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Original Article

Formulation Development and Evaluation of Diclofenac Sodium Sustained Release Tablet Using Factorial Design.

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Abstract

The objective of the study is to design Diclofenac sodium SR tablets employing a combination of HPMC K 4M, (hydrophilic polymer), ethyl cellulose (lipophilic polymer) and Sodium alginate (hydrophobic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized by 3^2– factorial design. Diclofenac SR tablets were formulated employing the selected combinations of HPMC K4M (Factor A) Sodium alginate (Factor B) and EC (Factor C) as per 3^2- factorial study and prepared by direct compression method. The SR tablets were evaluated for drug release kinetics and mechanism. For optimization, time for % cumulative drug release was taken as response (Y1), % swelling index taken as response (Y2) and the percent of HPMC as X1, percent of sodium alginate as X2 and percent of EC as X3. The polynomial equation describing the relationship between the response Y1, Y2, Y3 and the variables X1, X2 and X3 based on the observed data was worked out. Diclofenac release from the matrix tablets prepared employing HPMC K4M (Factor A) Sodium alginate (Factor B) and EC (Factor C) as per 3^2 factorial design was slow and spread over a longer period of time up to 10 h. The release depended on the composition of the matrix tablet. Diclofenac release from formulations (F-F8) was slow and spread over 8-10 h. Drug release from these tablets was diffusion controlled. Non fickian diffusion was the drug release mechanism. The optimized SR formulation (F3) prepared to give a slow release of Diclofenac over 10 h with a %CDR 81.88%. Diclofenac sodium release from the optimized SR formulation was diffusion controlled and release was by nonfickian (anomalous) diffusion mechanism. Based on the pharmacokinetics, Diclofenac SR tablets for b.i.d administration should contain a total dose of 100 mg of Diclofenac and the desired release rate (K0) is 10.85 mg/h. The drug release rate of optimized SR tablets formulated was found to be 7.37 mg/h, which is very close to the theoretical desired release rate. Hence the optimized formulation (F3) is considered as the best Diclofenac SR formulation developed.

Keywords: Factorial design, Diclofenac sodium, Sustain Release.

Introduction

For many decades, conventional drug delivery systems have been commonly used for drug administration. They have been known to provide a prompt release of the drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutic effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day1. Sustained release drug delivery systems are those formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The sustain release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of the drug to a tissue. Drug release from these systems should be at

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a desired rate, predictable and reproducible. Polymers which are used as release-retarding materials in the design of Controlled release drug delivery systems play a vital role in controlling the delivery of drugs from the systems. The success of Controlled drug delivery systems depends on how well the polymer regulates the release of drug from the system. A wide range of polymers and other release retarding polymers are available. Formulation and manufacture of SR matrix tablets are a less complicated approach widely used in industry for obtaining an oral controlled release. Matrix tablet formulation needs an efficient release retarding material which plays a critical role in regulating drug release from matrix tablets. The objective of the study is to design Diclofenac SR tablets employing a combination of HPMC K4M (hydrophilic polymer), Sodium alginate (hydrophobic polymer) and ethyl cellulose (lipophilic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized 3 factors at 2 levels (3^2) factorial design. Diclofenac sodium is a widely used nonsteroidal anti-inflammatory, analgesic and antipyretic drug. Controlled release formulation is needed for Diclofenac because of its short biological half life of 2.0 h. The drug also causes gastrointestinal disturbances, peptic ulceration with bleeding if present in large concentration in the gastrointestinal tract. Hence, Diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of Diclofenac.

Materials & Methods

Diclofenac sodium taken as gift sample from Wockhardt Pharmaceutical Pvt. Ltd, Aurangabad. HPMC K4M procured from Balaji Drugs, Surat, Gujarat, Ethyl cellulose procured from Modern Industries, Malegaon, Nashik and Sodium alginate, Lactose, Magnesium stearate and Aerosil procured from Research-Lab Fine Chem. Industries, Mumbai.

