e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.12, 2022

DESIGN & EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF DICLOFENAC SODIUM(BCS CLASS-II DRUG) BY USING NATURAL POLYMERS

Vishnu Kant * Dr. Gajendra Singh Rathore
Bhupal Nobles Institute of Pharmaceutical and Sciences, B. N. University, Udaipur (Raj) 313001
vkrai70@gmail.com
Phone no-9893248760

Abstract
The objective of this work was to study the effect of various matrixes forming, release retarding and mucoadhesive polymers on the release of BCS class II drugs. Actual aim of this research work was to design and develop an extended-release matrix tablets by using diclofenac sodium (DS). Actual aim of this research work was to design and developed an extended-release matrix tablets by using diclofenac sodium (DS). The drug excipient interaction study was done by FT-IR. The FT-IR spectrum shows no interaction between drug, guar gum, MCC, Lactose and HPMC because the entire characteristics peak was present in this spectrum.The direct relationship was observed between swelling index and HPMC and MCC concentration, and this concentration increase, swelling index was also increased. It has been observed that the cumulative percent drug release increase with increasing concentration of micro crystalline cellulose and HPMC(K100LV) and swelling index. The reason attributed to this fact is faster erosion of the gelled layer from the tablets containing higher amount of micro crystalline cellulose and HPMC (K100LV) and formulation DF7 showed higher swelling behavior and have higher percent of release rate then other formulations.In DF7 drug was less but overall release from the tablets was highest after 12 hrs. So, from the economical point of view, it is acceptable to get same release pattern with using less amount of drug and it may be also caused the lesser gastric irritation. Due to those reasons a DF7 matrix tablet was selected as best formulations as compared to all others.DF7 followed this model and diffusion exponent (1.13) was found greater than 1 (n>1) indicating the release of diclofenac sodium from the tablet followed super case transport.Super case transport corresponds to diffusion, erosion and swelling mechanism and also includes polymer disentanglement and further erosion, which may be due to the presence of matrix forming and swellable guar gum and erodible nature may due to the presence of MCC (disintegrating agent), lactose (hydrophilic diluents) and low viscous polymers like HPMC K100 LV.The *in vitro* release data of tablet formulation at initial stage was considered as the reference for release study. The *in vitro* release profile revealed that the release profile after 3 months of storage at accelerated condition was found to be similar to that of reference one. Based on the results it was confirmed that the tablet was stable after 3 months of storage at accelerated stability conditions, probably due to the fact that the stable excipients used to prepare the tablets, but further real time stability analysis is required to establish the stability and to determine the shelf life of the best selected formulation.
Keywords:controlled-release matrix tablets, diclofenac sodium; HPMC K100 LV;*in vitro* release

Introduction

Poorpatientcompliance,increasedchancesofmissingthedoseofadrugwithshorthalf-lifeforwhichfrequentadministrationisnecessary.Theunavoidablefluctuationsofdrugconcentrationmayleadtoundermedicationorovermedication.Atypicalpeak-valleyplasmaconcentrationtimeprofileisobtainedwhichmakesattainmentofsteady-stateconditiondifficult.Thefluctuationsindruglevelsmayleadtoprecipitationofadverseeffectsespeciallyofadrugwithsmall TherapeuticIndex(TI) wheneverovermedicationoccur [1].

Diclofenac sodium (DS) is a non-steroidal drug having a potent anti-inflammatory, analgesic, and antipyretic effect. It is an inhibitor of prostaglandin synthesize. It is used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosingspondylities, acute gout, and following some surgical procedures. It has an unpleasant taste and causes gastric irritation.

DS is mainly absorbed from the gastrointestinal tract. DS is a phenyl acetic acid derivative with a p*K*a value of 4.0; it is practically insoluble in acidic solution but dissolves in intestinal fluid and water. It is generally known that DS gets into blood within 30 min and reaches the maximum blood concentration (C_{max}) within 1.5–2.5 h following oral administration of an enteric coated tablet. The oral bioavailability is around 60% with an excretion half-life between 1.1 and 1.8 h. Diclofenac sodium inhibits prostaglandins synthesis and has short lasting antiplatlet action. Neutrophylchemotoxis and super oxide production at the inflammatory site are reduced.Diclofenac is well absorbed following oral dosing but, with administration of the enteric-coated preparation, the time to peak plasma concentration can be variable.There is some Presystemic elimination but about 60% pf the oral dose reaches the systemic circulation. A linear increase in AUC with dose has been reported over the range 25-150 mg in humans. Like many other NSAIDs, diclofenac is highly bound to plasma protein, mainly albumin, and the degree of binding has been shown to be >99.5%.Pharmacokinetic studies showed that a dose of 25mg of diclofenac sodium produces an effective blood level concentration of 0.7-1.5 µg/ml within 1.5-2.5 hr.The mean terminal elimination half life in humans is 1-2 hr. some of the metabolites show anti-inflammatory, analgesic and antipyretic activity [2-4].

The objective of this work was to study the effect of various matrixes forming, release retarding and mucoadhesive polymers on the release of BCS class II drugs. Actual aim of this research work was to design and develop an extended-release matrix tablets by using diclofenac sodium (DS). Diclofenac sodium is potent non-steroidal anti-inflammatory [NSAID] drug in with a potency, on the weight basis that is approximately 2-3 times that of Indomethacin, as a weight basis, its analgesic potency is 8 to 16 times greater than ibuprofen. Conventional dosage form has a short biological half-life of 1.1-1.8 hours and often need to be given at frequent intervals to maintain drug concentration in the blood within the therapeutic range. Diclofenac sodium is a phenyl acetic acid derivative with a p*K*a value of 4.0. As there is an inverse correlation between frequency of dosing and patient compliance, frequent dosing leads to patient noncompliance.

Therefore, by formulating an extended-release matrix tablets can achieve which decrease the dosing frequency and incidence of side effects, andReduction of total amount of drug administered over the period of treatment to improve better patient compliance.Due to these reasons, it is felt that drug needs to be formulated into extended-release matrix tablet.

MATERIALS AND METHODS

MATERIALS

Diclofenac Sodium was procured from Amoli Organics., Hyderabad, India**;** Guar gum, Lactose and Mg Stearate were purchased from CD H Laboratory, New Delhi, India; HPMC K100LV and HPMC K4M were collected from Colorcon Asia Pvt. Limited, Mumbai, India, where as Micro crystalline cellulose was procured from JRS Pharma LP, Patterson, NY, USAand Talcwas purchased from Oxford Laboratory, Mumbai, India.

METHODS

FORMULATION OF GASTRORETENTIVE FLOATING MATRIX TABLETS OF DICLOFENAC SODIUM

In the formula designed for Diclofenac sodium extended-release matrix tablets, following ingredients were used as they are well known and more commonlyused in the formulation of extended-release dosage form as per the literature survey [5-12]

Table: 1: Functions of various components used to prepare floating matrix tablet formulations of Diclofenac sodium

S.NO.	EXCIPIENTS	FUNCTIONAL CATEGORY
1	Diclofenac sodium	Active ingredient
2	Lactose	Diluents (Soluble)
3	Micro Crystalline Cellulose (Avicel PH-101)	Diluents (Insoluble)
4	Guar Gum	Matrix former (Insoluble)
5	HydroxyPropylMethylCellulose (Methocel K100LV)	Release retarding polymer
6	HydroxyPropylMethylCellulose (Methocel K4M)	Release retarding polymer
7	Magnesium stearate	Lubricants
8	Talc	Lubricants
9	Purified water	Solvent for Granulation

Table 2: Composition of different floating matrix tablet formulation of Diclofenac sodium

Formulation Code		DF1	DF2	DF3	DF4	DF5	DF6	DF7
S.NO.	INGREDIENTS	QTY / tab (mg)						
1.	Diclofenac sodium	100	100	100	100	100	100	75
2.	Guar Gum	100	100	100	100	100	100	100
3.	Lactose	90	40	60	40	40	25	40
4.	Micro Crystalline Cellulose (Avicel PH-101)	-	50	30	-	-	15	25
5.	Hydroxy Propyl Methyl Cellulose (Methocel K4M)	-	-	-	50	-	-	-
6.	HPMC K100 LV	-	-	-	-	50	50	50
7.	Magnesium stearate	6	6	6	6	6	6	6
8.	Talc	4	4	4	4	4	4	4
9.	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Total weight	300 mg	300 mg	300 mg	300 mg	300 mg	300mg	300mg

Manufacturing Procedure

1. Accurately weighed quantity of Diclofenac sodium, Guar gum and Lactose were taken in a Motor, mixed well and sifted through 40-mesh screen.
2. Then others materials were added one by one and finally granulated with water.
3. Wet mass was sieved using 16 mesh screen and granules obtained were air-dried in oven at 50 ° c for 2 hrs. Dried granules were sifted using 14 mesh screens.
4 Moisture contents of dried granules was controlled and maintained between 2-3%. If it was not within the limit then the granulation was further reprocessed.

5. Above blend with the target weight of 300mg, was compressed using 8.0 mm normal concave punches (RimekMachinary).

DRUG EXCIPIENT INTERACTION STUDY

The drug excipients interaction study was done by using FT-IR (FTIR-8300, Shimadzu, Tokyo, Japan). To determine the interaction, the IR spectrum of pure drug with excipientswas obtained by using KBr disk method.

EVALUATION OF PRECOMPRESSION PARAMETERS

FLOW PROPERTY

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the Preformulation stage to be poorly flowable, the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be precompressed or granulated to improve their flow properties. During the Preformulation evaluation of the drug substance, therefore its flowability characteristics should be studied [13-15].

BULK DENSITY

It varies substantially with the method of crystallization, milling or formulation. Usually, bulk density is of great importance when one considers the size of high dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. It can be determined by measuring the volume of a known mass of a powder sample that has been passed into a graduated cylinder.

Method:

Precompression studies were carried out after lubricating the prepared granules. Approximate amount (30 gm) of sample was introduced into a dry100ml cylinder without compacting and unsettled apparent volume, V_o was measured [Jyoti Scientific Ind. Gwalior (M.P)]**.**

Bulk Density = Mass/Volume

TAPPED DENSITY

It is a limiting density attained after tapping down usually in a device which lifts and drops a volumetric measuring cylinder containing powder at a fixed distance.

Method:

100ml graduated cylinder was mounted on a holder. Sample was carefully loaded without compacting and unsettled apparent volume, V_o was measured. This was then mechanically tapped by using suitable mechanical tapped density tester.

The cylinder was tapped 500 times initially and tapped volume, $V_a$was measured. Tapping was repeated to additional 750 times and tapped volume, $V_f$was measured.

$$\textbf{Tapped Density} = \frac{\textbf{Mass}}{\textbf{Final Volume}}$$

COMPRESSIBILITY INDEX AND HAUSNER RATIO

$$\text{Carr's Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} X100$$

Whereas V_0 is the initial volume and V_f is the final volume after tapping the powder.

