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Research Article

# CITRUS GUM MATRIX TABLETS FOR SUSTAIN RELEASE OF ACECLOFENAC: *IN VITRO* DRUG RELEASE AND SWELLING BEHAVIOR

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**ABSTRACT**

**Objective:** The main aim of the present study was to establish the potential of citrus gum as a novel pharmaceutical aid for the development of sustained release drug delivery systems.

**Materials and Methods:** Aceclofenac sustained release tablets with citrus gum powder and comparison studies of hydroxypropyl-methylcellulose (HPMC) K-100 were prepared by wet granulation technique. Compatibility of the drug with the gum was studied using differential scanning calorimetry and Fourier transform infrared spectroscopy. The physicochemical properties such as hardness, thickness, friability, uniformity of weight and the drug content of the formulated tablets were estimated.

**Results:** The comparative dissolution profiles of aceclofenac sustained release tablets prepared with citrus gum powder (20%) and HPMC K-100 (30%) was shown that the effect of polymer concentration, decrease in drug release rate was observed when citrus gum powder content in the matrix was increased.

**Conclusion:** The sustained release tablets shows that citrus gum powder by forming a matrix retards the release rate of drug and can be used as sustained release dosage form.

**Keywords:** Aceclofenac, Citrus gum powder, Sustain release polymer, Hydroxypropyl-methylcellulose K-100, Swelling behavior.

## INTRODUCTION

Polysaccharides are composed of many monosaccharide residues that are joined to each other by O-glycosidic linkages. The great diversity of structural features of polysaccharides, which originates from differences in the monosaccharide composition, linkage types and patterns, chain shapes, and degree of polymerization, dictates their physical properties, including solubility, flow behavior, gelling potential, and/or surface and interfacial properties. Polysaccharides, which are commercially available for use in food and nonfood industries as stabilizers, thickening and gelling agents, crystallization inhibitors, and encapsulating agents, etc., are also called hydrocolloids or gums. Polysaccharide gums occur in nature as storage materials, cell wall components, exudates, and extracellular substances from plants or microorganisms [1,2]. Polymers have been successfully investigated and employed in the formulation of solid, liquid and semi-solid dosage form and are specifically useful in the design of novel drug delivery systems [3]. Both synthetic and natural polymers have been investigated extensively for this purpose [4]. Synthetic polymers are toxic, expensive, have environment related issues, need long development time for synthesis and are freely available in comparison to naturally available polymers.

Citrus tree gum is obtained from the incised trunk of the tree family: Rutaceae (*Citrus limon (l.)* burm. f.) the gum is a complex polysaccharide comprising galactose, arabinose, rhamnose, glucose, glucurine acid and other sugar residues. Earlier, there was no report of citrus gum powder used as excipient. Non-steroidal anti-inflammatory drugs are highly effective in the treatment of rheumatoid and osteoarthritis but their long-term use results in gastrointestinal (GI) toxicity in a large number of cases like ulceration and stricture formation in esophagus, stomach and duodenum leading to severe bleeding, perforation and obstruction. Aceclofenac also has a wide spectrum of GI side-effects ranging from mild dyspepsia to gastric bleeding. Due to its short plasma half-life (3-4 hr) and GI toxicity parole, aceclofenac is an ideal candidate for preparing extended or controlled release drug products [5,6]. That can potentially avoid drug release in the upper position of the GI tract.

In the present study, it was envisaged to design sustained release formulation of aceclofenac with *C. limon* gum so as to minimize initial drug release in stomach and to reduce the possible gastro irritant and ulcerogenic effects of the drug.

## MATERIALS AND METHODS

### Materials

Citrus gum collected from various places of Krishna District, Andhra Pradesh (India). The plant was identified by Dr. Badraiah, Botanist, Head Department of Botany Osmania University, Hyderabad. The specimen no: 0115. Aceclofenac was purchased from yarrow chemicals) Ruthenium Red (Oxford Laboratory, Mumbai, Maharashtra, India). Polyvinylpyrrolidone K30, hydroxypropyl-methylcellulose (HPMC) 100 Cps, starch, talc, magnesium stearate and iso propyl alcohol used in the study were of analytical grade.

