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Formulation and *in vitro* Evaluation of Oral Floating Matrix Tablets of Diclofenac Sodium

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Abstract: The purpose of this research was to prepare floating matrix drug delivery system of Diclofenac sodium. Diclofenac sodium Floating matrix tablets were developed to prolong gastric residence time and increase its bioavailability Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. Floating matrix tablets containing 100 mg Diclofenac sodium were developed using different bees wax combinations. The tablets were prepared by melt granulation technique, using polymers such as Hydroxy propyl methyl cellulose (HPMC K15M), ethyl cellulose, bees wax alone or in combination with Cetyl alcohol and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate on floating properties were investigated. The formulation was optimized on the basis of acceptable tablet properties, floating lag time, and total duration of floating and *in vitro* drug release. The resulting formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. The results of dissolution studies, floating lag time indicates that formulations F6 exhibited good and controlled drug release. Applying the linear regression analysis and model fitting, the selected formulation F6 showed diffusion coupled with erosion drug release mechanism, followed first order kinetics.
Keywords: Diclofenac sodium, floating tablets, melt granulation, *in vitro* release.

INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes. Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects: (1) gastrointestinal (GI) physiology (2) physiochemical properties of the drug and (3) dosage form characteristics [1-6]. Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). Dosage form with prolonged GRT or gastro-retentive dosage form (GRDF) provides an important therapeutic option. Various approaches for preparation of gastro retentive drug delivery system include floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension system and sachet systems [7-8]. Among these, the floating dosage form has been used most commonly.

Floating drug delivery systems were first described by Davis in1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine [9-11].

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) having chemical name Sodium 2-[(2,6-dichlorophenyl)- amino] phenyl acetate. The most frequent adverse side effects occurring with Diclofenac sodium are gastrointestinal (GI) disturbances, peptic ulceration and GI bleeding, hence there is a potential need for a floating matrix dosage form for this drug to minimize gastric erosion

side effect. Its biological half-life on the other hand is very short, sustaining its anti-inflammatory activity only for a few hours and associated adverse effects; it is considered an ideal model drug for floating matrix drug delivery [12-18]. The present research work is an attempt to formulate rate controlled floating drug delivery system of Diclofenac sodium which is primarily absorbed from stomach, so by increasing the GRT of the drug, the bioavailability can be increased. As the drug is moderately weekly acidic drug, so the stomach is the major absorption site for the drug.

Basing on this fact the drug is made to float in the stomach using the mechanism of buoyancy by using gas generating agent ($NaHCO_3$,) and the drug is delivered in the sustained release dosage form by using Bees wax, Cetyl alcohol, as hydrophobic polymer. HPMC is used as swellable polymer to formation of gel layer for control release. Ethyl cellulose is used to retard the disintegration and also dissolution. Microcrystalline cellulose is used as diluents [19]. The study also includes various evaluation studies of Diclofenac sodium tablet and the effect of processing variables on it. A possible interaction between drug and polymers are also investigated by FTIR study.

So, the objectives of the present study of formulation and in-vitro evaluation of oral floating matrix tablets of Diclofenac sodium are

- to prepare floating matrix tablets of Diclofenac sodium using hydrophobic wax materials, Sodium bicarbonate as gas generating agent and
- to evaluate the *in vitro* release characteristics and to predict and correlate the release behavior of Diclofenac from the matrix.

MATERIALS AND METHODS:-

Materials

Diclofenac sodium and HPMC K15M were obtained as gift sample from Genovo Development services Ltd, R & D Center, Bangalore, Ethyl cellulose and Bees wax were purchased from HiMidei Laboratories PVT, Ltd. Mumbai, Cetyl alcohol was purchase from Bugoyne Burdiges & Co, Mumbai, Microcrystalline cellulose was purchase from Yarrow Chem Products, Mumbai, Sodium bicarbonate was purchase from Nice Chemicals, PVT, Ltd, Cochin, Magnesium stearate was purchase from Central Drug House, PVT, Ltd, Delhi and Talc was purchase from LOBA Chemie PVT, Ltd. Mumbai. All other reagents, solvents, chemicals used were of either pharamcopoeial or analytical grade.

