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PROBABLE USE OF *PROSOPHIS CUMANENSIS* FRUIT MUCILAGE AS RELEASE RETARDANT WITH POVIDONE: TAKING NIMESULIDE AS A MODEL DRUG

Sravanthi B, Sowmya PS, Hemanth P Kumar K, Hindustan Abdul Ahad*

PG Department of Pharmaceutics, Balaji College of Pharmacy, Anantapur, Andhra Pradesh, India

ABSTRACT

Keywords:

Nimesulide, *Prosopis cumanensis*, Povidone, matrix tablets, sustained release

For Correspondence:

Dr. Hindustan Abdul Ahad

PG Department of
Pharmaceutics, Balaji
College of Pharmacy,
Anantapur, Andhra Pradesh,
India

E-mail:

abduhindustan@rediffmail.com

Aim: The present research work was aimed to prepare Nimesulide sustained release matrix tablets using *Prosopis cumanensis* fruit mucilage and Povidone.

Method: Drug excipient compatibility studies were performed by using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopic studies. Various formulations of Nimesulide *P. cumanensis* fruit mucilage and Povidone were prepared. The DSC and FTIR studies revealed that the *P. cumanensis* fruit mucilage and Povidone are compatible with Nimesulide. The formulated tablets were evaluated for pre compression and post compression parameters including swelling behavior and release rate kinetics, which were found to be satisfactory within the limits.

Conclusion: *In vitro* dissolution study proved that the dried *P. cumanensis* fruit mucilage and Povidone in combination can be used as a matrix forming polymers for making sustained release matrix tablets.

INTRODUCTION

Prosopis cumanensis (Fabaceae family) is a shrub or small weed plant grows all over the world. The tree grows to a height of up to 12 m and has a trunk with a diameter of up to 1.2 m. The plant has characteristic thorns and yellow flowers ^[1]. The bark exudates a good amount of gum round the year.

Nimesulide (*N*-4'-nitro-2'-phenoxyphenyl methane sulfonamide) is a weakly acidic Non-Steroidal Anti-inflammatory drug (NSAID). Nimesulide chemical structure contains a sulfonamide moiety as the acidic group. Nimesulide shows high anti-inflammatory, antipyretic and analgesic activities in addition to low toxicity, a moderate incidence of gastric side effects and a high therapeutic index ^[2]. Nimesulide has a biological half-life of 1.8-4.7 hours. The oral absorption is uniform, rapid and complete. The normal adult dose of Nimesulide is usually 100-200 mg ^[3]. Hence we have selected Nimesulide for the development of once daily sustained release matrix tablets.

The objective of present investigation is to prepare and evaluate sustained release matrix tablets of Nimesulide using *P. cumanensis* fruits mucilage in combination with Povidone as release retardant in tablet dosage forms.

MATERIALS AND METHODS

Nimesulide was obtained as a gift sample from Waksman Selman Pharmaceuticals, Anantapur, India. *Prosopis cumanensis* fruits were collected from plants growing in local areas of Anantapur, India. The plant was authenticated at the Department of Pharmacognosy, Balaji College of Pharmacy, Anantapur, India. Povidone, Micro crystalline cellulose and Magnesium stearate were procured from SD Fine chemicals (Mumbai, India). All other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiment.

Extraction of mucilage

The fresh *P. cumanensis* fruits were collected and washed with water. The fruits were crushed and placed in water for 5–6 hours, boiled for 30 minutes and left to stand for 1 hour to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (in the quantities of three times the volume of filtrate) was added to precipitate the mucilage ^[4]. The mucilage was separated, dried in an oven at 40°C, collected, powdered, passed through a # 80 sieve and stored in air tight container till use ^[4, 5].

Evaluation of Pre compression parameters

Differential Scanning Calorimetric (DSC) analysis

Differential Scanning Calorimetry (DSC) thermo grams were obtained by a differential scanning calorimeter (Schimadzu DSC-50, Tokyo, Japan) at a heating rate of 10°C/min from 30-300°C in nitrogen atmosphere (20 ml/min) with a sample weight of 3mg.