### Isolation of *C. limon* gum

The citrus gum was collected and soaked in water for 5-6 hr, boiled for 30 minutes and left to stand for 1 hr to allow complete extraction of the gum into the water. The gum was filtered using a multi-layer muslin cloth bag to remove the dirt and foreign matter from the solution. Acetone (in the quantities of three times the volume of filtrate) was added to precipitate the gum [7]. The gum was separated, dried in an oven at 35°C, collected, ground, passed through a 80 sieve and stored in desiccator at 30°C and 45% relative humidity till use.

### Characterization of citrus gum powder

The citrus gum powder was characterized for phyto – physicochemical properties. The phyto-chemical examinations such as ruthenium red test, Molisch test and iodine test confirm the presence of mucilage, carbohydrates and polysaccharides, respectively. The surface analysis (Joel, model 840, Japan) was determined by scanning electron

microscope (SEM). The citrus gum was evaporated with carbon and then sputtered with gold to make the sample electrically connected. Carbon was layered to a thickness of approximately 10 nm and gold was layered to approximately 25 nm. The physicochemical properties such as loss on drying, pH and viscosity were determined according to Indian pharmacopoeial procedure [8]. The pH of 1% solution was measured using a digital pH meter by dispersing the citrus gum in 25 ml of distilled water. The viscosity of the citrus gum (2%w/w) was determined using RVDV II + viscometer (Brookfield Engineering India, Mumbai, Maharashtra, India). Prior to the study, the sample was filled in the sample adapter and allowed to stand for 24 hr undisturbed for complete relaxation of the sample. Viscosity was determined using spindle S2 8, at 50 rpm using a constant temperature bath maintained at 20°C. The acute toxicity study was carried out according to the organization for economic co-operation and development guidelines by using female Swiss albino mice and each approximately of 20.0 kg by body weight.

**Flow ability of citrus gum powder**

*Angle of repose*

Angle of repose was determined by Neumann's method and calculated using the formula, for un-lubricated, as well as lubricated granules.

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

Where, h = height of the pile, r = radius of the pile base

**Tapped density (TD)**

An accurately weighed granule from each formulation was lightly shaken to break any agglomerates formed, and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TD of granules was determined by the following formula.

$$TD = \text{Total weight of powder}/\text{Tapped volume} \quad (2)$$

**Carr's compressibility index**

It is a simple index that can be determined on small quantities of granules. In theory, the less compressible a material, the more flowable it is. The compressibility index of the granules was determined using following formula.

$$\text{Carr's index}(\%) = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad (3)$$

**Hausner's ratio**

It is the ratio of TD and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict granules flow properties. In general, a value <1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. And >1.5 indicates that the poor flow, in between these values passable.

**Bulkiness**

Specific bulk volume or reciprocal of bulk density is called as bulkiness. The bulkiness was calculated according to the following equation:

$$\text{Bulkiness} = 1/\text{Bulk density} \quad (4)$$

**Percent porosity**

Percent porosity was calculated according to the following formula:

$$\text{Percent porosity} = V_b - V_t/V_b \times 100 \quad (5)$$

Where $V_b$ is the apparent volume of tablet calculated from tablet dimensions, $V_t$ is a true volume calculated from the true density of the material.

**Differential scanning calorimetry (DSC)**

The DSC thermograms of aceclofenac, citrus gum and mixture of aceclofenac/citrus gum (1:1) were generated by a DSC (Shiamdzu, Japan) at heating rate of 10°C/min from 60 to 200°C. Accurately 12 mg of sample was taken in a standard pan and placed at sample stage. Nitrogen flow was set at 50 $cm^3$/minutes and the nitrogen flow rate to the chamber was 80 $cm^3$/minutes.

**Fourier transforms infrared spectroscopy (FTIR)**

FTIR spectra of aceclofenac, *C. limon* gum powder and mixture of aceclofenac/*C. limon* gum powder were recorded at room temperature in KBr pellets by applying 6000 kg/$cm^2$ pressure by using Shiamdzu instrument in the region between 400 and 4000/cm.

**Formulation of sustained released matrix tablets of aceclofenac**

The aceclofenac matrix tablets were prepared by wet granulation technique. 200 mg of aceclofenac, various proportions of citrus gum/HPMC (50, 100, 150 and 200 mg) and microcrystalline cellulose were granulated with isopropyl alcohol solution of starch (25 mg). Granulates were passed through 18# mesh screen and dried at 40°C for 2 hrs. The dried granulate was mixed with other formulation components, 2 mg each of magnesium stearate and talc as shown in Table 1 and then lubricated granules were evaluated for flow properties [9-10] such as bulk density, TD, %porosity, Hausner ratio, Carr's index, angle of repose, bulkiness. Then granules were compressed by using a 10 mm single station tablet punching machine, using flat faced punches 2.8.