METHODS:-

PREPARATION OF STANDARD CURVE OF DICLOFENAC SODIUM:-

Solutions ranging from 2 to 10 µg/ml were prepared by using ethanol and 0.1 N HCl Absorbance was measured for each solution at λ_{max} of 276 nm, using PC Shimadzu UV Spectrophotometer. . Correlation coefficient was found to be 0.9996 in 0.1 N HCl.

PREPARATION OF FLOATING TABLETS BY MELT GRANULATION TECHNIQUE:-

Floating tablets, each containing 100 mg Diclofenac were prepared by a conventional melt granulation technique. The composition of various formulations of the tablets with their codes is listed in Table. The composition with respect to polymer combination was selected on the basis of trial preparation of tablets. The amount of bees wax was decreased gradually and the reduced amount of bees wax was replaced by Cetyl alcohol. As per each formulation batch code required quantity of bees wax and Cetyl alcohol, were weighed and melted separately in a large china dish over a water bath. The drug was added to the molten wax and mixed well. Previously weighed quantities of Ethyl cellulose, HPMC, Microcrystalline cellulose and Sodium bicarbonate were added to the drug-wax mixture and mixed well. After thorough mixing the china dish was removed from water bath and cooled. The coherent mass was then scrapped from the china dish and was passed through sieve no.30.

Table 1:- FORMULAE FOR DICLOFENAC SODIUM FLOATING MATRIX TABLETS

INGREDIENT (mg per tablet)	Formulation									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Diclofenac Sodium	100	100	100	100	100	100	100	100	100	100
BEES WAX	90	90	90	90	90	90	80	70	60	55
Cetyl alcohol	-	-	-	-	-	20	30	40	50	55
HPMC K 15 M	64	64	64	64	64	64	64	64	64	64
Ethyl cellulose	30	30	30	30	30	30	30	30	30	30
Microcrystalline cellulose	60	50	40	35	30	30	30	30	30	30
Sodium bicarbonate	-	10	20	25	30	30	30	30	30	30
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3
Total Weight of tablet (mg)	350	350	350	350	350	350	350	350	350	350

EVALUATION OF GRANULES:-

Prior to compression into tablets, the granules were evaluated for properties such as;

a) Angle of repose:-

Flowability of different batch of granules was determined by calculating angle of repose by fixed height method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

$$\Theta = \tan^{-1} (h / r)$$

Where, θ = Angle of repose, h = Height of the pile and r = Average radius of the powder cone

b) Bulk Density:-

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

$$D_b = M / V_0$$

Where, M is the mass of powder and V_0 is the Bulk volume of the powder.

c) Tapped density:-

It was determined by placing a graduated cylinder, containing a known mass of drug- excipients blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by $D_t = M / V_t$

Where, M is the mass of powder and V_t is the tapped volume of the powder

d) Powder flow properties:-

The flow properties were determined by

i) Carr's Index (I):-

It is expressed in percentage and is expressed by $I = D_t - D_b / D_t$

Where D_t is the tapped density of the powder and D_b is the bulk density of the powder

ii) Hausner ratio:-

It is expressed in percentage and is expressed by $H = D_t / D_b$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

COMPRESSION OF TABLETS:-

After evaluation of granules were then compressed into tablet by direct compression technique using Hand operated tablet press Machine.

EVALUATION OF TABLETS:-

a) Weight Variation:-

20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

b) Thickness and diameter:-

The thickness and diameter of the tablets was measured by Vernier Calipers. It is expressed in mm**.**

c) Hardness:-

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in kg / cm^2**.**

d) Friability (F):-

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (**%**). 20 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 mins (100 revolutions). The tablets were weighed again (W_{final}). The % friability was then calculated by $F = W_{initial} - W_{final} / W_{initial} * 100$

e) Content Uniformity:-

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 5ml of Methanol and made up to volume with 0.1N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 276 nm using 0.1 N hydrochloric acid as blank.

f) In vitro buoyancy study:-

The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

g) In vitro dissolution studies:-

The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 276 nm using a UV/Visible spectrophotometer.

