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Research Article

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DESIGN AND IN VITRO EVALUATION OF DICLOFENAC SODIUM MATRIX TABLETS

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ABSTRACT

Diclofenac Sodium is a Non-steroidal Anti-inflammatory Drug commonly used for the treatment of Rheumatoid arthritis, Osteoarthritis, Ankylosing Spondylitis and Periarticular disorders. In this work 100 mgs of Diclofenac sodium Tablets were prepared by Direct Compression method. Pre & Post compression studies were carried out followed by In vitro release studies.

Keywords: Diclofenac Sodium, Matrix tablets, In-vitro release studies.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Solid medicaments may be administered orally as powders, pills, cachets, Capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug. The stringent formulations requirements of modern medicaments, the many advantages of tablet and capsule medication, couple medication, coupled with expanding health services and the commitment need for the large scale economic manufacture, have led to a steady decline in the prescribing of powders and pills. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian pharmacopoeia

pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on a amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer.

These immediate release dosage forms have some limitations such as:
1. Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliances.
2. A typical peak valley plasma concentration time profile is obtained which makes attainment of steady state condition difficulty.
3. The unavailable fluctuation in the drug concentration may lead to under medication or over medications as the CSS values fall or rise beyond the therapeutic range.
4. The fluctuations drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever over medications occurs.
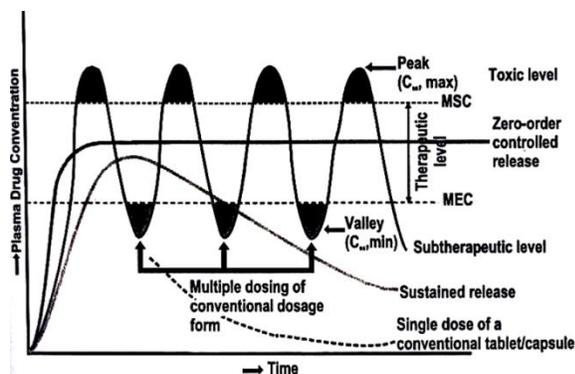
Fig 1: A hypothetical plasma concentration- time profile from conventional multiple dosing and single doses of sustain release and control delivery system

Controlled release Dosage form: Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.

Classification of Matrix Tablets: On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types:
1. Hydrophobic Matrices (Plastic matrices): The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acryl ate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices: These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices: The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swell able controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups
a. Cellulose derivatives: methylcellulose 400 and 4000cPs;Hydroxyethylcellulose;Hydroxypropyl methylcellulose (HPMC) 25, 100, 4000 and 15000 cPs; and sodium carboxymethylcellulose.
b. Non cellulose natural or semi synthetic polymers: Agar-Agar, carob gum, Alginates, Molasses, polysaccharides of mannose and gelatos, chitosan and modified starches.
c. Polymers of acrylic acid: Coraopolis 934, the most used variety.

4. Biodegradable Matrices: These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices: These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds by the use of dilute alkali.
II. On the Basis of Porosity of Matrix: Matrix system can also be classified according to their porosity and consequently, macro porous; micro porous and non-porous systems can be identified:
1. Macro porous Systems: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusing molecule size.

2. Micro porous System: Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusing molecules size.
3. Non-porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Advantages of Matrix Tablets:
• Easy to manufacture
• Versatile, effective and low cost
• Can be made to release high molecular weight compounds.
Disadvantages of the matrix systems:
• The remaining matrix must be removed after the drug has been released.
• The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusion resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Methods Used To Achieve Controlled Release Of Orally Administered Drugs:
A Diffusion controlled systems: Basically diffusion process shows the movement of drug molecules from a region of higher concentration to one of lower concentration. These systems of two types:
I) Reservoir type: A core of drug surrounded by polymer membrane which controls the release rate, characterizer's reservoir devices.
Advantages: Zero order delivery is possible; release rate varies with polymer type.