Preformulation study:

a) Melting point

Melting point of Diclofenac sodium was determined by using Melting point apparatus (VEEGO Model-Vmp-0)

b) Assay:

Dissolve about 450 mg Diclofenac sodium accurately in 25 ml glacial acetic acid & titrate with 0.1M Perchloric acid determining the end point potentiometricaly carries out blank titration. Each ml of 0.1M Perchloric acid is equivalent to 0.03181 gm of $C_{14}H_{10}Cl_2NNaO_2$

c) Infrared spectroscopy:

IR spectroscopy study of Diclofenac sodium was done by using FT-IR spectrophotometer (S). The spectra were scanned over the wavelength region of 400 cm^{-1}. The procedure consisted of dispersing a sample of KBr and compressing into the disc by applying of pressure consisted of 5 tons for 5 minutes in a hydraulic press. The pellets were placed in the light path and the spectrum was obtained.

d) Differential Scanning Calorimetry:

Differential Scanning Calorimetric studies of pure Diclofenac Sodium samples were carried out at the 10^0C/min between the temperature range 30^0C-300^0C under a nitrogen flow of 2-bar pressure.

e) UV Spectrophotometer:

UV spectrum of Diclofenac sodium solution in distilled water was scanned at 400 to 200 nm. The wavelength of maximum absorption (λ max) was determined.

f) Calibration Curve of Diclofenac sodium:

Preparation of standard stock solution:

Accurately weighed 10 mg of Diclofenac sodium was transferred to 100 ml of volumetric flask and volume was made up to the mark with 0.1 N HCL pH 1.2 and pH 6.8 phosphate buffers separately to obtained strength of 100 mc/ml. This was further diluted to give the solutions of concentration 2-20 mcg/ml. these solutions were measured for absorbance on UV spectrophotometer at 273 nm and 276nm, plotted against the concentration to give the standard calibration curve.

Formulation of Tablet

Diclofenac SR tablet formulation was optimized by 3^2 – factorial design. In the 3^2 – factorial design the two levels of HPMC K4M

are 15 % and 44.50 % the two levels of Sodium alginate 5% and 40.50% and the two levels of ethyl cellulose are 1 % and 20 %. Diclofenac SR tablets were formulated employing the selected combinations of HPMC K4M, Sodium alginate and EC as per $^{3}2$ – factorial study.

Preparation of Diclofenac sodium SR tablets:

The SR tablets were prepared by direct compression method as per the formulae given in Table 1. The required quantities of Diclofenac sodium, HPMC K4M, Sodium alginate and ethyl cellulose were thoroughly mixed in a dry mortar by following geometric dilution technique. The lubricants Aerosil and magnesium stearate were passed through mesh No. 60 on to the dry powder. Desired amount of the blend was directly compressed into a tablet machine using a tablet compression machine (R&D Tablet PRESS 8 Station D- Tooling) to a hardness of 8-9 Kg/cm2. Before compression the surface of the die and punches were lubricated

Evaluation of Powder Blend

The powder blend Diclofenac sodium was evaluated by bulk density, tapped density, compressibility index, Haussner's ratio and angle of repose.

Bulk density: An accurately weighed quantity of powder, which was previously passed through sieve # 40 and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation mark on the cylinder as ml. The volume measured was called as the bulk volume and the bulk density is calculated by following formula,

$$\textbf{Bulk density } (\rho_0) = \frac{M}{V_0}$$

Where,

M = mass of powder taken

V_0= apparent unstirred volume

Tapped Density

After measuring bulk volume the same measuring cylinder was set into tapped density apparatus. The tap density apparatus was set to 10 taps.