Fourier Transform Infrared (FTIR) Spectroscopic analysis

The FTIR spectrums of pure drug, excipient and Formulation (F-5) blend were studied by using FTIR spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.0502 mg sample in 300.0070 mg KBr). The scanning range was 500 to 4000 cm^{-1} and the resolution was 1cm^{-1} . This spectral analysis was employed to check the compatibility of drugs with the excipients used.

Flow properties of formulation blend

The formulation blend was evaluated for flow properties viz., Angle of repose ^[6], Loose Bulk Density ^[6], Tapped Bulk Density ^[6], Compressibility index ^[7] and Hausner's ratio ^[8]. The experiments were conducted in triplicate.

Preparation of matrix tablets

Sustained release matrix tablets of Nimesulide with *P. cumanensis* fruit mucilage and Povidone were prepared by using different drug: mucilage ratios as shown in Table 2. *P. cumanensis* fruits mucilage and Povidone were used as matrix forming materials while microcrystalline cellulose as a diluent and Magnesium stearate as a lubricant ^[9]. All ingredients used were passed through a # 100 sieve, weighed and blended. The granules were prepared by wet granulation technique and compressed by using 10 mm flat faced punches. The compositions of formulations were showed in Table No 1. These matrix tablets were evaluated for their physical properties as per official and Pharmacopoeia methods.

Table No 1: Formulae of matrix tablets

Ingredients (mg)	Formulations				
	F-1	F-2	F-3	F-4	F-5
Nimesulide	100	100	100	100	100
<i>P. cumanensis</i> fruits mucilage	10	20	30	40	50
Povidone	10	10	10	10	10
Micro crystalline cellulose	75	65	55	45	35
Magnesium stearate	5	5	5	5	5
Total weight of tablet	200	200	200	200	200

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation F-1, F-2, F-3, F-4 and F-5 were studied. One tablet from each formulation was kept in a Petri dish containing phosphate pH 7.4. At the end of 2 hours, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 2 hours till the end of 12 hours. The % weight gain by the tablet was calculated by the following equation ^[9].

$$S.I = \{(M_t - M_0) / M_0\} \times 100$$

Where, S.I = Swelling Index, M_t = Weight of tablet at time 't' and

M_0 = Weight of tablet at time 0.

***In vitro* drug release studies**

Release of Nimesulide from the matrix tablets was studied using a six basket USP XXIV dissolution apparatus taking 900 ml of HCl (pH 1.2) solution for first 2 hours and phosphate buffer (pH 7.4) for next 10 hours. The dissolution media were maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. The speed of rotation of basket was maintained at 50 rpm. The basket was covered with 100 mesh nylon cloth to prevent the escape of the beads ^[10]. The samples were withdrawn at 30 min intervals. The samples were filtered and suitably diluted to determine the absorbance at 276 nm using UV/ Visible single-beam spectrophotometer-117 (Systronics Corporation, Mumbai, India). The drug release experiments were conducted in triplicate ($n = 3$). The *in vitro* dissolution rates were further treated mathematically with zero order, first order, Higuchi ^[11], Korsmeyer Peppas ^[12] and Hixon Crowell's ^[13] Models.

RESULTS AND DISCUSSION

The DSC thermo gram of Nimesulide Pure drug showed a short endothermic peak at 147.92°C . The thermo gram of formulation (F-5) showed an endothermic peak at 145.36°C indicating a slight change in terms of shifting towards the lower temperature (Fig. 1A and 1B).