HAUSNER RATIO

It is also used to evaluate the flowability of drug substance.

Hausner ratio = tapped density / bulk density

ANGLE OF REPOSE

The angle of repose was determined by fixed funnel method. A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and granules were filled in funnel. Then funnel was opened to release the granules on the paper to form a smooth conical heap. The height and radius of the heap was measured and the angle of repose was calculated by using the following formula.

$$\theta = \tan^{-1} h/r$$

Where, θ = Angle of repose, h = Height of heap and r = Radius

EVALUATION OF MATRIX TABLETS [13-26]:

EVALUATION OF POST COMPRESSION PARAMETERS

Hardness:

Tablet hardness was determined by using a Tablet Monsanto Hardness Tester(Monsento, Mumbai, India).

Weight variation Test:

To study weight variation, 20 tablets of each formulation were collected randomly during compression and weighed using an electronic balance to obtain average weight of each tablet. Also, the individual tablet was weighted.

Limit: Weight of all individual tablets should be in the limit of average wt±5%.

Friability:

The test was carried out by using Roche Friabilator [Jyoti Scientific Ind. Gwalior (M.P)]. Ten tablets were taken and carefully dedusted prior to testing. The tablets were weighed accurately, and placed the tablets in the drum. The drum was allowed to rotate 100 times, and after that the tablets were removed. Removed loose dust from the tablets as before, and weighed accurately.

The % Friability was determined by using following formula:

$$\% \text{ Friability} = (\text{Initial Weight} - \text{Final Weight}) \times 100/\text{Initial Weight}$$

A maximum loss of mass not greater than 1.0 % is considered acceptable.

Thickness:

Thickness of the tablets was measured byVernier caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

Uniformity of drug content

For drug content, 10 tablets of diclofenac sodium were weighed accurately and powdered, powder equivalent to 50 mg of diclofenac sodium was shaken with 60 ml of methanol in 200 ml volumetric flask, and volume was further adjusted with methanol. Finally, 5 ml of this was diluted to 100 ml with methanol, and drug content was determined by UV-Spectrophotometer (UV-1800, Shimadzu, Japan) at 276 nm using calibration curve based on standard solutions [26].

Drug content was calculated by following formula.

$$\% \text{ Drug content} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

SWELLING BEHAVIORS OF EXTENDED-RELEASE MATRIX TABLETS: [16, 17, 27]

The extent of Swelling was measured in terms of % weight gain by tablet. Swelling behaviors of all the diclofenac sodium tablet formulations were studied. Three tablets from each formulation were kept in Petri dish. At the end of one hr tablets weights were withdrawn, soaked with tissue paper, and weighed. Then for every 2 hr. weights of tablets were noted, and the process was continued till the end of 12 hrs. % weight gain by tablet was calculated by formula;

Swelling Index (SI) = [(Mt –Mo) /Mo] x 100,

Where, S.I = Swelling Index

Mt = weight of tablet at time t

Mo = weight of tablet at time t = 0.

In -Vitro dissolution studies [16, 17, 28]

Drug release profiles of **diclofenac sodium** were evaluated in vitro using a dissolution test apparatus(FTIR-8300, Shimadzu, Tokyo, Japan). The USP paddle method was used to perform the dissolution profiles of Diclofenac Sodium from Various tablets formulations. The test for all the formulations was carried out in 900 mL 0.1 N HCl for 1st 2 hrs, and phosphate buffer pH 6.8 after 2ndhrs, maintained at 37 ± 0.5° C at a paddle rotation speed of 100 rpm. Withdrawing 5 mL filtered samples at preselected intervals up to 12 hours monitored progress of the dissolution. The release rates from these hydrophilic polymeric matrices were conducted in a medium of changing pH by starting with a tablet in HCl solution (pH=1. 2) for first 2 hours. Then, the tablets were immersed into a phosphate buffer (pH=6.8) for another 10 hours. The sample solutions were analyzed for Diclofenac Sodium by UV absorbance at 274.5 nm & 276.3 respectively, Cumulative percentage of drug release was calculated and the mean of three determinations was used in data analysis.

IN - VITRO DRUG RELEASE KINETIC STUDIES [16, 17, 28]

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer-Peppas model. The regression coefficient R^2 value nearer to 1 indicated the model fitting of the release mechanism.

The most direct assessment of a drug's release from various tablet formulation or product is accomplished through in-vivo bioavailability measurements. The use of in-vivo studies is restricted however for several reasons: the length of time needed to plan, conduct and interpret the study, the highly skilled personnel required for human studies, the low precision and high variability typical of the measurements, the high cost of the studies, the use of human subjects for nonessential research and the necessary assumption that perfect correlation exists between diseased patients and healthy human subjects used in the test.

Consequently, in-vitro tests have been extensively studied, developed and used as an indirect measurement of drug availability especially in the preliminary assessment of formulation factors and manufacturing methods that are likely to influence bioavailability.

The main objective in the development of in-vitro dissolution test is to show that the release of drug from tablet is as close as possible to 100%

MODELING AND COMPARISON OF DISSOLUTION PROFILES

Several theories and kinetic models describe the dissolution of drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of generic equation that translates the dissolution curve function of some parameters related with the pharmaceutical dosage forms. Drug dissolved from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of test time. Some analytical definitions of the Q (t) functions are commonly used such as zero order, first order, Higuchi, Peppas-Korsmeyer models. These models are used to characterize drug dissolution/release profiles.

MATHEMATICAL MODEL

1. ZERO ORDER MODELS [29]

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate).

The following relation is used to express the model:

$$\mathbf{Q_t = Q_o + k_o t}$$

where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution, k_o is the zero-order release constant.

For practical purposes the equation is rearranged:

Percentage of drug released = kt

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

2. FIRST ORDER MODEL

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit of time diminish.

The following relation is used to express the model:

$$\mathbf{\log Q_t = \log Q_o + kt/ 2.303}$$

where Q_t is the amount of drug released in time t, Q_o is the initial amount off drug in the solution, kis the first order release constant

For practical purposes the equation is rearranged:

Log % drug unreleased = kt / 2.303

This model is applicable to study of hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

3. HIGUCHI MODEL

Higuchi describes drug release as a diffusion process based in Fick's law, square root time dependent.

The following relation is used to express the simplified Higuchi model:

$$\mathbf{Q_t = kt}$$

whereQ_t**is** the amount of drug dissolved in time t and k is the Higuchi release constant.

For practical purposes the equation is rearranged:

Percentage of drug released = kt

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

4. PEPPAS-KORSMEYER MODEL

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

The following equation is used to express the model:

$\underline{Q_t} = kt^n$

Q_∞

where Q_t is the amount of drug dissolved in time t,Q_∞ is the amount of drug dissolved in infinite time, n is the release exponent indicative of the drug release mechanism and k is the kinetic constant incorporating structural and geometrical characteristics of tablet.

For practical purposes the equation is rearranged:

Log percentage of drug released = log k+ n log t

Peppas (1985) used n value in order to characterize different release mechanism concluding for values of n = 0.5 for fickian diffusion and higher values for n between 0.5 and 1.0 or n = 1.0 for mass transfer following a non fickian model

STABILITY STUDIES

The optimized batch was used for the stability study. Tablets were tested for a period of three months at 40°C with 75% RH, for their drug content and other parameters (Newtronics Pvt. Ltd). After 90 days all the quality control tests of tablet including drug contents of that formulation were determined. *In vitro* release study was also carried out for the same formulation after stipulated time period of time intervals. Methods followed for all the quality control tests were discussed in earlier section.The stored products were evaluated for various tablet characteristics including dissolution rate. The drug content of the tablet was determined spectrophotometrically using UV-Vis spectrophotometer [30].

Data analysis

Results are expressed as mean values and the significance of the difference observed was analyzed by the Student's t-test. In all tests, a probability value of $p < 0.05$ was considered statistically significant.

RESULT AND DISCUSSION

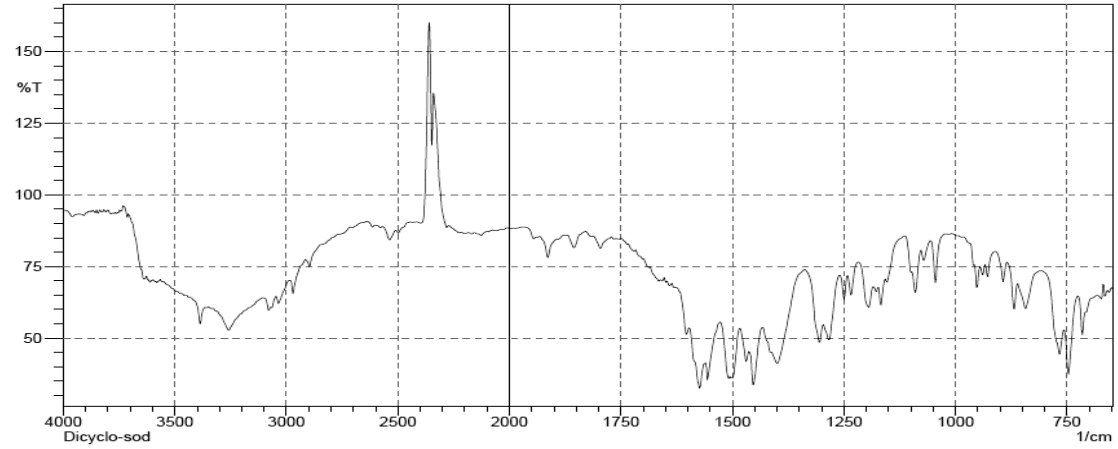

Fig. 1: FTIR Spectra of DS the major peaks are obtained at 1573.91, 767.67, 1504.46, 746.45, 1284.49 and 1305.81 $cm^{-1.}$

The FTIR spectrum of sample drug (**Diclofenac Sodium-DS**) shows the peak values which are characteristics of the drug and the spectrum was shown in fig. 1.Identification of drug was done by its UV and *IR* spectra. The infrared spectral assignment of both the drugs showed the characteristic peak value of drug which showed the identity of drugs [2,3, 31-32].

