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EFFECT OF HYDROPHILIC DRUG RELEASE RETARDANTS ON MATRIX TABLETS OF ACECLOFENAC SODIUM FOR ORAL SUSTAINED DRUG DELIVERY

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ABSTRACT

The successful optimization and development of drug entity, design of dosage form then plays important role. Aceclofenac sodium a novel NSAID used in the treatment of rheumatoid arthritis, frequency of administration may cause certain GI-adverse effects. The purpose of the present research work was to develop sustained release matrix tablets of aceclofenac sodium by wet granulation technique using different concentrations of locust bean gum (LBG) and hydroxyl propyl methyl cellulose (HPMC-K15M) as rate controlling polymer matrices. The solubility studies of aceclofenac were conducted to select suitable dissolution media. The drug excipients mixtures were subjected to preformulation by FTIR, DSC and XRPD studies. The different in-process and finished product quality controlled tests of the formulations were evaluated. *In-vitro* drug release potential was estimated in simulated gastric fluid pH1.2 for initial 2h, mixed phosphate buffer pH6.8 up to 6 h and simulated intestinal pH 7.4 at end of 12h studies. While increasing the concentrations of polymers significantly affects physicochemical properties of tablets and found within the limits. The release of drug from the tablets in pH1.2 is negligible. Under neutral conditions the tablets will swell and the drug release depend on swelling and erosion process resulting optimum level of drug released in a sustained manner and exhibited Higuchi model kinetics. The entire process is feasible in an laboratory scale and demands pilot study.

Key words: Aceclofenac sodium, Sustained release, Matrix tablets, HPMC, Locust bean gum, Higuchi Matrix Kinetics.

1. INTRODUCTION

Aceclofenac sodium is non-steroidal anti-inflammatory drug used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is rapidly and completely absorbed after oral administration, high bound plasma protein, peak plasma concentrations are reached 1 to 3h. The biological half-life of the drug is 1.8 – 3.5 h and dosing frequency 2-3 times daily with dose range 100 - 200mg [1]. Due to its short biological half-life requires multiple oral dosing to maintain the plasma drug concentration constantly during the entire period of therapy. It leads to fluctuation in the drug blood levels and dose related adverse effects like abdominal pain, gastritis, constipation, etc. The oral multiple dosing also fails to release the drug at the desired rate and in the desired amount which often results in poor patient compliance and inefficient therapy. [2]

An oral sustained / controlled release drug-delivery system should be able to achieve optimum therapeutic drug concentration in the blood with minimum fluctuation, improving therapy, safety, efficacy and patient compliance. [3] The matrix tablets are one of the least complicated approaches to the manufacture of oral sustained release dosage forms by direct compression or wet-granulation techniques of active drug, retardants and other additives. The release of the drug from the tablets by dissolution controlled as well as diffusion/erosion controlled mechanisms. [4] The drug release is controlled by adding the active drug into swellable hydrophilic or insoluble non-swellable matrix materials.

The hydroxyl propyl methyl cellulose (HPMC) and Locust bean gum (LBG) are hydrophilic swellable polymers used as coating agents, stabilizing agents, tablet binders, viscosity modifiers and suspending agents in various pharmaceutical products. [5] These are also commonly used to design of certain novel drug delivery products either oral or per-oral route of administration. The hydrophilic polymers have been widely used as drug release modifiers in several sustained / controlled drug delivery systems of their advantageous properties over synthetic polymers such as biocompatibility, biodegradability, ability to modify the properties of aqueous environment capacity to thicken, emulsify, stabilize, encapsulate, swell and to form gels1.[6] The hydrophilic polymers generally known as hydrogels respond in to surrounding conditions such as pH, ionic strength, and temperature of the medium, the polymer hydrate in water forming a gel layer at the matrix periphery which controls the release of drug from the formulated system. The pH-sensitivity of hydrogels is an important

factor in designing for controlled drug delivery systems for water insoluble drugs having pH sensitivity in the GI-tract. [7]

Generally, most of the oral sustained release tablets are enter into the GI-tract and the fluid slowly penetrate through the outer layer of polymer matrix system which induces the dissolution, swelling and formation of thick hydrodynamic layer. Further, drug moves from a higher concentration region of the biological membrane to lower concentration side. The concentration gradient will developed, which acts as the driving force to activate the diffusion of drug out of the system. The inside of the system should have lower water content initially than the surrounding medium to control the diffusion of a drug effectively in a sustained manner, finally, the diffused drug partition between the body fluid and plasma enters into systemic circulation. [8]

The aim of the present study, which was to develop oral products namely matrix tablets of aceclofenac sodium were prepared by wet granulation techniques by using locust bean gum [LBG], hydroxyl propyl methylcellulose (HPMCK15M), as release retardants and Avicel PH 101 as diluent. The effects of polymer and diluent ratio on the certain preliminary characterizations of tablets such as hardness, average weight, percentage of weight variation, percentage friability, and percentage of drug content, swelling ratio and in-vitro drug release potential were evaluated according to pharmacopeias methods.

2. MATERIAL AND METHODS

2.1 Materials

Aceclofenac sodium was obtained as a gift sample from Microlabs Bengaluru, Karnataka. India. Locust bean LBG was gum gift sample from LBG- Sicilia Natural gums, Ragusa-Italy. HPMC-Methocel K15M was gift sample from Colorcon Asia Private Ltd. Goa. AvicelPH101 was gift sample from Signet Chemicals Pvt, Ltd. Mumbai. Plasdone29/32 and PolyplasdoneXL were gift samples from ISP Singapore PTE Ltd., Singapore. Magnesium stearate and Purified talc were purchased from Loba chemicals Mumbai. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

2.2 PREFORMULATION STUDIES

2.2.1 Development of calibration curve

A stock solution of aceclofenac sodium was prepared by dissolving 100mg of pure drug in little quantity of methanol, magnetically stirred at 50 rpm for 30 minutes. Then the volume

was adjusted up to 100 ml with pH 1.2 acidic buffer, pH 6.8 and pH 7.4 phosphate buffers in a 100 ml volumetric flask to obtain the concentration 1000 µg/ml. From the stock solution, prepare different concentration of aliquots which are diluted with respective buffers, subjected to scanning between 200 - 400 nm in a UV- Visible spectrophotometer (Shimadzu 1201, Japan). The absorption maxima of aceclofenac sodium were obtained at λ max 275 nm. Accurately measured 10 ml of the above stock solution was further diluted up to 100 ml with corresponding buffers to obtain a working standard solution containing 100µg/ml. The different aliquots of working standard solution were diluted serially with sufficient buffers to obtain the concentration below Beer's range of 2 – 20 µg / ml. A calibration curve for aceclofenac sodium was obtained by measuring the absorbance at λ max 275 nm [9]. The procedure was performed in triplicate to validate the development of calibration curve.

2.2.2 FT-IR Spectroscopic Analysis

Drug polymer interactions were studied by FT-IR spectroscopy. Two milligrams of aceclofenac sodium alone, mixture of drug and polymer were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 450-4000cm^{-1} was recorded taking air as the reference and compared to study any interference.

2.2.3 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behaviors of drug alone and mixture of drug and polymer. The instrument comprised of calorimeter (DSC-60), flow controller (FCL-60), thermal analyzer (TA-60) and operating software (TA-60). The samples were heated in sealed aluminum pans under nitrogen flow (80ml/min) at a scanning rate of 10 ^{0} C/min from 25 to 450°C. Empty aluminum pan was used as reference. The heat flow as a function of temperature was measured for the drug and drug -polymer mixture.

2.2.4 X-Ray Powder Diffractometry (XPRD)

The X-ray diffraction patterns of pure drug and the drug loaded formulations were recorded using Philips X-ray powder Diffractometry (Model; PW 1710) with copper target to investigate the effect of granulation on crystallinity of drug. Powder X-RD patterns were recorded using a radiation at 30kv and 25mA, scanning speed 20/min^{-1}, over the 4^0 to 40^0 diffraction angle (2θ) range.