• Disadvantages: System must be physically from important sites.
• Difficult to deliver high molecular weight compounds.
• Increased cost per dosage unit, potential toxicity if system fails.
• Flicks first law of diffusion describes the diffusion process.
  $J = -D \, dc/dx$

  Where, D= diffusion coefficient in area/time
  Dc/dx = change of concentration 'c' with distance 'x'

II) Matrix type: Matrix system is characterized by a homogenous dispersion of solid drug in a polymer mixture.
Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.
Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system. Higuchi has delivered the appropriate equation for drug release from this system,
$M = k \, t^{1/2}$, Where, M= amount of drug released per unit area, K= constant

III) Dissolution Controlled Systems:
Reservoir type: Drug is coated with a given thickness coating, which is slowly dissolved in the content of gastro intestinal tract. By altering layers of drug with the rate controlling coats as shown in figure no.1, a pulsed delivery can be achieved. If the Outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.
Matrix type: It can either be a drug impregnated sphere or a drug impregnated tablet, this will be subjected to slow erosion.

METERIALS AND METHODS

EVALUATION OF PRE-COMPRESSION PARAMETER:
1. Angle of Repose: The powders were allowed to flow through the funnel fixed to a stand at a definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.
$Tan\theta = h/r$, $\alpha = \Theta tan^{-1}(h/r)$ Where Θ = angle of repose, h = height of the heap, r = radius of the heap
2. Bulk density: A quantity of powder was transferred to a measuring cylinder and the occupied by the powder in terms of ml was recorded.
Bulk density=Weight of powder in gm/volume of packing in ml
3. Tapped density: The powder in the measuring was tapped 100 times on a plain hard wooden surface and volume occupied in ml was noted.
Tapped density =weight of powder in gm/tapped volume in ml
4. Carr's Index: The flow ability of powder can be evaluated by comparing the bulk density (D_o) and tapped density (D_s) of powder and the rate at which it is packed down.
Carr's index is calculated by –   Compressibility index (%) = $D_t - D_o / D_t * 100$
Where D_o = bulk density D_t = tapped density
5. Hausner's ratio: It is the ratio of tapped density to bulk density.
Hausner's ratio = D_t / Do, Where Do= bulk density t = tapped density

PREPARATION OF MATRIX TABLETS OF DICLOFENAC SODIUM:
DIRECT COMPRESSION METHOD: All powdered ingredients like Diclofenac sodium, hydroxypropylmethyl cellulose, Xanthan gum, MCC, PVP, Talc, Magnesium stearate were weighed accurately and mixed well in a dry clean mortar in a geometrical order where used and tablets were prepared by direct compression technique. Desired amount of blend was directly compressed into tablets

using tablet compression machine (RIMEC, MINI PRESS-1).Before compression the surface of the die

Table 1: FOMULATION OF CONTROLLED RELEASE MATRIX TABLETS OF DICLOFENAC SODIUM

FORMULATION CODE	F1	F2	F3	F4	F5
DRUG(mg)	50	50	50	50	50
XANTHAN GUM(mg)	45	55	45	35	30
HPMC	20	-	20	25	15
MCC	60	60	35	40	60
PVP	35	40	60	62	55
TALC	6	10	5	4	5
MAGNESIUM STEARATE	4	5	5	4	5

Fig 2: Formulations

EVALUATION FOR POST COMPRESSIVE PARAMETERS:

All prepared matrix tablets were evaluated for the following parameters.

1) Thickness of tablet: Thickness and diameter were measured using a calibrated vernier caliper. 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.

and punches were lubricated.

2) 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.

3) 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.

4) 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=I-F/I*100, Where, I =Initial weight of tablets = weight after friability.

% Friability of tablets less than 1% was considered acceptable.

5) Drug Content Uniformity: Weigh and powder 20 tablets. Weigh accurately a quantity of powder containing 50mg of Diclofenac sodium shake with 60 ml of methanol in 100ml volumetric flask dilute to volume with methanol. Dilute 5ml of this solution to 100ml with methanol and measure the absorbance at 285nm using blank as a reference.

% PURITY=observed abs/specific abs*wt. of sample/ label claim*100/DF

6) Dissolution studies: Freshly prepared test media of 1000ml was places in dissolution vessels of dissolution test apparatus USPXXIV model. Samples of the matrix tablet of Diclofenac sodium (after weighing) was placed in basket was immersed in dissolution media and maintained at $37.5+1^0$c and was rotated at the speed of 75rpm. 5ml of samples were withdrawn at fixed time interval, and this was immediately replaced with the same volume of fresh test media. The sample withdrawn were filtered and estimated spectrophotometric ally at 285nm cumulative amount of drug release at each interval was calculated by using standard graph of Diclofenac sodium. Dissolution studies were performed for all Formulations. The mean values and standard deviation were calculated.