Evaluation of drug release mechanism by various kinetic models

Data obtained from in vitro release studies were fitted to various kinetic equations to find out the mechanism of drug release from tablet. The kinetic models used were

- Zero Order Release kinetic model
- First Order Release kinetic model
- Hixson Crowell cube root equation
- Higuchi square root equation

RESULTS AND DISCUSSION:-

Diclofenac Sodium is a water insoluble drug. Its poor inherent compressibility coupled with associated side effect posses a significant challenge for developing floating tablets. For developing floating tablets with desirable drug release profile, cost effectiveness and broader regulatory acceptance combination of HPMC, Ethyl cellulose, Bees wax, and Cetyl alcohol was chosen as release controlling polymers. Sodium bicarbonate was added as a gas generating agent.

Evaluation of the pre-compression parameters of formulated granules:-

Formulation of proper powder/granule blend is the key factor in the production of tablet dosage form involving floating extended release of drug from matrix type particle. Physical parameters such as specific surface area, shape, hardness, surface characteristics and size can be significantly affect the rate of dissolution of drugs contained in a complex system. The formulated granule blends of different formulations (F1 to F10) were evaluated for angle of repose, tapped density, bulk density, Carr's index and Hausner ratio. The results of angle of repose (<25) indicated good flow properties of the entire formulated granule blend. The compressibility index value were recorded, result in good to excellent flow properties.

Formulated powder blends density; porosity and hardness are often interrelated properties and are likely to influence compressibility, porosity, dissolution profile and properties of tablets made from it. The results of percentage porosity indicating that the packaging of the granule blend may range from close to loose packaging and also confirming that particle are not of greatly different sizes. All these results indicate that the formulated granule blend possessed satisfactory flow properties and compressibility.

Results of Post Compression Properties of Diclofenac Sodium Tablets:-

Evaluation of the formulated floating tablets:-

The tablets of different formulations (F1 to F10) were evaluated for various parameters viz; thickness, diameter, hardness, friability, percentage weight variation and percentage drug content. All the formulations showed uniform thickness and diameter. In a weight variation test, the pharmacopoeial limit for the percentage deviation for the tablets of more than 350mg is ± 5%. The average percentage deviation of all tablet formulations was found to be with in the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Drug content was found to be uniform among different batches of the tablets, and the percentage of the drug content was more than 96%. The hardness of all the formulation was between 4.0 to 5.5 kg/cm^2. The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability.

Table 2: - Results of pre-compression parameters of formulated granules

Formulation code	AOR in degree = $\tan^{-1}$ (h/r)	Bulk Density	Tapped Density	Carr's index	Hausner Ratio
F1	15.1	0.57	0.71	19.0	1.24
F2	12.4	0.55	0.67	16.9	1.22
F3	10.2	0.55	0.70	19.9	1.27
F4	14.0	0.54	0.73	21.5	1.35
F5	17.7	0.53	0.67	20.8	1.26
F6	16.6	0.57	0.74	23.1	1.29
F7	19.2	0.56	0.74	23.7	1.30
F8	18.7	0.57	0.73	22.8	1.32
F9	20.8	0.58	0.72	18.7	1.24
F10	20.3	0.55	0.71	19.0	1.24