DRUG EXCIPIENT INTERACTION STUDY:

Evaluation of Diclofenac sodium interaction with the other components by the FTIR study:

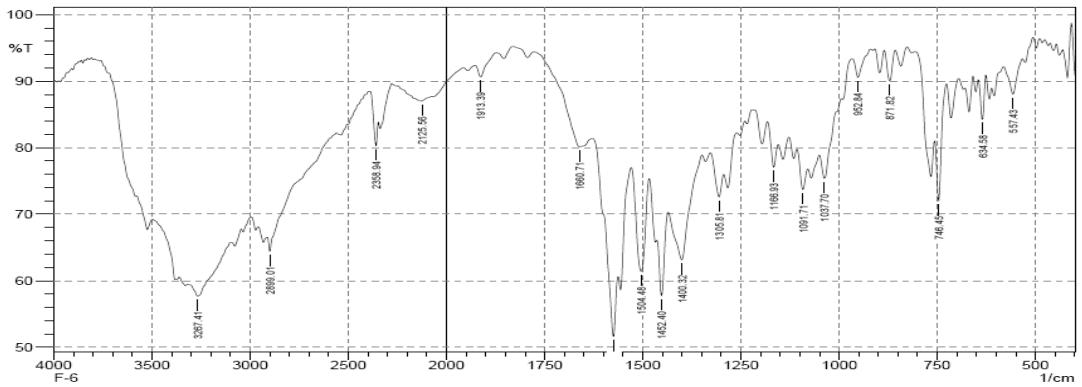

Fig. 2: FTIR Spectra of formulation DF6 & the major peaks are obtained at 1573.91, 1504.46, 1452.40, 1400.32, 1305.81, 1091.71 and 746.45 cm^{-1}.

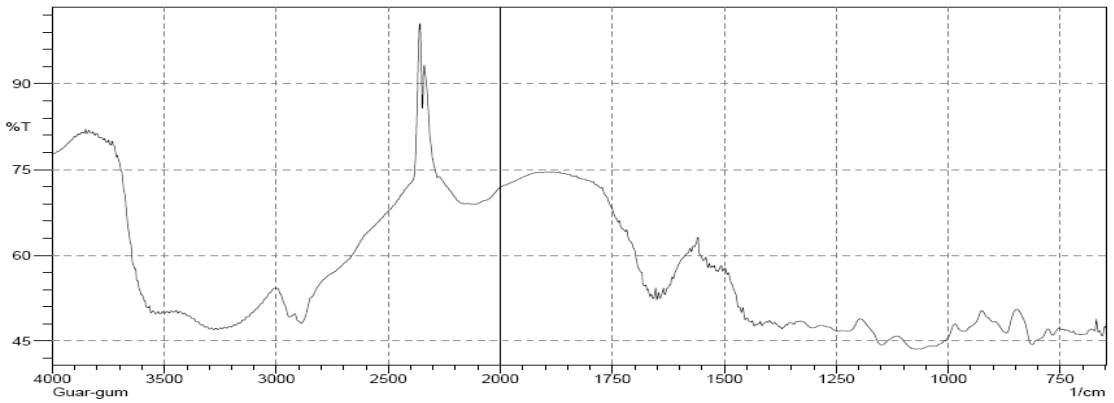

Fig. 3: FTIR Spectra of guar gum & the major peaks are obtained at 3261.63, 2889.37, 1660.71, 1149.57, 1072.42 and 813.96 cm^{-1}.

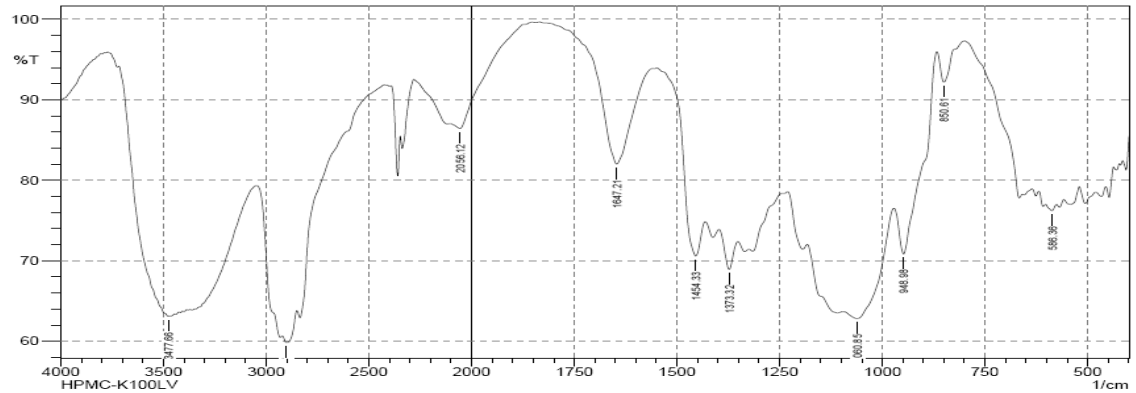

Fig. 4: FTIR Spectra of HPMC (LV-100) & the major peaks are obtained at 2902.87, 1647.21, 1373.32, 1060.85, 848.98 and 586.36 cm^{-1}.

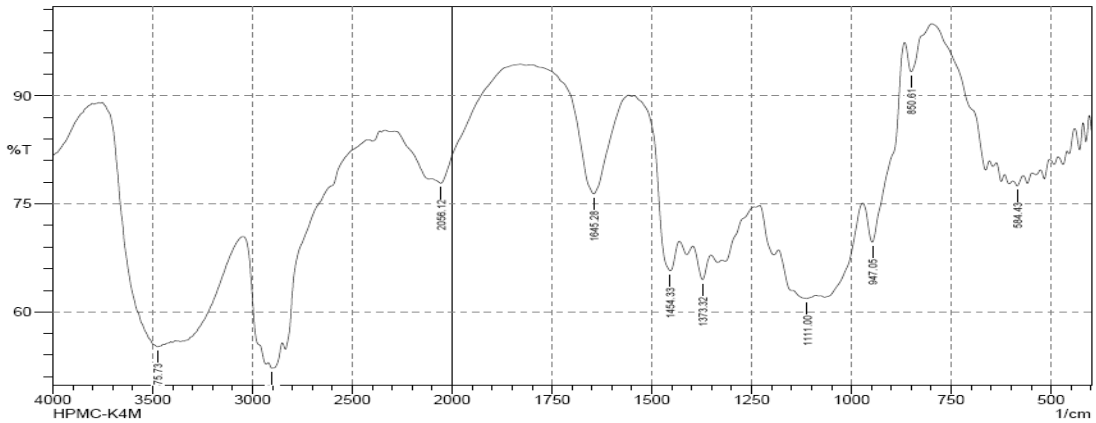

Fig. 5: FTIR Spectra of HPMC (K4M) & the major peaks are obtained at 2902.87, 1645.28, 1454.33, 1373.32, 1111.00, 947.05 and 584.43 cm^{-1}.

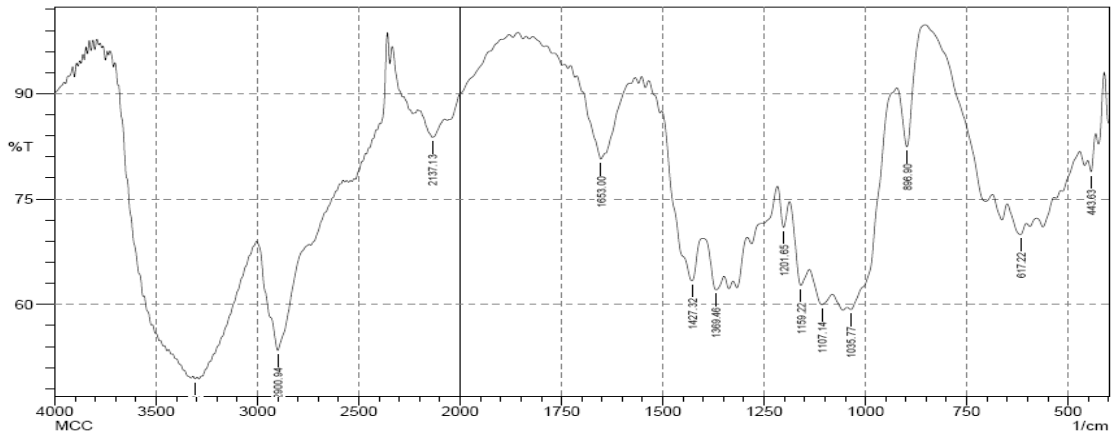

Fig. 6: FTIR Spectra of MCC & the major peaks are obtained at 3489.23, 2974.23, 1639.49, 1421.54, 1369.46, 1290.38, 1138 and 1232.51 cm^{-1}.

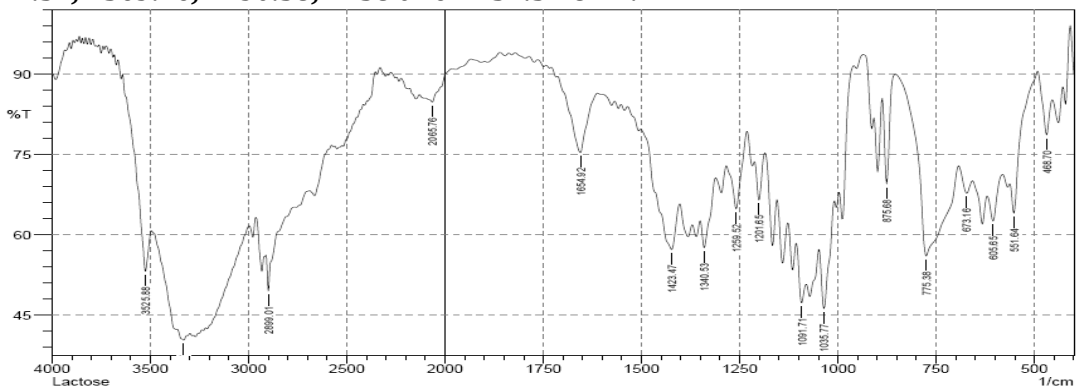

Fig. 7: FTIR Spectra of Lactose (the major peaks are obtained at 3331.07, 2899.01, 1654.92, 1423.47, 1340.53, 1091.71, 1035.77, 775.38 and 605.65 cm^{-1}).

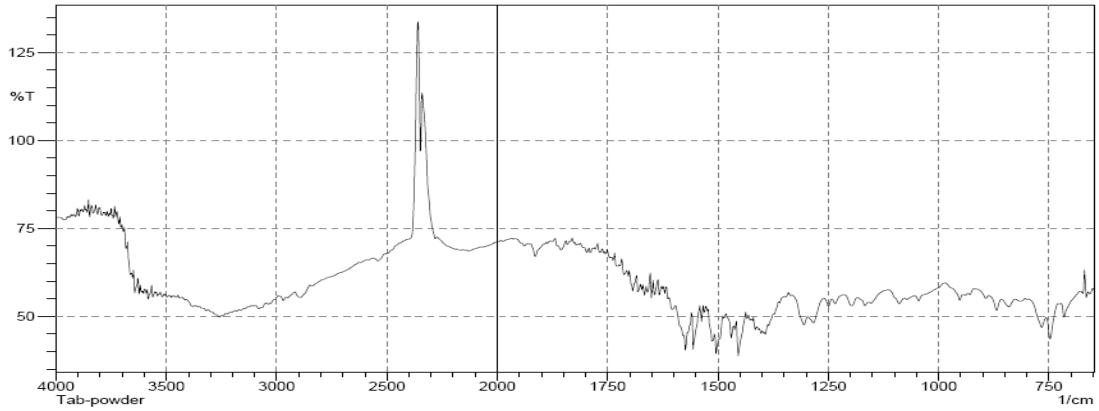

Fig. 8: FTIR Spectra of 1:1 mixture of DS and Guar gum & the major peaks are obtained at 1573.91, 1502.55, 1305.81, 1284.59, 767.67 and 746.45 cm^{-1}.