**Evaluation of tablets**

*Appearance and dimension (thickness and diameter)*

The tablets were visually observed for capping, chipping, and lamination. The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets were determined using a Vernier-Caliper. Ten tablets from each type of formulation were used, and average values were calculated.

**Tablet hardness**

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/$cm^2$. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/$cm^2$.

**Percent friability**

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in roche friabilator, which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of <1% in weight is generally considered acceptable. Percent friability (%F) was calculated as follows.

$$\text{Friability} = 100 \times (1 - W2)/W1 \quad (6)$$

Where, W1: Initial weight before friabilator, W2: Final weight after friabilator.

**Table 1: Formulation of different batches of aceclofenac sustained release tablets using citrus gum as matrix polymer**

| Ingredients (mg) | F1[a] | F2[a] | F3[a] | F4[a] | F5[b] | F6[b] | F7[b] | F8[b] |
|---|---|---|---|---|---|---|---|---|
| Aceclofenac | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Citrus gum | 50 | 100 | 150 | 200 | | | | |
| HPMC K-100 Cps | | | | | 50 | 100 | 150 | 200 |
| Microcrystalline cellulose | 221 | 171 | 121 | 71 | 221 | 171 | 121 | 71 |
| Starch | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

[a]Formulation batches F1, F2, F3, F4 contains citrus gum with 10%, 20%, 30%, 40% matrix polymer respectively, [b]Formulation batches F5, F6, F7, F8 contains HPMC K-100 with 10%, 20%, 30%, 40% matrix polymer respectively. HPMC: Hydroxypropyl-methylcellulose

**Weight variation**
A total of 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with an average value to find the deviation in weight. The test was performed according to the official method.

**Drug content**
Twenty tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets equivalent to 200 mg of aceclofenac was extracted with pH 7.4 phosphate buffer and the solution was filtered through Whatmann filter paper. The absorbance was measured at 274 nm after suitable dilution.

***In vitro* release studies**
The dissolution rate of aceclofenac from the tablets was studied in 900 ml of 1.2 pH HCl buffer for first 2 hrs and remaining (up to 24 hrs) in 7.4 pH phosphate buffer using electrolab-TDT-08L USP2 dissolution test apparatus with paddle stirrer at 50 rpm. A temperature of 37±1°C was maintained throughout the study. One tablet containing 200 mg of aceclofenac was used in each test. Samples of dissolution media (5 ml) were withdrawn and filtered through a filter paper (0.45 µm) at each time intervals of every 1 hr, suitably diluted and assayed for aceclofenac using UV spectrophotometer at 274 nm respectively. The dissolution sample withdrawn at each time was replaced with fresh dissolution sample.

**Quantification of the water uptake determination**
For conducting water uptake studies, the dissolution jars were marked with the time points of 0.5, 1, 2, up to 9 hrs. One tablet was placed in each dissolution jar containing 900 ml of phosphate buffer pH 7.4 buffers at 37±0.5°C, and the apparatus was run at 100 rpm using paddle. The tablets were taken out after completion of the respective stipulated time span as mentioned above and weighed, after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to the following equation

$$Q = 100 (W_w - W_i)/W_w \quad (8)$$

Where, Q is the percentage of the liquid uptake, $W_w$ and $W_i$ are the masses of the hydrated samples before drying and the initial starting dry weight, respectively. The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using the following equation

$$E = 100 (W_i - W_f)/W_i \quad (9)$$

Where, $W_f$ is the final mass of the same dried and partially eroded sample.

The entire process was repeated to get 3 values for each time point, and the average was calculated [12].

**Characterization of drug release kinetics**
In order to describe the kinetics of the release process of drug in the different formulations, zero-order ($Q_t = Q_0 + K_{0t}$), first-order ($l_n Q_t = l_n Q_0 + K_{1t}$), Higuchi ($Q_t = KH_{t½}$) and Korsmeyer-Peppas ($Q_t/Q_8 = K_{tn}$) models. A value of n = 0.5 indicates Case I (Fickian) diffusion or square root of time kinetics, 0.5 < n < 1 anomalous (non-Fickian) diffusion, n=1 Case II transport and n > 1 Super Case II transport [13].