The tapped density was determined by using the following formula,

$$\textbf{Tapped density } (\rho_t) = \frac{M}{V_f}$$

Where,

M = weight of sample powder taken

V_f = tapped volume

Carr's Index (Compressibility Index): It is one of the most important parameters to characteristics the nature of powder and granules. It can be calculated from the following equation**,**

$$\textbf{Carr's index (\%)} = \frac{tapped\ density - poured\ density}{tapped\ density} x\ 100$$

Haussner's Ratio: Haussner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by following formula [28, 29].

$$\textbf{\textit{Haussner's ratio}} = \frac{tapped\ density}{poured\ density}$$

Angle of Repose: Flow ability of Diclofenac sodium was determined by using a fix height method. A funnel with 10mm inner diameter of the stem was fixed at a height of 2 cm over the platform. About 10 g of sample slowly passed along the wall of funnel till the tip of the pile formed touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of power cone was measured. Angle of repose was calculated from three averages using following formula [28, 29].

$$\textit{tan}\ \theta = \frac{2h}{D}$$

Where,

θ = Angle of repose

h = Height of powder cone

r = Radius of the powder cone

Evaluation of Tablet

Diclofenac sodium tablet were evaluated thickness, hardness, friability, weight variation, content uniformity and in- vitro dissolution study.

Thickness: Thickness and diameter were measured using a calibrated vernier calliper. 3 tablets of each formulation were picked

randomly and thickness was measured individually. Tablet thickness should be controlled within a ± 5% variation of standard value [28].

Hardness: Hardness was measured using Monsanto Hardness tester that measures the pressure required to break diametrically placed matrix tablets by applying pressure with coiled spring [28].

Friability: The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (W initial) and transferred into Friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were taken out weighed again (W final). The %

Friability was then calculated by:

$$F= (1-W0 - W) 100$$

Weight variation: Method: Uncoated tablets complies this test. The average weight is determined by weighing 20 tablets. Not more than two tablets deviate from the average weight by a percentage greater than that given and no tablet deviates by more than double that percentage.

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 or less than 324 mg	7.5
324 mg or more	5

Drug Content Uniformity: Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 100 mg of Diclofenac sodium was dissolved in 100 ml of pH 6.8 phosphate buffer stirred for 60 min and filtered. 1mL of the filtrate was diluted to 100 ml with pH 6.8 phosphate buffer. Absorbance of this solution was measured at 276 nm using pH 6.8 phosphate buffers as blank and content of Diclofenac sodium was estimated.

In-vitro Dissolution Study: The tablet samples were subjected to in-vitro dissolution studies using USP Type 2 dissolution apparatus at 37±2°C and 50 rpm speed. As per the official recommendation of USFDA, 900 ml of pH 6.8 Phosphate buffer (next 8hrs) was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time intervals and. The dissolution media volume was complimented with fresh and equal volume of blank media (0.1 N HCL). The aliquots were filtered and scanned with appropriate dilution and amount of Diclofenac sodium released from the tablet samples was determined spectrophotometrically at a wavelength of 276 nm by comparing with the standard calibration curve.

Release kinetics: In order to establish the mechanism of drug release the in-vitro drug release data was fitted to four popular exponential equations (zero order, first order, Higuchi, and Korsmeyer Peppas.

Results and Discussion

Formulation and manufacture of SR matrix tablets are a less complicated approach widely used in industry for obtaining an oral controlled release. Matrix tablet formulation needs an efficient release retarding material which plays a critical role in regulating drug release from matrix tablets. The objective of the study is to design Diclofenac SR tablets employing a combination of HPMC K 4M, (hydrophilic polymer), ethyl cellulose (lipophilic polymer) and Sodium alginate (hydrophobic polymer) for better controlled release. Diclofenac SR tablet formulation was optimized by 3^2 – factorial design. Optimization of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes conform to certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, swelling index and stability. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal.