Table 3:– Results of Post Compression Properties of Diclofenac Sodium Tablets

Formulation code	% of Weight Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	350 ± 4	5.3± 0.01	9.9±0.01	4.0± 0.01	0.28± 0.01	96.6
F2	350 ± 5	5.5± 0.01	9.9±0.02	5.0± 0.01	0.22± 0.01	96.1
F3	350 ± 4	5.3± 0.01	9.9±0.01	5.0± 0.01	0.18± 0.01	97.0
F4	350 ± 3	5.3± 0.01	9.9±0.02	5.0± 0.01	0.44± 0.01	96.1
F5	350 ± 2	5.4± 0.01	9.9±0.01	4.5± 0.01	0.38± 0.01	96.1
F6	350 ± 4	5.2± 0.01	9.8±0.02	5.0± 0.01	0.49± 0.01	95.6
F7	350 ± 3	5.5± 0.01	9.9±0.01	5.0± 0.01	0.41± 0.01	97.0
F8	350 ± 4	5.3± 0.01	9.9±0.01	5.0± 0.01	0.28± 0.01	96.6
F9	350 ± 3	5.4± 0.01	9.9±0.01	5.0± 0.01	0.25± 0.01	95.6
F10	350 ± 4	5.3± 0.01	9.9±0.01	5.0± 0.01	0.28± 0.01	96.6

In vitro Buoyancy study:-

From the results of floating behaviour studies, it was found that as the concentration of effervescent mixture increase, the floating lag time, floating duration and matrix integrity decreased and vice versa. A reverse trend was observed on increasing the polymer concentration. The initial batches of F1 prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces Co_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml, and the tablet becomes buoyant. To study the effect of sodium bicarbonate concentration on floating lag time, batches F1 to F10 were selected. It was found that as the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate 30 mg was essential to achieve optimum in vitro buoyancy (i.e, floating lag time of 4 to 5 minutes and floating duration of 12 hours). Further increase in concentration of sodium bicarbonate does not show any significant effect on floating behaviour. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. Thus 30 mg concentration of sodium bicarbonate was kept constant for batches F5 to F10, which showed floating lag time between 4 and 5 minutes and remained floating for more than 12 hours. The relationships between the amounts of gas generating agent and the floating lag time as well as the duration of floating are shown in Table. It was observed that the floating lag time for this system is in the range of 15 to 4 min and floatation was achieved maximum at gas generating quantity of 30 mg within 4 min. Therefore the formulation F5 to F10 was selected for In-vitro Dissolution study of floating matrix tablet.

Table 4 - Results of in vitro Buoyancy Study of Diclofenac sodium matrix tablet

Formulation code	Amount of Sodium bicarbonate (mg)	Buoyancy Lag Time	Total Floating time
F1	0	Did not float	Did not float
F2	10	30min	>4 hrs
F3	20	18 min	>6 hrs
F4	25	10 min	>8 hrs
F5	30	5 min	>12 hrs
F6	30	5 min	>12 hrs
F7	30	5 min	>12 hrs
F8	30	4 min	>12 hrs
F9	30	4 min	>12 hrs
F10	30	4min	>12 hrs

In Vitro Dissolution Studies:-

Based upon Floating lag time and total floating time formulation F5 to F10 were selected for dissolution study. The results obtained from *in vitro* dissolution studies of all the six formulations were given in figures. In Formulation F5, F6, F7, F8, F9 and F10 were showed 72.21 %, 75.02 %, 59.85%, 58.52%, 58.07% and 57.96 % drug release at the end of 12 hours respectively. Incorporation of higher amount of cetyl alcohol in formulation F7, F8, F9 and F10 was found to be less drug release characteristics due to excess amount of Cetyl alcohol in comparison to Formulation F5 and F6. The drug released from all the formulations diffusion coupled with erosion drug release mechanism, followed first-order kinetics. The regression coefficient was found to be higher (0.9878) in formulation F6. Formulation F6 was selected as a best optimized formulation among the all formulation because it gives with a sustained release of more than 75 % drug release at the end of 12 hrs.

