement of swelling rate of the sustained release matrix tablet was carried out to gain insight the observed

phenomenon of drug release with the rates of polymer hydration[16-17]. The swelling studies were carried out by measuring the initial diameter, height and weight of the sustained release matrix Tablet and placed in dissolution medium (phosphate buffer pH 7.4) at 37 ± 0.5^0 C. Swollen tablets were withdrawn from the medium, extra buffer present on the matrix surface was gently wiped with the soft tissue paper and the swelling index were measured at predetermined time interval.

The swelling ratio was then calculated using the following formula:

$$SR = W_g - W_o / W_o$$

Where, SR = Swelling Ratio

W_o = Initial weight of tablet

W_g = final weight of tablet

The weight of tablet was noted after every hour.

Stability studies

From the formulated SR matrix tablet formulation Guar gum and Tamarind gum which shows appropriate study for selected stability study. The stability study was carried out according to USP FDA stability guidelines and ICH guidelines short term stability testing carried at low, high, medium temperature[18]. Sampling was carried out for 3 months. The samples were analyzed by physical absorbance and drug content was evaluated at regular interval of time.

RESULT AND DISCUSSION

Drug – excipients interaction studies

The FTIR and X-ray diffraction studies were carried out to understand the solid state interaction in tablets. The FTIR and X-ray diffraction of pure drug, individual polymers, drug-polymers physical mixture (proportion same as the tablet composition) were recorded. The observed peak values of each were evaluated with the standard peak values of the drug and other excipients. No major interactions were observed. All these confirmed the suitability of all excipients with the drug to formulate the sustained release matrix tablets. The X- ray diffraction pattern of Guar gum and Tamarind gum did not show any peak, which indicates that the structure was completely amorphous. Thus Guar gum and isolated Tamarind gum was used for further studies.

Characterisation of the blend

The pre- compression parameters of granules were evaluated and shown in the **Table** 2. In the present study, Guar gum and tamarind gum was used, as a hydrophilic matrix carrier in designing of oral controlled drug delivery system. Good flow of powders is essential during punching. The present investigation involves the preparations of Guar gum and Tamarind gum with excipients by direct compression process.

The angle of repose of the major components of the tablet formulations were determined by the funnel method. The angle of repose is considered an indirect measurement of powder flowability. The angle of repose of the Guar gum (F1-F5) and Tamarind gum (F6-F10) formulation was found to be less than 30^0, which indicates that it has good flow properties. The compressibility index also indirectly measures the flow ability of powder mass. The compressibility index or Carr's index of the formulation F1 to F5 by using Guar gum and the formulation F6 to F10 by using Tamarind gum were found to be in the range of 12.46 to 13.69 and 12.50 to 14.54 respectively. These values confirmed that both the compressibility and flowability was good and within the limits.

The results of the study indicated that the drug, polymers and with other excipients was suitable for direct compression into a matrix tablet to give uniform dose.

Characterization of fabricated sustained release matrix tablet

Matrix tablets of Aceclofenac were prepared by the direct compression method and subjected to the various evaluation tests **(Table: 3)**. The content distribution of each formulation was uniform and the quantity of drug for all formulations was less than 0.15%. The thickness of all formulations was ranged from 4.02 to 4.12 mm and from 0.3982 to 0.3993 respectively. The tablet hardness depends on the ratio of the polymer added to the drug. The formulation F5 was less hard than the other formulation, whereas F2 was harder than the other guar gum formulations of the Aceclofenac Sustained release matrix tablet.

In case of the Tamarind gum matrix tablet the formulation F10 was less hard than the other formulations, and the F7 formulation showed that it was harder than the other formulations. But all these results of hardness showed that they are within the pharmacopoieal requirements. A small difference between formulations is related to the type and percentage of the retarding polymer. Since tablet hardness is not a perfect index to evaluate the strength of the tablet friability percentage was also used to test hardness of tablet. For all the prepared formulations, friability percentage was less than 1% being in the acceptable range. The average weight deviation percentage of 20 tablets taken from each formulation was less than ± 0.5%.