**Similarity factor**
The similarity factor ($f_2$) is a logarithmic transformation of the sum-squared error of differences between the test $T_j$ and reference products $R_j$ over all time points,

$$f_2 = 50 \log \{[1 + (1/m) \Sigma w_j |R_j - T_j|^2]^{-0.5} \times 100\}$$

where $w_j$ is an optional weight factor, This method is more adequate to compare dissolution profile when more than three or four dissolution time points are available and can only be applied if the average difference between $R_j$ and $T_j$ is <100. If this difference is higher than 100, normalization of the data is required.

**Stability studies**
Accelerated stability study was carried out to observe the effect of temperature and relative humidity on optimized formulations ($F_2$), by keeping at 40°C, in airtight high-density polyethylene bottles for 3 months, at RH 75±5%. Physical evaluation and *in vitro* drug release was carried out each month for 3 months.

## RESULTS

**Phyto and Physicochemical Tests of *C. limon (l.)* burm. f. Gum Powder**
The gum powder was characterized for phyto-chemical examinations, pH, viscosity and loss on drying to assess the citrus gum powder as excipient (swellable polymer) for developing sustained release tablets of aceclofenac. In ruthenium red test observed pinkish red color, indicates the presence of mucilage. In Molisch test pinkish red ring formed, it indicates the presence of carbohydrates, in Iodine test observed blue spots under microscopic study indicates the presence of polysaccharides and in Mayer's test no color change indicates the absence of alkaloids.

**Micromeritic properties of *C. limon (l.)* burm. f. gum powder**
The pH of citrus gum powder solutions (1% w/v) was 6.8. Viscosity and loss on drying of citrus gum powder were found to be 1.35 CP and 1.2%. In acute toxicity studies, the animals survived until the completion of the studies. Bulk density and TD of citrus gum powder

**Table 2: Micromeritic and post-compression properties of aceclofenac sustained release tablets**

| Parameters | Citrus gum[a] | | | | HPMC K-100[b] | | | |
|---|---|---|---|---|---|---|---|---|
| Percentage of polymer (Batch) | 10% (F1) | 20% (F2) | 30% (F3) | 40% (F4) | 10% (F5) | 20% (F6) | 30% (F7) | 40% (F8) |
| Angle of repose (Ø°) | 32.34 (0.03) | 31.56 (0.02) | 32.23 (0.03) | 30.16 (0.05) | 32.56 (0.05) | 32.24 (0.04) | 31.40 (0.05) | 32.75 (0.03) |
| Bulk density (g/ml) | 0.513 (0.004) | 0.542 (0.005) | 0.562±(0.004) | 0.582 (0.003) | 0.518 (0.006) | 0.512 (0.002) | 0.518 (0.004) | 0.553 (0.003) |
| TD (g/ml) | 0.641 (0.002) | 0.638 (0.003) | 0.672 (0.005) | 0.675 (0.004) | 0.650 (0.003) | 0.630 (0.006) | 0.618 (0.003) | 0.700 (0.006) |
| Carr's index (%) | 19.96 (0.1) | 15.04 (0.3) | 16.3 (0.05) | 13.7 (0.2) | 20.30 (0.2) | 18.75 (0.03) | 16.18 (0.02) | 21.1 (0.05) |
| Hausner ratio | 1.20 (0.02) | 1.17 (0.05) | 1.19 (0.05) | 1.15 (0.03) | 1.20 (0.04) | 1.20 (0.05) | 1.19 (0.03) | 1.20 (0.04) |
| Bulkiness | 1.949 (0.03) | 1.845 (0.05) | 1.779 (0.02) | 1.715 (0.06) | 1.930 (0.04) | 1.953 (0.03) | 1.930 (0.03) | 1.808 (0.02) |
| Percentage of porosity | 0.159 (0.02) | 0.211 (0.01) | 0.164 (0.05) | 0.187 (0.02) | 0.146 (0.04) | 0.182 (0.02) | 0.220 (0.03) | 0.140 (0.04) |
| Thickness (mm) | 3.1 (0.3) | 4.0 (0.1) | 3.2 (0.4) | 3.8 (0.5) | 4.2 (0.1) | 4.0 (0.3) | 4.4 (0.2) | 3.9 (0.4) |
| Diameter (mm) | 10.25 (0.10) | 9.2 (0.08) | 10.50 (0.12) | 9.8 (0.14) | 9.85 (0.12) | 10.53 (0.08) | 11.2 (0.16) | 9.6 (0.18) |
| Content uniformity (%) | 94.50 (1.02) | 98.48 (0.97) | 96.24 (0.95) | 95.38 (0.99) | 97.46 (1.02) | 95.06 (1.01) | 97.20 (0.970) | 98.77 (1.04) |
| Weight variation (mg) | 500.15 (0.13) | 499.50 (0.16) | 498.25 (0.14) | 501.34 (0.22) | 498.25 (0.20) | 501.20 (0.16) | 499.26 (0.14) | 500.34 (0.13) |
| Hardness (kg/cm$^2$) | 6.2 (0.3) | 6.3 ( 0.4) | 6.6 (0.6) | 6.8 (0.3) | 5.8 (0.4) | 6.2 (0.4) | 6.5 (0.3) | 6.6 (0.5) |