The drug excipient interaction study was done by FT-IR. The FT-IR spectrum shows no interaction between drug, guar gum, MCC, Lactose and HPMC because the entire characteristics peak was present in this spectrum (Fig 1 and 3-8). FT-IR Spectrum (Fig. 1) of pure Drug (diclofenac sodium), the major peaks were obtained at 1573.91, 767.67, 1504.46, 746.45, 1284.49 and 1305.81 cm^{-1}. Whereas the physical mixtures of drug FTIR Spectra of 1:1 mixture of DS and Guar gum were studied and the major peaks were obtained at 1573.91, 1502.55, 1305.81, 1284.59, 767.67, 746.45 cm^{-1}(Fig. 8). But FTIR Spectra of DF1 showed at 1573.91, 746.45, 1502.55, 1452, 1305.81, 873.75 cm^{-1} and DF6 (Fig. 2) was shown major peaks at 1573.91, 1504.46, 1452.40, 1400.32, 1305.81, 1091.71 & 746.45 cm^{-1}.

From the above all data, it can be concluded the following points. The IR spectra of drug was compared with that of the standard peak available in official book USP, IP and identified as Diclofenac sodium. The UV spectra of the drug were recorded and the obtained λ_{max}values were compared with the peaks those are given in reference books. It was found to be the same. The co-efficient of correlation obtained from the standard plot showed linearity in the analytical method. Compatibility studies were carried out to ascertain any interaction of the drug with the excipients used in the preparation of matrix tablets, which may be interfere the dissolution of the drug actively as well as stability of the product. Therefore, a medicated formulation along with the pure drug sample was subjected FTIR analyses. In analyses of the FTIR spectra of the pure drug and the drug-excipients mixture and it was also compared with prepared formulations**.**

DEVELOPMENT OF FORMULATION:

In the formula designed for Diclofenac sodium extended-release matrix tablets, following ingredients were used as they are well known and more commonlyused in the formulation of extended-release dosage form as per the literature survey. For the formulation of extended-release matrix tablets of Diclofenac sodium, Lactose and microcrystalline cellulose were used as diluents which provide channels for the drug to diffuse from the Guar Gum /HPMC matrix and improve tableting characteristics. Release kinetics of Diclofenac Sodium from these swollen matrices was principally regulated by lactose, even in the presence of MCC [11,12, 33-37]**.**

Hydrophilic polymers are widely used in the formulation of modified–release oral dosage forms. Various synthetic polymers (HPMC, Na-CMC, polymethacrylate, etc.) and natural materials (xanthan, guar gum, and chitosan) have been tried by various researchers. It has been shown that in hydrophilic matrices, swelling as well as erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug release rate [38,39].

Recently the potential of guar gum as an inexpensive and flexible carrier for oral extended-release drug delivery has been highlighted. Guar gum formulations are relatively insensitive to changes in

stirring speed of dissolution test, compaction pressure, or storage under accelerated stress conditions. However, guar gum alone may not sustain drug release satisfactorily requiring the addition of other hydrocolloids like HPMC in relatively large amounts [40].

HPMC of K100LV and K4M were used to control the release of drug. It was chosen because it has faster hydration rate and for freely soluble drugs like Diclofenac Sodium, a rapid rate of hydration is necessary to form a protective gel layer, which prevent the quick penetration of gastric fluids into the tablet core. The potential advantages of natural gums as extended–release excipients are their high viscosity, low cost, and commercial availability. The ultimate goal of our work is to provide natural gum based extended-release systems that are inexpensive, in terms of raw material and manufacturing costs, and suitably robust to accommodate a variety of drugs. On the basis of preliminary studies using drug and gum in different ratio and studying their dissolution it was decided to go for 1:1 ratio which gave the best release of drug.

EVALUATION OF PRECOMPRESSION PARAMETERS

EVALUATION OF PRECOMPRESSION PARAMETERS OF DICLOFENAC SODIUM

Table 3:Evaluation of precompression parameters of Diclofenac sodium granules

Formulations→ / Parameter ↓	DF1	DF2	DF3	DF4	DF5	DF6	DF7
Bulk density g/cm^3	0.68	0.66	0.68	0.69	0.69	0.64	0.67
Tapped density g/cm^3	0.74	0.73	0.76	0.78	0.77	0.75	0.76
Compressibility Index %	8.10	9.58	10.52	11.5	10.38	14.66	11.84
Hausner's ratio	1.09	1.10	1.12	1.13	1.12	1.17	1.13
Angle of repose (Ɵ)	23.05	23.54	24.33	25.10	23.85	29.54	24.66

These are the measures of propensity of powder to be compressed and reflect the relative importance of interparticulate interaction. In a freely flowing powder, interparticulate interaction is less significant and so bulk density and tapped density will be closer in value**.** For poorer flowing material, interparticulate interaction is more and significant difference is also observed between bulk density and tapped density.

Both bulk density and tapped density of granules blend DF formulations were determined. The bulk density was varied in between a range of 0.64 to 0.69 g/cm^3 and tapped density was found to be in range between 0.73 to 0.78 g/cm^3.

Compressibility index was carried out, it was found between 8.1% to 14.66% indicating that the granules blend has mixed properly with the lubricating agents, which were used to improve the flow property of the granules before compression. If the % compressibility index is in the range of 5-15, seems to be excellent flow, whereas if it is in the range of 12-16, then flowability of granules may be good.

Hausner's ratio was carried out, it was found between 1.09 to 1.17, all the values were < 1.25, so it is good to flow. The results were shown in table 3.

The angle of repose for the formulated granules blend (DF1-DF7) was carried out and the results were shown in table 3. It concludes the entire formulations blend was found to be range between 23.05° to 29.54°. It showed that granules have good flow properties. From these values it can be concluded that all the granules were good flowability.

EVALUATION OF POST COMPRESSION PARAMETERS

POST COMPRESSION PARAMETERSOF MATRIX TABLETS OF DICLOFENAC SODIUM

Table 4: Physical parameter of Diclofenac sodium matrix tablets

Formula-toions	Hardness Kg/cm^2	Average Weight(mg)	Friability	Thickness (mm)	Drug Content (%) Mean± S.D
DF1	6	301.01 ± 3.77	0.83%	4.2	103± 0.87
DF2	6	300.20 ± 2.46	0.72 %	4.2	99.5±0.50
DF3	6	300.80 ± 2.19	0.70%	4.2	100.2±0.53
DF4	6	300.90 ± 2.33	0.43 %	4.1	100.6±1.00
DF5	6	301.00± 3.55	0. 44 %	4.2	100±0.88
DF6	6	301.03 ±2.98	0. 42%	4.0	101±1.24
DF7	6	300.11 ± 1.30	0.43 %	4.2	101±0.87

* Every formulation (trial batch) was evaluated from their physical unofficial quality control tests. The following table gives a concise result of the same.

All the tablet formulations (DF) passes the weight variation test, the percentage weight variation was within the IP limit i.e, below ± 5.0 %. The hardness of all the formulations was found approx 6 Kg/cm^2. The friability of Formulation AF1-AF7 was found to be in the range of 0.42-0.83%, which was within the IP limit i.e below 1%. Thickness of all the tablets were approx 3mm. The drug content of all the formulation was found in the range of 99.5- 103 % which was within acceptable limit (table 4).

SWELLING BEHAVIORS OF EXTENDED-RELEASE MATRIX TRIAL TABLETS OF DICLOFENAC SODIUM:

Swelling behaviors of extended-release matrix trial tablets:

Table 5: The effect of swelling index behaviors on different formulations

Time (hrs)	Swelling Index (Mean ± S.D)						
	DF1	**DF2**	**DF3**	**DF4**	**DF5**	**DF6**	**DF7**
1	52.15±0.33	72.64±1.83	47.39±6.27	55.48±10.97	61.01±5.99	58.36±3.55	61.68±0.69
2	73.64±1.57	86.93±2.90	69.21±1.01	77.18±2.53	80.17±2.49	74.97±1.57	77.51±0.69
4	91.47±3.77	107.19±2.26	87.92±3.77	91.47±6.97	96.12±5.19	107.53±1.01	110.63±1.32
6	115.83±3.24	121.37±0.69	113.39±2.76	111.18±2.40	114.39±1.014	120.26±1.84	123.58±1.52
8	112.18±4.15	117.27±3.16	113.51±1.67	122.48±1.67	124.58±2.95	132.00±2.16	135.65±2.13
10	105.20±5.22	115.83±1.57	108.74±0.69	125.35±5.29	130.89±0.33	145.29±9.64	152.93±1.91
12	100.00±5.11	112.51±2.21	107.19±0.69	117.05±0.50	120.48±3.73	141.08±7.67	149.05±0.69

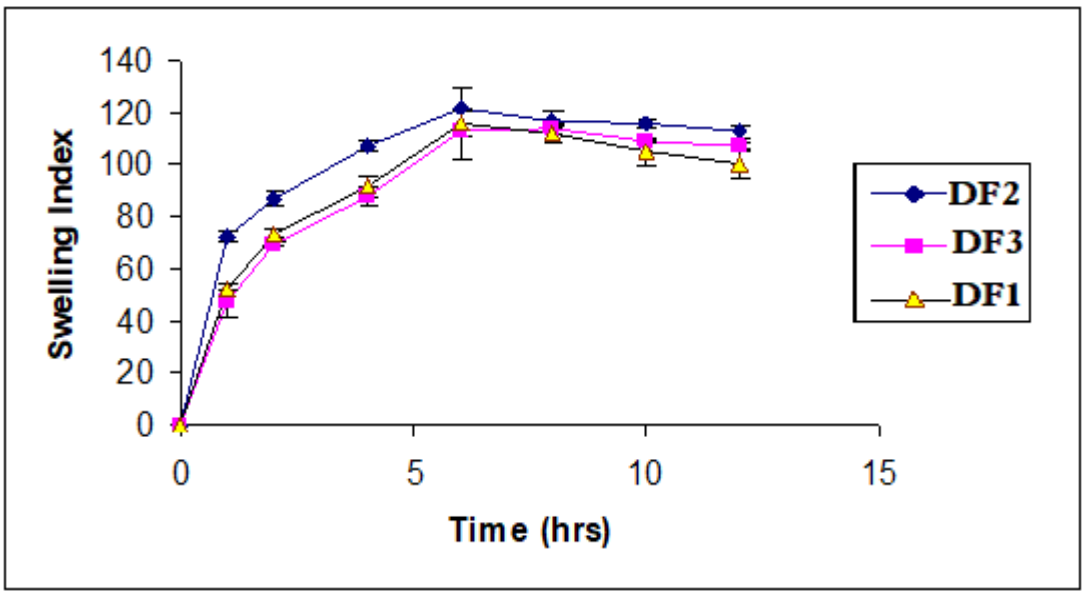

Fig. 9: Plot of swelling index behaviors on formulations DF1, DF2 and DF3.