The Drug content was assayed by UV Spectrophotomeric method of Guar gum matrix tablet formulation F1 to F5 was found to be 98.22%- 99.45% drug content. Also the drug content by the UV Spectrophotomeric method of Tamarind gum matrix tablet formulation F6 to F10 was

found to be 98.43- 99.49% drug content. It showed that % drug content of F1 to F5 and F6 to F10 were within the pharmacopoieal limits.

***In vitro* release study**

The percentage of drug release from the formulated sustained release matrix tablets was performed in the gastric and intestinal fluids. The drug release was performed for first two hours with the pH of 1.2 (0.1N HCl) and the rest up to 24 hrs with phosphate buffer of pH 7.4. The release of drug from the matrix tablet using Guar gum for 2 hrs was in the range of 9-20% whereas, the release from the matrix tablets containing Tamarind Gum is in the range of 10-30%. This may be due to the amount of polymer present in the Aceclofenac Sustained release matrix tablet.

When compared with the formulations F1 to F5 using Guar Gum, F5 showed a slow sustained release up to 24 hrs **(Fig 1&2).** The release of drug in the formulation F2 was in the optimized condition as required. This may be due to the swellable polymers (Guar Gum) when exposed to the dissolution medium; tablet surface becomes wet and hydrated to form a gel layer. The gel layer increases as the concentration increases and retards the rate of drug release.

Similarly the drug release from the formulations F6 to F10 by using the Tamarind gum, slow release of the drug was seen in the formulation F10. This may be due to the high concentration of polymer loading which in turn increases the viscosity of the gel matrix, which resulted in a decrease of the effective diffusion coefficient of the drug .

By comparing the Guar gum matrix tablet of Aceclofenac of **(F2)** formulation with Tamarind gum matrix tablet of Aceclofenac of **(F7)** formulation, the Tamarind gum matrix tablet showed that the release of drug is in a desirable sustained manner for 24 hours.

The mechanism of drug release from polymeric matrices showed the swelling phenomenon. The mechanism of drug release involved the disentanglement and erosion of polymer. Guar gum matrix tablets and Tamarind matrix tablets release process involves the penetration of water in the dry matrix, hydration and swelling of the polymer and diffusion of the drug dissolved in the matrix.

Using Korsmeyer and Peppa's model, '**n**' values for the formulation F1 to F5 showed from 0.61 to 0.76 and from F6 to F10 formulation as 0.50 to 0.81.The '**n**' values showing between the range of 0.5 to 1 is called anomolus kinetics (non-Fickian) suggesting diffusion and erosion mechanism takes place. So Guar gum matrix tablet and Tamarind gum matrix tablet followed diffusion and erosion mechanism.

Swelling index

The process of the drug release from Guar gum matrix **(fig 3)** and tamarind gum matrix **(fig 4)** involves water penetration in to the matrix by hydration and swelling of the polymer and drug dissolution and diffusion out of the matrix. As the polymer concentration increases, swelling index was found to increase. The swelling behavior indicated the rate at which this formulations absorbed water from dissolution media and swelled. It has been observed that the cumulative percent drug release decreases with increasing concentration of polymer and swelling index.

The formulation of the thick gel structure during the diffusion and erosion causes the delay in the drug release from the matrix tablet.

Stability study

According to ICH guidelines, three months accelerated stability study (40 ± 2^0C/ 75±5% RH) for the optimized formulations of Guar gum matrix tablet (F2) and Tamarind gum matrix tablet (F7) showed negligible change for the parameters like appearance, weight variation, thickness, hardness and drug content.

CONCLUSION

The present study was carried out with Hydrophilic natural gums i.e. with Guar gum and Tamarind gum. Using the hydrophilic polymers Sustained release matrix tablets of Aceclofenac was prepared. The Guar gum matrix tablet of Aceclofenac and Tamarind gum matrix tablet of Aceclofenac was formulated by direct compression method and comparative study was done for all the parameters.