RESULTS:
Table 2: PRE COMPRESSIVE PARAMETERS OF DICLOFENAC SODIUM TABLETS

FORMULATION CODE	BULK DENSITY	TAPPED DENSITY	ANGLE OF REPOSE	CARR'S INDEX	HAUSNERS RATIO
F1	0.406	0.521	19	22.16	0.751
F2	0.387	0.525	20	25.61	0.754
F3	0.376	0.537	22	29.27	0.705
F4	0.390	0.535	22	28.70	0.712
F5	0.364	0.530	24	26.65	0.730

Table 3: POST COMPRESSIVE PARAMETERS OF DICLOFENAC SODIUM TABLETS

FORMULATION CODE	HARDNESS (kg/cm^2)	FRIABILITY (%)	THICKNESS (mm)	DRUG CONTENT (%)	WEIGHT VARIATION (%)
F1	8.20	0.41	3.20	90.0	2.325
F2	8.45	0.40	3.23	90.2	2.225
F3	9.23	0.22	3.45	93.2	2.330
F4	10.20	0.37	3.15	94.0	2.350
F5	8.00	0.32	3.18	90.3	2.312

Table 4: Formulation 1

Time	Absorbance	Concentration (μg/ml)	Total amount of drug release in mg	% drug release	% drug remaining
1hr	0.062	0.601	5.425	40.2%	93.2%
2hr	0.065	0.622	5.597	42.5%	94.0%
3hr	0.070	0.641	5.761	50.8%	94.2%
4hr	0.076	0.666	6.003	68.9%	93.6%
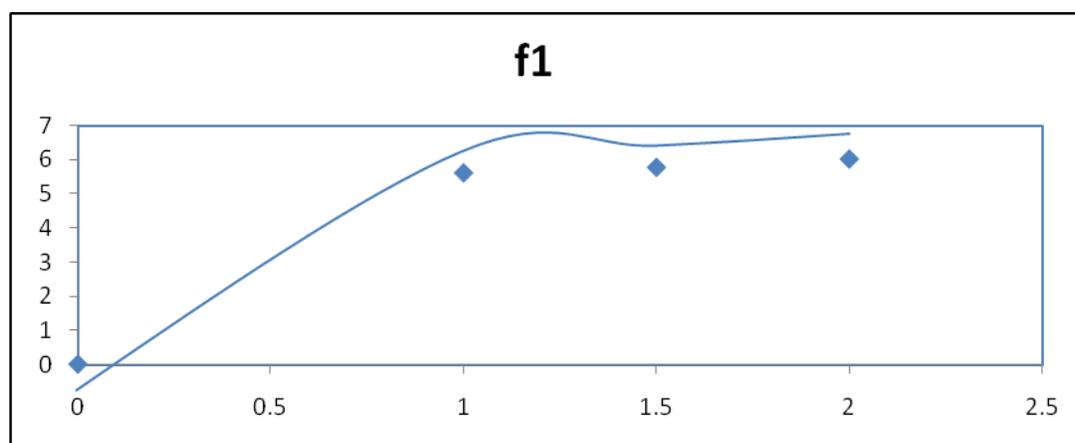
Fig 3: In vitro release study of formulation F1 in phosphate buffer pH-7.4