[a]Formulation batches F1, F2, F3, F4 contains Citrus gum with 10%, 20%, 30%, 40% matrix polymer respectively, [b]Formulation batches F5, F6, F7, F8 contains HPMC K-100 with 10%, 20%, 30%, 40% matrix polymer respectively, TD: Tapped density, HPMC: Hydroxypropyl-methylcellulose

was found to be 0.76 g/ml and 0.86 g/ml. Angle of repose, Carr's index and Hausner's ratio of citrus gum powder were found to be 30.30,1.13 and 12.3 (Table 2).

**DSC study**

DSC studies had also been carried out in order to predict any energy level changes that might interfere with the formulations behavior. Fig. 1 clearly shows that pure aceclofenac shows a sharp endothermic peak at 151°C showing its crystalline nature. Aceclofenac physical mixture clearly shows a peak at 154°C. Slight difference is due to the incorporation of drug into the polymer. Incorporation of aceclofenac into citrus gum did not influence the thermal properties.

**FTIR spectroscopy**

The FTIR spectral analysis of aceclofenac and the physical mixture of aceclofenac and excipients were performed, pure aceclofenac spectra (Fig. 2) showed absorption band at 1790.01 (1790-1710) functional group Ester HOOC-O-C=0, secondary amine C-N stretch 1167.2018 (119-1130), secondary amine, NH bend 1574.10 (1650-1550) 0-H bend, hydrogen bonded 3398.87 (3570-3200), alkyl substituted hydrogen C-H stretch 2970.35 (3100-2800). The same absorption bands were present in the physical mixture (drug: Citrus gum) of tablet formulation. The IR-spectrum showed that there is no chemical and physical interaction between drug and excipients.

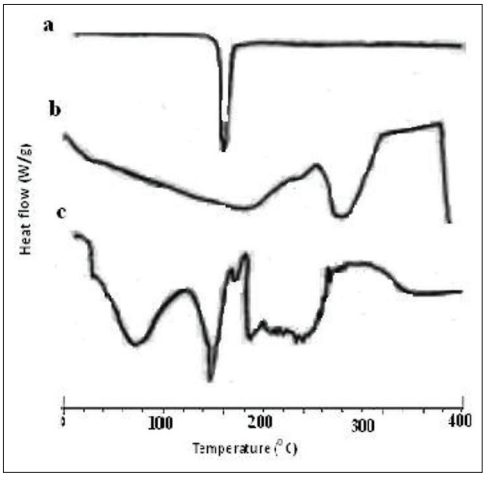


**Fig. 1: Differential scanning calorimetry (DSC). DSC thermogram of (a) aceclofenac, (b) *Citrus limon* gum, (c) Drug and *C. limon* gum physical mixture**