The FTIR study showed that there was no interaction between Aceclofenac, Guar gum, and Tamarind gum or with other excipients .The micromeretic properties i.e. angle of repose, bulk density, tapped density, compressibility index for the blends of Aceclofenac and Guar gum and the mixture for the mixture of Aceclofenac and Tamarind gum showed that they are within the pharmacopoieal limits.

The evaluation of the various parameters for the blends of the tablet and the evaluation of tablets of Guar gum matrix tablet and Tamarind gum matrix tablet showed an acceptable range.

The *in vitro* release study for 24 hrs of Guar gum matrix tablet formulation F1, F2 , F3, F4 and F5 were found to be as (96.54%), (97.10%), (93.11%), (79.34%), (65.75%) respectively. Among these F1 to F5 formulations, the **F2** formulation showed more percentage drug release and was sustained.

The *in vitro* release study of Tamarind gum matrix tablet formulation F6 , F7, F8, F9, and F10 showed the release as (97.34%), (98.07%), (89.95%), (83.98%), (68.98%)

respectively. Among these F6 to F10 formulations, the **F7** formulation showed more % drug release and was sustained.

The mechanism of drug release from polymeric matrices showed the swelling phenomenon. The mechanism of drug release involved the disentanglement and erosion of polymer. Guar gum matrix tablets and Tamarind matrix tablets released process involved the penetration of water in the dry matrix, hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

Using Korsmeyer and Peppa's model, '**n**' values for the formulation F1 to F5 showed between 0.61 to 0.76 and F6 to F10 formulation between 0.50 to 0.81.

The '**n**' value showing between the ranges of 0.5 to 1 is called anomolus kinetics (non-Fickian) suggesting diffusion and erosion mechanism. So Guar gum matrix tablet and tamarind gum matrix tablet followed diffusion and erosion mechanism.

The swelling index of Guar gum matrix tablet showed that if the polymer concentration increases, swelling index increase and percentage drug release decreases. Also likewise the swelling index of Guar gum matrix tablet showed that if the polymer concentration increases swelling index increase and percentage drug release decreases.

While comparing percentage of drug release from the F7 of Tamarind gum matrix tablet with F2 of Guar gum matrix tablet formulation, **F7** formulation showed the sustained drug release for up to 24 hrs. Hence it can be concluded that the Tamarind gum which is a natural polymer can be used as promising drug release retardant in comparison to the Guar gum.

REFERENCES

1. Kudela V, Hydrogels, Encyclopedia of polymer science and Engineering, Wiley New York, 1987; 7:703-807.
2. Bamba M, Puisieux F, Marty FP, Carstensen JT, Release mechanisms in gel forming sustained release preparation, Int. J. Pharm. 1979;2: 307-315.
3. Emeje MO, Kunle OO, and Ofoefule SI, The effect of the molecular size of carboxy methyl cellulose on the rate of hydration matrix erosion and drug release, Drug Delivery Tech., 2005; 5:56-60.
4. Manuel E, Antonios K and Merlena V, Development and evaluation of oral multiple unit and single unit hydrophilic controlled-release systems. Pharm Sci. Tech., 2000; 4: 34-37.
5. Talukdar MM. and Kinget R, Swelling and drug release behavior of Xanthan gum matrix tablets, Int J. Pharm, 1995; 120: 63-73.
6. Banker GS, Carztensen JT, in Modern Pharmaceutics 4th edition Marcel Dekker Inc New York 1998, 167.
7. Gowada RV, Shivkumar HG, Indian J Pharm Sci , 2007; 69(2):251.
8. Mutalik S, Naha A, Usha AN, Rajnitha K, Musmade P, Arch Pharm Res, 2007; 230(2): 222.
9. Gwen MJ, Joseph RR, Rhodes CT, Modern pharmaceutics, Marcel Dekker, Inc volume 1996; 72(3): 581.
10. USP-30 NF-25, the Official compendium of standards, the United States of pharmacoepeial convention 2007.
11. Nokano M, Ogata A, *In- vitro* release characteristics of matrix tablets, Study of Karaya gum and guar gum as release modulators, , Indian. J. Pharm Sci, 2006; 68(6): 824-826.
12. Ei-Arini SK, Leuen Berger H, Modeling of drug release from polymer matrices effect of drug loading Int J Pharm Sci 1995: 141-148.
13. The United State Pharmacopeia 24, NF 19, United State Pharmacopoieal convention Rockville M.D, Asian Edition, 2000, 1462-5, 1913-4.
14. Korsmeyer RW, Gurny R, Doelkar E, Buri P, Peppa's NA, Mechanism of solute release from porous hydrophilic polymers, Int J Eur Pharm 1983; 15:25-35.
15. Sujja Areevath.J, Munday D, Cox PJ, Khan KA, Relationship between swelling, erosion and drug release in hydrophilic natural gum mini matrix formulation Eur J Pharm. Sci, 1998; 207-217.
16. Abrahamsson B, Alpsten M, Bake B, Larsson A, Sjorgre J, *In-vitro* and in- *vivo* erosion of two different hydrophilic gel matrix tablet Eur J Pharm Biopharm, 1998; 46:69-75.
17. Renuka Gupta, Kamalinder Singh K, Indian J Pharm Sci, 2007; 69(3): 408.
18. Stability testing of new drug Substances and products, European medicines, Agency, August 2003, EME 2006, CPMP/ ICH/ 2736 99 EMEA 2006.