Table 5: Formulation 2

Time	absorbance	Concentration (μg/ml)	Total amount of drug release in μg	% drug release	% drug remaining
0.5hr	0.030	0.28139	2.26051	1.980	98.00
1hr	0.033	0.27174	2.42566	2.211	96.70
1.5hr	0.035	0.33009	2.79081	2.243	97.60
2hr	0.036	0.31961	3.12849	2.411	95.05
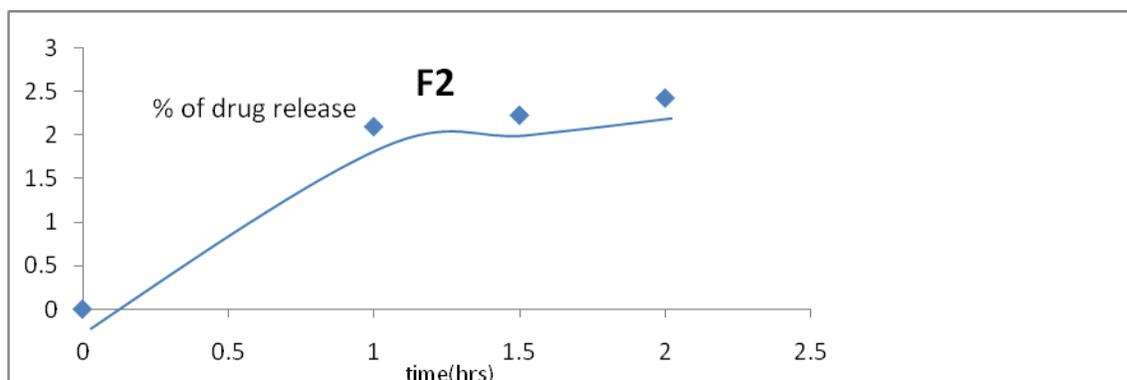
Fig 5: In vitro release study of formulation F2 in phosphate buffer pH-7.4

**Table 6: Formulation 3**

Time	absorbance	Concentration (μg/ml)	Total amount of drug release in μg	% drug release	% drug remaining
0.5hr	0.41	0.37431	3.16876	2.695	95.205
1hr	0.42	0.38266	3.23394	2.427	97.073
1.5hr	0.045	0.42101	3.49909	2.9959	96.141
2hr	0.046	0.43853	3.74677	3.0157	96.743
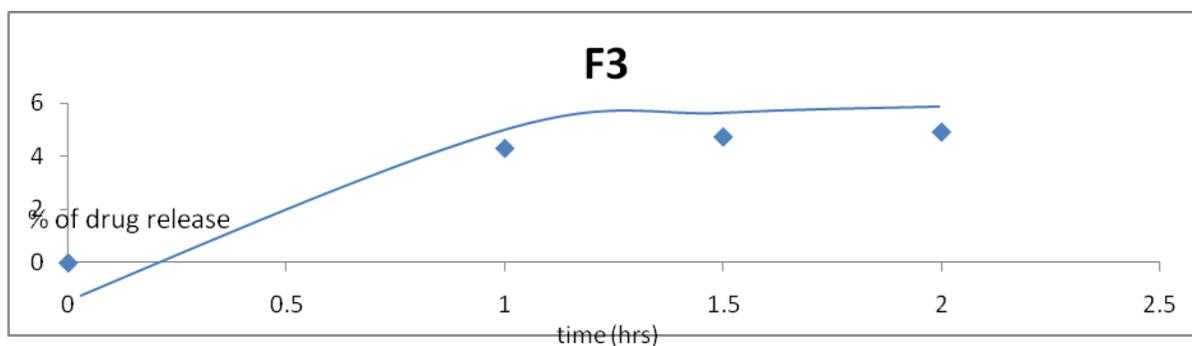
Fig 6: In vitro release study of formulation F3 in phosphate buffer pH-7.4

Table 7: Formulation 4

Time	absorbance	Concentration (μg/ml)	Total amount of drug release in μg	% drug release	% drug remaining
0.5hr	0.022	0.2268	2.0212	1.415	93.26
1hr	0.022	0.2483	1.8567	1.627	9.40
1.5hr	0.032	0.2633	2.5505	1.858	96.00
2hr	0.033	0.3209	2.7082	2.147	98.823
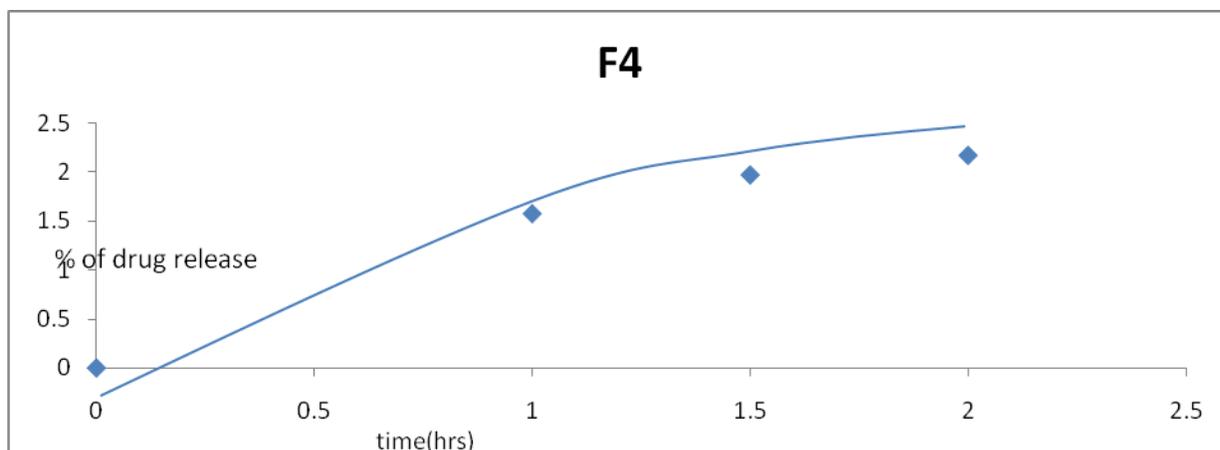
Fig 7: In vitro release study of formulation F4 in phosphate buffer pH-7.4