2.3 Preparation of aceclofenac sodium matrix tablets

Ten batches of aceclofenac sodium matrix tablets were prepared corresponding to various drugs to polymer ratio by wet granulation technique. All the ingredients were passed through sieve No.60 mesh ASTM prior to weighing. Required quantities of drug, polymer, diluent and disintegrant were mixed thoroughly in a mortar and added sufficient volume of granulating solution (Plasdone K29/32 in isopropyl alcohol). The wet mass was passed through sieve No.16 and the granules were dried at 50°C for 30 minutes. The dried granules were passed through sieve No's 22/44. The granules retained on sieve No. 44 meshes were mixed with 15% of fines (granules that passed through sieve No. 44). The required quantities of talc and magnesium stearate were finally added as glidant and lubricant. Based on theoretical weight of each tablet, the filling capacity of the lower punch was adjusted and the tablets compressed into 500 mg weight by using a single-punch tablet compression machine (Cadmach, Ahmedabad, India) at 6-7 kg/cm^2 hardness. Table 1 summarizes the batch details of aceclofenac sodium matrix tablets.

Table.1. Batch details for the formulation of aceclofenac sodium matrix tablets

Ingredients	Batch Code									
	AF-1	AF-2	AF-3	AF-4	AF-5	AF-6	AF-7	AF-8	AF-9	AF-10
Aceclofenac	200	200	200	200	200	200	200	200	200	200
LBG	25	50	100	150	200	-	-	-	-	
HPMC K15M	-	-	-	-	-	25	50	100	150	200
Avicel PH 101	225	200	150	100	50	225	200	150	100	50
Plasdone K29/32	10	10	10	10	10	10	10	10	10	10
Polyplasdone XL	10	10	10	10	10	10	10	10	10	10
Mag. stearate	15	15	15	15	15	15	15	15	15	15
Purified talc	15	15	15	15	15	15	15	15	15	15
Theoretical weight of each tablets = 500 mg										

2.4 PHYSICOCHEMICAL EVALUTION OF MATRIX TABLETS

2.4.1 Micromeritic properties of granules

The flow characteristics of the different batches formulated granules were measured by determining their angle of repose using fixed-base cone method. A glass funnel was secured with its tip positioned at a fixed height (H) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the funnel. The height and radius of the heap was measured. [10] The experiment was repeated in triplicate, the angle of repose (tan θ) was calculated using the formula;

$$\text{Angle of repose}[\theta] = \tan^{-1}(h/r)$$

H = cone height, r = radius of circular base formed by the granules on the ground.

The bulk and tapped densities of the formulated granules were evaluated by using the bulk density apparatus. Known weights of formulated granules were transferred into a 50cc graduated measuring cylinder. The cylinder was fixed on bulk density apparatus and the timer knob was set for 100 tapings. Then, the initial bulk volume and final volume after 50 tapings were noted. The experiment was repeated in triplicate. [11] The respective densities of different batches of granules were calculated by using the following formulas;

$$\text{Bulk density [gm /cc]} = \frac{\text{Mass of the sample (g)}}{\text{Bulk volume (ml)}}$$

$$\text{Tapped density [gm/cc]} = \frac{\text{Mass of the sample}}{\text{True volume}}$$

Compressibility index or Carr's index value of formulated granules was computed according to the following equation;

$$\text{Carr's index (CI \%)} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio of granular powder was determined by comparing the tapped density to the bulk density by using the equation;

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.4.2 Weight variation, Hardness and Friability

The uniformity of weights of tablets was determined according to the method mentioned in Indian pharmacopeia [12]. Weighed 10 tablets individually in an electronic balance and their average weight were determined. The standard deviation was calculated using the following formula;

Average weight (gm) = Total weight of the tablets /10

Standard deviation (%) = (Iw – Aw / Aw) x 100

[Where, Iw = Individual weight of the tablets, Aw = Average weight of the tablets]

For each formulation, the hardness of 10 randomly selected matrix tablets was examined using a Pfizer hardness tester (A-101 Secor India). The tablet hardness or crushing strength was measured in kg/cm2.

The percentage of friability was evaluated by using Roche friabilator (USP EF-2 Electro Lab). Ten or twenty tablets from each batch were weighed and placed in the plastic chamber.

The chamber rotated for 4 minutes or 100 revolutions. During each revolution the tablets falls from a distance of 6 inches after 100 revolutions and were removed from the chamber and reweighed. The percentage of weight loss or friability was determined by the following formula;

Friability (%) = Loss in weight of tablets / Initial weight x 100

2.4.3 Swelling behavior of tablets

The swelling ratio of three matrix tablets from each formulation was determined. The three matrix tablets were each weighed and placed in a glass beaker containing 500 ml of phosphate buffer at pH 6.8 ± 0.1 at 37 °C with continuous stirring at 50 rpm. After 0.5, 2, 4 and 6 hours' time period intervals the tablet was removed and blotted with tissue paper. The tablet was weighed on a digital balance (GE-412 Sartorius) and the final weight of the tablet was noted after prescribed time. The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point[13]. The extent of swelling was measured in terms of percentage weight gain by the tablet was calculated by the following formula;

Swelling index (S.I) = [(Mt-Mo) / Mo] X 100

[Where, Mt = weight of tablet at time =t and Mo = weight of tablet at time t=0]

2.4.4 Determination of drug content uniformity

Five tablets of each batch were weighed and powdered. The quantity of the powder equivalent to 200 mg of aceclofenac sodium was suspended in 100 ml of phosphate buffer containing 10 ml of methanol. The resulting solution was transferred into a stoppered conical flask and the flask was shaken for a period of 12 hours by using a mechanical shaker at room temperature. Next day it was stirred for 15 minutes. The solution was filtered, after suitable dilution; the drug content in the filtrate was analyzed at λ max 275 nm using UV-Visible spectrophotometer (Shimadzu 1201). [14] The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Each experiment was carried out in triplicate (n=3). The actual drug content was determined by using the following relationship;

$$\text{Drug content} = \frac{(k \times \text{Absorbance} \pm B) \times \text{bath volume} \times \text{dilution factor}}{1000}$$

2.4.5 In-vitro drug release studies

The various batches of the compressed matrix tablets of aceclofenac sodium was subjected to estimation of drug release in the simulated gastric fluid of pH 1.2 from 0 - 2 hours and simulated intestinal fluid (SIF) pH of 7.4 up to 12 hours by using dissolution test apparatus USP XIII paddle type (Model-TDT-08L, Electrolab Mumbai, India). The drug loaded matrix tablets were put into the basket rotated at a constant speed 75 rpm in 900 ml dissolution medium of pH 1.2 containing 2% w/v sodium lauryl sulfate was used for initial 2 hours and continued the test by changing the dissolution media pH 7.4 phosphate buffers up to the end of 12 hours and maintained temperature 37^0C. Samples (5ml) were withdrawn at different time intervals over a period of 12 hours. After each sampling, equal volume of the medium was replaced with same volume of fresh medium. The sample was filtered through 0.45µ membrane filter and diluted with appropriate dilution with respective medium. Then estimate the aceclofenac sodium concentration in the solution by using UV-Visible spectrophotometry (Shimadzu 1201, Japan) measured at λ max 275 nm. [15, 16] The absorbance of the samples was measured at different time intervals and the concentration, amount of drug released and the percentage of drug release were calculated using the following formulas;

Concentration (µg/ml) = Slope X Absorbance ± Intercept

$$\text{Drug released} = \frac{C \times VD \times DF}{1000} \times 100$$

Where; C= Concentration (µg/ml), VD= volume of dissolution media, DF= dilution factor.

$$\text{Percentage drug release (\%)} = \frac{\text{Amount released}}{\text{Drug content}} \times 100$$

2.4.6 Mechanism of drug release kinetics studies

The data obtained from the in-vitro dissolution studies was subjected to kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V2 software. The in-vitro drug release drug release data of the formulations was analyzed with various kinetic equations like zero-order (% release v/s time), first- order (Log % retained v/s time), Higuchi matrix (cumulative % drug released vs. square root of time) and Korsemeyer and Peppas equation (Log cumulative percent drug released versus log time).[17] The coefficients of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots.