COMPARATIVE STUDIES OF IN VITRO DRUG DISSOLUTION PROFILE:

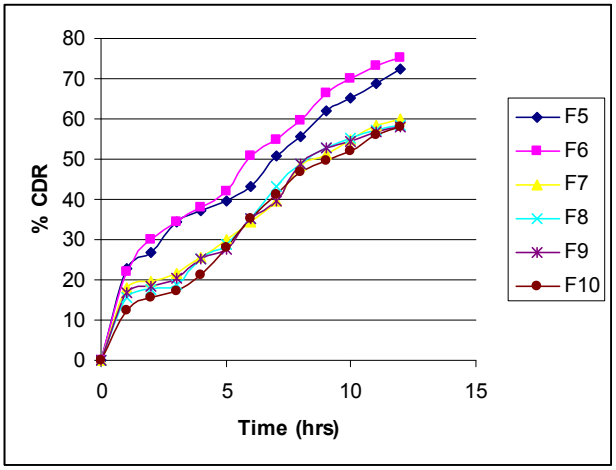

Figure 29:- Zero order curve for Comparison formulations F5 to F10

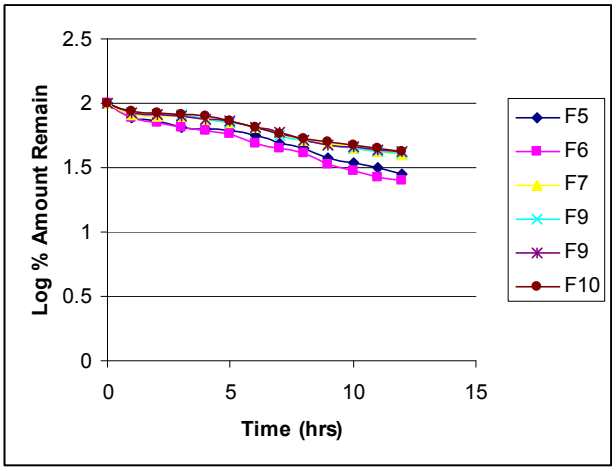

Figure 30:- 1st order curve for Comparison formulations F5 to F10

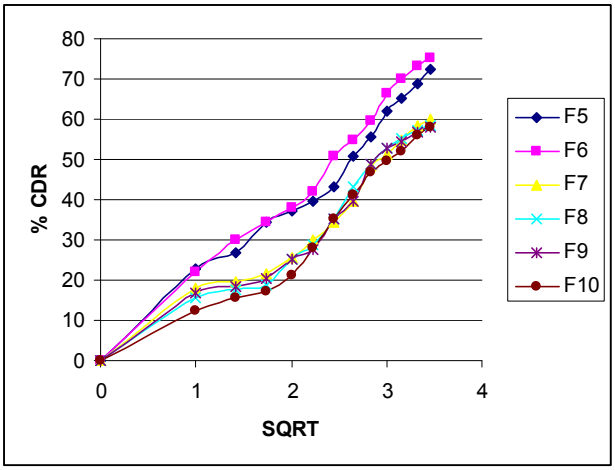

Figure 31:- Higuchi curve for Comparison formulations F5 to F10

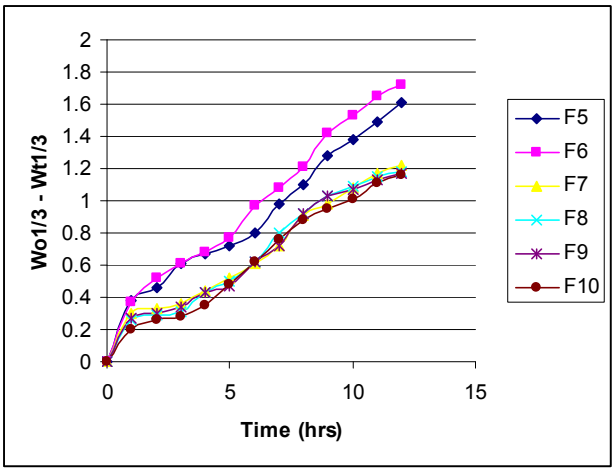

Figure 32:- Hixson-Crowell curve for Comparison formulations F5 to F10

Table 5: - FOR CORRELATION COEFFICIENT (R^2) OF ALL MODELS

Formulation code	Zero order	1st order	Higuchi	Hixson-Crowell
F5	0.8271	0.98	0.9799	0.9785
F6	0.8355	0.9878	0.9862	0.9849
F7	0.9155	0.9785	0.9421	0.9787
F8	0.9355	0.9796	0.9309	0.9784
F9	0.9229	0.9741	0.9319	0.9738
F10	0.9609	0.9871	0.3167	0.9866

Compatibility study by FTIR:-

FTIR Spectra of Drug (Diclofenac sodium) and optimized formulation F6 (Drug and Polymer mixture) were shown in table and figures. The studies revealed that there was no significant interaction between drug and polymer.