Table 8: Formulation 5

Time	Absorbance	Concentration (µg/ml)	Total amount of drug release in µg	% drug release	% drug remaining
0.5hr	0.040	0.34631	3.25679	2.481	94.219
1hr	0.037	0.41857	3.62713	3.0089	93.914
1.5hr	0.064	0.41702	3.81318	3.247	93.843
2hr	0.062	0.5131	4.6079	3.684	93.306
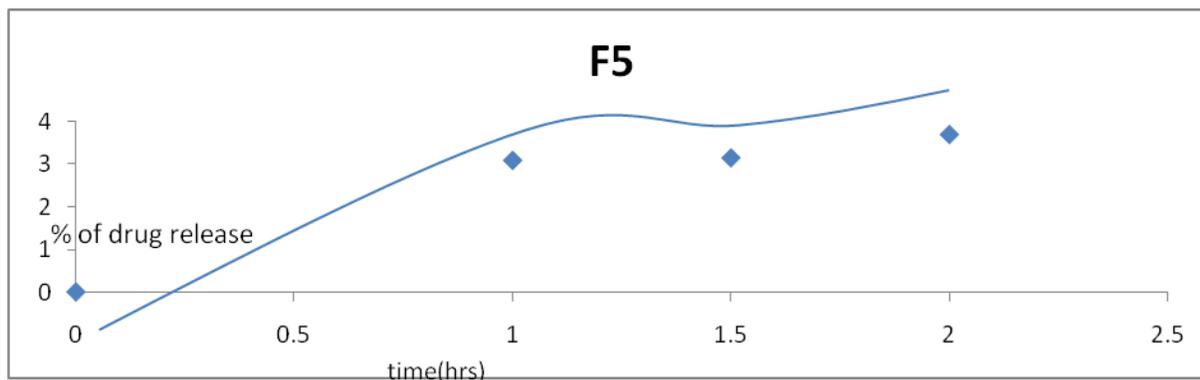
Fig 8: In vitro release study of formulation F5 in Phosphate buffer pH-7.4
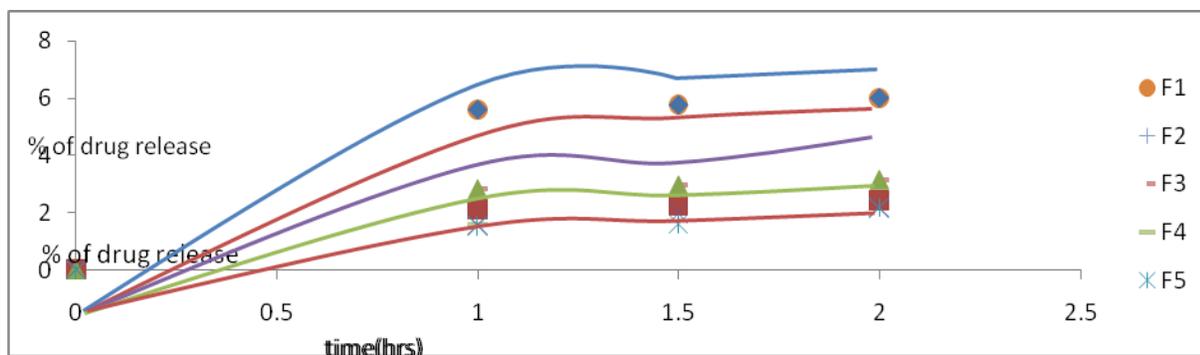
Fig 9: Comparison of drug release profiles of all formulations (F1-F5) of phosphate buffer Ph7.4