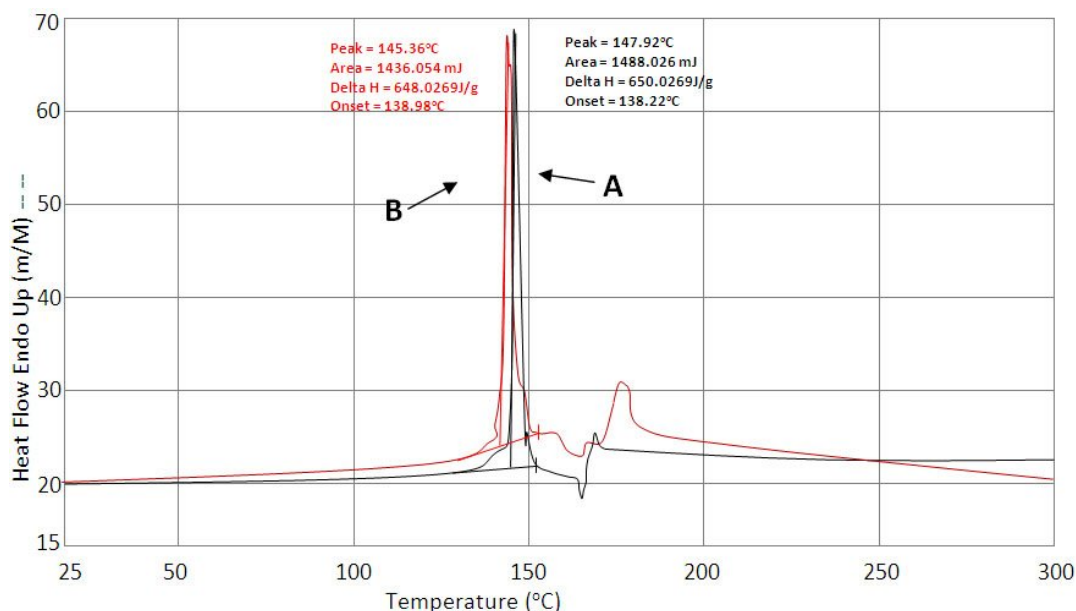


Fig. 1: The DSC thermo grams of A) Nimesulide; B) matrix tablets (F-5)

The FTIR spectrum revealed that the characteristic peaks in spectrum of Nimesulide were observed even in the spectrum of formulation (F-5). The FTIR spectrums were showed in Fig. 2, 3 and 4.