Zero-order kinetics: The drug release followed by zero-order was estimated by using the following equation;

$Q_t = Q_0 + K_0 t$

Where Q is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times Q =0), and K_0 is the zero order release constant. When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics with a slope equal to K_o.

First-order kinetics: The drug release followed to first-order was estimated by using the following equation;

$\text{Log } c = \text{Log } Co - K_t / 2.303$

Where: C = Amount of drug remained at time (t). Co = Initial amount of drug, K=First-order rate constant (hr^{-1})

When the calculated data was plotted as log cumulative percent drug remaining versus time obtained a straight line that indicates that the release follows first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slop values.

Higuchi's matrix model: This model explains the release of drug from matrix devices mainly by diffusion of drug from the matrix layer. The drug release from the formulations was determined by using the following Higuchi's classical diffusion equation.

$Q = [DE / \tau (2A - E Cs) C_{st}]^{½}$

Where; Q = Amount of drug released at time (t), D = Diffusion co-efficient of the drug in the matrix, A = Total amount of drug in unit volume of matrix, Cs = the solubility of the drug in the matrix, E = Porosity of the matrix, τ = Tortuosity and t = time (hrs.) of which Q amount of drug is released.

The above equation can be simplified if one assumes that D, Cs and A are constant. The equation becomes

$Q = Kt^{½}$

When the data was plotted by cumulative percentage of drug release versus square root of time shows a straight line. This was indicates that the drug was released by diffusion mechanism.

Korsemeyer and Peppas model: This model was generally used to analyze the release of the drug from polymeric dosage forms, when the release mechanism is not well known or when more than one type of release occurs corresponding to time (t). In order to understand the

mode of drug release from swellable matrices, the data is fitted to the following Peppas equation

$M_t / M_\infty = K t^n$

Where, Mt is the amount of drug released at time (t). M∞ is the amount of drug released at infinite time (t). K is the kinetic rate constant depends on structural and a geometric characteristic of the product and n is the diffusional exponent which indicates the release mechanism. [18]

The above equation can be simplified by applying log on both sides then we get:

Log Mt / M∞ = Log K + n Log t

When the data is plotted as log percentage of drug release versus log time shows a straight line with a slope equal to 'n' (diffusional co-efficient) and the 'K' (coefficient of correlation) can be obtained from y-intercept.

2.4.7 Stability studies for formulated products

Selected batches of the formulated aceclofenac sodium matrix tablets were packed in transparent polyvinyl chloride blisters of 0.2 mm thickness. The studies were conducted according to the ICH for zone IV in the desiccators with saturated salt solution for up to 6 months maintaining proper temperature and relative humidity (RH). i. e. 25±2^{0}C with 60±5% relative humidity (RH) 40 ±2^{0}C with 75±5% relative humidity (RH) and Room temperature (under normal ambient conditions). [19] Samples were withdrawn at 1.0, 2.0, 3.0, and 6.0 months intervals and evaluated physical appearance by visual inspection, drug content was estimated.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies

The preformulation is the preliminary study for investigation and detail understanding of the physicochemical and chemical dynamics of drug substances through stability under the conditions to select correct form of drug and non-drug components for developing optimal drug delivery system. [20] Based on the preformulation results, proper excipients are used in the manufacturing of protocol products and to optimize the release of drug for an extended period at the site of action.

3.1.1 Development calibration curve

The development of standard calibration curves of aceclofenac sodium in SGF pH 1.2, pH 6.8 and 7.4 PBS was generated by UV-visible spectrophotometric technique at absorption

maxima 275nm. The calibration curves were developed by a plot absorbance vs concentration showed good linearity within a particular range (Fig 1a, 1b, 1c). The standard curves of aceclofenac sodium reveal that the drug obeys beer's law in concentration range of 2 – 20µg/ml. The linear regression equation was generated and used to calculate the amount of drug present in the formulated dosage forms i.e. SGF pH 1.2 (y = 0.021 x - 0.00232, R2= 0.9990), pH 6.8 PBS (y= 0.058x - 0.05963, R2=0.9995), and pH 7.4 PBS (y= 0.098x + 0.12615, R2 = 0.9980).

3.1.2 FT-IR spectroscopy

The FTIR spectras, observed that the characteristic absorption peaks of pure aceclofenac sodium was obtained at 3276.5, 2915.5, 1716.5, 1589.3, 1279.6 and 749.4cm-^{1} corresponding to NH- stretching, C=O stretching of –COO and –COOH group respectively (Fig 2a). The characteristic absorption peaks of LBG were observed in the region of 3186.4, 2925.6, 1705.6, 1528.4, 1450.5, 1350.25 and 774.5 cm^{-1} (Fig 2b). The characteristic peak at 3186.4 cm^{-1} represents O–H stretching vibration and 2925.6 cm^{-1} corresponding to C–H stretching of the –CH_2 groups. The peaks found at 1705.6 to and 1528.4 cm^{-1} represent the ring stretching of galactose and mannose of LBG. On other hand, the peaks observed in the region of 1350.25 to 1450.5cm^{-1} are corresponding to symmetrical deformations of CH_2 and COH groups. The lower wave number observed at around 774.5 cm^{-1}are due to ring stretching and ring deformation of α-D-(1-4) and α-D-(1-6) linkages. The physical mixture of aceclofenac sodium and LBG characteristic peaks at wave numbers 3124.2, 2856.5, 1710.8, 1538.2 and 774.5 cm^{-1} corresponding to NH- stretching, C=O stretching of –COO and –COOH groups respectively (Fig 2c). FTIR spectra of HPMC K15M show the characteristic peaks at wave numbers 2815.33, 1706.56, 1485.32, 1385.36 and 782.60 cm-1 corresponding to C-H stretching, C=C stretching in the aromatic ring and peaks at 1485.32, 1385.36 cm-1 which can be assigned to the C-H deformation (Fig 2d). FTIR spectrum of physical mixtures of aceclofenac sodium and HPMC K15M showed absorption peaks at wave numbers 2932.86, 1718.33, 1507.52, 1252.82 and 748.45 cm^{-1} corresponding to C-H stretching and C-H deformation (Fig 2e). The IR spectra's of individual polymer and physical mixtures of drug and polymer were compared with the spectra of the pure drugs. The spectral data suggests that the major peaks for drugs are obtained as nearer value and there were no considerable changes in IR peaks in all physical mixtures of drug and polymer. This indicates that the drugs were molecularly dispersed in the polymers or in drug loaded formulations thus thereby indicating the absence of any interactions.

3.1.3 Differential scanning calorimetry (DSC)

DSC is a well-established method often used as a qualitative technique to characterize physical and chemical changes in either enthalpy or heat capacity of a crystalline drug in the polymer matrix during the manufacturing process. The pure aceclofenac sodium shown a sharp endothermic peak at 158.50^{0}C followed by corresponding meting point (Fig 3a). However, the drug-loaded matrix tablets were shown a sharp endothermic peak in between the range of 193 to 195^{0}C (Fig 3b, 3c). The extra obvious peak of the pure aceclofenac sodium at 158.5^{0}C was not observed in the thermograms of prepared matrix tablets. The results indicate that there were no changes in thermal behavior of drug during the manufacturing process and it was molecularly dispersed in different hydrogel matrices.

