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Al $^{3+}$ ion cross-linked matrix tablets of sodium carboxymethyl cellulose for controlled release of aceclofenac: Development and *in-vitro* evaluation

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ABSTRACT

Treatment of musculo-skeletal disorders with non-steroidal anti-inflammatory drugs (NSAIDs) produces extensive gastric adverse effects. Aceclofenac, a novel NSAID, loaded sodium carboxymethyl cellulose and Aluminium hydroxide matrix tablets was prepared by wet granulation method with an aim to minimize the drug release at gastric mucosa and provide prolonged release at the small intestine. The effect of formulation variables like polymer/ $Al(OH)_3$ ratio, drug load and processing variable like compression force on the extent of in-vitro drug release in acid solution (pH 1.2) and phosphate buffer solution (pH 6.8) was studied. The concentration of Aluminium hydroxide significantly influenced the drug release behavior from the matrix tablets. At low concentrations it gave slower release, while at higher concentration it produced faster release. Drug load and hardness of the tablets produced considerable variation in drug release. Compatibility of the drug in the tablets was evaluated through FTIR, XRD and DSC analyses. The drug release in acidic pH was minimal (3-8%) from all the batches observed. This study reveal that proper selection of formulation and processing variables could produce a tablet dosage form that can be effectively used to control the drug release in stomach and prolong the same at small intestine.

Key words: Ionotrophic gelation, Aluminium hydroxide, NSAIDs, drug release, gastric adverse effect.

INTRODUCTION

Non-steroidal anti inflammatory drugs (NSAIDs) are extensively used for symptomatic treatment of musculo-skeletal disorders like rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [1,2]. However, long term therapy with these drugs may produce minor gastric irritation to severe bleeding, ulceration and perforation of gastric mucosa due to inhibition of synthesis of prostaglandins and direct contact of the drug with mucosa [3]. Generally, enteric coating of the dosage form is widely adopted as a solution to the problem. However, due to all or none hypothesis and considerable delay in gastric emptying, dose–dumping as well as intra- and inter-subject variation in the onset of therapeutic action may be exhibited by drugs administered as enteric coated [4]. Thus, rational dosage form for delivery of NSAIDs is which can minimize the drug release in the gastric mucosa. Again, drugs having shorter biological half life need to be administered frequently, and thus have several disadvantages.

Development of an oral sustained release dosage form is of much interest to a pharmaceutical house as they provide prolonged duration of action of drugs having short biological half-life, and reduce dose-related toxicity, dosing frequency, and patient non-compliance [5,6]. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. Also, pharmaceutical industries prefer tablet dosage form because of the ease of manufacturing using the simple and economical tablet manufacturing infrastructure [7,8]. Matrix tablets as a tool for sustained release of the drug has gained much importance now-a-days. Recently much research efforts have been directed to the use of natural polymers to prepare such dosage forms. Native biopolymers have the advantage of being biodegradable and biocompatible which would reduce or eliminate their side effects in

biomedical applications [9]. Again, biopolymers can be engineered for various chemical modifications [10] and thus many functional characterizations can be imparted to them [11].

Among the wide range of biopolymers available, cellulose is the most abundant of them in nature [12]. Sodium carboxymethyl cellulose (SCMC), a semi synthetic derivative of cellulose, is widely used ranging from flocculation, drag reduction, oil drilling operation [13] to food industries, cosmetics and pharmaceuticals [14]. SCMC has been widely used in pharmaceuticals as thickening, gel forming, suspending agent and drug delivery. SCMC has been used for IPN beads with gelatin for drug delivery system [15]. SCMC as a matrix material for tablet production has also being explored widely. However, easy solubility in water, substantial swelling and rapid erosion of SCMC matrix tablet are some of the limitations to make it an ideal matrix material. The unique property of SCMC to crosslink with cations by the process of ionotrophic gelation has made it possible to encapsulate simvastatin in simple and mild conditions [16]. This character can be used as a solution to the problem of swelling and erosion of matrix tablets prepared with SCMC. When carboxylate groups of the polymer comes in contact with Al^{3+} ions it will form a rigid gel like structure which could prevent substantial swelling and erosion and thus, may help in prolonging the duration of drug action.

In this present investigation, aceclofenac (ACF) loaded aluminium carboxmethyl cellulose (Al-CMC) matrix tablets were prepared by ionotropic gelation with Al^{3+} ions with an aim that the formulation will be able to minimize the drug release in stomach to avoid the harsh effects of NSAIDs and can provide controlled release in small intestine. The concentration of aluminium ions on the extent of ionotrophic gelation has been studied. The in-vitro drug release pattern from various matrix tablets prepared under different conditions has also been studied in acidic (pH1.2) media and in PB solution (pH 6.8). Compatibility of the drug in the matrix tablets has been assessed by conducting FTIR, XRD, and DSC analysis. Aceclofenac, a novel NSAID, has been used as a model drug in this study. Its short biological half life requiring frequent administration makes it a potential candidate for controlled release preparation.

MATERIALS AND METHODS

2.1. Materials

Aceclofenac (ACF) was obtained as a gift sample from Torrent Pharmaceuticals Pvt Ltd ,Baddi, India. Sodium Carboxymethyl Cellulose [SCMC, Medium Viscosity (MVCMC),High Viscosity (HVCMC)], Aluminium hydroxide [$Al(OH)_3$],magnesium stearate, sodium bicarbonate, sodium hydroxide, methanol, and potassium dihydrogen phosphate were purchased from S.D. Fine-Chem, Mumbai, India. All materials were of laboratory reagent grade and used as received. Double-distilled water was used throughout the experiment.

2.2. Preparation of matrix tablet

The tablets are prepared by conventional wet granulation method. ACF, SCMC, and $Al(OH)_3$ previously passed through #60 mesh screen were mixed in a stainless steel bowl. The powder blend was moistened with the required amount of water and then granulated using #18 mesh screens. The granules were dried at 60°C for sufficient period of time and the moisture content of the granules as measured using the IR Moisture Meter was found to be confined within 0.85% to 1.2%. The dried granules were then passed through #22 mesh screen, mixed with magnesium stearate, and compressed into tablet using a flat-faced 10-mm punch in a ten-station rotary minipress tablet machine (RIMEK, Karnavati Engineering, Gujarat, India). The tablets were prepared under the following conditions:

1. Keeping the amount of drug (100mg) constant, the ratios of MVCMC: $Al(OH)_3$ (1:1 to 5:1 w/w) were varied (tablets F1-F3, F13)

2. Keeping the amount of drug (100mg) constant and the ratios of total polymer:$Al(OH)_3$ (1:1w/w) constant, the weight ratios of HVCMC to MVCMC was varied from 10-60% w/w (tablets F4-F6).

3. Keeping the amount of drug (100mg) constant and the ratios of total polymer:$Al(OH)_3$ (1:1w/w) constant, the weight ratios of MVCMC:HVCMC (40:60% w/w) constant, hardness (2-6 kgf) of the tablets were varied (tablets F6-F8).

4. Amount of ACF was varied from 50 to 150 mg, keeping the ratios of total polymer:$Al(OH)_3$ (1:1w/w) constant, the weight ratios of MVCMC:HVCMC (40:60% w/w) constant and hardness (4 kgf) constant (tablets F9-F10).

5. Keeping the amount of drug (100mg) constant, ratios of total polymer:$Al(OH)_3$ (1:1w/w) constant, the weight ratios of MVCMC:HVCMC (40:60% w/w) constant and hardness (4 kgf) constant , the total amount of polymer and $Al(OH)_3$ was varied from 200 to 400 mg, to get tablets of weight ranging from 304 to 504 mg (tablets F11-F12).

6. Keeping the amount of drug (100mg) constant, the weight ratios of MVCMC: $Al(OH)_3$ (1.67:1 to 2.5:1 w/w) was varied (tablets F14-F15).

Duplicate batches of each tablet formulation having a batch size of about 100 tablets were prepared. The composition of the tablets is shown in table 1.

Table 1: Composition of matrix tablets

Formulation code	Amount of Drug(mg)	MVCMC (mg)	HVCMC (mg)	$Al(OH)_3$ (mg)	Mag St (mg)	Hardness (kgf)
F1	100	250	0	50	4	4
F2	100	200	0	100	4	4
F3	100	150	0	150	4	4
F4	100	135	15	150	4	4
F5	100	105	45	150	4	4
F6	100	60	90	150	4	4
F7	100	60	90	150	4	2
F8	100	60	90	150	4	6
F9	50	60	90	150	4	4
F10	150	60	90	150	4	4
F11	100	40	60	100	4	4
F12	100	80	120	200	4	4
F13	100	275	0	25	4	2
F14	100	250	0	150	4	4
F15	100	250	0	100	4	4

2.3. Evaluation of granules

2.3.1. Bulk density

Both poured (or fluff) bulk (Do) and tapped bulk densities (DF) were determined, according to the method reported previously [17], whereby a fixed quantity of granules from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. The initial volume was observed, and then cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in the volume was noted [18].