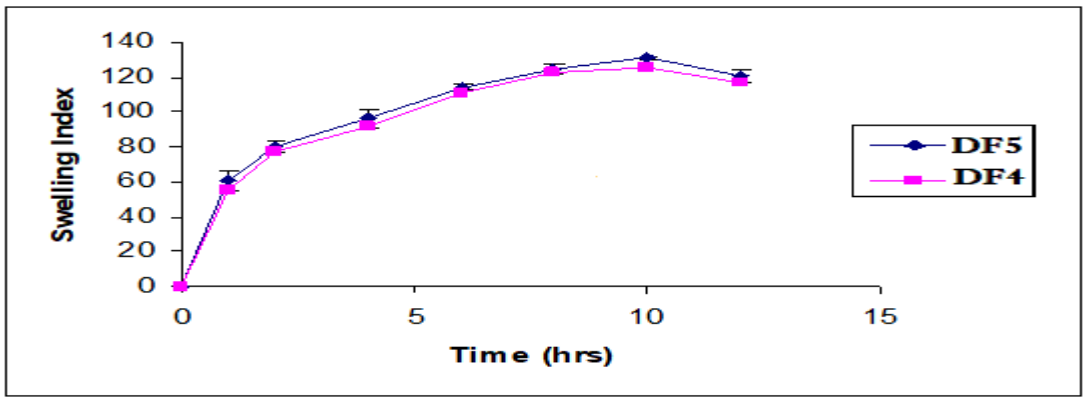

Fig. 10: Plot of swelling index behaviors on formulations DF4, DF5.

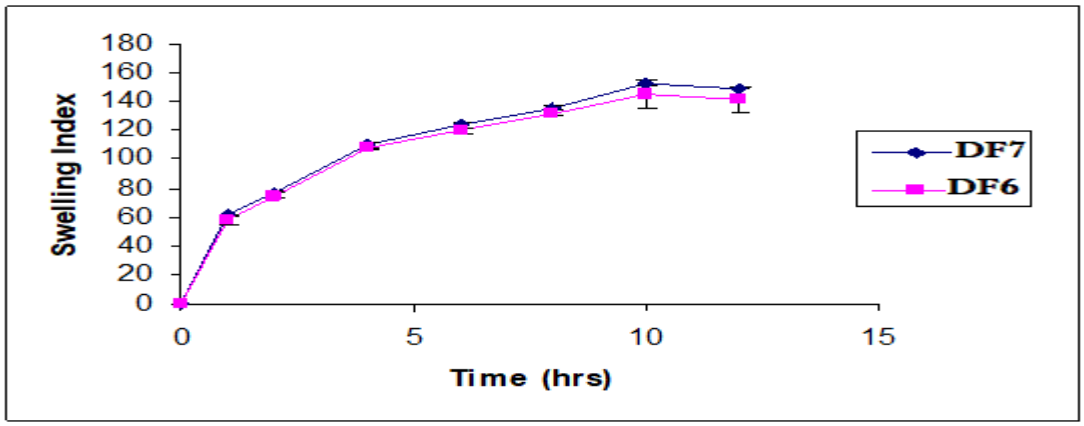

Fig. 11: Plot of swelling index behaviors on formulations DF6, DF7.

The swelling behaviors of different DF formulations were analyzed. DF7 has grater swelling index then other formulation within 12hrs in which drug was incorporated 75 mg with guar gum (100mg) and HPMC100LV (50mg) with 25mg of MCC and 40mg of lactose.

In DF5 and DF6 formulations the guar gum and HPMC (K100LV) were present in the same amount, but the swelling of DF6 was more than DF5, it may be due to the presence of MCC in DF6

formulation. In DF6 formulations, the amount of MCC was less than DF7 and also the swelling was more in DF7.

Among the DF1, DF2 and DF3 swelling index of DF2 was slightly more because MCC was used in higher amount than DF1 and DF3. Swelling of DF4 was further more than DF2 because here HPMC (K4M) was replaced with MCC, which contributed greater swelling than DF2. But the swelling of DF4 was less than DF5, DF6 and DF7 because in DF5, DF6, DF7 contained only HPMC K100LV (low viscous) that was replaced in place of HPMC K4M (high viscous).

***IN-VITRO* DISSOLUTION STUDY:**

Formulation code: DF1

This formulation was prepared with guar gum and no single HPMC grade and MCC were used in this formulation.

Apparatus: Paddle type R.P.M.:100

Sampling volume: 5ml Volume: 900ml

Media: 0.1(N) HCl pH 1.2 [first 2hrs.] & Phosphate buffer pH 6.8 [last 10 hrs]-by solvent changing methods Temperature: 37± 0.5ºc

Changes made in the formula to improve the drug release of DF2:

Some amounts of Micro Crystalline Cellulose were added here and better drug released profile was observed as compared to DF1 formulations that may be due to better swelling of the tablets. This formulation was prepared with guar gum and no single HPMC grade was used in these formulations.

Changes made in the formula to improve the drug release of DF3:

Quantity of Micro crystalline cellulose was reduced and weight of lactose was increased and it was observed much better released of drug as compared to the DF1 and DF2. But selling index was observed in between these two formulations, which may be due to the presence of less amount of MCC than DF2 formulations and more amount of highly water-soluble diluents lactose.

Changes made in the formula to retard the drug release of DF4:

Similar amount of lactose was used as it was in case of DF2 formulations but the quantity of lactose was reduced further as compared to DF3 formulations and MCC was replaced by HPMCK4M. Release of the drug was almost similar as DF1 formulations and it was slightly greater than that but lesser than DF2 and DF3 formulations. Slight changes of swelling index were observed and it was greater than DF1-DF3 formulations.

Changes made in the formula to retard drug release of DF5:

Same amount of HPMC K100LV was added instead of HPMC K4M, but lactose quantity was kept the same. Better released of the drug was observed as compared to the DF1-DF4 formulations, it may be due to more swelling and more hydrophilicity of this polymer.

Changes made in the formula to retard the drug release of DF6:

Same amount of HPMC K100LV was added as it was in DF5 formulations, but lactose quantity was reduced slightly and MCC was added. Better and more released of the drug was observed as compared to the DF1-DF5 formulations, it may be due to much more swelling and more hydrophilicity of these excipients.

Changes made in the formula to retard drug release of DF7:

Table 6: Drug release profile (%CDR) of DF7 formulation

TIME	Total amount of drug release (mg) Mean± S.D.	Cumulative % release Mean± S.D.
1	3.72±0.052	4.89±0.181
2	5.57±0.269	7.33±0.354
3	8.35±0.789	18.33±0.701
4	11.73±0.089	22.79±0.439
5	15.58±0.573	27.86±0.404
6	19.75±0.290	33.35±0.733
7	26.26±0.532	41.92±0.716
8	30.41±0.458	47.39±0.845
9	35.55±0.097	54.15±0.309
10	40.11±0.411	60.16±0.853
11	45.11±0.249	66.75±0.341
12	52.12±0.374	75.35±0.472

Quantity of the Diclofenac sodium was reduced in DF7 formulation, amount of lactose and MCC was further increased from the earlier trial. It was observed almost more than 75 % of the drug was released within 12 hrs and better swelling of the tablets among the all-others formulation. And it was selected as best formulations.

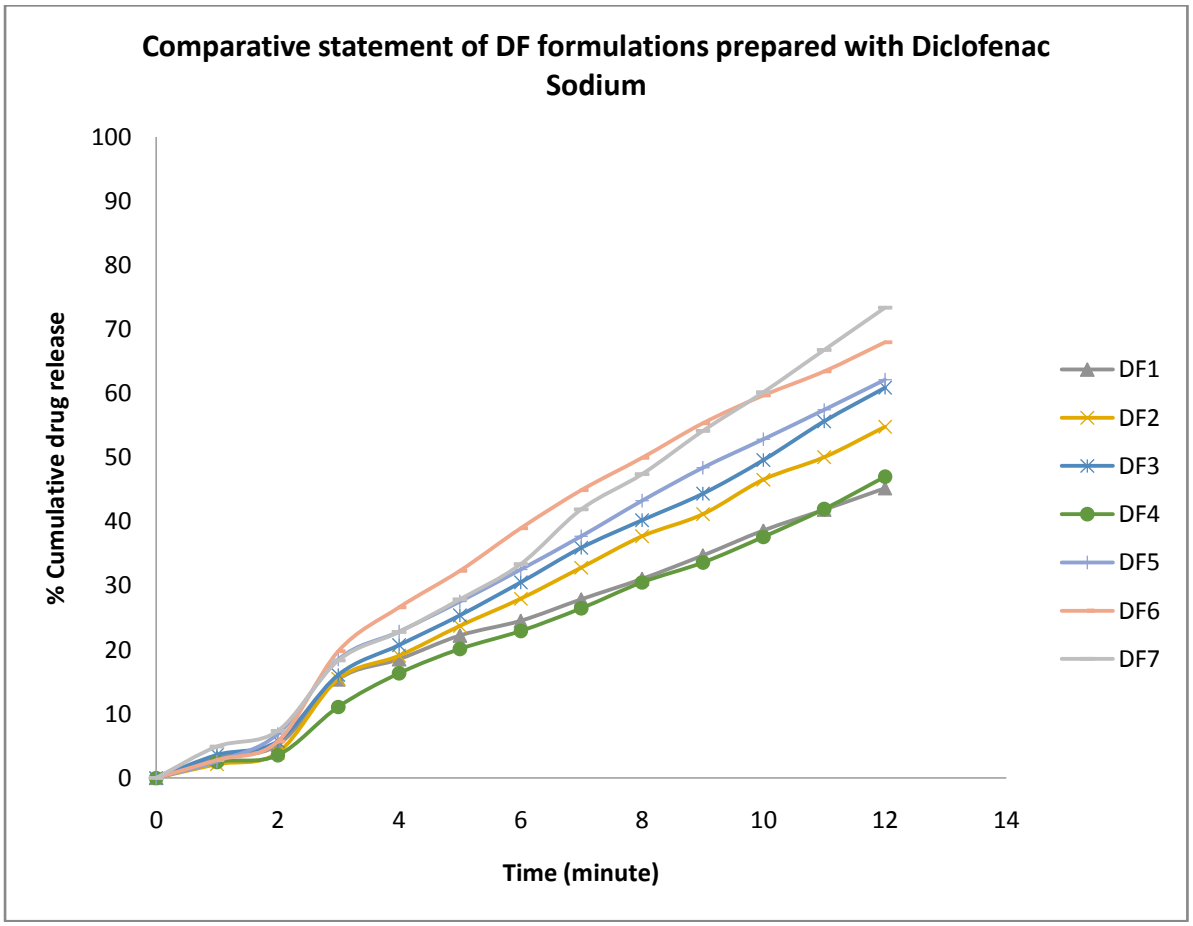

Fig: 12: Dissolutions profiles: A comparative statement of DF formulations prepared with Diclofenac Sodium