3.1.4 X-Ray Powder diffractometery (X-RPD)

The distribution of the drug in the polymeric matrix is very important to maintain the theoretical potency and stability in the manufacturing process. However, the drug can crystallize during the formulation resulting decreased aqueous solubility rate due to its polymorphic changes such as particle size, shape, density, melting point etc. The XRPD is an important technique in pharmaceutical field because to investigate the fundamental physical features about the crystalline nature of solid substances.

The X-ray powder diffraction patterns of pure drug were compared with drug-loaded matrix tablets. The relative intensity of peaks were observed in XRPD patterns and calculated by using D8 TOOLS software. The intensity of the pure aceclofenac sodium peaks observed at 8.72, 14.47, 22.26, and 25.95(2θ) (Fig 4a). The peaks intensity of formulated aceclofenac sodium matrix tablets AF-4 at 13.98 and 16.76 (2θ) (Fig 4b). The aceclofenac sodium matrix tablets AF-9 shows peaks at intensity 14.16 and 16.65(2θ) (Fig 4c). The XRPD scan of plain aceclofenac sodium shown sharp intense peaks of crystallinity whereas the drug-loaded matrix tablets exhibited halo pattern with less intense followed by denser peaks. This result indicates that decrease in the degree of crystallinity due to partial amorphization of the drug in the polymeric matrix. Thus, there were no appreciable changes in the crystallinity of drug during the manufacturing process.

3.2 Micromeritic properties of precompressed granules

From the Table 2, the granules of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, carr,s index, hausner's ratio. Increasing the

concentration of polymer and diluent ratio decreases the angle of repose. The angle of repose (<30) indicates good flow properties of the granules due to formation of high compact matrix in the granulation process. The bulk and tapped density values were obtained in the acceptable range indicating good packability of the granules in the tablet die cavity and minimizes weight variation of compressed tablets. Compressibility index and hausner's ratio values were obtained in the range 18.04 to 8.35 and 1.22 to 1.08 respectively. This indicates the prepared granules have excellent compressibility and good flow properties to get acceptable hardness to the tablets.

Table 2 Micromeritic properties of pre-compressed matrix granules of aceclofenac sodium

Formulation Code	Bulk density (g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
AF-1	0.336 ± 0.05	0.410 ± 1.23	18.04	1.22	21.25
AF-2	0.366 ± 0.55	0.438 ± 0.85	16.45	1.20	19.20
AF-3	0.397 ± 0.25	0.468 ± 0.68	15.17	1.17	17.65
AF-4	0.428 ± 0.38	0.496 ± 0.42	13.70	1.15	14.25
AF-5	0.467 ± 0.47	0.523 ± 0.22	10.70	1.11	12.65
AF-6	0.316 ± 0.15	0.385 ± 0.82	17.60	1.21	22.60
AF-7	0.338 ± 0.22	0.407 ± 0.78	16.95	1.20	20.70
AF-8	0.376 ± 0.15	0.447 ± 0.65	15.88	1.18	19.45
AF-9	0.423 ± 0.28	0.488 ± 0.74	13.36	1.15	17.22
AF-10	0.446 ± 0.66	0.508 ± 0.88	12.25	1.13	16.40

Data are expressed as mean ±SD of at least triplicate

3.3 Effect of polymer to diluent ratio on physicochemical properties of matrix tablets

3.3.1 Effect of locust bean gum and Avicel PH101

The depicted Table 3, illustrates that the weight variation of the matrix tablets was observed within pharmacopeia limit complied below ±5% w/w of standard deviation from the average. However, the average weight of the matrix tablet of the batch AF-3 was obtained very nearer to theoretical weight. The higher concentration polymer and diluent ratio influences the formation of dense matrix granules and uniform size, ultimately increases flow properties which minimizes weight variation of formulated matrix tablets. The hardness of the formulated tablets obtained within the acceptable range of 5.6 to 6.6 kg/cm^2 followed by decreasing the percentage of friability except the batch AF-1. This indicates the low concentration of LBG used in the formulation decreases the mechanical strength due to the formation of loose matrix with higher concentration of Avicel pH 101.The percentage of

aceclofenac sodium content in the tablets of batches AF-1 to AF-5 was observed in the range of 84.76 ± 0.6 to 93.42 ± 0.24 respectively (Table 3). It was stated that the percentage of drug content increases by mainly increasing the concentration of LBG entrapped more quantity of drug due to formation of dense matrix during compression.

The Figure 5 reveals that the percentage of swelling ratio of aceclofenac sodium matrix tablets containing various concentrations of LBG and AvicelPH10 was obtained in the range of 176.30 to 238.60 at the end of 6 hours. The result suggests that by increasing the concentration of both polymer and diluent could influence the percentage of swelling ratio. The formulation AF-1 containing high level of Avicel PH101 (above 200mg) which shows higher swelling ratio in initial hours followed by erosion at the end of 6 hours due to its fibrous nature, forms larger pores which rapidly increase the water penetration into the interior layer of polymeric gel network and decrease the resistance of gel layer in higher pH level. [21] The formulation of batch AF-5 containing more concentration of polymer and less concentration of diluent decreases the swelling ratio gradually but increases the erosion. The formulation AF-4 shows steady state swelling ratio for 6 hours. This states that the presence of higher level of LBG enhance the gel formation inhibiting water penetration into interior layer of polymeric gel and thus gradually swells with an increased time period.

The depicted results in the figure 6, illustrates that the aceclofenac sodium release from the matrix tablets in SGF pH 1.2 for initial 2 hours was obtained less than 30%w/w due to poor solubility of LBG and aceclofenac sodium in this environment. The maximum amount of aceclofenac sodium release (>70 % w/w) from the matrix tablets in SIF pH 7.4 at 6 hours followed by sustaining up to 12 hours. The formulated tablets of batch AF-4 were released in sustain manner compared to AF-1 because of optimum concentration in polymer to diluent ratio. By increasing the polymer proportion in the tablets forms a thick hydrodynamic gel layer that take a prolonged time to diffuse un-dissolved hydrophobic nature of aceclofenac sodium into bulk of the dissolution medium. Thus, the results clearly explain that the polymer and diluent ratio modified the drug release in a sustained manner.

3.3.2 Effect of HPMC K15M and Avicel PH101

From the Table 3, the weight variation of the matrix tablets observed within pharmacopeia limit and complied below ± 5% w/w of standard deviation from the average. The average weight of the matrix tablet of the batch AF-9 was obtained very nearer to theoretical weight. This suggested that by increasing the polymer and diluent ratio influences the formation of

uniform size granules which ultimately increases the flow properties and minimizes the weight variation. The hardness of the formulated tablets obtained within acceptable range of 5.5 to 7.1 kg/cm^2 followed by decreasing the percentage of friability except the batch AF-6. This indicates the low concentration of HPMC K15M used in the formulation decreases the mechanical strength due to the lower compressibility of Avicel pH 101 forms loose matrix granules. The percentage of aceclofenac sodium content in the matrix tablets of batches AF-6 to AF-10 was found in the range of 88.95 to 96.42 respectively. It was stated, that the percentage of drug content increases with higher concentration HPMC K15M due to formation of dense matrix entrapped more quantity of drug.

The figure 7, explains that the percentage of swelling increases with an increase in the concentration of polymer and diluent in the matrix system. The percentage of swelling ratio of aceclofenac sodium matrix tablets containing various concentrations of HPMC K15M and AvicelPH10 were obtained in the range of 168.20 to 246.32 at the end of 6 hours. The result suggests that increasing the concentration of both polymer and diluent could influence the percentage of swelling ratio. The formulation AF-6 containing higher level of Avicel PH101 (above 200mg) shows higher swelling in initial hours followed by erosion at the end of 6 hours because Avicel PH101 is a hydrophilic fibrous excipient which rapidly increases the water penetration into interior layer of polymeric gel network and increases erosion of less viscous gel layer. The formulation AF-9 shows steady state swelling ratio for 6 hours. The formulation of batch F-10 containing more concentration of polymer and less concentration of diluent increases the swelling ratio gradually but decreases the erosion. This states that the presence of higher level of HPMC K15M enhances the formation of thick gel acts as a barrier inhibiting the water penetration into interior layer of polymeric gel and thus gradually swells with increased time period.