2.3.2. Hausner's factor

Hausner found that the ratio DF/ DO was related to interparticle friction and, as such, could be used to predict powder flow properties [18].

2.3.3. Compressibility percentage

The compressibility index of the granules was determined by Carr's compressibility percentage [18].

$$\text{Compressibility \%} = (DF - DO)/ DF * 100$$

2.4. Physical testing of tablets

Weight variation test (using Precisa Electronic Balance, model XB 600M/C, Switzerland), diameter measurement (using Digimatic Caliper, model CD-6″CS, Mitutoyo Corporation, Japan), hardness test (using Monsanto type hardness tester), and friability test (using Friabilator, Veego, Mumbai, India) were done following the usual methods.

2.5. Potency test of tablet

Ten tablets were weighted and powdered in a glass mortar. A quantity of the powder equivalent to about 10 mg ACF was transferred into a 250-ml volumetric flask and 150 ml USP phosphate buffer (PB) solution (pH 6.8) was added. The stoppered flask was shaken for 24 h in a mechanical shaker and volume was made up to the mark with the buffer solution. The mixture was filtered and an aliquot following suitable dilution was analyzed at 274 nm using a spectrophotometer (model UV-2400 PC series, Shimadzu, Japan) for ACF content and finally potency of the tablet was determined using a calibration curve constructed using PB solution of pH 6.8. The reliability of the above analytical method was judged by conducting recovery analysis at three levels of spiked drug solution in the presence or absence of the polymer and the excipients and for three consecutive days.

The recovery averaged 98.7±3.64%.

2.6. Morphological examination of tablet
A tablet was placed in a Petri dish and immersed in 75 ml 0.1 (N) HCl solution (pH 1.2). The liquid was removed carefully after 4 h with a syringe, and photographs of the tablet was taken with a digital camera fitted with zoom lens (Sony cybershot DSC-W290, China) at every hour. Tablet was also immersed in 75 ml of USP PB solution (pH 6.8). Photograph of the tablet was taken at the end of 4 hrs.

2.7. In Vitro release study
In vitro drug release study was carried out in acidic solution 0.1 (N) HCl (pH 1.2) for 4 h and in USP PB solution (pH 6.8) using USP II dissolution rate test apparatus (model TDP-06P, Electro Lab, Mumbai, India). One weighed tablet was placed in 900 ml acidic solution (37± 1°C) and rotated with paddle at 75 rpm. Aliquot was withdrawn at different times and replenished immediately with the same volume of fresh solution. The withdrawn samples following suitable dilution were analyzed spectrophotometrically at 274 nm for acidic and buffer solution. The amounts of drug released in acidic medium and PB solution were calculated from the calibration curves drawn, respectively, in 0.1 (N) HCl and PB solution (pH 6.8). Each release study was duplicated.

2.8. Compatibility of drug in matrix tablets:
2.8.1. Fourier transform infrared analysis
Fourier transform infrared (FTIR) spectra of pure ACF, physical mixture, and powdered tablet were recorded in FTIR spectrophotometer (Perkin-Elmer model RX-1, UK). The samples were mixed with KBr and converted into pellets at 100 Kg pressure using a hydraulic press. The spectra were taken in the wavelength region of 4,000–400 cm−1.

2.8.2. Differential scanning calorimetry
Differential scanning calorimetry (DSC) thermograms of ACF, physical mixture, and powdered tablet were obtained in the following way: a weighed amount (4.8 to 6.2 mg) of a sample was kept in hermetically sealed aluminum pan and heated at a scan speed of 10°C/min over a temperature range of 30–300°C in a differential scanning calorimeter (Perkin-Elmer model Pyris Diamond TG/DTA, UK) which was calibrated against indium. DSC thermo grams were also obtained in an atmosphere of air in a differential scanning calorimeter (DTG-60H, Shimadzu, Japan) under similar operating conditions.

2.8.3. X-Ray diffraction analysis
The qualitative X-ray diffraction analysis (XRD) studies were performed using an X-ray diffractometer (Miniflex XRD, Rigaku corporation,Tokyo, Japan). Pure ACF, physical mixture, and powdered tablet were scanned from 5° to 50°diffraction angle (2θ) range under the following measurement conditions: Ni-filtered Cu-Kα (λ = 1.54) radiation; voltage, 40 kV; Current, 40 mA; scan speed, 1°/min.

2.9. Viscosity measurement
Viscosity of 1 % (w/v) aqueous solution of the blended polymers in formulations represented F4-F6 were measured in a Brookfield viscometer using spindle no .M1 (Toki Sangyo viscometer, model no. TV-10, Japan).

2.10. Erosion study
Drug free matrix tablets having different Total Polymer/$AL(OH)_3$ ratios (1:1 to 5:1 w/w) were weighed and placed in wire baskets and immersed in 500ml USP PB solution (pH 6.8) at 37 ◦C for 4h.The baskets were removed from the solution and were then dried in an oven at 50°C for 24-h time period, allowed cooling at room temperature and finally weighed in an electronic balance (Precisa Electronic Balance, model XB600M/C Switzerland) until constant weight was achieved (final dry weight, W2).
The tablet erosion (ES) at different times was estimated from the following equation [19]:

$$ES=(W1-W2)/W1*100$$

W1=Initial weight of tablet
W2=Final dry weight.
The percentage remaining of tablets after erosion was calculated from the following equation:

% remaining = 100 - ES

2.11. Statistical analysis
Each formulation was prepared in duplicate, and each analysis was duplicated. The effect of formulation variables on drug release was tested for significance level by using analysis of variance (ANOVA, single factor) with the aid of GraphPad InStat. Difference was considered significant when $p<0.05$.

RESULTS AND DISCUSSION

3.1. Physical characterization of tablets

The physical testing of the tablets revealed the following information: the weight of the tablets was confined within ± 5% of the average weight, diameter varied from 10.10 to 10.17 mm with MSD 0.230% (n = 10),the maximum friability found was 0.88% and the drug content varied within ±5% of the labeled amount. All these variation were found to comply with the requirements of official compendium.

3.2. Compatibility of drug in tablets:

3.2.1. FTIR analysis

Interaction of drug with polymer in the matrix tablets were studied through FTIR analysis of pure ACF and drug loaded tablets. FTIR spectrum of ACF (fig 3) showed characteristics peaks at 3319 cm^{-1}, 2936 cm^{-1}, 1715 cm^{-1}, 1508 cm^{-1}, 1254 cm^{-1}, 666 cm^{-1} representing respectively OH stretching vibration, CH stretching vibration, COO^- asymmetric stretching and C=0 stretching, C=C aromatic ring stretching, C-O-C stretching and C-Cl stretching. Drug loaded matrix tablets generated the respective peaks at 3312 cm^{-1}, 2945 cm^{-1}, 1715 cm^{-1}, 1500 cm^{-1}, 1254 cm^{-1}, 660 cm^{-1} that were almost at the same wave numbers as those of the pure drug. This indicates the absence of any interaction of the drug with the polymer.