Standard graph

$y = 0.014x + 0.023$
$R^2 = 0.996$
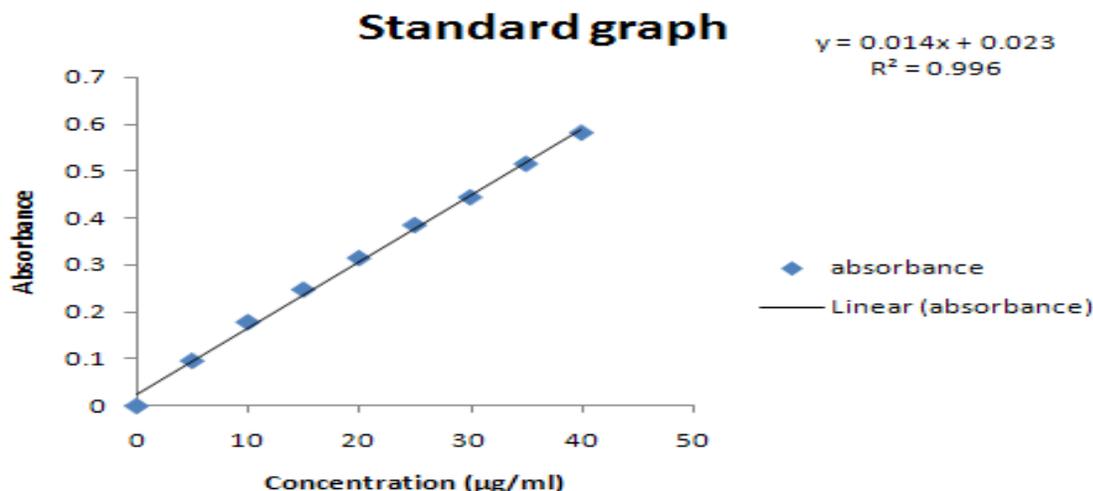
Fig 10: Standard graph

DISCUSSIONS

Matrix tablets of Diclofenac sodium were prepared using water soluble polymer and water insoluble polymer. Polymers used are HPMC, XANTHAN GUM, PVP, and MCC. The best matrix release formulations were selected. Standard graph of diclofenac sodium in phosphate buffer pH 7.4 are shown in graph no 2.Good linearity was observed with the plot. Its r^2 value is 0.9993 which is very nearer to 1 and hence obeys Beer Lambert Law.

Standard graph of Diclofenac sodium in acidic buffer pH 2 are shown in graph no 1. Good linearity was observed with the plot. Its r^2 value is 0.9995 which is very nearer to 1 and hence Obeys Beer Lambert Law. The drug release from hydrophilic matrix tablets is controlled by a hydrated viscous layer formed at the tabled periphery, its gel layer acts as barrier to drug release. In each case the weighed quantity of drug and polymer were mixed and compressed. The powdered drugs & additives were compressed into tablets of appropriate dimensions (reasonable thickness). The compressed tablets were tested for hardness, thickness, diameter, weight variation and evaluated for drug content uniformity, drug release profiles was compared with pure drug. All the batches of matrix tablets prepared were found to be uniform with respect to the physical parameter tested. Hardness, friability and content uniformity test were performed in triplicate and the results are shown as an average with standard deviation. The dissolution rate studies were performed by using USP XXIV dissolution tested employing rotating basket 100 rpm the dissolution media is stimulated G1 fluids and the study was continued for 12 hours. At suitable times, samples of 5ml were withdrawn by means of pipette or plastic syringe fitted with per filter and it was immediately replaced with fresh dissolution medium. The drug release data for HPMC, PVP, MCC, Xanthan Gum, Methyl cellulose were shown in table and graph. The mean cumulative percentage of Diclofenac sodium released at various time intervals from all formulations are compared and showed in among all formulations.

Conclusion: By comparing all formulations from F-1 to F-5, F-2 formulation shows good release.

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