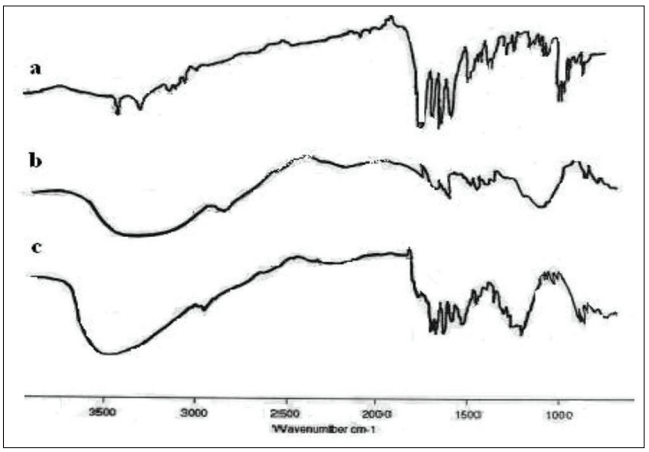


**Fig. 2: Fourier transforms infrared (IR) spectroscopy. (a) IR spectra of aceclofenac, (b) IR spectra of *Citrus limon* gum, (c) IR spectra of drug and *C. limon* gum physical mixture**

**SEM**

The water soluble gum was characterized for surface characters by SEM. The SEM microphotograph showed that the gum was smooth and crystalline in nature as shown in Fig. 3a and b.

**Pre-compression parameters**

The prepared granules were evaluated porosity, bulk density, TD, Carr's index, Hausner's ratio, angle of repose. The bulk density was found to be 0.512-0.582 g/ml, TD 0.618-0.700 g/ml, angle of repose was found to be 30.16-32.75, Carr's index was found to be 13.7-21.10, Hausner' ratio and % porosity was found to be 1.15-1.2, 0.146-0.220.

**Post-compression parameters**

The prepared tablets were evaluated thickness, diameter, hardness, friability, weight variation, content uniformity and packing fraction. The thickness and diameter of the tablets were found to be 3.1 to 4.4 mm and 9.2-11.2 mm. The hardness of the prepared tablets was all within the acceptable range of 5.8-6.8 Kg/cm$^2$. Weight loss in the friability test was <1% in all the case.

**Data of *in vitro* drug release studies**

The comparative dissolution profiles of aceclofenac sustained release tablets prepared with citrus gum powder (20%) and HPMC K-100 (30%) is shown in Fig. 4. Sustained release tablets with drug–polymer ratio 1:0.5 (F2) showed 94.30% total drug release at the end of 24 hr. However, tablets with greater drug–polymer ratio - viz., F1, F3 and F4 were found effective in sustaining the drug release beyond 24 hr. Dissolution profile of the HPMC 100 Cps based matrix tablets showed that at levels of drug–polymer ratio F7 (1:0.75), the profile was close to the profile obtained by citrus gum powder based matrix tablets F2.

**Quantification of the water uptake determination**

The swelling behavior of formulations F2, F7 was studied, and the swelling index was calculated with respect to time as shown in Fig. 5. As time increases, the swelling index was increased, because weight

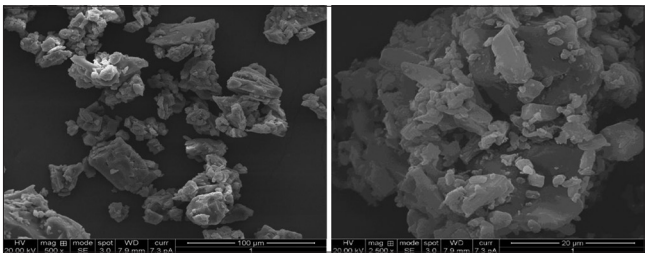

**Fig. 3: Scanning electron microscopy microphotograph. (a) *Citrus limon* gum, (b) Aceclofenac with 2.5% *C. limon* gum**