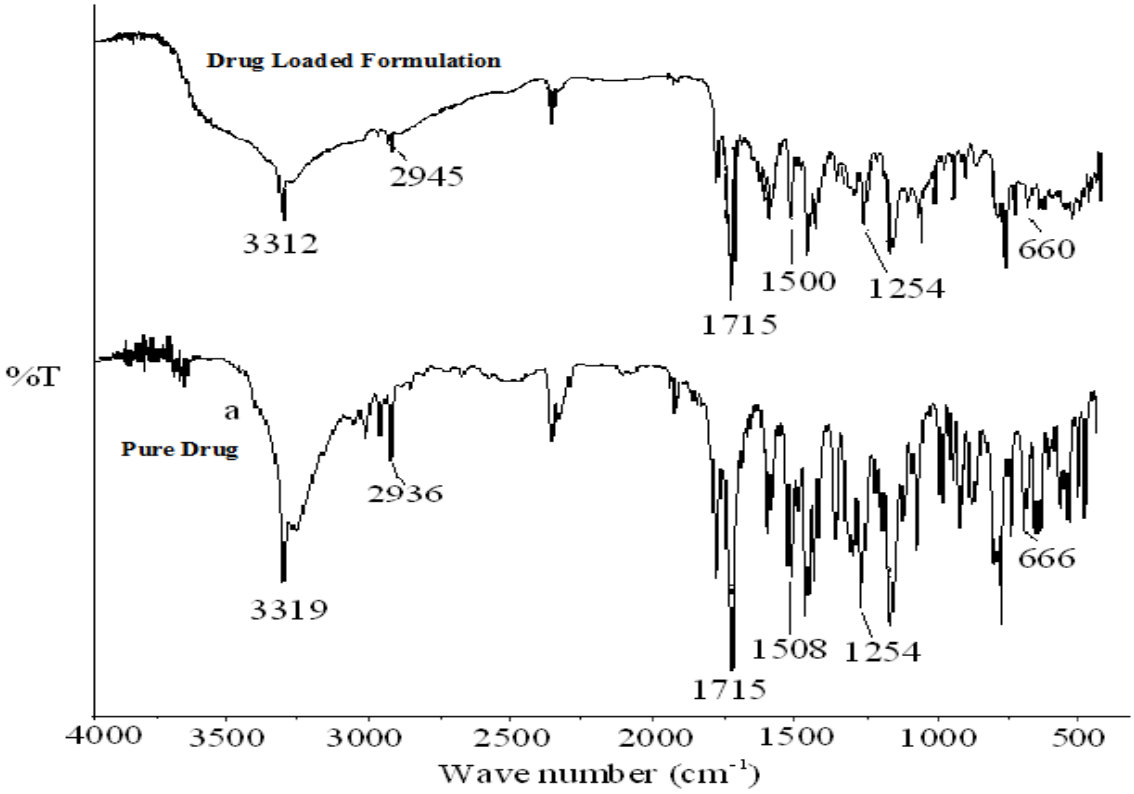

Figure 3: FTIR spectra of aceclofenac, aceclofenac loaded matrix tablet (Formulation F6)

3.2.2. DSC analysis

DSC thermogram of pure ACF, and drug-loaded tablet obtained under nitrogen atmosphere are shown in fig 1. A sharp endothermic peak corresponding to the melting point of ACF was found at 152.49 ◦C (fig 1). However, drug-loaded matrix tablet (fig 1) did not show sharp endothermic peak. The disappearance of the melting endothermic peak of the drug indicates that the drug might have been molecularly dispersed or converted into amorphous form during the preparation of matrix tablet. Research reports are available in literature which state that drugs become molecularly dispersed or undergo amorphization during the preparation of cross-linked CMC beads [16] and chitosan–polyethylene glycol–g-acrylamide hydrogel microsphere [20]. On the other hand, reports are also available stating that the endothermic peak of ACF did not disappear and no solid state transformation took place during the preparation of chitosan enteric coated tablets [21].

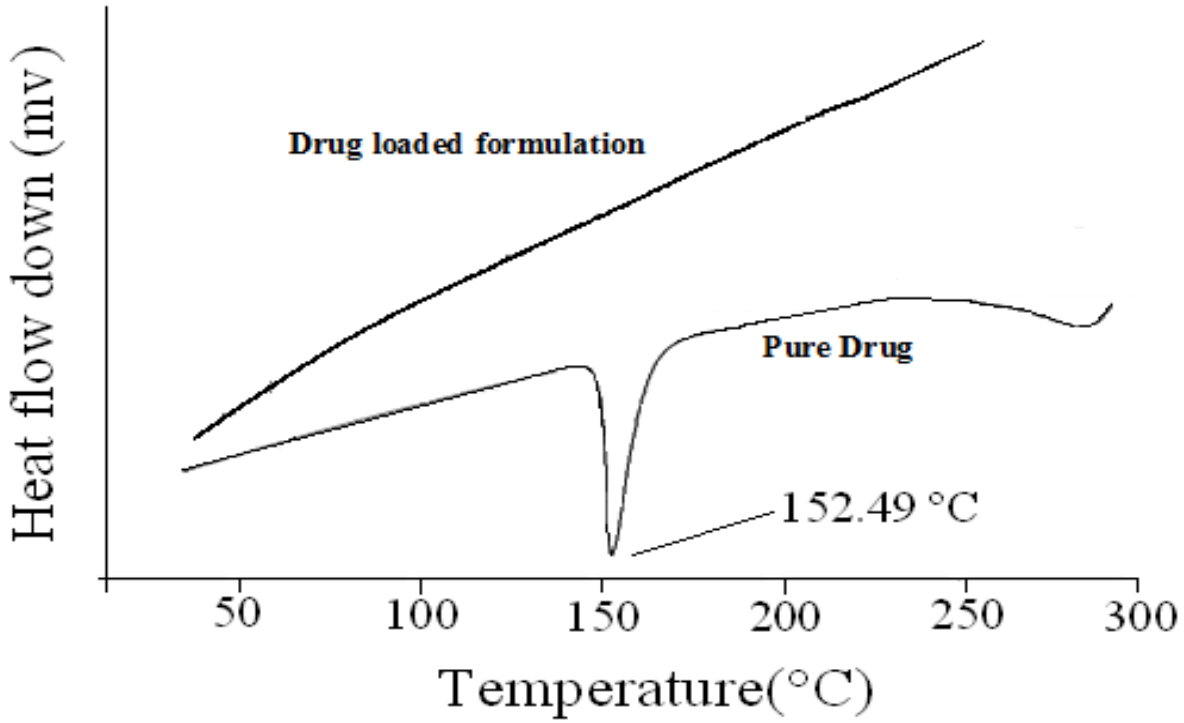

Figure 1: DSC thermograms of aceclofenac, aceclofenac loaded matrix tablet (Formulation F6)

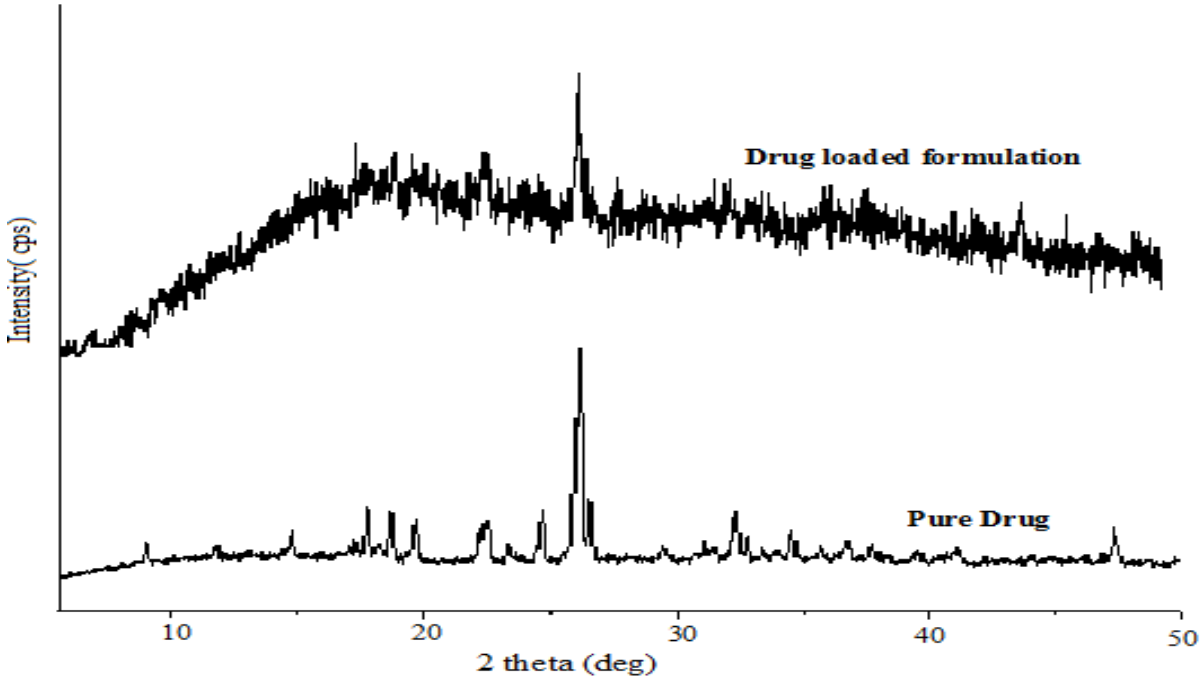

Figure 2: X-ray diffractograms of pure ACF, powdered tablet (Formulation F6)

3.2.3. XRD analysis

The XRD diffractograms of ACF and drug-loaded tablet are shown in fig 2. XRD trace of ACF showed reflection to the inter planner distance of 5.01, 4.76, 3.96 and 3.41 Å respectively at 17.66, 18.62, 22.4 and 26.09 ° 2θ. The drug loaded matrix tablet showed reflection to the inter planner distances of 4.75, 3.97, 3.41 Å respectively at 18.65, 22.34, 26.09° 2θ. The results demonstrated that the characteristic peaks of the drug appeared almost at the same 2θ values in the XRD chart of drug loaded matrix tablet, although the intensity of the peaks was considerably reduced. It clearly indicated that the crystallinity of the drug was retained in the matrix tablet. Although inconclusive without further experimentation, it may be stated that without being transformed into amorphous form, ACF might have

been entrapped into the solid network of the matrix structure formed by SCMC and Aluminium hydroxide formed by ionotrophic gelation.