Gradient drug released plot of various matrix tablets:

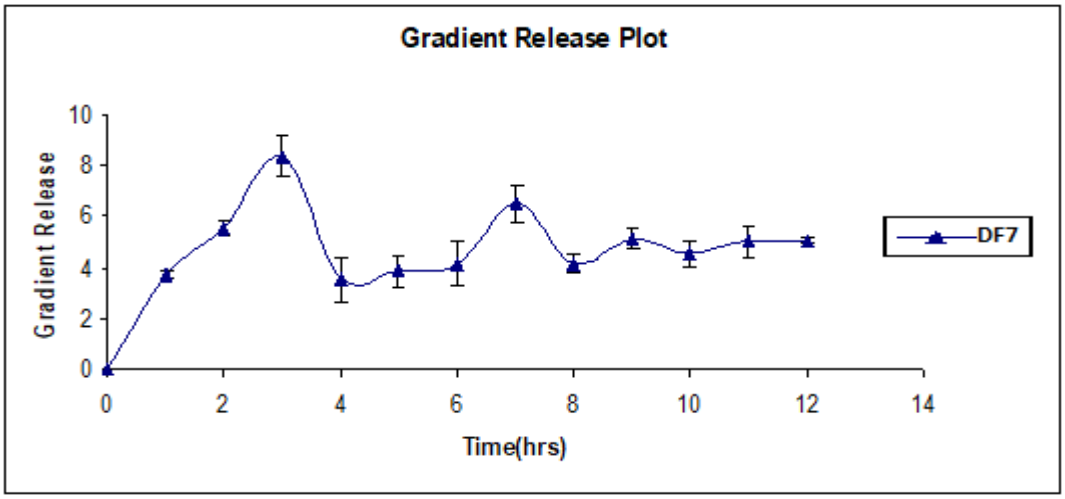

Fig. 13:Gradient drug released (hr^{-1}) plot of formulation DF7

From all the gradient release plot it was seen that for DF7 formulation, initial release was less than all the other prepared formulations and the maintenance concentration of Diclofenac sodium was more or less same as it was in other formulations. In DF7 drug was less but overall release from the tablets

was highest after 12 hrs. So, from the economical point of view, it is acceptable to get same release pattern with using less amount of drug and it may be also caused the lesser gastric irritation. Due to those reasons a DF7 matrix tablet was selected as best formulations as compared to all others.

RELEASE KINETIC STUDY

Table 7: Drug released kinetic model reports for k and n values.

Formulation code	Order of release pattern				
	Zero order	First order	Higuchi Model	Peppas model	
	$k \times 10^2$	$k \times 10^2$	$k \times 10^2$	$k \times 10^2$	n
DF1	403	4.997	172	335	1.086
DF2	472	6.701	220	237	1.325
DF3	503	7.668	225	354	1.170
DF4	383	7.668	237	236	1.230
DF5	532	8.152	246	333	1.235
DF5	605	9.810	279	330	1.301
DF7	453	6.609	215	335	1.133

Table 8: Drug released kinetic model reports for values of correlation coefficient.

Formulation code	Order of release pattern			
	Zero order	First order	Higuchi model	Peppas model
DF1	0.9839 P<0.1	0.9924 P<0.05	0.9865 P<0.1	0.9603 P<0.1
DF2	0.9904 P<0.05	0.99 P<0.05	0.9858 P<0.1	0.9563 P<0.1
DF3	0.9949 P<0.05	0.9875 P<0.1	0.9786 P<0.1	0.9766 P<0.1
DF4	0.9918 P<0.05	0.9822 P<0.1	0.9807 P<0.1	0.9648 P<0.1
DF5	0.993 P<0.05	0.9899 P<0.05	0.9898 P<0.1	0.9688 P<0.1
DF5	0.9834 P<0.1	0.9926 P<0.05	0.9924 P<0.05	0.9543 P<0.1
DF7	0.9946 P<0.05	0.9807 P<0.1	0.9693 P<0.1	0.9846 P<0.1

From the above table it can be concluded that the all formulations followed mixed order kinetics likes zero order, first order release kinetics, and it was also followed the Higuchi model kinetics &Peppas model. It is seen that DF2, DF3, DF5 and DF7 tend to zero order release more than first order (from r^2 value). It is acceptable from any control release formulation to fit more in zero order models than first order models. The *in vitro* release data of all the tablet formulations were subjected to evaluation of release kinetics to identify the release mechanism. The release kinetics and release mechanism of DF7 tablet formulations are presented in Tables 7&8. The release of diclofenac sodium from the DF7

tablets formulation followed mixed order kinetic, but the high value of R^2 in Higuchi model (0.9693) of DF7 revealed that the release of diclofenac sodium from this formulation followed diffusion controlled as well as release of the drug from the matrix tablets was constant, which was further confirmed by the R^2 values (0.9946) in Zero order model rather than first order model.

The release data when fitted to the Korsmeyer-Peppas model it was found that formulations DF7 followed this model and diffusion exponent (1.133) was found greater than 1 (n>1) indicating the release of diclofenac sodium from the tablet followed super case transport.Super case transport corresponds to diffusion, erosion and swelling mechanism and also includes polymer disentanglement and further erosion, which may be due to the presence of matrix forming and swellable guar gum and erodible nature may due to the presence of MCC (disintegrating agent), lactose (hydrophilic diluents) and low viscous polymers like HPMC K100 LV.

The same results were found for all others DF matrix tablets. But the high R^2 value (0.9846) of Korsmeyer-Peppas model clearly indicated the release mechanism of diclofenac sodium from different tablets formulation were strongly dependent on model. Gradient release plot also proved that the release of the drug from the matrix tablets was constant, so by this formulations release pattern can be controlled in a better way and finally controlled and extended release formulations was prepared and developed successfully.

Joshi, Yogesh *et al.*, 2013, was studied to find out the potential of gum from the fruits of Aeglemarmelos to act as a release modifier in the formulation of Diclofenac sodium sustained release matrix tablets. Among all theformulations, AM-4 showed a slow and complete drug release of 98.86% over a period of 12 hr andthereby exhibited a satisfactory sustained drug release phenomenon [5]. Kumar, G *et al.*, 2013,designed and characterized sustained release matrix tablets of Diclofenac sodium employing naturalpolymers like Tamarind seed polysaccharide (TSP) and Guar Gum in view to improve therapeuticaction and patient compliance by reducing dosage frequency. The resultssuggest that the developed sustained releasematrix tablets preparedemploying TSP and Guar Gum ofDiclofenac sodium could perform betterthanconventional dosageforms,leadingtoimproveefficacyandbetterpatientcompliance[6].Garje V. A, *et al.*,2013was developed an oral sustained release dosage form of diclofenac sodium, with chitosanas a sustained release polymer, and to evaluate the prepared dosage form forphysical parameters,likeweightuniformity,hardness,friability,anddrugcontent.TheDiclofenac sodium tablets were prepared by wet granulation method, with a solvent such as distilled water, lactose was used asdiluents, talc 1% was used as lubricant. The result from in-vitro drug release studies indicated that theformulationsbatch-2 & batch-3, withpolymerconcentrations1:1.1&1:1.3resp.Preparedbywetgranulation using distilled water as a solvent, were found to be release the drug at a steady state overan extended period of time upto 24 hrs [7]. UpendraNagaich*et al.*, 2014, was investigated the effectof various concentrations of natural and synthetic polymers on in vitro drug release from sustainedrelease matrix tablets. HPMC K4M and acacia gum were used as synthetic(hydrophilic) and natural (hydrophobic) polymers respectively. On comparing in vitro release of optimizedformulation with marketed preparation, it was concluded that F3 was found to be more efficient andpromisingthanmarketedpreparation[8].EhabMostafaElzayat*etal.*, 2017,waspreparedandevaluatedmulti-layeredmatrix tabletsof diclofenac using Eudragit RL/RSblendtoachievebothimmediate and sustained therapeutic effects. Diclofenac potassium (25 mg) was incorporated in anouterimmediate release layerto provide immediate pain reliefwhereas Diclofenac sodium (75 mg)was incorporated in the inner core to provide extended drug release. Themulti-layeredtabletswereprovedto be bioequivalent with the commercially available tablets and were in agreement with the observed in-vitro drug release results. Stable physical characteristics and drug release profiles were observed inboth long term and accelerated conditions stability studies[41].Abdul Ahad*et al.*,2010,weredesigned matrix tablets of Diclofenac sodium using Hibiscus rosa-sinensis leaves mucilage and tostudy its release retardant activity in prepared sustained release

formulations. Hibiscus rosa-sinensisleaves were evaluated for physicochemical properties. Different matrix tablets of Diclofenac sodium Hibiscus rosa-sinensis leaves mucilage were formulated. Itwas concluded that Hibiscus rosa-sinensis leaves mucilage can be used as an effective matrix formingpolymer,to sustain the release of Diclofenac sodium from the formulation[42].ThanikachalamSivakumara*et al.*, 2007, were prepared megaloporous controlled release tablets of Diclofenac sodium (DS) with two kinds of granules. One of them is the restraining-phase matrix granule (RMG) and itcontrols the release rate of the drug. The otherone is the soluble housing-phase matrixgranule(HMG) and controls liquid penetration into the system. Carnauba wax and Eudragit L 100 polymerswere used to constitute the restraining and housing matrix phases, respectively. From the above analysis, it is evident that the release mechanism of DSfrom matrix tablet is influenced by both hardness and polymer contents. The stability profiles indicatethatthe physico-chemicalpropertiesofthetabletsarenotaffectedonstorage at45°C/75%RHupto6 months [43]. G. N. K. Ganesh *et al.*, 2010, were fabricated sustained release tablets of Diclofenac sodium usingCashewnuttreegum,HPMCandCarbopol.It is cleared through the dissolution profile ofDiclofenac sodium from matrix tablets prepared using different polymerswere indicated an increasein the polymer ratio retarded the drug release to a greater extent [44]. Ehab Ibrahim Taha *et al.*, 2015,werepreparedDiclofenac sodium (DS)matrix tabletsbydirectcompressionmethodunderdifferent compression forces (5, 10, 15 and 20 KN), using ethylcellulose as matrix forming material. Data obtained revealed that, upon increasingcompression force the in vitro drug release was sustained and the Tmax value was four hours (forformulations compressed at 15 and 20 kN) compared to the conventional voltarine® 50 tablets (Tmaxvalue of 2 hours [45]. Basawaraj S Patil*et al.*, 2010, was developed HPMC matrix tablets for oralcontrolled/ sustained release of water-soluble Diclofenac Potassium. Sustained release matrix tabletscontaining 100 mg of Diclofenac Potassium were developed using different drug polymer ratio ofHPMC.Applying the exponential equation, all the tablets (exceptD5) showed diffusion dominated drug release. The mechanism of drug release from D5 was diffusioncoupled with erosion [46].