For optimizing Diclofenac SR tablet formulation employing HPMC K4M, Sodium

alginate and EC, a $^{3}2$ factorial design was used. In the 3^2 –factorial design the two levels of HPMC K4M are 15 % and 44.50 % the two levels of Sodium alginate 5% and 40.50% and the two levels of ethyl cellulose are 1 % and 20 %. Diclofenac SR tablets were formulated employing the selected combinations of HPMC K4M, Sodium alginate and EC as per 3^2-factorial study. The SR tablets were prepared by direct compression method as per the formulae given in Table.5 and were evaluated for in-vitro drug release kinetics, swelling. The results for evaluation of prepared matrix tablets viz. Hardness, weight variation, variety, drug content uniformity was founded in the range of 8.5±0.02 to 9.5±0.4, 299.12±0.58 to 302.20±1.11, 0.50 to 0.91, 96.3±0.90 to 99.8±0.10 respectively for all formulations and showed all values within the limit. The friability of the tablets was found to be less than 1% which was considered within the limit. The drug content of the all formulations was found to be within the limits. From the Fig 9.4, 9.5, 9.6 and Table 9.6 the formulation F1-F8 shows drug release rate of 99.85% in 9 h, 99.18 at 10 h, 81.88% in 10 h, 102.2% in 10 h, 87.86% in 10 h, 76.08 % in 10 h, 94.57% in 10 h and 79.17% in 10 h respectively. The formulation F3 will show better retardation of drug release 81.88% in 10 h. All formulations prepared by using factorial design, in which the better formulation F3 prepares by concentration of polymer HPMC K4M, Sodium alginate and Ethyl Cellulose (50:5.60:1.0) in combination showed a desired release rate up to10 h. In above all formulations in which the F3 formulation having good drug release study up to 10 hours (81.88%). As per USP limit not less than 75% drug release upto 10hr. So the F3 formulation follows the USP limit. The results of kinetic models viz. Zero order, Higuchi, first order, Peppas model of all formulations (F1-F8). The optimize batch F3 give r^2 value 0.996, 0.980, 0.915 and 0.997 respectively (Table- 9.8). The formulations prepared were found to release the drug by diffusion mechanism. The F3 formulation follows the Zero order drug release, which gives the highest r^2 value 0.996. All the formulation shows a good stability, all tablet formulations are kept in environmental test chamber for 45 days at 40^0C and room temperature. The F3 formulation is stable, according to ICH guidelines and therefore it shows that the F3 formulation is an optimized formulation than all other formulations.

Conclusion

Diclofenac sodium release from the matrix tablets prepared employing the selected combinations of HPMC K4M (Factor A) Sodium alginate (Factor B) and EC (Factor C) as per 3^2- factorial design was slow and spread over a longer period of time upto 10h. The release depends on the composition of the matrix tablet. Diclofenac sodium tablet release from the formulations (F1-F8) was slow and spread over 8-10h. Drug release from these tablets was diffusion controlled mechanism (zero order kinetic). The optimized SR formulation prepared to give a slow release of Diclofenac over 10h with a percent drug release and swelling index indicating validity of the optimization technique employed. Diclofenac sodium release from the optimized SR formulation (F3) was diffusion controlled and release was by non-fickian (anomalous) diffusion mechanism. Based on the pharmacokinetics, Diclofenac sodium SR tablets b.i.d administration should contain a total dose of 100mg of Diclofenac sodium and the desired release rate (7.37 mg/h. The release rate of optimized SR tablets formulated was found to be 7.37mg/h, which is very close to the theoretical desired release rate. Hence the optimized formulation is considered as the best Diclofenac SR formulation is considered as his best Diclofenac SR.

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Table 1. Characterization & UV absorbance of Diclofenac Sodium.

Sr. No	Test	Specification	Test Result
1	Description	White powder	White powder
2	Melting point	283-284^{0}C	282-283^{0}C
3	Assay	99.9%	99.86%

Sr. No	Concentration (ppm)	Absorbance (276nm)
1	**2**	**0.242**
2	**4**	**0.525**
3	**6**	**0.714**
4	**8**	**0.920**
5	**10**	**1.172**

Table 2. Selection of Factor and Level.

Coded level	Independent Factors		
	HPMC-K4M	**Sodium alginate**	**Ethyl cellulose**
Lower level (-1)	15 mg	5 mg	1 mg
High level (+1)	44.50 mg	40.50 mg	20 mg

Table 3. Layout of Actual Factorial design.

Run	HPMC-K4M	Sodium alginate	Ethyl cellulose
1	44.50	40.50	1.00
2	15.00	5.60	20.00
3	15.00	5.60	1.00
4	44.50	5.60	20.00
5	44.50	40.50	20.00
6	15.00	40.50	20.00
7	15.00	40.50	1.00
8	44.50	5.60	1.00

Table 4. Compositions of Tablets.