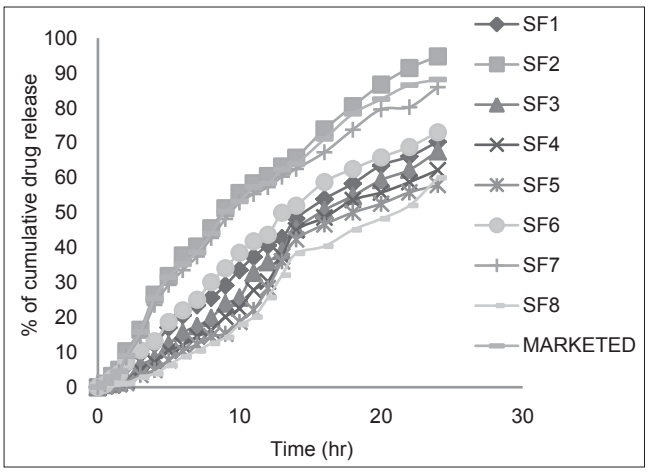


**Fig. 4: Dissolution profile of aceclofenac sustained release tablets**

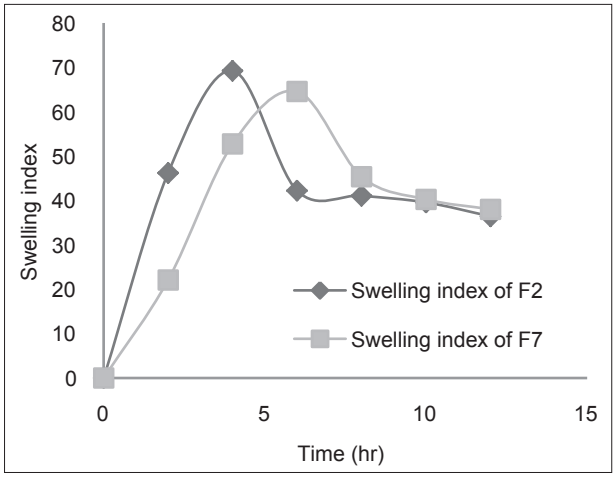


**Fig. 5: Swelling index of aceclofenac sustained release tablets**

gain by tablet was increased proportionally with rate of hydration up to 4 hr for formulations F2 and F7 and up to 6 hr. Later on, it decreases gradually due to dissolution of the outermost gelled layer of the tablet into the dissolution medium.

**Release kinetics of aceclofenac sustained release tablet formulations**

The optimized formulations (F2, F7) were followed zero-order kinetics; the $R^2$ values were found to be 0.971 and 0.987. Anomalous diffusion mechanism was explained by Higuchi model; the $R^2$ values were found to be 0.980 and 0.979 (Table 3).

**Similarity factor of aceclofenac sustained release tablets**

The $f_1$ values should be close to 0 and values $f_2$ should be close to 100. In general, $f_1$ values lower than 15 (0-15) and $f_2$ values higher than 50 (50-100) show the similarity of the dissolution profiles. Food and Drug Administration and European Medicines Agency declared similarly if $f_2$ is between 50 and 100. Similarity factor of aceclofenac sustained release tablets was found to be $f_1$ = 4.05 (not more than 15) and $f_2$ = 78.34 (limits 50-100). It indicated similarity the formulation SF2 and marketed product.

**Stability studies**

The results of stability studies of matrix tablets of aceclofenac (F2) revealed that there was no significant change in hardness, drug content, and dissolution profiles. Thus, formulation was stable at accelerated conditions of temperature and humidity.

## DISCUSSION

The citrus gum powder was used as matrix forming polymer for developing sustained release tablets of aceclofenac. The pH of citrus gum powder solutions (1% w/v) was suitable for solid oral dosage form. Acute toxicity studies show that zero toxicity was found using gum in the biological system, which could be used as safe excipient for developing oral solid dosage form. Micromeritic property of citrus gum shows that it had good and free flowing property. Data from FTIR and DSC studies shows compatibility between drug and polymer ruling out any interaction. The results of prepared granules evaluations were shown that there was no significant difference in their bulk densities and tapped densities in all the prepared granules. The results of micromeritic properties were shown that aceclofenac sustained release granules has free flowing, these values were found to be within the Indian Pharmacopoeia limits. The content uniformity and weight variation of all batches SF1 to SF8 of tablets within the specified the Indian Pharmacopoeia limits. All the batches of tablets complied with the requirements of the Indian Pharmacopoeia which states that not more than one tablet weight should none by more than 5% of the mean tablet weight. The dissolution profile showed

**Table 3: Drug release mechanism of aceclofenac sustained release tablets**

| Kinetic model | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Zero order | 0.985 | 0.971 | 0.990 | 0.970 | 0.974 | 0.982 | 0.987 | 0.974 |
| First order | 0.950 | 0.952 | 0.945 | 0.920 | 0.967 | 0.951 | 0.968 | 0.948 |
| Higuchi model | 0.993 | 0.980 | 0.988 | 0.988 | 0.987 | 0.982 | 0.979 | 0.965 |
| Koresemeyer peppas model | 0.949 | 0.967 | 0.933 | 0.909 | 0.898 | 0.964 | 0.951 | 0.911 |