3.3. Evaluation of granules:

The prepared granules were evaluated for bulk density, hausner ratio and compressibility index and the results are indicated in the table 2. Granules of formulation F0 prepared with only medium viscosity SCMC showed hausner ratio and compressibility index of 1.65 and 25 respectively. It was also observed that it is very difficult to granulate the drug-polymeric mass due to its rubbery and sticky nature. The above values indicate the cohesiveness (internal friction between the particles) of the powder and, consequently, very poor flowability. Thus granules prepared with only SCMC are not suitable for compression into tablets and are thus not discussed any further. In order to incorporate good flowability to the granules, addition of an excipient in the form of $Al(OH)_3$ was thought to be suitable. Granules composed of SCMC and $Al(OH)_3$ were prepared and the results in terms of bulk density, hausner ratio and compressibility index are observed. Granules of F13 showed relatively good flow properties as indicated by the values of hausner ratio and compressibility index. When compressed, tablets of hardness 2Kgf could only be produced and that the tablets also showed a high percentage of friability. Thus, though incorporation of $Al(OH)_3$ imparted some compressibility into the granules of F13, but since the tablets lacked the required minimum hardness and showed higher friability, they were not evaluated for in-vitro release study any further. This amount of Aluminium hydroxide corresponds to the minimum amount that must be present for satisfactory compression and tabletting. Apart from formulations F0 and F13, the granules of all remaining batches showed satisfactory values of hausner ratio and compressibility index and were thus subjected to further studies. From the above made observations, it is clear that $Al(OH)_3$ acts as a binder. In the absence of $Al(OH)_3$, the granules that were too sticky and rubbery in nature and posed considerable problem in granulation, became less sticky and rubbery in nature and were very easily granulated when $Al(OH)_3$ was incorporated. Thus apart from acting as a binder in the tablet manufacturing, it also acts as a good excipient and aided in wet granulation process.

Table 2: Physical properties of granules

Formulation code	Hausner ratio	Compressibility index
F1	1.25	20
F2	1.176470588	15
F3	1.151515152	13.157895
F4	1.205882353	17.073171
F5	1.184210526	15.555556
F6	1.2	16.666667
F7	1.176470588	15
F8	1.2	16.666667
F9	1.194444444	16.27907
F10	1.19047619	16
F11	1.170731707	14.583333
F12	1.176470588	15
F13	1.282051282	22
F14	1.136363636	12
F15	1.184210526	15.555556

3.4. In-vitro release study:

3.4.1. Effect of aluminium hydroxide: $Al(OH)_3$ was incorporated as an excipient in the tablet for dual purpose. Firstly, in the absence of $Al(OH)_3$, the granules were not suitable for tabletting & it was very difficult to granulate the drug-polymeric mass due to its rubbery and sticky nature. Secondly, based on literature it was thought that when the tablets come in contact with aqueous medium, Al^{3+} ions liberated from $Al(OH)_3$ will bind with the COOH group of SCMC through the ionotropic gelation method and will form insoluble matrix which in turn will provide prolongation of drug release [16]. The effect of $Al(OH)_3$ on drug release in acidic medium was observed for 4 hrs from tablets prepared with 100 mg drug loading at 4kgf hardness and indicated by formulation F1-F3. The amount of drug released in acid was minimal (7% of drug load at the end of 4 hrs) fig 5. This drug release behavior was also verified from the area under the curves (AUCs) measured from the cumulative percent drug release versus time curves using trapezoidal rule. One way ANOVA revealed that AUC values are comparatively same ($p=0.40$), indicating insignificant difference amongst the formulations. SCMC possess COOH groups which can bind with Al^{3+} ion through ionotropic gelation process forming water insoluble gel matrix of Al-CMC. The release of a drug through such an ionically cross linked polymeric matrix depends on the extent of swelling of the polymer which in turn, is controlled by the pH of the aqueous medium. Similar to calcium alginate, which converts to alginic acid and swells to a very less extent in acid solution of low pH [22], Al-CMC may be converted in to their corresponding acid forms in solution of low pH. The unionized carboxyl groups of the

Table 3: Derived release parameters of matrix tablets.

Formulation code	AUC (% mg h/ml) up to 4 h in acidic medium (mean ± SD, n=3)	AUC (% mg h/ml) till complete release in PB (mean ± SD, n=3)	t50% in PB solution (min) Mean ± SD (n=3)	t80% in PB solution (min) Mean ± SD (n=3)
F1	12.47±2.33	435.96±4.96	212.18±4.86	345.11±5.9
F2	10.33±0.78	430.69±1.47	149± 3.14	261.1±2.62
F3	11.49±1.07	331.39±1.89	120.8±1.63	202.6±3.03
F4	10.92±0.90	410.49±1.33	234.5±3.17	364.2±3.04
F5	9.04±0.33	492.35±4.91	261.4±3.24	453.8±6.3
F6	7.66±1.05	477.62±4.50	313±3.28	508.5±3.62
F7	9.16±1.44	511.02±0.45	293.5±2.67	479±0.63
F8	7.05±0.42	394.78±2.43	385.8±1.47	627±3.21
F9	6.58±0.38	450.46±3.43	349.4±3.53	508.8±3.58
F10	18.75±1.10	498.12±3.68	278.8±1.11	493.2±3.39
F11	11.07±0.19	383.05±2.51	241.6±3.7	414±1.69
F12	6.84±0.36	377.72±3.77	419.5±1.02	617.2±3.84
F13	-	-	_	_
F14	1.68±1.02	394.97±2.98	252.89±1.98	413.86±4.98
F15	2.54±1.09	410.07±3.22	232.28±2.22	370.65±3.37

Table 4: Derived parameters of formulations.

Formulation code	Rate of erosion at the end of 4h	Viscosity of 1%(w/v) solution(cP)
F1	28.84%	-
F2	41.42%	-
F3	56.45%	-
F4		150.25
F5		191.063
F6		250.146

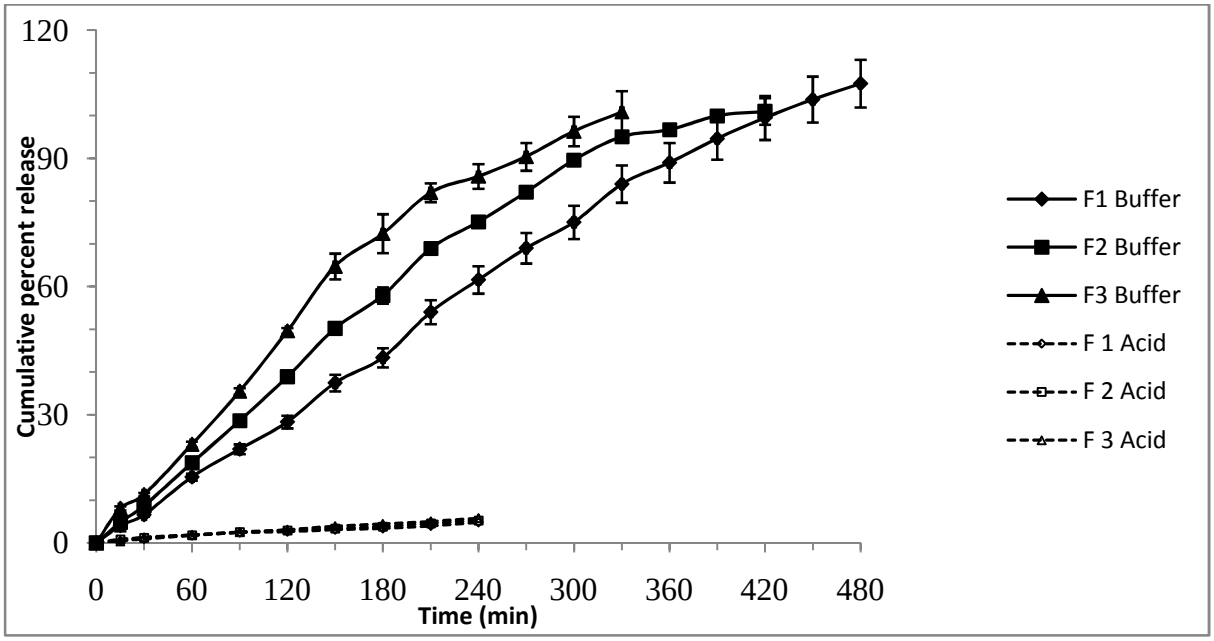

Figure 5: Effect of Aluminium Hydroxide on release profiles of aceclofenac from matrix tablets in HCl buffer (pH 1.2) (dotted line) and in phosphate buffer solution (pH 6.8) (Firm line and filled markers). Key: F1 buffer filled rhombus, F2 buffer filled square, F3 buffer filled triangle, F1 Acid open rhombus, F2 Acid open square, F3 Acid open triangle.

polymers exert little electrostatic repulsive forces and hence, relaxation of the macromolecular chain does not take place [23]. As a result, the tablets do not swell in acidic solution to a great extent and drug release takes place slowly. Figure 4A, B, C shows the appearance of tablets which were kept in acidic solution for 4 h. As is evident, the tablets didn't swell much at the end of every hour. The tablets also didn't develop any cracks or fissures which would have accelerated the rate of drug release.