Figure 8, illustrates that the aceclofenac sodium release from the matrix tablets in SGF pH 1.2 for initial 2 hours was obtained as less than 20 %w/w due to poor solubility of aceclofenac sodium in this environment. The maximum amount of aceclofenac sodium release (>50 % w/w) from the matrix tablets in SIF pH 7.4 at 6 hours followed by sustaining up to 12 hours. The formulation AF-9 gives optimum drug release compared to AF-6. In higher concentration of HPMC K15M in the matrix tablets prolongs the drug release due to formation of thick hydrodynamic diffusion gel layer in the dissolution process that take a

prolonged time to diffuse un-dissolved hydrophobic nature of aceclofenac sodium into bulk of the dissolution media.

3.4 Analysis of various drug release kinetics

The in-vitro drug release of all the batches of F-1 to F-10 aceclofenac sodium matrix tablets was treated with various kinetic models. The mechanism of drug release was determined by using PCP-DISSOv2.08 software. The in vitro drug release pattern of batches AF-1 to AF-5 were found to be highest correlation co-efficient (r2) in the range of 0.9968, 0.9969, 0.9961, 0.9959, 0.9929 corresponding to huguchi matrix followed to Korsemeyer – Peppas model with coefficient of correlation (r2) in the range 0.9944, 0.9951, 0.9956, 0.9991, 0.9987 and diffusion coefficient (n) values are 0.5810, 0.5895, 0.5996, 0.6033, 0.6199 respectively (Table 4). The formulations AF-6 to AF-10 shows highest regression coefficient (r2) values were obtained in the range of 0.9453, 0.9866, 0.9896, 0.9945, 0.9835 corresponding to huguchi matrix followed to Korsemeyer – Peppas model with coefficient of correlation (r2) values in the range 0.9538, 0.9962, 0.9968, 0.9976 0.9957 and the values of diffusion coefficient (n) are obtained 0.5496, 0.6830, 0.6915, 0.8925, 0.8965 respectively (Table 4) The results describes that the release mechanism from the batches of AF-1 to AF-5 matrix tablets shows highest correlation co-efficient corresponding to huguchi matrix followed to krosemeyer – peppas model. The formulation batches of AF-6 to AF-10 shows the mechanism of drug release zero-order followed to krosemeyer - peppas mixed order kinetics. All the formulation batches have shown the diffusion co-efficient (n) values in the range of 0.5810 to 1.185.This indicates, the drug release from matrix tablets by both diffusion and erosion mechanisms followed by super case-II transport.

3.5 Stability studies

No significant changes was observed for the formulated aceclofenac sodium matrix tablets in their physicochemical parameters such as drug content, average weight, and hardness after 01, 02, 03, 04, 05 and 06 months when kept at 25^0C / 60% RH, 40^0C / 75% RH and room temperature (Table 5). Based on these observations, it was concluded that developed formulations of aceclofenac sodium matrix tablets are physically and chemically stable and retain their pharmaceutical properties at various temperature and humidity conditions over a period of 6 months.

Table 3 Physicochemical evaluation of the formulated matrix tablets of aceclofenac sodium

Evaluation parameters					
	Average weight(mg)	**S. D. (%)**	**Hardness (kg/cm2)**	**Friability (%)**	**Drug content (%)**
AF1	494.50	1.61	5.6 ± 0.10	0.84 ± 0.02	84.76 ± 0.6
AF2	492.25	1.23	6.0 ± 0.15	0.70 ± 0.05	85.98 ± 0.58
AF3	490.20	0.80	6.2 ± 0.08	0.56 ± 0.04	89.40 ± 0.70
AF4	500.10	0.40	6.5 ± 0.12	0.132 ± 0.07	92.52 ± 0.12
AF5	482.15	0.84	6.6 ± 0.50	0.124 ± 0.14	93.42 ± 0.24
AF6	488.50	2.86	5.5 ± 0.10	0.118 ± 0.02	88.95 ± 0.81
AF7	490.20	2.65	5.8 ± 0.25	0.85 ± 0.05	91.98 ± 0.56
AF8	494.60	1.21	6.0 ± 0.92	0.65 ± 0.04	93.52 ± 0.75
AF9	500.30	0.80	6.5 ± 0.18	0.55 ± 0.07	95.52 ± 0.22
AF10	498.40	0.60	7.1 ± 0.55	0.44 ± 0.014	96.42 ± 0.28

Data are expressed as mean ±SD of at least triplicate

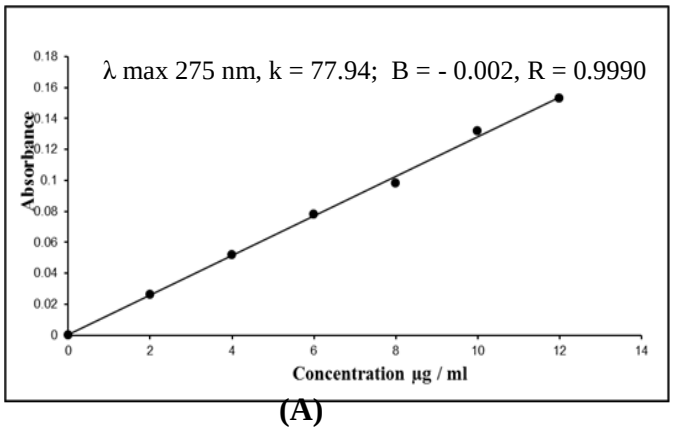
Table 4 *In-vitro* drug release of aceclofenac sodium matrix tablets fitted with various kinetic models

Batch code	**Various Kinetic Models**								
	Zero-order		**First order**		**Huguchi matrix**		**Korsmeyer-peppas equation**		
	r^2	**K_0 (h^{-1})**	**r^2**	**K_1(h^{-1})**	**r^2**	**KH($h^{-1/2}$)**	**r^2**	**K_{KP} (h^{-n})**	**n-values**
AF1	0.8987	9.819	0.9337	-0.3059	0.9968	29.209	0.9944	25.239	0.5810
AF2	0.9087	9.570	0.9459	-0.2673	0.9969	28.407	0.9951	24.102	0.5895
AF3	0.9155	9.342	0.9665	-0.2347	0.9961	27.683	0.9956	22.991	0.5996
AF4	0.9333	8.868	0.9953	-0.1913	0.9959	26.164	0.9991	21.407	0.6033
AF5	0.9387	8.400	0.9968	-0.1642	0.9929	24.732	0.9987	19.539	0.6199
AF6	0.8830	8.650	0.8668	-0.2438	0.9453	25.517	0.9538	22.838	0.5496
AF7	0.9382	8.789	0.8950	-0.1820	0.9866	25.852	0.9962	18.128	0.6830
AF8	0.9792	8.877	0.9282	-0.1756	0.9896	24.512	0.9968	17.865	0.6915
AF9	0.9865	7.712	0.9287	-0.1745	0.9945	23.252	0.9986	16.895	0.8925
AF10	0.9883	7.702	0.9297	-0.1736	0.9845	22.965	0.9957	15.652	0.7265