Sr. No	Name of ingredients	Formulation code							
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1	Diclofenac sodium	100	100	100	100	100	100	100	100
2	HPMC-K4M	44.5	15.0	15.0	44.50	44.50	15.00	15.00	44.50
4	Sodium Alginate	40.50	5.60	5.60	5.60	40.50	40.50	40.50	5.60
5	Ethyl cellulose	1.00	20.0	1.00	20.00	20.00	20.00	1.00	1.00
6	Lactose	120	140	160	153	190	145	180	136
7	Magnesium Stearate	1	1	1	1	1	1	1	1
8	Aerosil	1	1	1	1	1	1	1	1

Each formulation contains 1% Magnesium Stearate, 1% Aerosil of total weight.

Table 5. Precompression evaluation parameter (F1-F8).

Batch code	Angle of repose (ϴ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Haussner's ratio
F1	21.62±0.09	0.54±0.06	0.634±0.04	14.51±0.86	1.1697±0.05
F2	20.85±0.10	0.53±0.08	0.626±0.07	15.33±0.25	1.1811±0.07

F3	21.75±0.13	0.52±0.12	0.617±0.09	14.42±0.53	1.1655±0.05
F4	21.83±0.15	0.54±0.12	0.628±0.08	14.89±0.27	1.1749±0.09
F5	22.97±0.08	0.54±0.08	0.629±0.07	14.94±0.68	1.1757±0.07
F6	20.68±0.09	0.53±0.09	0.598±0.06	16.38±0.41	1.186±0.06
F7	21.33±0.08	0.50±0.09	0.644±0.06	14.75±0.55	1.1730±0.07
F8	22.97±0.16	0.54±0.15	0.635±0.05	15.11±0.72	1.1781±0.06
(n=3, ±S.D) (S.D= Standard deviation)					

Table 6. Post-compression evaluation parameter (F1-F8).

Formulation Code	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Weight variation (%)	Content Uniformity (%)
F1	3.4±0.2	8.5±0.02	0.51	301.98±0.91	98.03±0.15
F2	3.2±0.4	9.0±0.4	0.80	300.92±1.20	98.8±0.22
F3	3.6±0.1	8.6±0.6	0.79	300.12±1.09	99.8±0.10
F4	3.3±0.3	9.5±0.4	0.91	299.12±0.58	96.3±0.90
F5	3.4±0.8	9.3±0.2	0.50	302.32±1.03	97.0 ±0.22
F6	3.4±0.1	9.0±0.2	0.85	301.13±0.99	98.78±0.37
F7	3.5±0.4	8.8±0.3	0.72	300.94±1.57	99.0±0.081
F8	3.3±0.5	8.5±0.04	0.87	302.20±1.11	98.9±0.31
(n=3, ±S.D) (S.D= Standard deviation)					

Table 7. Cumulative % Drug Release (F1-F8).

Time (hr)	% Cumulative Drug release (Mean±S.D)							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	15.42±1.2	13.24±3.22	7.37±1.16	14.83±1.4	10.85±3.64	6.16±2.45	12.07±0.95	6.57±1.62
2	25.83±2.4	22.54±1.87	15.33±1.1	24.39±2.9	19.02±1.4	14.78±1.63	25.35±1.6	19.41±1.25
3	39.22±3.2	30.75±2.43	24.01±0.92	35.34±3.15	26.95±2.4	19.69±2.57	34.88±2.5	26.67±1.39
4	51.90±1.7	43.43±1.67	33.03±1.6	43.52±1.84	32.70±3.26	25.40±2.80	46.42±1.3	35.27±2.87
5	63.73±1.3	56.74±2.98	40.88±1.30	52.42±1.2	41.21±1.34	32.57±3.26	54.60±2.31	44.76±2.8
6	70.78±1.67	67.31±3.10	54.11±2.1	65.42±2.31	49.35±2.48	42.18±2.3	61.14±1.30	56.51±2.4
7	81.52±2.98	72.20±1.87	62.19±1.4	72.47±3.21	56.78±2.21	49.69±1.69	67.25±2.50	59.54±3.68
8	91.25±3.22	80.77±2.43	67.27±1.85	78.01±1.43	68.82±1.6	60.10±2.44	75.96±2.61	64.48±2.64
9	99.85±1.10	93.73±3.21	75.63±2.65	92.12±1.72	81.38±2.35	69.37±1.53	85.62±1.9	71.62±3.18
10	-	99.18±1.67	81.88±1.34	102.2±3.4	87.86±1.63	76.08±1.77	94.57±1.33	79.17±3.78

Table 8. Characterization of swelling index (F1 -F8).