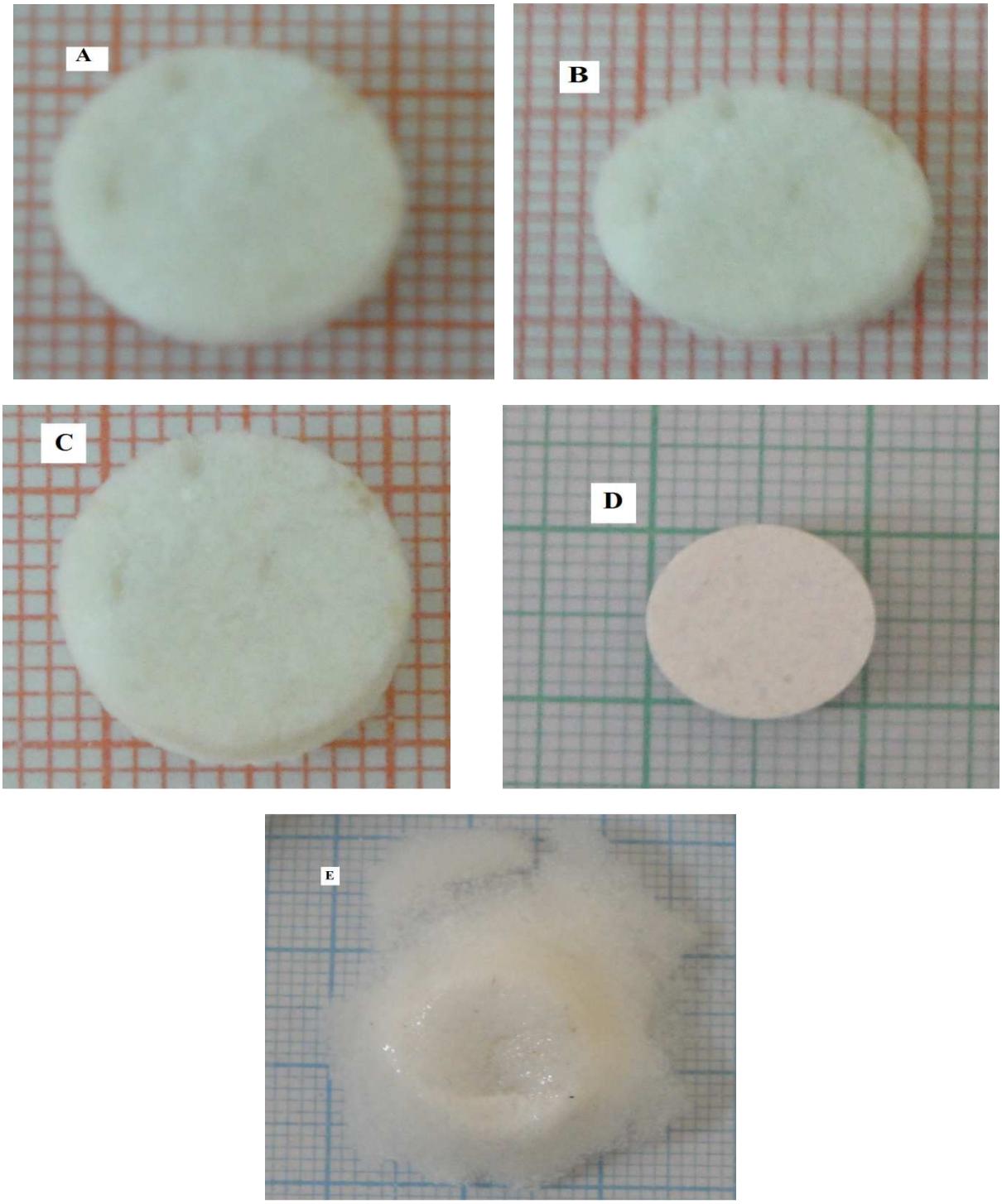

Figure 4: Photo images of CMC matrix tablets hydrated for 4 hr in acid media (pH 1.2) and 2hr in PB solution (pH 6.8). A,B,C in acidic media at 0hr, 2hr, 4hr respectively and D,E in pH 6.8 at 0hr and 4 hr respectively.

The effect of $Al(OH)_3$ on drug release behavior in PB solution was observed from the same batches as mentioned earlier. As evident from the fig 5, increase in amount of $Al(OH)_3$ produced faster release. While tablets of formulation F1 released the total loaded drug in 8 hrs, the release of drug from F3 was almost complete at 5.5 hrs. Theoretically, increase in amount of $Al(OH)_3$ would have sustained the release of drug in PB solution. Since, more Al^{3+} ions would be available to bind with COOH groups of SCMC and would result in the formation of rigid and viscous gel layer [16] which would provide diffusional resistance to the influx of the dissolution medium and the efflux of the dissolved drug out of the matrix. The results are thus not in harmony with the general trends. A possible explanation of this anomalous behavior is as follows. Here, Al^{3+} ions bind with the COOH groups of SCMC to from a dense and rigid gel structure. This gel formation depends on the concentrations of the cations present. At optimum concentrations, the Al^{3+} ions are able to cross-link more efficiently with the COOH groups. Beyond a certain

concentrations of $Al(OH)_3$, an excess of the cations will not be able to cross-link and thus would act as a channeling agent favoring faster drug release. This result is in agreement with other observations [7]. They observed that the system comprising of calcium gluconate in combination with sodium alginate failed to control the release of the drug for a prolonged period of time. They attributed that the presence of the calcium ions could have a channeling effect that facilitates more rapid media penetration into the inner layers of the matrix. In formulations F1-F3, as the amount of $Al(OH)_3$ is increased, per unit weight of SCMC decreased and thus provided an excess of the cations which didn't crosslink and resulted in a faster drug release. Moreover, as $Al(OH)_3$ is insoluble in the aqueous media, the excess of it increases the rate of erosion of the tablets, which also accounts in faster drug release. Morphological evaluation of the tablets kept in PB solution for 4 hr showed an increased rate of erosion as the amount of $Al(OH)_3$ was increased. The results are shown quantitatively in table 4**.** Fig 4D, E also indicates this observation. This observation was verified by preparing special batches wherein the amount of SCMC was kept constant and the amount of $Al(OH)_3$ was gradually increased. These batches are indicated by F1, F14, and F15. When the tablets are placed in both the acid and PB solution, increase in amount of the crosslinker ions Al^{3+} produced a slower drug release as shown in the fig 5A**.**