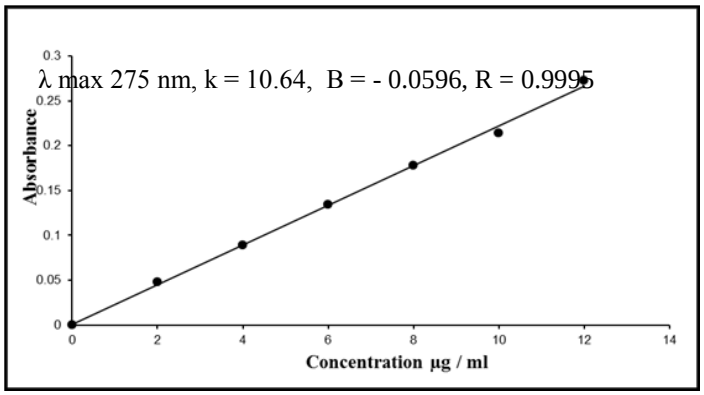
Where K_0 is zero order proportionality constant, r^2 is the regression coefficient; K_1 is the first order release rate constant, K_H is the Higuchi constant, K_{KP} is peppas equation constant. n = Diffusion exponent related to mechanism of drug release, according to equation Mt/M=Ktn ,

Table 5. Stability evaluation of formulated aceclofenac sodium matrix tablets

Sampling Interval (months)	Stability conditions					
	Room temp ^{0}C	25^{0}C/60% RH	40^{0}C/75% RH	Room temp ^{0}C	25^{0}C/60% RH	40^{0}C/75% RH
	Drug content (mg /tablet)			Physical characteristics		
				Appearance	Average weight (mg)	Hardness (kg/cm2)
0	199.52	199.52	199.52	No significant change	500.50	6.2 ± 0.8
1	199.52	199.52	199.48	No significant change	500.50	6.2 ± 0.8
2	199.52	199.50	199.45	No significant change	500.55	6.2 ± 0.8
3	199.50	199.50	199.40	No significant change	500.62	6.0 ± 0.8
4	199.50	199.45	199.40	No significant change	500.42	5.9 ± 0.8
5	199.42	199.25	199.10	No significant change	500.10	5.8 ± 0.8
6	199.15	189.20	185.60	Slight change in color	500.05	5.5 ± 0.8



(A)



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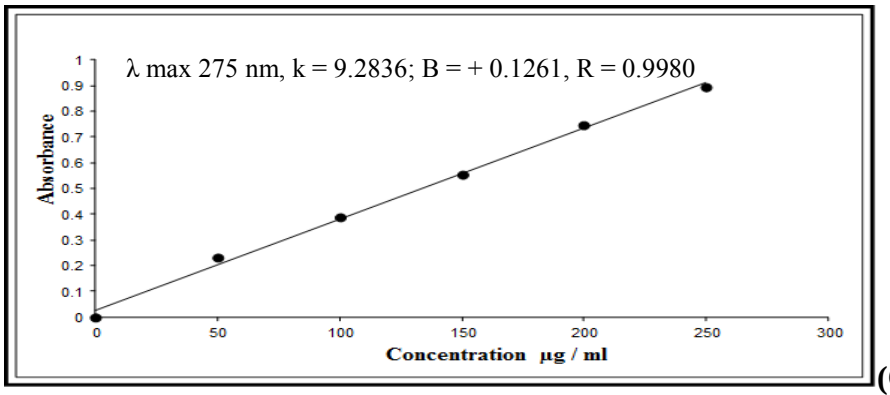


(C)

Figure 1 Standard calibration of aceclofenac sodium in A) pH 1.2 buffer solutions B) pH 6.8 phosphate buffer solutions, C) pH 7.4 Phosphate buffer solutions

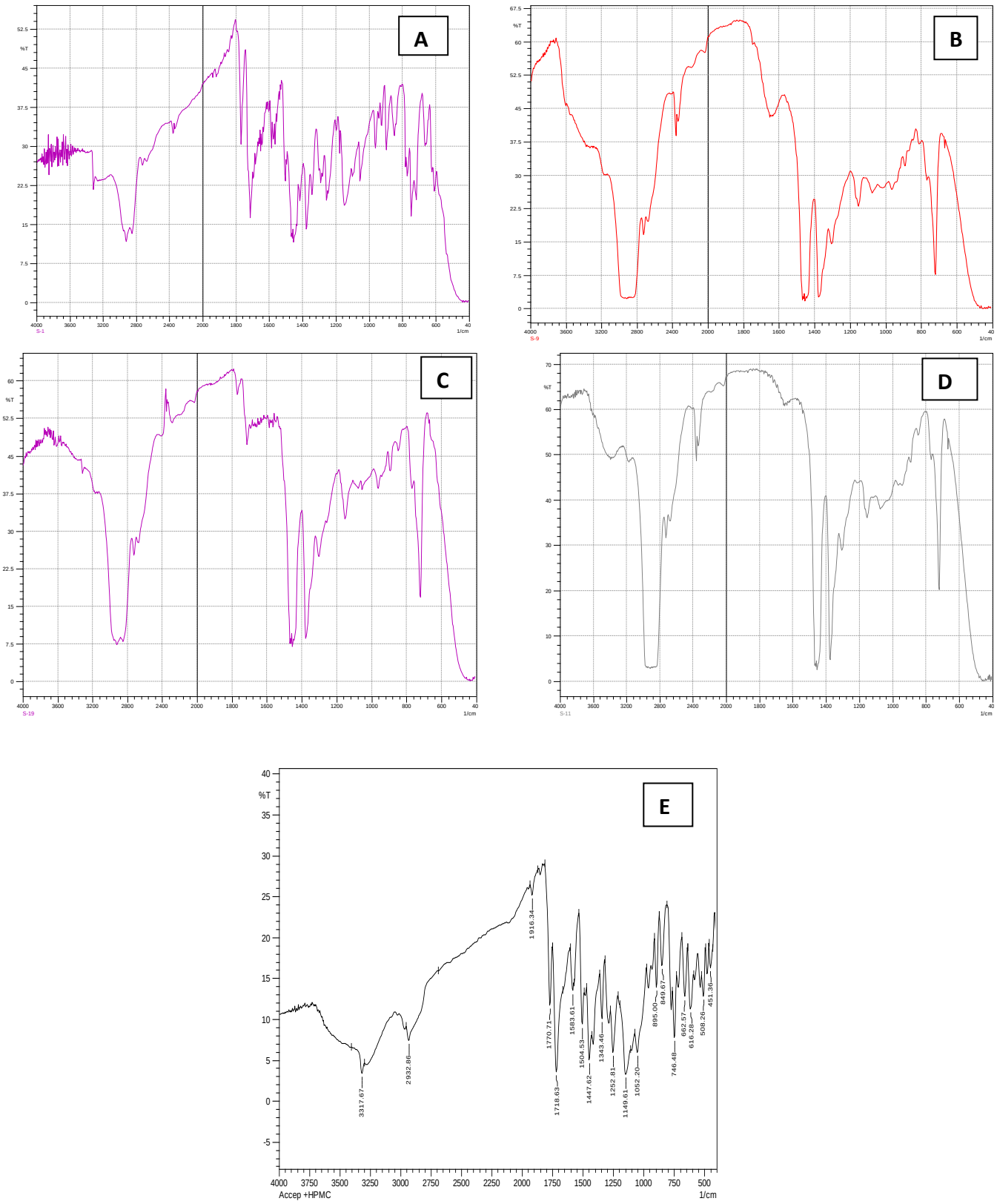


Figure 2. FTIR-Spectra of A) Pure aceclofenac sodium, B) LBG, C) Physical mixture aceclofenac sodium and LBG, D) HPMC K15M, E) Physical mixture of aceclofenac sodium and HPMC K15M