[a]Formulation batches F1, F2, F3, F4 contains Citrus gum with 10%, 20%, 30%, 40% matrix polymer respectively, [b]Formulation batches F5, F6, F7, F8 contains HPMC K-100 with 10%, 20%, 30%, 40% matrix polymer respectively

that the effect of polymer concentration, decrease in drug release rate was observed when citrus gum powder content in the matrix was increased. This may be due to the reason that the polymer in higher concentrations in the tablets might have produced dense matrix around the drug particles, providing more barriers for them to escape and dissolve. HPMC 100 Cps based matrix tablets of aceclofenac were used for comparative study. Aceclofenac release increased as the percent amount of HPMC 100 Cps level in the tablet increased. Drug release is controlled by the hydration of HPMC 100 Cps, which forms a gelatinous barrier layer at the surface of the matrix. In addition, the resistance of such a gel layer to erosion is controlled by the viscosity grade of the HPMC 100 Cps. Dissolution profile of the HPMC 100 Cps based matrix tablets showed that at levels of drug–polymer ratio (1:0.75), the profile was close to the profile obtained by citrus gum powder based matrix tablets F2. These matrix tablets provided slow and complete release of aceclofenac over 24 hr and were suitable for once a day (24 hr) administration. Means reduce the gastric irritation. Sustained release formulation of aceclofenac with *C. limon* gum so as to minimize initial drug release in the stomach that will reduce the possible gastro irritant and ulcerogenic effects of the drug. A direct relationship was observed between swelling index and polymer concentration, and as polymer concentration increases, swelling index was increased. It has been observed that the cumulative percent drug release decreases with increasing concentration of polymer and swelling index.

The *in vitro* drug released data were assessed using various kinetics models. Formulations containing citrus gum were best fitted with a majority of the kinetic models and followed Higuchi or zero-order kinetics. It was found that the *in vitro* drug release of aceclofenac was best explained by Higuchi equation as the plots showed the highest linearity. This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics or Higuchi kinetics. Drug content, hardness, disintegration time and dissolution profile of the optimized formulation F2 no significant changes before and after accelerated stability studies.

## CONCLUSION

The sustained release tablets of aceclofenac prepared with citrus gum and HPMC K-100, from the result F2 were selected as the best formulation. It is shown that citrus gum powder by forming a matrix retards the release rate of drug and can be used as sustained release dosage form.

## REFERENCES

1. Perepelkin KE. Polymeric materials of the future based on renewable plant resources and biotechnologies: Fibres, films, plastics. Fibre Chem 2005;37(6):417-30.
2. Lam KS. New aspects of natural products in drug discovery. Trends Microbiol 2007;15(6):279-89.
3. Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustained-release carriers. Drug Dev Ind Pharm 2000;26(10):1025-38.
4. Uhrich KE, Cannizzaro SM, Langer RS, Shakesheff KM. Polymeric

systems for controlled drug release. Chem Rev 1999;99(11):3181-98.
5. British National Formulary. 57th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2009. p. 554.
6. Mutalik S, Manoj K, Reddy MS, Kushtagi P, Usha AN, Anju P, *et al.* Chitosan and enteric polymer based once daily sustained release tablets of aceclofenac: *In vitro* and *in vivo* studies. AAPS PharmSciTech 2008;9(2):651-9.
7. ElijahI N, Conway BR. Characterization of *Grewia* gum, a potential pharmaceutical excipient. J Excip Food Chem 2010;1(1):30-40.
8. Indian Pharmacopoeia-II. Delhi: Indian Pharmacopoeia Commission; 1996. p. 554-5.
9. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Mumbai: Varghese Publishing House; 1987. p. 182-203.
10. Sharma S, Gupta GD. Formulation and characterization of fast dissolving tablet of promethazine theoclate. Asian J Pharm 2008;2(1):70-2.
11. Odeku OA, Itiola OA. Evaluation of the effects of *Khaya* gum on the mechanical and release properties of paracetamol tablets. Drug Dev Ind Pharm 2003;29(3):311-20.
12. Schwartz JB, Simonelli AP, Higuchi WI. Drug release from wax matrices. I. Analysis of data with first-order kinetics and with the diffusion-controlled model. J Pharm Sci 1968;57(2):274-7.
13. Korsmeyer RW, Gurny R, Decker EM. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983;15(1):25-35.