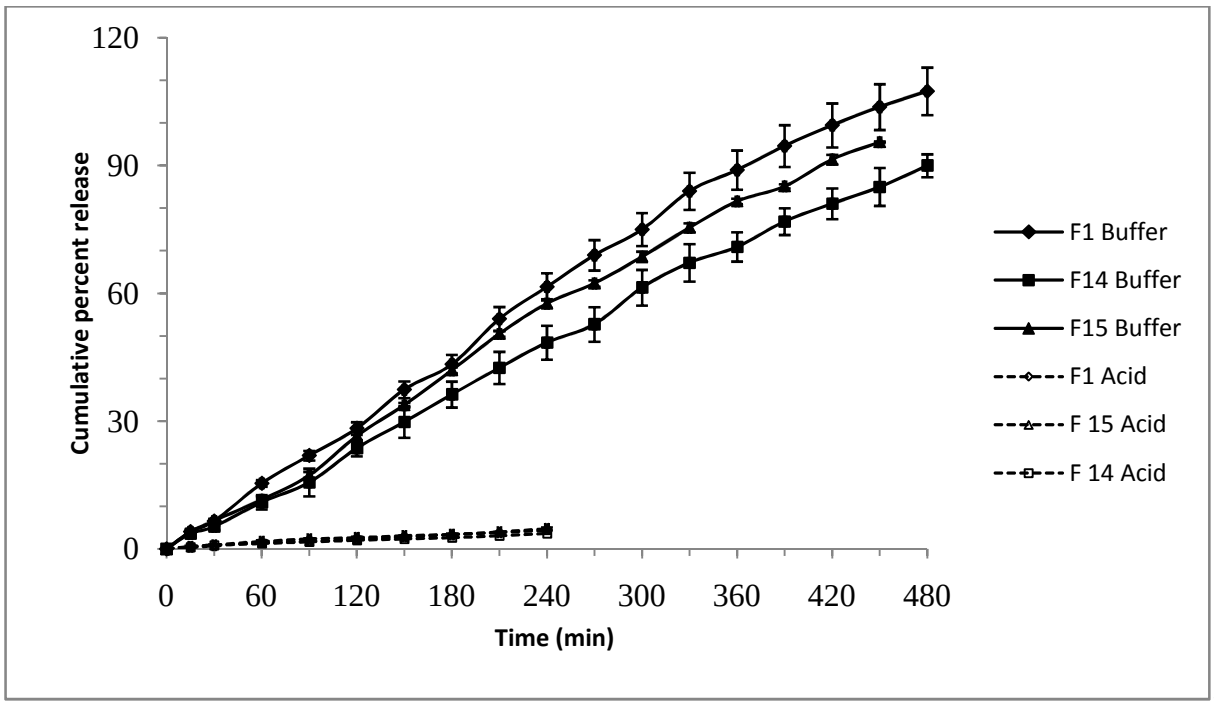

Figure 5A: Effect of Aluminium Hydroxide on release profiles of aceclofenac from matrix tablets in HCl buffer (pH 1.2) (dotted line) and in phosphate buffer solution (pH 6.8) (Firm line and filled markers). Key: F1 buffer filled rhombus, F14 buffer filled square, F15 buffer filled triangle, F1 Acid open rhombus, F14 Acid open square, F15 Acid open triangle.

This result is in harmony with the general trend that an increase in amount of cross linking cations produced a slower release from the matrix tablets [22]. The possible explanation has been given earlier. Again, when larger amount of $Al(OH)_3$ was used in tablet formulation, more Al^{3+} ions became available to bind with SCMC during the wet massing stage of tablets preparation. As a result, a better and stronger gel was formed. As the concentration of Al^{3+} ions increases per unit weight of SCMC, stronger gel of AlCMC is formed that delay the influx of the dissolution medium and the efflux of the dissolved drug out of the matrix. As a result, drug is released in a more sustained manner as the amount of $Al(OH)_3$ is increased. From the spectrum of observations made, it can be concluded that $Al(OH)_3$ is a versatile tablet excipient since it not only aids in tablet manufacturing process, but also act as a binder and a crosslinking agent, which when used at optimum concentration will slow the drug release from the matrix.

3.4.2. Effect of blend polymer: With an aim to further retard the drug release, substitution of medium viscosity SCMC with high viscosity SCMC was thought off. The effect are observed in batches represented as F4-F6 prepared with 100mg drug load at 4kgf hardness and increasing amount of medium viscosity SCMC substituted with high viscosity SCMC. As a result of this, the release of the drug from the matrix in both acid and PB solution decreased in order of increase in amount of HVCMC incorporation as seen from the graph shown in figure 6. The values of $t_{50\%}$ and $t_{80\%}$ (table 3) increased respectively from 234 min to 313 min and 364 min to 508 min respectively. A possible explanation of this behavior is given. When blends of high and medium viscosity comes in contact with

dissolution media, it forms a gel structure upon cross linking between Al^{3+} ions of $Al(OH)_3$ and that of COOH groups SCMC by the process of ionotrophic gelation. Incorporation of high viscosity SCMC increases the availability of COOH groups. As the amount of HVCMC is increased, the gel layer becomes more strong and viscous. Determination of viscosity of 1 % (w/v) solution revealed that as the amount of high viscosity SCMC was increased, the viscosity of the solution increased from 150.25 to 250.14 cp (table 4**).** A more viscous gel layer would prevent the dissolution fluid to enter the matrix and thereby release the drug by the efflux of the same. Moreover, drug release decreased from high viscosity SCMC formulation because of more polymer entanglement and more gel strength. Increase in gel strength would contribute to a lesser rate of polymer erosion [24]. For all these reasons, the diffusion coefficient of the drug and dissolution through the matrix decreases and results in a lower drug release [25]. Similar observations of increase in polymer viscosity resulting in slower drug release have also been reported [26,27].

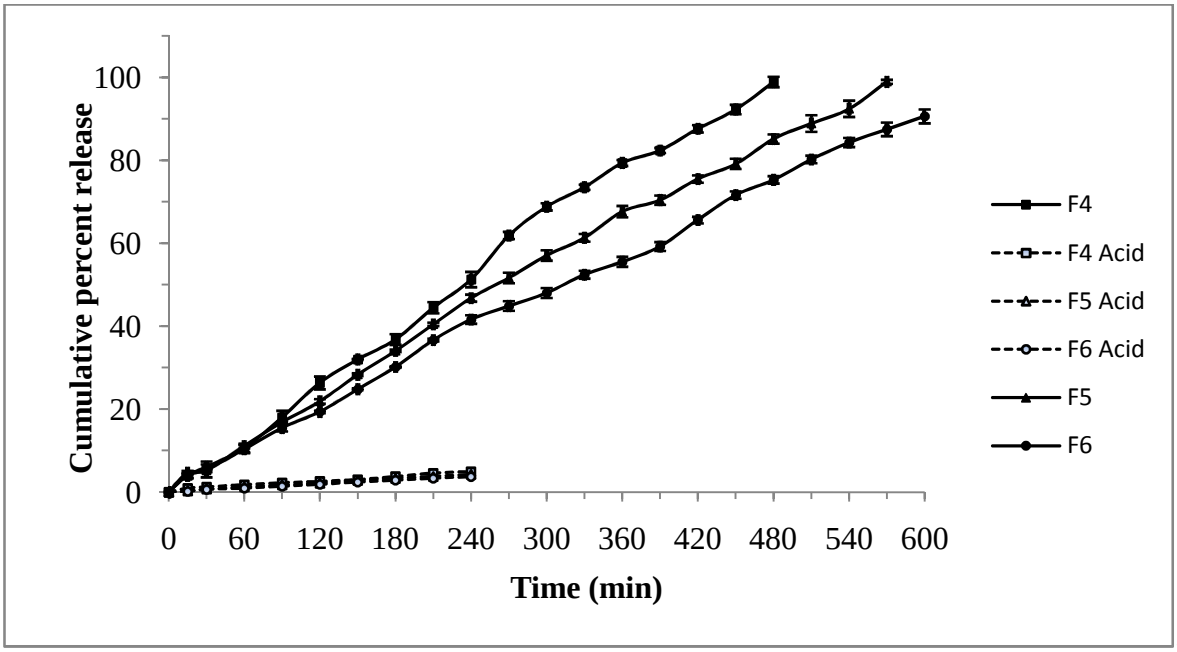

Figure 6: Effect of polymer blend on release profiles of aceclofenac from matrix tablets in HCl buffer (pH 1.2) (dotted line) and in phosphate buffer solution (pH 6.8) (Firm line and filled markers). Key: F4 buffer filled square, F5 buffer filled triangle, F6 buffer filled circle, F4 acid open square, F5 acid open triangle, and F6 acid open circle.

3.4.3. Effect of compression force: ACF tablets (F6-F8) having potency 100 mg were prepared at various compression force (2-6 kgf), to impart hardness to the tablets and the drug release profiles are represented in the figure 7. It was evident from the figure that increase in compression force decreased the release rate of the drug from the tablets. Increase in compression force should reduce the tablet porosity which hinders greater liquid penetration in to the matrix, causing delayed dissolution of the drug from the matrix. The drug release becomes faster as the hardness is decreased because of larger matrix porosity of the tablet, which allowed greater penetration of the dissolution fluid into the matrix, thus enhancing greater drug diffusion and dissolution. Such an effect has also been reported [28,29].

3.4.4. Effect of drug load: The effect of drug load (50 to 150 mg) on its release was studied with tablets F6, F9, F10 prepared at 4 kgf hardness. The figure 8 indicates that increasing in drug loading of the tablets, tended to increase the drug release marginally faster. The release profiles of the drug from the tablets appeared to be almost overlapping. Although ANOVA test of AUC values indicated significant difference ($p< 0.05$) table. The reason for the above observation can be explained as follows. Increase in drug loading of the tablets, increased the concentration gradient and thus, drug diffusion through gel layer becomes faster resulting in faster drug release. Similar results have been reported in matrix tablet prepared by sodium alginate and calcium gluconate [22].