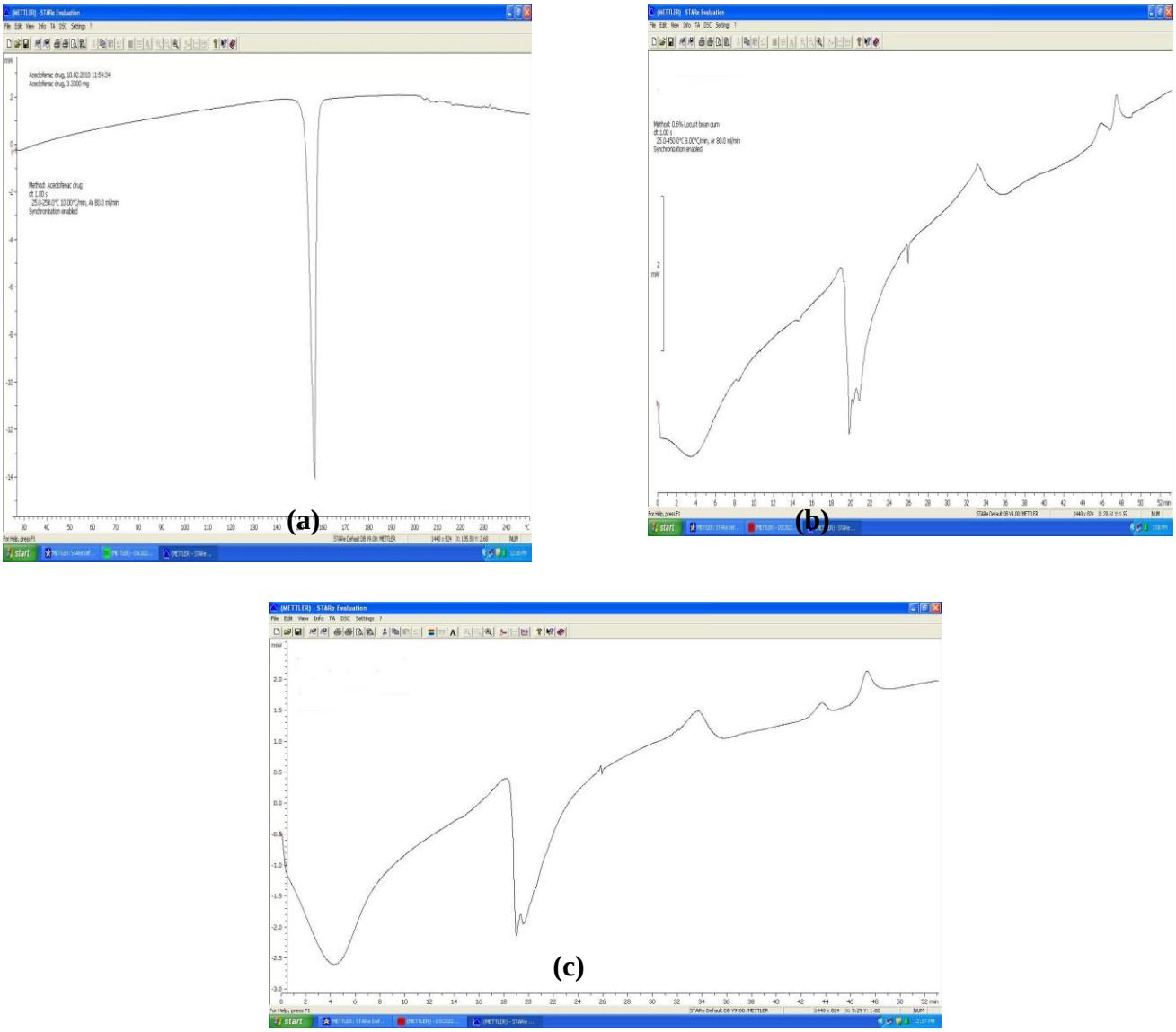
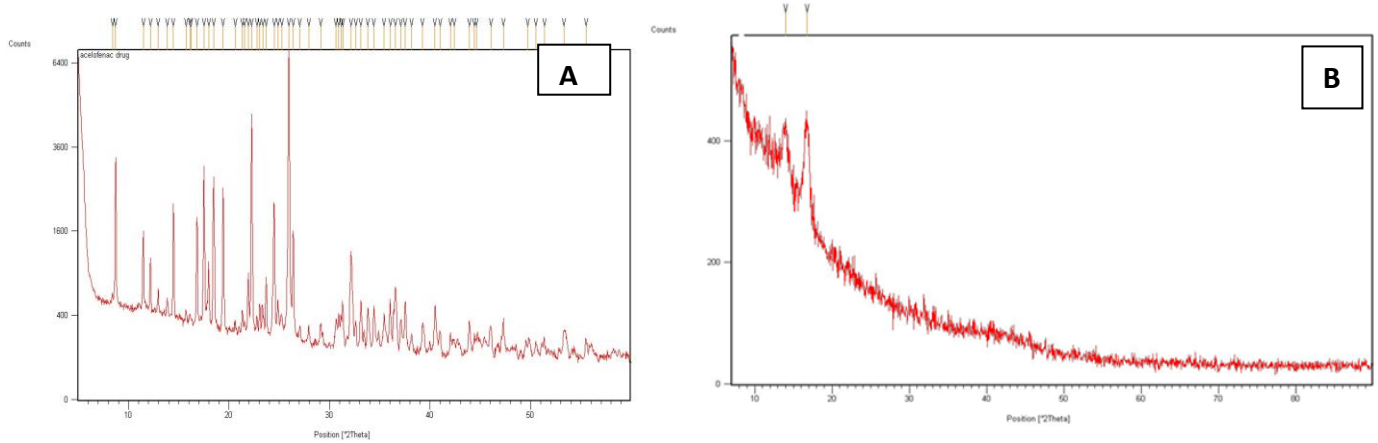


Figure 3 DSC Thermo-grams of a) pure aceclofenac sodium b) Aceclofenac sodium matrix tablets (AF-4), c) Aceclofenac sodium matrix tablets (AF-9)



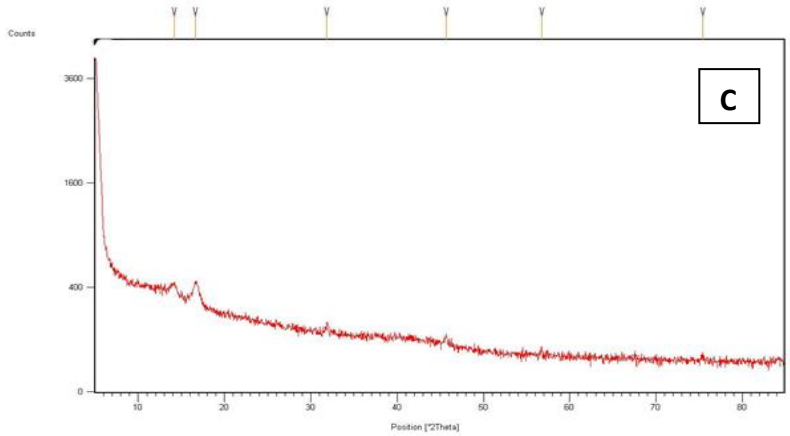


Figure 4 X-Ray diffraction patterns of A) Pure aceclofenac sodium B) Matrix tablets containing LBG as retardant (AF-4), C) Matrix tablets containing HPMC K15M as retardants (AF-9)