Table 7: - FOR FTIR DATA INTERPRETATION

Bonds/Group	Absorption range in cm^{-1}	Pure Drug	Formulation F6
- NH	3600-3200	3259.70	3246.20
C=O	1900-1500	1660.70	1654.92
C=C	1900-1500	1853.59	1851.66
C-C	1300-800	1070.49	1060.85
C-H	3800-2700	2899.01	2848.56
COO^-	1610-1550	1573.91	1579.70
C-N	1280-1350	1305.81	1303.88
C-Cl	850-550	842.89	844.82

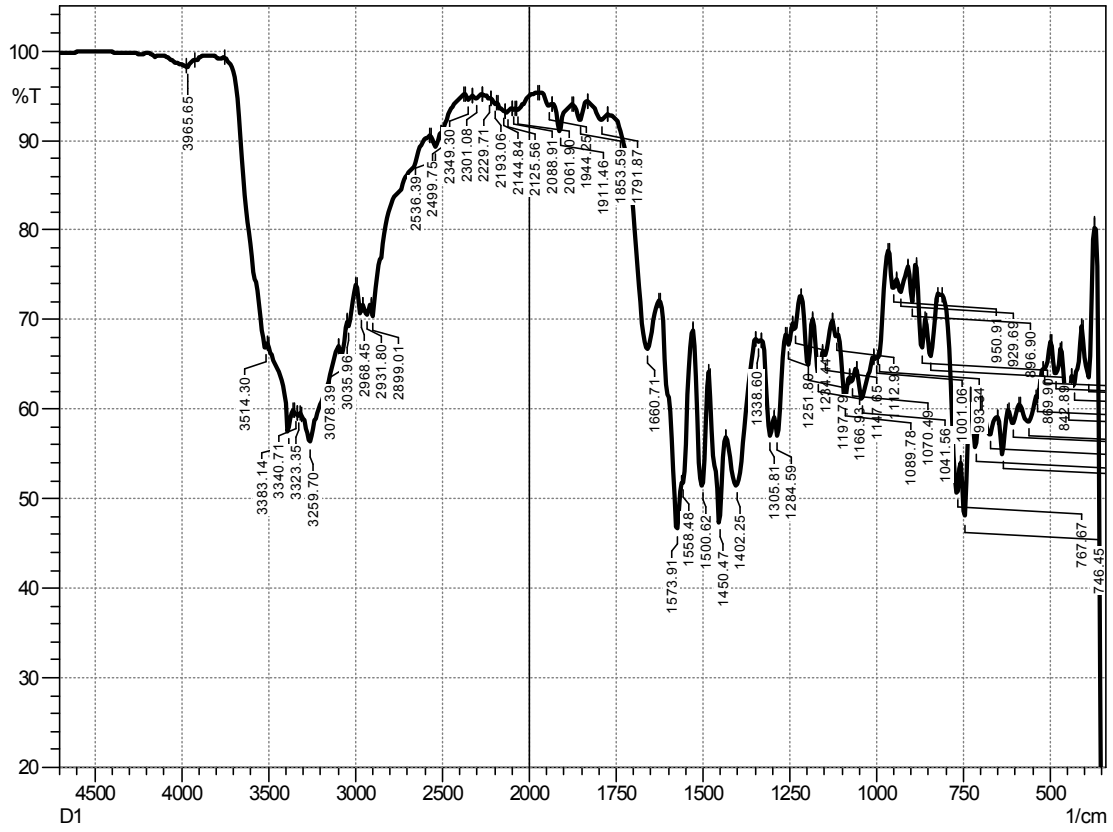

Figure 33:- FTIR SPECTRA OF PURE DRUG (DICLOFENAC SODIUM)