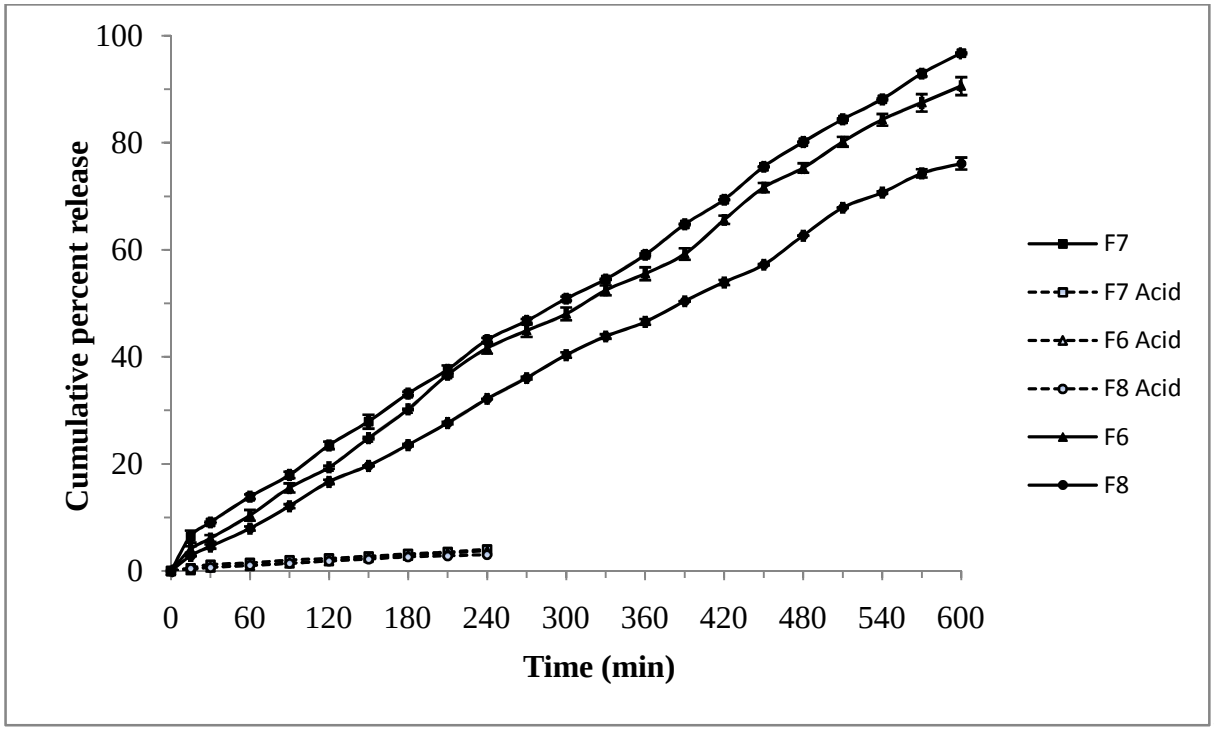

Figure 7: Effect of tablet hardness on release profiles of aceclofenac from matrix tablets in HCl buffer (pH 1.2) (dotted line) and in phosphate buffer solution (pH 6.8) (Firm line and filled markers). Key: F7 buffer filled square, F6 buffer filled triangle, F8 buffer filled circle, F7 acid open square, F6 acid open triangle, and F8 acid open circle.

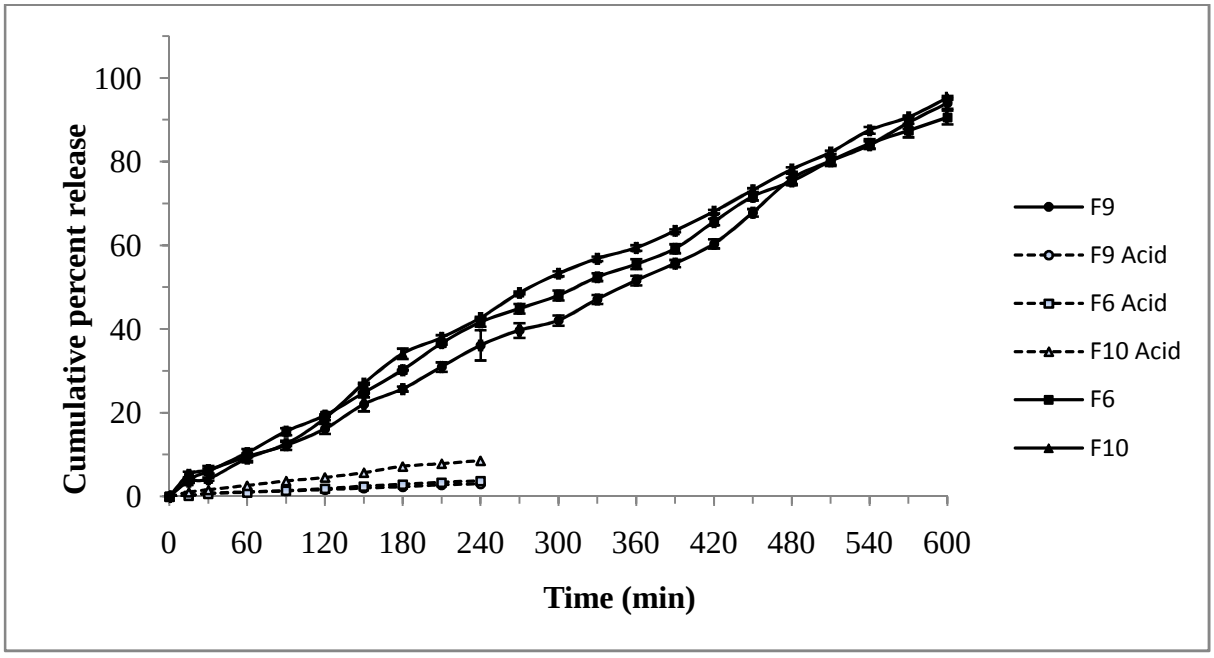

Figure 8: Effect of drug load on release profiles of aceclofenac from matrix tablets in HCl buffer (pH 1.2) (dotted line) and in phosphate buffer solution (pH 6.8) (Firm line and filled markers). Key: F6 buffer filled square, F10 buffer filled triangle, F9 buffer filled circle, F6 acid open square, F10 acid open triangle, and F9 acid open circle.

3.4.5. Effect of total polymer: The effect of total polymer on the drug release rate was studied with tablets F6, F11-F12 prepared with 100 mg drug load at 4 kgf hardness. Increase in total polymer/$Al(OH)_3$ concentration gave a more sustained release of the drug from the tablets in both media as seen from the figure 9. The release of a drug from a swell able matrix is dependent on the degree of gelation, hydration, chain relaxation and on the rate of erosion. As the amount of total polymer/$Al(OH)_3$ was increased, the gel structure formed ionotrophically by the cross linking of Al^{3+} ions with carboxylate ions of SCMC was much more rigid and strong. A more rigid gel layer would mean a slower rate of erosion [24] and chain relaxation, as also the swelling will be less. The tablet

formulations were found to swell to different extent forming a gel like structures, which is dependent on the total polymer/cross linking agent proportion. Also the gel structure eroded to a lesser extent as the polymer/$Al(OH)_3$ concentration was increased. More ever, drug release from matrices is dependent on the influx of dissolution fluid to the matrix core and efflux of the dissolved drug. A complex gel like structure formed would thus act as a diffusion barrier and would thus prevent the efflux of the drug from the gel structure [30]. All these factors results in decrease of drug release rate with the increase of total polymer. Similar observations were reported [31,32].