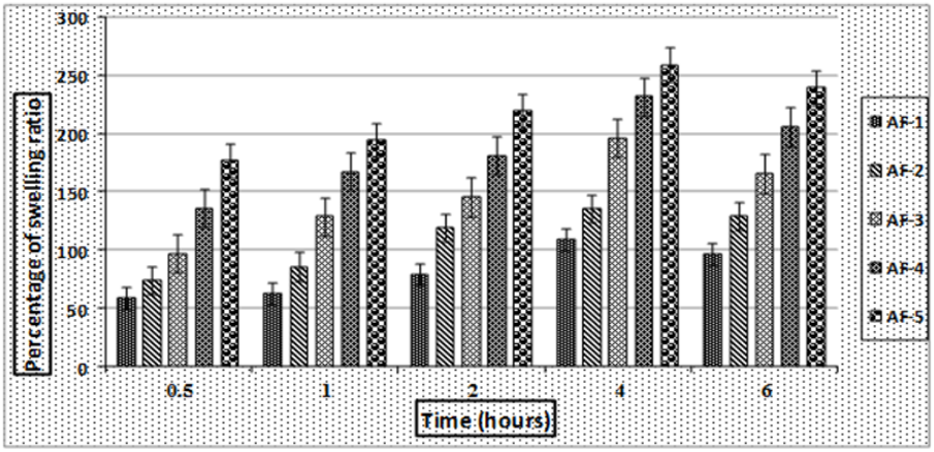


Figure 5 Effect of LBG and Avicel PH101 on swelling behaviors of aceclofenac matrix tablets in pH 6.8 PBS

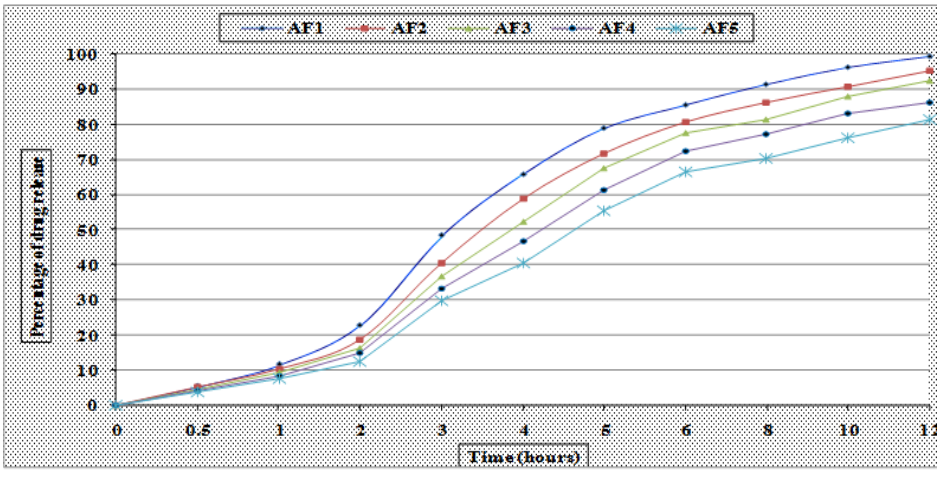


Figure 6 Effect of LBG and Avicel PH101 on *In-vitro* drug release profiles of formulated matrix tablets of aceclofenac sodium

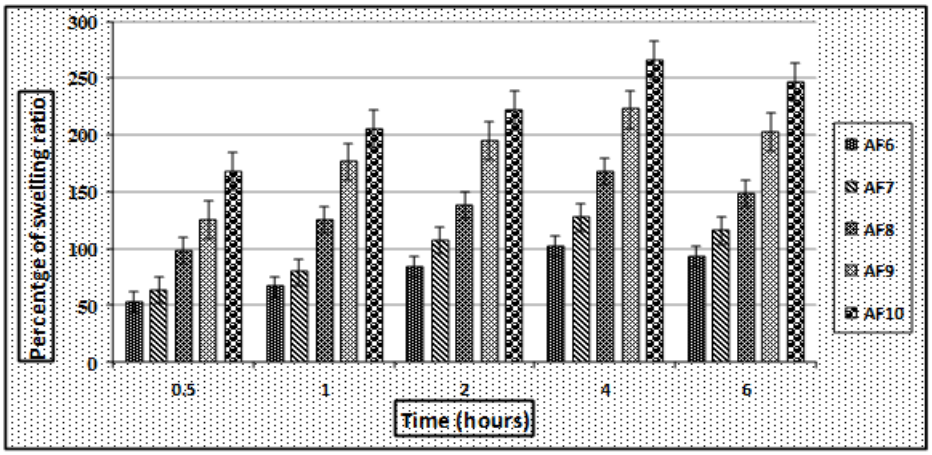


Figure 7 Effect of HPMC K15M and Avicel PH101 on swelling behaviors of aceclofenac matrix tablets in pH 6.8 PBS

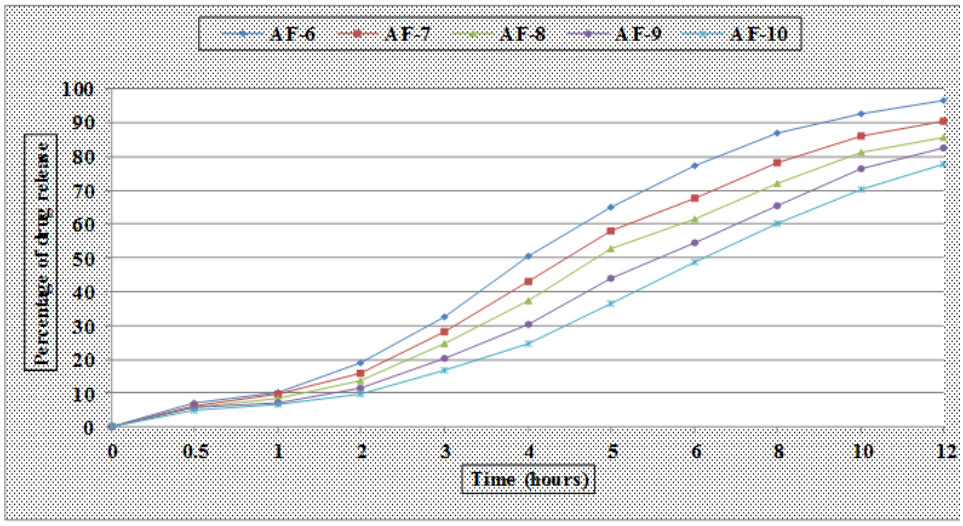


Figure 8 Effect of HPMC K15M and Avicel PH 101 on *In-vitro* drug release profiles of formulated matrix tablets of aceclofenac sodium

CONCLUSION

In the present research work, the aceclofenac sodium oral sustained release matrix tablets have been developed by using hydrophilic release retardants and investigated the effects of polymer and diluent ratio on physicochemical properties and drug release potential. All the micromeritic properties of the granules show acceptable ranges that are free flowing during the compression of tablets. The compressed tablet properties such as percentage of drug content, hardness, average weight and weight variation obtained an acceptable range and the values meet pharmacopeias limits. The swelling behaviors of formulated tablets remarkably increase with optimum proportion of polymer and diluent level. The optimum proportion of HPMC K15M and Avicel PH101 shows the gradual swelling behavior and gives a great

contribution to sustain the drug release for extended period of time. The in-vitro drug release significantly decreases with variable concentration of polymer and diluent ratio. The formulated drug loaded matrix tablets in SGF pH 1.2 show less than 20% w/w of drug release due to hydrophobicity of drugs, but maximum amount of drug release (>60 %w/w) in pH 7.4 at 6 hours followed by sustaining up to 12 hours. The kinetic drug release mechanism of formulated aceclofenac sodium matrix tablets was found to be linear and close correlation with huguchi matrix diffusion followed to Korsmeyer and Peppa's model and good regression co-efficient was observed due to diffusion and erosion mechanism of polymeric chains and shown the diffusion co-efficient (n) values in the range of 0.5810 to 1.185. This indicates, the drug release from matrix tablets by both diffusion and erosion mechanisms followed by super case-II transport. The developed formulations of aceclofenac sodium matrix tablets are physically and chemically stable and retain their pharmaceutical properties at various temperature and humidity conditions over a period of 6 months. Based on the investigated results, it was concluded that the polymer and diluent ratio modify the release of drug in different environmental pH conditions, capable of exhibiting the sustained release properties, environmentally stable and feasible for further scale up industrial production.

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