Time (hr)	Swelling index (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	49.17	45.24	25.18	66.28	42.42	40.62	37.04	25.04
2	63.21	59.17	38.01	70.19	55.71	51.01	45.21	38.78
3	70.09	70.26	46.22	76.52	66.91	60.00	60.01	49.32
4	85.63	81.25	61.04	85.04	73.81	75.01	72.45	55.01
5	97.04	87.09	79.54	93.37	81.62	86.41	87.32	64.91
6	86.11	75.03	91.21	82.97	84.09	76.32	84.31	65.00
7	81.39	70.97	98.41	78.01	71.83	66.01	77.11	63.22
8	77.94	64.52	87.01	72.68	68.04	63.02	72.01	59.80

Table 9. Release Kinetics of Diclofenac Sodium Matrix Tablets.

Sr No	Formulation code	Zero order kinetics (r^2)	First order kinetics (r^2)	Higuchi (r^2)	Peppas (n)
1	F1	0.991	0.853	0.950	0.997
2	F2	0.995	0.829	0.936	0.994
3	F3	0.996	0.980	0.915	0.997
4	F4	0.961	0.881	0.937	0.996
5	F5	0.993	0.890	0.902	0.991
6	F6	0.992	0.989	0.881	0.994
7	F7	0.989	0.873	0.955	0.994
8	F8	0.987	0.981	0.940	0.979

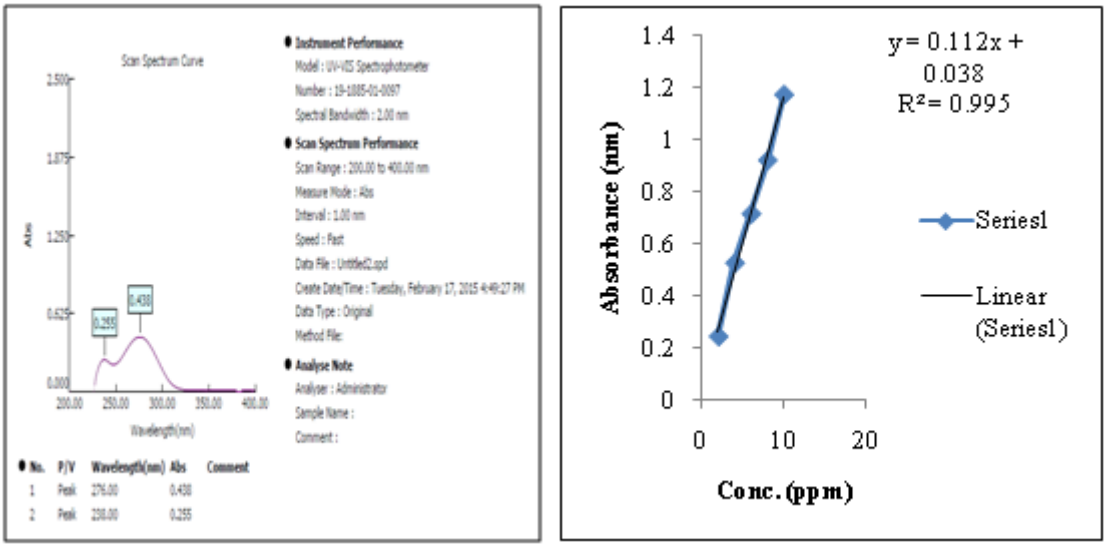

Fig. 1. UV absorbance & Calibration curve of Diclofenac sodium in pH 6.8 phosphate buffer.