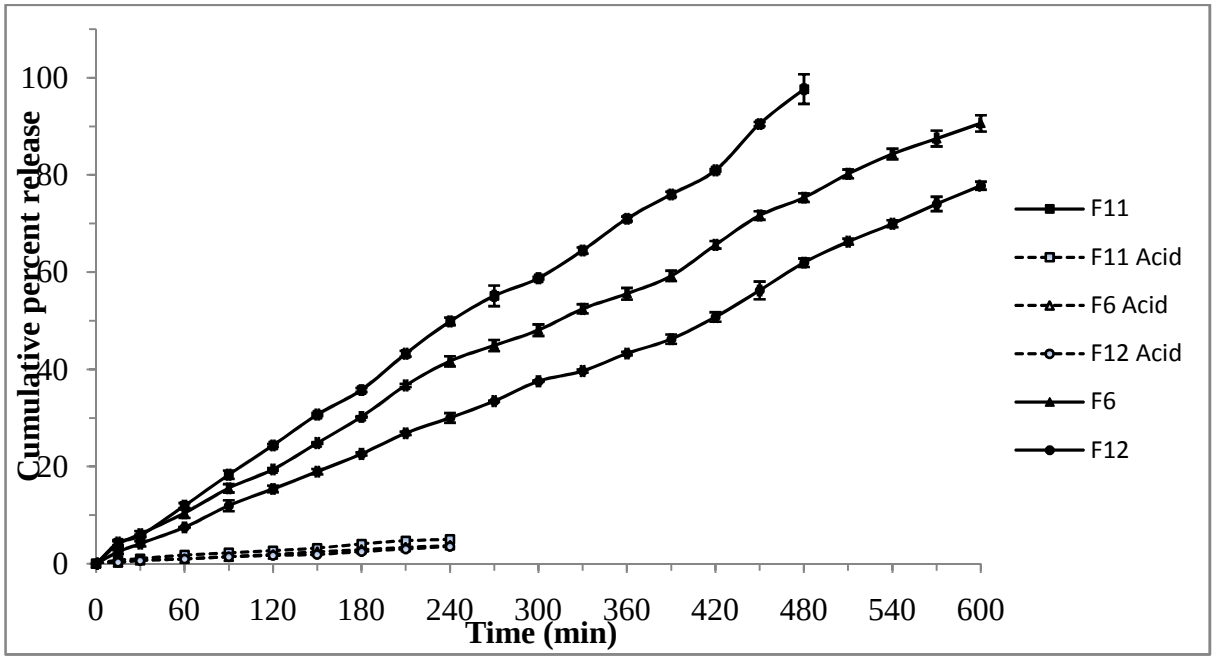

Figure 9: Effect of total polymer on release profiles of aceclofenac from matrix tablets in HCl buffer (pH 1.2) (dotted line) and in phosphate buffer solution (pH 6.8) (Firm line and filled markers). Key: F11 buffer filled square, F6 buffer filled triangle, F12 buffer filled circle, F11 acid open square, F6 acid open triangle, and F12 acid open circle

3.5. Dynamic drug release:

After oral administration a dosage form goes through various pH conditions in the gastrointestinal tract. In order to simulate the dynamic changing environment, the dissolution study of matrix tablets were done in acid solution (pH 1.2) for 2 h and then transferred in PB solution (pH 6.8) till complete drug release. As seen from the fig 10, drug release at the end of 2 hr in acidic solution pH 1.2 was minimal with only 3% of the loaded drug being released from the batches observed. While in PB solution pH 6.8, 75-90% of the loaded drug was released at the end of 10 hr depending on the formulation variables. It can, therefore, be concluded from the above results that the tablets are capable of minimizing the release of ACF in the stomach and then provide controlled release in the intestine. Such release behavior is highly desirable for dosage forms loaded with NSAIDs, in order to reduce the various gastric adverse effects produced by those groups of drugs. Again, ACF has a very short half life and thus needs to be administered frequently. Sustaining the release of ACF for a prolonged period of time would reduce the problems associated with frequent administration. From the results it seems that the matrix tablets prepared by ionotrophic gelation of Al^{3+} ions and carboxylate ions are ideal for delivery of ACF like drug candidate. It achieves the dual target of controlling the drug release at gastric mucosa, thereby bypassing the severe gastric adverse effects associated with it and at the same time provides prolonged drug release at the intestinal pH. It is expected in the days to come that a lot of effort will be given for successful delivery of NSAIDs and a spectrum of new innovative, cost effective and patient friendly formulations will be developed.

3.6. Kinetics of drug release

The release of a drug from a swell able matrix is dependent on the degree of gelation, hydration, chain relaxation and polymer erosion. The mechanism of drug transport through matrix tablets was evaluated by fitting the drug release data (upto60%) to the classical power law expression [33]:

$Mt/M\infty=kt^n$

where M_t and M_∞ are, respectively the amounts of drug released at time t and at infinite time; k represents a constant incorporating structural and geometrical characteristic of the dosage forms; n denotes the diffusion exponent indicative of the mechanism of drug release. Values of n ranging from 0.45 to 0.5 indicate Fickian or diffusion

controlled release, values of n ranging from 0.89 to 1.0 indicate Case II transport mechanisms. Values of n intermediate between the above limits indicate anomalous or non-Fickian transport.

Values of n have been calculated from the above equation by fitting the drug release data up to 60%. In all the formulations, in acid, the values of n ranged from 0.69 to 0.88 indicating the drug release followed anomalous or non fickian transport. Where as in buffer the values of n are between 0.85 to 1.04, indicating that the drug release follows case 2 transport mechanisms.

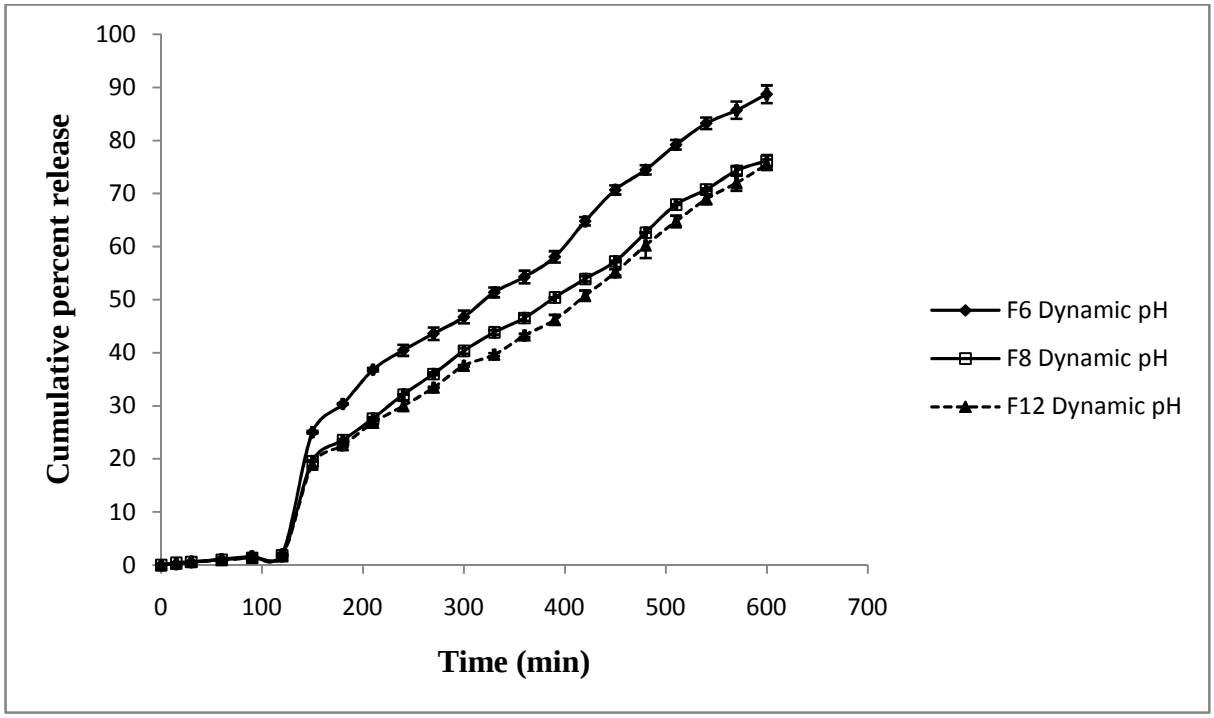

Figure 10: Dynamic drug release from matrix tablets. Key: F6 solid line and filled marker, F8 solid line and open marker triangle, F12 dotted line and filled marker.

CONCLUSION

High and medium viscosity CMC and $AL(OH)_3$ in different ratios were used as matrix material for the preparation of matrix tablet by wet granulation method using ionotrophic gelation technique. FTIR, DSC, XRD study demonstrated the apparent absence of any interaction of the drug with the formulation additives. In-vitro drug release study was carried out for 4 hrs in acidic solution (pH 1.2) and in PB solution for 10 hrs. The study shows that there is minimum drug release in acidic media and that the release of drug in PB solution was extended for over 10 hrs. Aluminium hydroxide considerably influenced the tabletting process and release of drug from the matrix tablets. The relative swelling, viscosity & erosion of the gel network were responsible for the drug release. There was significant effect on drug release behavior on variables drug loading, compression force and total polymer. From the above findings it can be concluded that ionotrophic gelation of SCMC and Al^{3+} ions could be a suitable method for preparation of matrix tablet intended to minimize drug release at gastric mucosa and target it at small intestine.

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