TABLE No: 1 Formulation of Sustained release matrix Tablet with Guar gum (F1-F5) and Tamarind Gum (F6- F10)

S.No	Ingredient	Formulations									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Aceclofenac	50	50	50	50	50	50	50	50	50	50
2	Polymer	100	125	150	175	200	100	125	150	175	200
3	MCC	250	225	200	175	150	250	225	200	175	150
4	Total weight	400	400	400	400	400	400	400	400	400	400

TABLE No. 2 Micromeritic properties of the Blend of Aceclofenac with Guar gum and Tamarind gum

S.No	PARAMETER	Formulations									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Wt variation(gm)	0.40± 0.04	0.39± 0.01	0.40± 0.04	0.40± 0.02	0.40± 0.03	0.40± 0.03	0.40±0. 03	0.40 ±0.02	0.40±0. 02	0.40±0. 04
2.	Hardness(N)	11.16	12.00	11.54	11.76	11.43	11.09	10.33	10.37	10.40	10.28
3.	Thickness(mm)	4.13	4.13	4.11	4.13	4.12	4.06	4.07	4.07	4.02	4.60
4.	Friability(gm)	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39

TABLE No.3 Evaluation parameters for fabricated Sustained release Guar Gum and Tamarind gum matrix tablets

PARAMETER	FORMULATIONS				
	F6	F7	F8	F9	F10
Wt variation(gm)	0.40± 0.03	0.40±0.03	0.40 ±0.02	0.40±0.02	0.40±0.04
Hardness(N)	11.09	10.33	10.37	10.40	10.28
Thickness(mm)	4.06	4.07	4.07	4.02	4.60
Friability(gm)	0.39	0.39	0.39	0.39	0.39