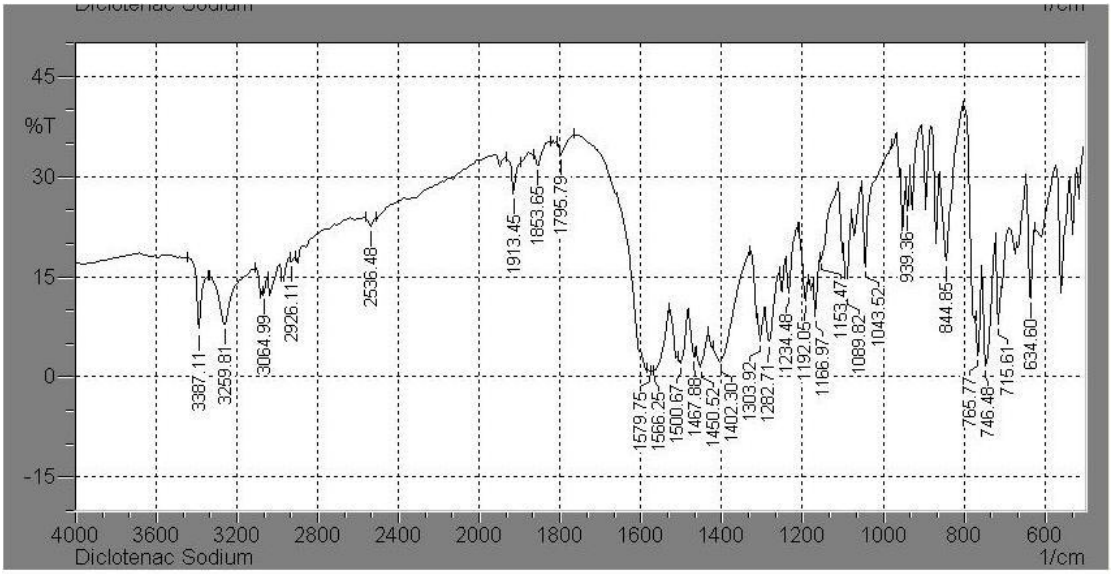

Fig. 2. FTIR Spectrum of Diclofenac sodium.

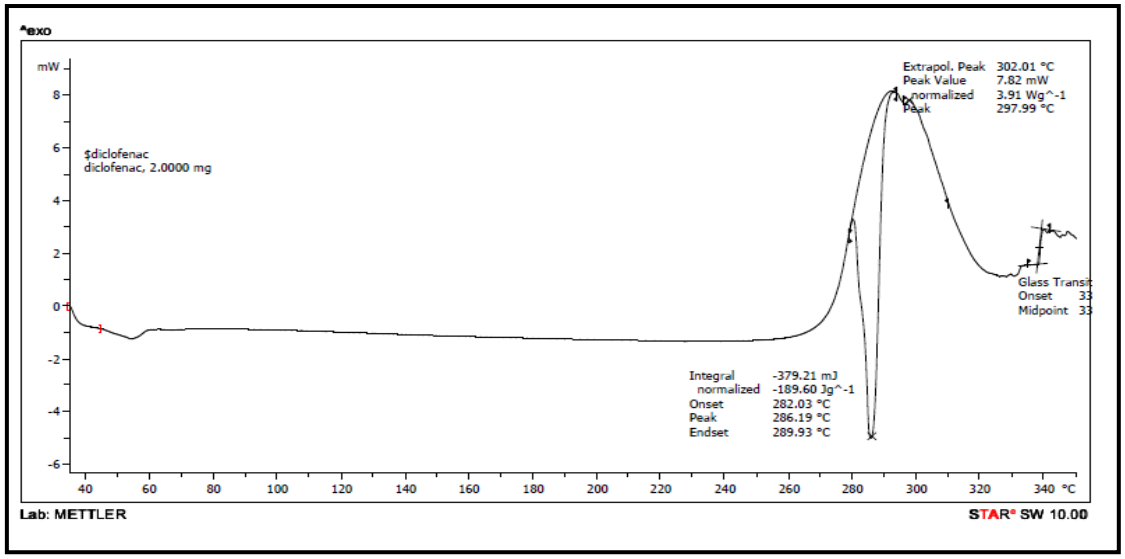

Fig. 3. DSC Thermogram of Diclofenac sodium.