STABILITY STUDIES OF BEST SELECTED TABLET FORMULATIONS AS PER ICH GUIDELINES

Stability of a pharmaceutical preparation can be defined as “the capability of a particular formulation (dosage form or drug product) in a specific container and closer system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its self-life” [30].
The stability of a product can be evaluated if its degradation impurities, it’s assay, its dissolution and disintegration time does not generate/alter considerably after 6 months of accelerated stability testing at 40°C and 75% RH as per the ICH guidelines.
Among the different tablet formulations, AF7 and DF7 showed highest released of drug. Therefore, formulations AF7 and DF7 were selected for further studies.

Table 9: Quality control test parameters of DF7 tablets at different time intervals during accelerated stability study

Parameters	Initial	After 90 days
Physical appearance	**White to off white**	**No change**
Weight variation (mg)	300.11	300.46
Thickness (mm)	4.2	4.3
Hardness (kg/cm^2)	6	6
Friability (%)	0.43	0.41
% Drug content Uniformity	101	100

***In vitro* drug release studies**		
Time (Hrs)	**% Cumulative drug release**	
	Initial	**After 90 days***
0	**0**	**0**
1	4.89	4.97
2	7.33	7.85
3	18.33	18.85
4	22.79	23.12
5	27.86	28.25
6	33.35	33.88
7	41.92	42.45
8	47.39	48.55
9	54.15	55.64
10	60.16	61.25
11	66.75	67.88
12	75.35	76.02

**In vitro* release study at different time intervals were carried out on six tablets and the mean value is presented.

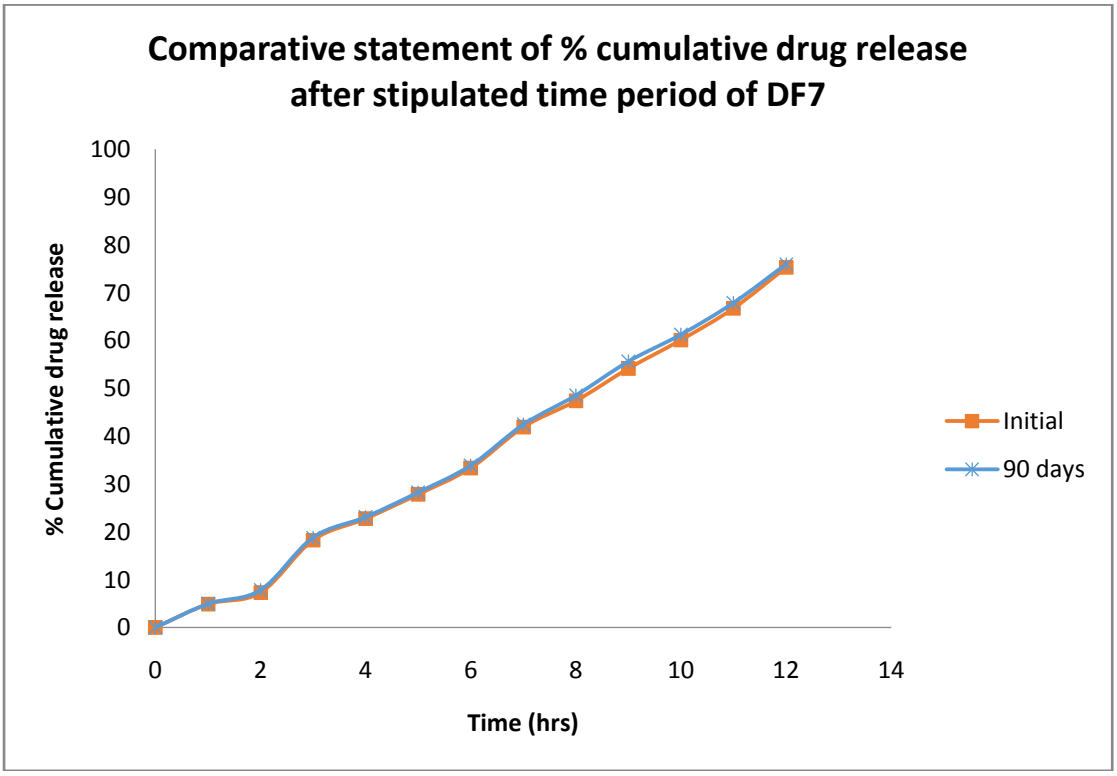

Figure 14: *In vitro* release profile of tablet formulation (DF7) after different time intervals (Mean ± S.D.; n = 3).

The evaluated quality control test parameters of stability studies at different time intervals are presented in Table 9. There were no significant changes in the test parameters like: physical appearance, weight variation, diameter, thickness, hardness, friability and drug content uniformity test were observed in tablets after 3 months of storage at accelerated stability conditions. The *in vitro* release data of tablet formulation at initial stage was considered as the reference for release study. The *in vitro* release profile (Figure 14) revealed that the release profile after 3 months of storage at

accelerated condition was found to be similar to that of reference one. Based on the results it was confirmed that the tablet was stable after 3 months of storage at accelerated stability conditions, probably due to the fact that the stable excipients used to prepare the tablets, but further real time stability analysis is required to establish the stability and to determine the shelf life of the best selected formulation.

CONCLUSION:

Actual aim of this research work was to design and developed a controlled-release matrix tablets by using diclofenac sodium (DS).

The drug excipient interaction study was done by FT-IR. The FT-IR spectrum shows no interaction between drug, guar gum, MCC, Lactose and HPMC because the entire characteristics peak was present in this spectrum.

It showed that granules have good flow properties. From these values it can be concluded that all the granules were good flowability.

All the tablet formulations (DF) passes the weight variation test, the percentage weight variation was within the IP limit i.e, below ± 5.0 %. The hardness of all the Formulations was found approx 6 Kg/cm^2. The friability of Formulation DF1-DF7 was found to be in the range of 0.42-0.83%, which was within the IP limit i.e below 1%. Thickness of all the tablets were approx 3mm. The drug content of all the formulation was found in the range of 99.5- 103 % which was within acceptable limit. The formulated matrix tablets met the pharmacopeial requirement of uniformity of the weight. All the tablets conformed to the requirement of % friability, thickness and assay which was carried out as per I.P method and were well and within acceptable limits.

The extent of Swelling was measured in terms of % weight gain by tablet. Swelling behaviors of formulations DF1, DF2, DF3, DF4, DF5, DF6 and DF7 was studied. The swelling index was calculated with respect to time as time increase, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to 8 h. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium**.** The direct relationship was observed between swelling index and HPMC and MCC concentration, and this concentration increase, swelling index was also increased. It has been observed that the cumulative percent drug release increase with increasing concentration of micro crystalline cellulose and HPMC(K100LV) and swelling index. The reason attributed to this fact is faster erosion of the gelled layer from the tablets containing higher amount of micro crystalline cellulose and HPMC (K100LV) and formulation DF7 showed higher swelling behavior and have higher percent of release rate then other formulations.

Micro crystalline cellulose was not incorporated into the formulation DF1, compared to formulation DF2. In this case, the swelling behavior of micro crystalline cellulose allowed further penetration of medium, resulting in rapid erosion of the guar gum matrices and thus the release rate was lesser in case of DF1than the DF2. From all the gradient release plot it was seen that for DF7 formulation, initial release was less than all the other prepared formulations and the maintenance concentration of Diclofenac sodium was more or less same as it was in other formulations. In **DF7** drug was less but overall release from the tablets was highest after 12 hrs. So, from the economical point of view, it is acceptable to get same release pattern with using less amount of drug and it may be also caused the lesser gastric irritation. Due to those reasons a DF7 matrix tablet was selected as best formulations as compared to all others.

From kinetic study, it can be concluded that the all-formulations dose follows zero order, first order release kinetics as well as it is also following the Higuchi model kinetics &Peppas model. From the all values of rare approximately close to each other, so all formulation follows the mixed order release kinetics. The release data when fitted to the Korsmeyer-Peppas model it was found that formulations **DF7** followed this model and diffusion exponent (1.133) was found greater than 1 (n>1) indicating the release of diclofenac sodium from the tablet followed super case transport.Super case

transport corresponds to diffusion, erosion and swelling mechanism and also includes polymer disentanglement and further erosion, which may be due to the presence of matrix forming and swellable guar gum and erodible nature may due to the presence of MCC (disintegrating agent), lactose (hydrophilic diluents) and low viscous polymers like HPMC K100 LV.The same results were found for all others DF matrix tablets. But the high R^2 value (0.9846) of Korsmeyer-Peppas model clearly indicated the release mechanism of diclofenac sodium from different tablets formulation were strongly dependent on model. Gradient release plot also proved that the release of the drug from the matrix tablets was constant, so by this formulations release pattern can be controlled in a better way and finally controlled and extended-release formulations was prepared and developed successfully.

The inverse relationship was noted between of HPMC (K100LV) and HPMC (K4M) in release rate of Diclofenac sodium because HPMC (K4M) high molecular weight and viscosity then HPMC (K100LV), so resulted in slower release rate due to formation of a thick gel structure and further retarding penetration of the dissolution medium and leach out the Diclofenac sodium from continuous viscoelastic matrix, that retard the drug release from tablet matrix Lactose is the most useful filler for tablet formulations. It is freely water soluble and would modify the drug release for undergoing solution. While amount of lactose is increasing in the formulation DF3, release rate was markedly increase compared to formulation DF2 because lactose diffuses outwards through the gel layer, increasing the porosity and decreasing the tortuosity of diffusion path of drug. In the trial DF7, the quantity of Diclofenac sodium was reduced and quantity of lactose and micro crystalline cellulose was increased, the percent of release rate was increase compare to formulation F6 and finalized formulation **DF7**.

The evaluated quality control test parameters of stability studies at different time intervals it can be revealed that there were no significant changes in the test parameters like: physical appearance, weight variation, diameter, thickness, hardness, friability and drug content uniformity test were observed in tablets after 3 months of storage at accelerated stability conditions. The *in vitro* release data of tablet formulation at initial stage was considered as the reference for release study. The *in vitro* release profile revealed that the release profile after 3 months of storage at accelerated condition was found to be similar to that of reference one. Based on the results it was confirmed that the tablet was stable after 3 months of storage at accelerated stability conditions, probably due to the fact that the stable excipients used to prepare the tablets, but further real time stability analysis is required to establish the stability and to determine the shelf life of the best selected formulation.