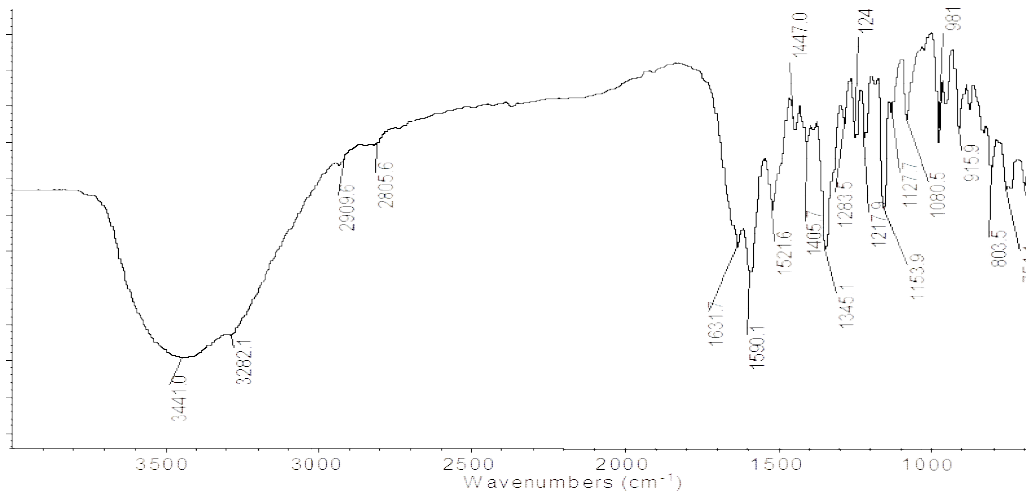


Fig. 2: IR Spectrum of Nimesulide Pure drug

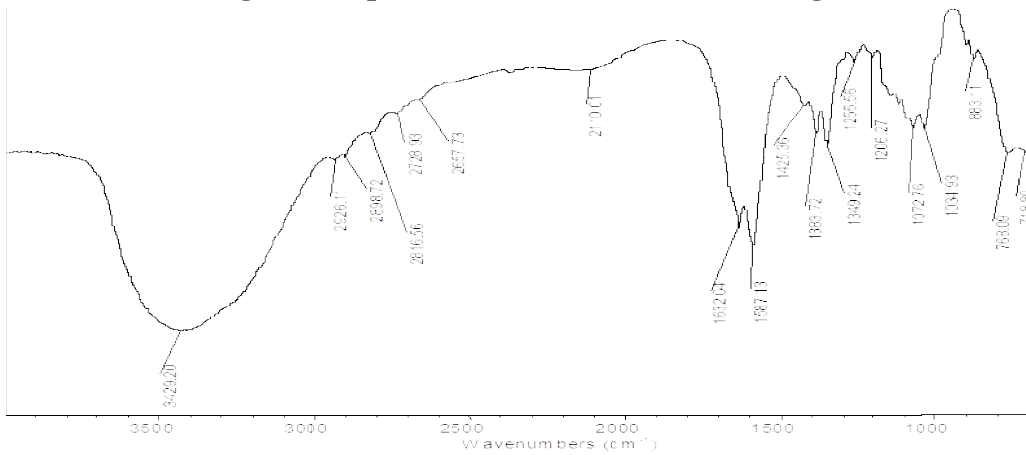


Fig. 3: IR Spectrum of Placebo tablets

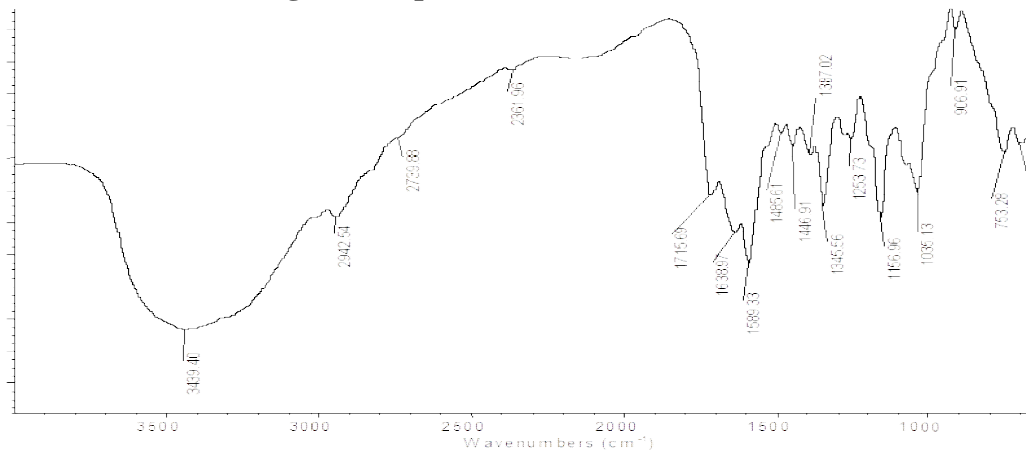


Fig. 4: IR Spectrum of formulated matrix tablets (F-5)

All the formulation blends showed excellent flow properties and excellent compressibility index and tabulated in Table No 2.

Table No 2: Flow properties of formulation blend

Formulation	Angle of repose ($^{\circ}$)	Loose Bulk Density (g/cm^3)	Tapped Bulk Density (g/cm^3)	Carr's Index (%)	Hausner's ratio
F-1	18.07 \pm 0.01	0.56 \pm 0.01	0.65 \pm 0.02	14.09 \pm 0.02	1.16 \pm 0.021
F-2	20.22 \pm 0.02	0.57 \pm 0.05	0.68 \pm 0.02	14.41 \pm 0.08	1.20 \pm 0.001
F-3	23.20 \pm 0.04	0.56 \pm 0.02	0.67 \pm 0.04	14.71 \pm 0.02	1.18 \pm 0.002
F-4	24.10 \pm 0.01	0.56 \pm 0.02	0.65 \pm 0.02	14.10 \pm 0.02	1.14 \pm 0.001
F-5	22.01 \pm 0.02	0.62 \pm 0.01	0.75 \pm 0.01	17.31 \pm 0.04	1.21 \pm 0.001

All values were expressed as mean \pm S.D; Number of trials (n=5)