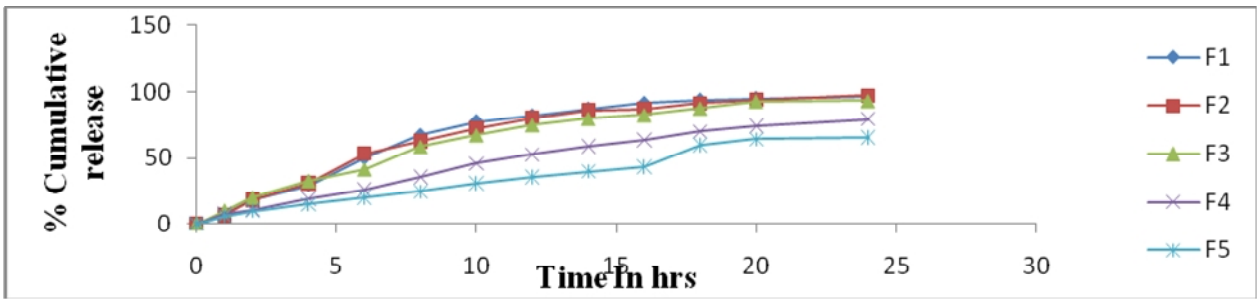

FIG 1 Graph showing the comparative % drug release from Guar gum matrix tablets

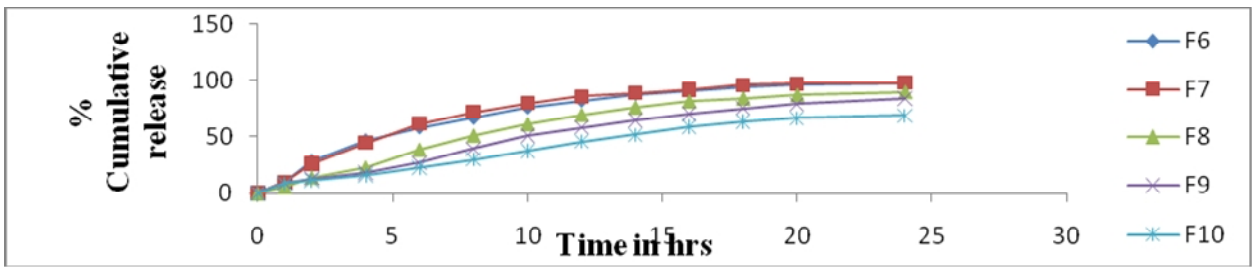

FIG 2 Graph showing the comparative % drug release from Tamarind gum matrix tablets

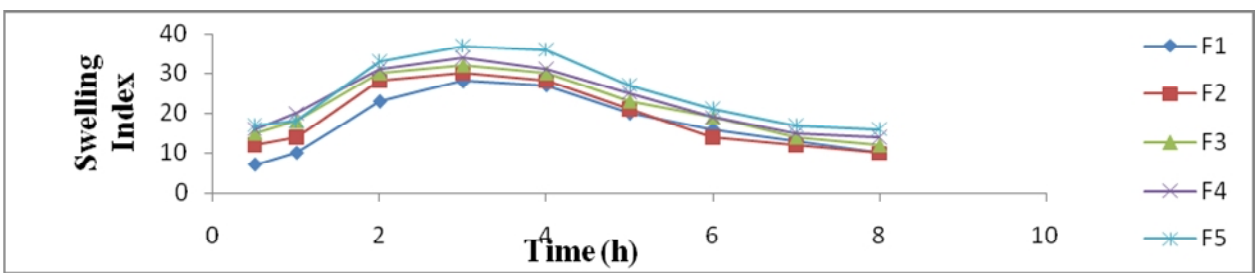

FIG 3 Graph showing swelling index for fabricated Guar gum matrix tablet

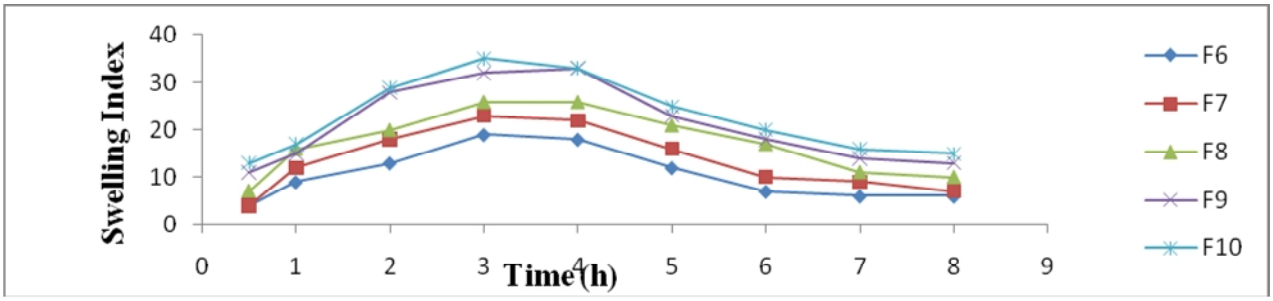

FIG 4 Graph showing swelling index for fabricated Tamarind gum matrix tablet

Source of support: Nil, Conflict of interest: None Declared