Finally, it can be concluded that matrix tablets were prepared and developed successfully with the help of diclofenac sodium by using various matrix forming polymers and by changing other variables to control the drug release patterns and further it can be confirmed by the clinical setting of both the best selected formulations to get *IVIVC* data.

REFERENCES:

1. Shargel L,YuABC. Modified release drug products. In: Applied Biopharmaceutics andPharmacokinetics.4thed.McGrawHill.1999:169-171.
2. Al-Badr A A,Mekkowi AG. Analytical profiles of Diclofenacsodium. In Analytical profiles of drugs substances, Vol.19; Florey, K. Ed. Acadmic press: New Yark,1990; pp 123-140.
3. Dollery, C. Therapeutic Drugs, Churchill livirgstone, London, 1999: D88-D91.
4. Tripathi, K. D. Essentials of medical pharmacology. Ed. Jaypee Brothers: New Delhi, 2003: 178.
5. Joshi, Yogesh& Kumar, Ratendra&Teotia, U. Formulation and Evaluation of Diclofenac sodium Sustained Release Matrix Tablets Using AegleMarmelos Gum. International Journal of Current Trends in Pharmaceutical Research. 2013;1: 174-180.
6. Kumar, G. & Rao, M. & Reddy, Kishore Kumar & Kumar, K. & Gangadhar, S. V. N. Development and evaluation of Diclofenac sodium sustained release matrix tablets employing natural polymers. World Journal of Pharmaceutical Research.2013; 2:2541-2550.
7. Garje V.A, Nagargoje S.S, Phanse V.R, Kshirsagar R.R, Formulation and evaluation of SR release

matrix tablets of Diclofenac sodium by using chitosan as a natural polymer, 14 February 2013; Pharmatutor-art-1651. https://www.pharmatutor.org/articles/formulation-evaluation-sr-release-matrix-tablets-diclofenac-sodium-chitosan-natural-polymer

8. UpendraNagaich, CharuBharti, Ashok Kumar Pal, Neha Gulati. Diclofenac sodium Loaded Sustained Release Matrix Tablet Possessing Natural and Synthetic Polymers: Formulation and in vitro Characterization, Indian Journal of Pharmaceutical Education and Research,48 (supplement), Oct-Dec, 2014:49-55.
9. Miranda A, Millan M, Caraballo I. Investigation of the influence of particle size on the excipient percolation thresholds of HPMC hydrophilic matrix tablets. Journal of Pharmaceutical Sciences.2007; 96(10):2746-2756.
10. Kale, V. V.; Kasliwal, R. H.; Avari, J. G. Effect of matrix geometry on drug release from Guar Gum matrix tablet. Ind. Drugs, 2005:42:84-86.
11. Krishnaiah, Y. S. R.; Muzib, Y. I.; Bhaskar, P.; Satyanarayana, V.; Latha, K. Pharmacokinetic evaluation of Guar Gum based colon targeted drug delivery system of tinidazole in healthy human volunteers. Drug Del. 2003; 10:263-268.
12. Deodatt, A. W.; Abu; Serajuddin, T.M..; Jacobson, H. Preformulation testing in pharmaceutical dosage forms. Tablets Vol. 1, 2nd ed., revised and expanded. Lieberman, Lachman. Schwartz, Marcel dekker, Inc. 1989:2-3.
13. Deodatt, A. W; Abu; Serajuddin, T.M.; Jacobson, H. Preformulation testing in pharmaceutical dosage forms. Tablets Vol. 1, 2nd ed., Revised and expanded by Lieberman, Lachman, Schwartz, Marcel Dekker Inc. 1989:54-56.
14. Eugene, F.F.; Timothy, A. H..Preformulation in The Theory and practice of Industrial pharmacy, 3rd ed. by Lachman, Liebermann, Kanig, 1990:183-184.
15. Borguist P, Korner A, Larsson A. A model for the drug release from a polymeric matrix tablets-effect of swelling and dissolution, J Controlled Release, 2006; 113:216-225.
16. Siepmann J, Peppas NA, HPMC matrices for controlled drug delivery: new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics, PharmResearch,2000;16:1748-1756.
17. Kumar R, Patil MB, Patil SR, Paschapur MS. Formulation and evaluation of effervescent floating tablet of famotidine. International Journal of Pharm Tech Research, 2009;1(3):754-763.
18. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: a review. International Journal ofPharmTech Research, 2009;1(3):623-633.
19. Zaware SR, Gaikwad PD, Bankar VH, Pawar SP. A Review on floating drug delivery system. International Journal of Pharmaceutical Sciences, 2010; 2(3):834-847.
20. BCS classification system. Highlight of the FDA‟s draft guidance, www.fda.gov
21. Sakarkar DM, Kshirsagar RV, Deshbhratar RM. Studies on formulation and invitro evaluation of gastroretentive drug delivery system of carbamazepine. International Journal of Chem Tech Research, 2010;2(1):108-113.
22. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers, Eur J Pharm Biopharm , 2010;74(2):332-9.
23. Sheu MT, Chen RN, Ho H-O, Yu CY. Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. European Journal of Pharmaceutical Sciences, 2010; 39:82–89.
24. Shah SH, Patel J K, Patel NV. Formulation and evaluation of effervescent floating tablet of Levofloxacin against H.pylori infection. Der Pharmacia Sinica,2010;1 (3):232-244.
25. Markhade DM,Fulzele, S.B.; Satturawar, P.M.; Joshi, S.B. Gum copal and gum damer : novel matrix forming materials for sustained drug delivery. Ind. J. Pharm. Sci. 2006: 68:53- 58.
26. Sheu MT, Chen RN, Ho H-O, Yu CY. Development of swelling/floating gastroretentive drug

delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. European Journal of Pharmaceutical Sciences, 2010; 39 :82–89.
27. Sakarkar DM, Kshirsagar RV, Deshbhratar RM. Studies on formulation and invitro evaluation of gastroretentive drug delivery system of carbamazepine. International Journal of Chem Tech Research, 2010;2(1):108-113.
28. HDZalte, R. B. Saudagar, Review on sustained release matrix tablet, IJPBS, 3(4), OCT- DEC, 2013:17-29.
29. Shah SH, Patel J K, Patel NV. Formulation and evaluation of effervescent floating tablet of Levofloxacin against *H.pylori* infection. Der Pharmacia Sinica,2010;1 (3):232-244.
30. Indian Pharmacopeia. Controller of Publication, Delhi, 2007; 1,2:153,58.
31. Dooley, Mukta, Spencer, Caroline M, Dunn, Christopher J. Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. Adis International Drugs, 2001; 61(9):1351-1378.
32. Brogden, Wiseman, Lynda R. Aceclofenac: a review of its pharmacodynamic properties and therapeutic potential in the treatment of rheumatic disorders and in pain management. Adis International Drugs, 1996; 52(1):113-124.
33. Al-Saidan, SM,Krishnaiah, Y. S. R.; Patro, S. S.; Satyanarayana, V. In-vitro and in-vivo evaluation of Guar Gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. AAPS Pharm. Sci. Tech. 2005; 6: E14-E21.
34. Varshosaz, J.; Tavakoli, N.; Kheirolahi, Use of hydrophilic natural gums in formulation of sustained release matrix tablets of tramadol hydrochloride. AAPS Pharm. Sci. Tech.2006; 7: E1-E7.
35. KrishnaiahYSR, Devi AS,Nagesware RL,Bhasker, P.R.; Karthikeyan, R. S.; Satyanarayana, Guar Gum as a carrier for colon specific delivery, influence of metronidazole and tinidazole on in vitro release of albendazole from Guar Gum matrix tablets. J. Pharm. Pharm.Sci.2001; 4: 235-243.
36. Al-Saidan, SM,Krishnaiah,Y. S. R.; Satyanarayana,V. Rao.Invitro and invivo evaluation of Guar Gum based matrix tablets of rofecoxib for colonic drug delivery. Drug. Dev. 2005:2, 155-163.
37. Siepmann J,Streubel, A.; Peppas, N.A. Understanding and predicting drug delivery from hydrophilic matrx tablets using the sequential layer model. Pharm. Res. 2002; 19:306-314.
38. Yeole PG,Galgattae, I. B. ; Nakhat, P. D. Design and evaluation of xanthan gum based sustained release matrix tablet of diclofenac sodium. Ind. J. Pharm. Sci. 2006; 2:185-189.
39. L Lachman, HA Lieberman, Joseph L Kanig. The theory and practice of Industrial pharmacy, Verghesh publishing house, 3rd edition, 1990:346.
40. Basak SC, Jayakumar BM and Mani KPL. Formulation and release behavior of sustained release Ambroxol HCL HPMC matrix tablet. Ind J Pharm Sci 2006; 68 (5):594-598.
41. EhabMostafaElzayataAli Abdelzaher Abdel-RahmancSayed Mohamed AhmedcFars KaedAlanaziabWalidAbdulazimHabibaHishamSulimanAbou-AudadAdel Sakre, Formulation and pharmacokinetics of multi-layered matrix tablets: Biphasic delivery of diclofenac, SaudiPharmaceutical Journal, 2017;25(5), July:688-695.
42. Abdul Ahad, Chitta Suresh Kumar, Kishore Kumar Reddy B, Ravindra BV, Sasidhar CGS, Abhilash C, Sagar NRV, Designing and evaluation of Diclofenac sodium sustained release matrix tablets using hibiscus rosa-sinensis leaves mucilage, International Journal of Pharmaceutical Sciences Review and Research, 2010; 1(2), March – April, Article 006:29-31.
43. ThanikachalamSivakumara, Prabal Kumar Mannaa, ThanikachalamSundarRajanb, Mahmoud Ahmedc, RajappanManavalana, Design and Evaluation of Diclofenac sodium Megaloporous Matrix System Aimed for Colonic Drug Delivery, Iranian Journal of Pharmaceutical Sciences Winter 2007; 3(1):1-12.
44. GNKGanesh, RSureshkumar, NJawahar ,V Senthil, D NagasamyVenkatesh and M. ShanmukhaSrinivas , Preparation and Evaluation of Sustained Release Matrix Tablet of Diclofenac sodium using Natural Polymer, J. Pharm. Sci. & Res. 2010;2 (6):360-368.
45. Ehab Ibrahim Taha, Gamal Abdel GhanyShazly, Gamaleldin Ibrahim Harisa, NahlaSedikBarakat,

FouzaKayem Al-Enazi and Ibrahim MostafaElbagory, Formulation and in vivo evaluation of Diclofenac sodium sustained release matrix tablet: Effect of compression force, Pak. J. Pharm. Sci., 2015;28(2), March:573-579.

46. Basawaraj S Patil, Upendra Kulkarni and Parikh Bhavik, Formulation and evaluation of diclofenac potassium matrix tablets, IJPSR (2010); 1(8) (Suppl.):88-92.