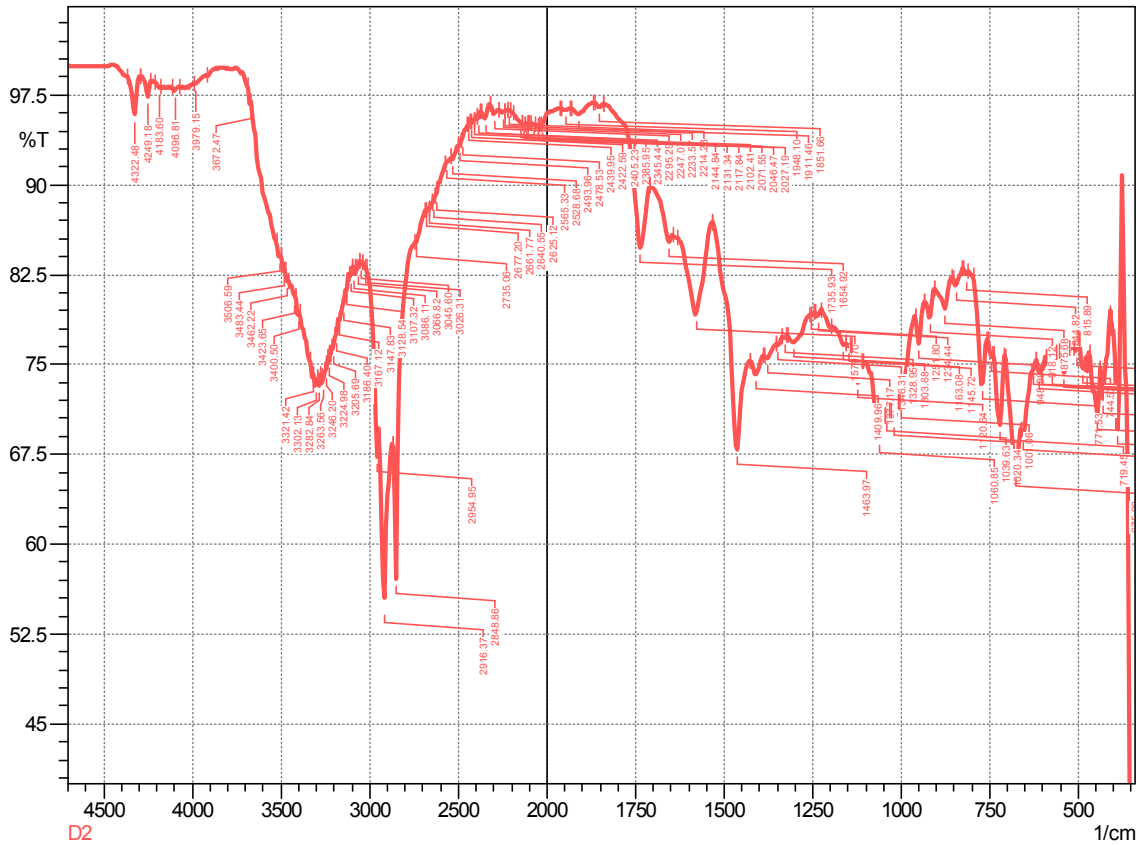

Figure 34: - FTIR SPECTRA OF FORMULATION F6

CONCLUSION:

The present study was aimed at developing an oral floating system for Diclofenac sodium with the use of wax materials, swellable polymer, release retardant and an alkalizing agent which proved to be an ideal formulation, as it released the drug in a controlled manner for extended period of time by maintaining the buoyancy. The study reveals that, the release of drug, Diclofenac sodium exhibited diffusion coupled with erosion drug release mechanism, followed first-order kinetics. The optimized formulation gives the best result in terms of the floating lag time (5minutes) and floating duration of 12 hours, and drug release more than 75 % at the end of 12 hours. This result is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the floating matrix dosage forms. The dose can be reduced and possible incomplete absorption of the drug can be avoided.

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