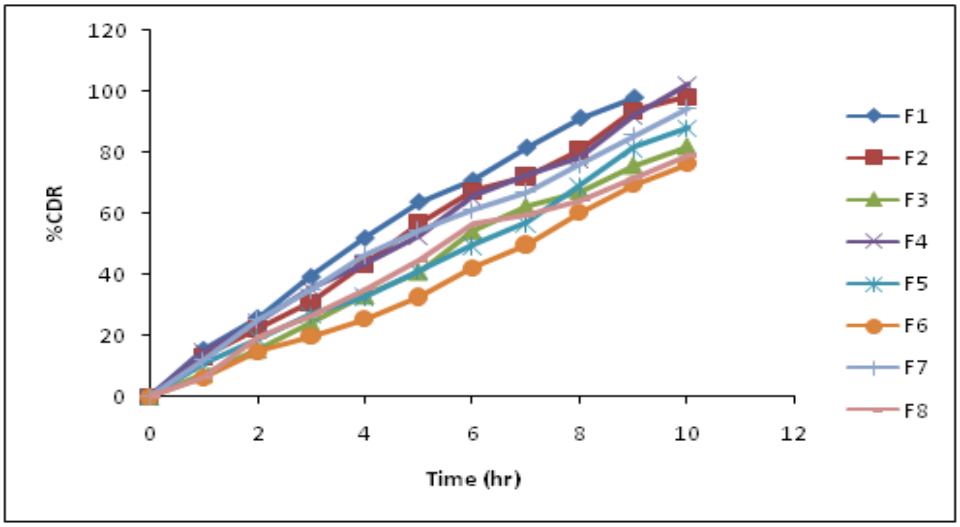

Fig.5. *In-vitro* Drug Release Profile of F1-F8.

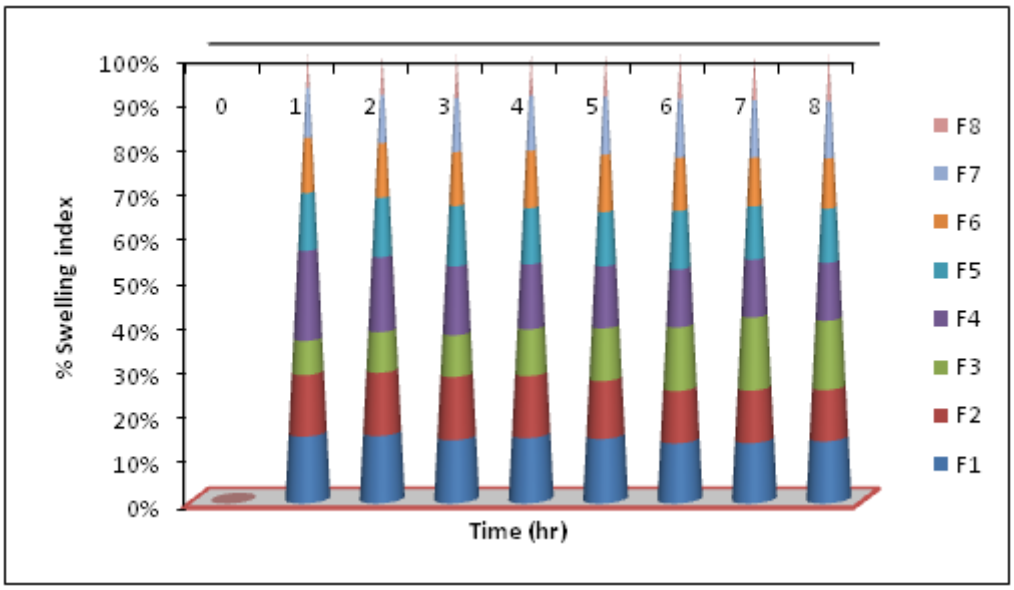

Fig.6. Swelling index plot for F1-F8.

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