The formulated tablets showed uniformity in swelling and the values plotted and shown in Fig. 5. The thickness of formulated tablets was uniform and was ranged from 5.7 \pm 0.53 to 6.1 \pm 0.06mm. The formulated tablets passed the hardness as it was more than 4 kg/cm² (5.52 \pm 1.08 to 6.87 \pm 1.05 kg/cm²). All the formulated tablets showed good mechanical strength as the loss on friability was less than 1% (0.15 \pm 0.01 to 0.89 \pm 0.04%). The drug content in the formulated tablets was ranged from 99.8 \pm 1.64 to 100.8 \pm 1.37%. All these values were shown in Table No 3. *In vitro* drug release profile of Nimesulide from formulated matrix tablets were studied using zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell's models which were shown in Fig. 6, 7, 8, 9 and 10 respectively. The mathematical models revealed that the drug release from these formulations was by swelling of polymer and erosion of matrix tablets. The rate of release was faster in matrix tablets of F-1 batch and slower in F-5 batch. This result shown that as the proportion of *P. cumanaensis* fruits mucilage increased, the overall time of release of the drug from the matrix tablet was also increased (release retarding).

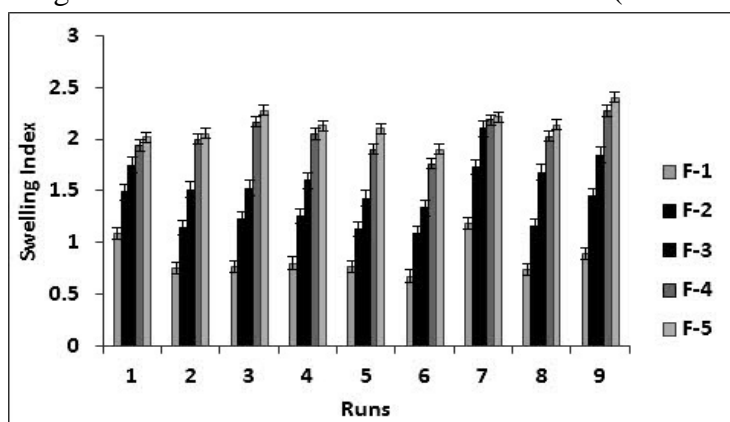


Fig. 5: Swelling Index of matrix tablets

Table No 3: Post compression parameters of formulated matrix tablets

Formulation	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F-1	5.9±0.08	5.52±1.08	0.49±0.08	99.9±0.25
F-2	5.9±0.05	6.52±1.14	0.15±0.01	100.8±1.37
F-3	5.7±0.53	6.87±1.05	0.89±0.04	99.9±1.81
F-4	6.1±0.06	6.58±0.52	0.73±0.04	99.8±1.64
F-5	6.0±0.09	6.02±0.29	0.68±0.01	100.1±2.05

All values were expressed as mean ±S.D; Number of trials (n=5)

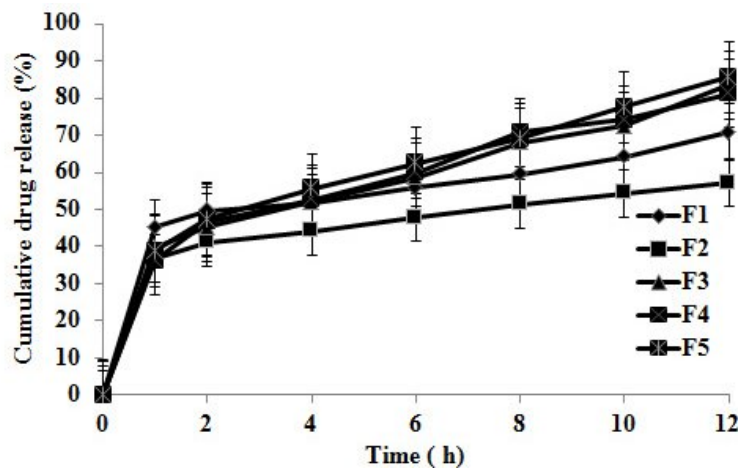


Fig. 6: Zero order plots of matrix tablets

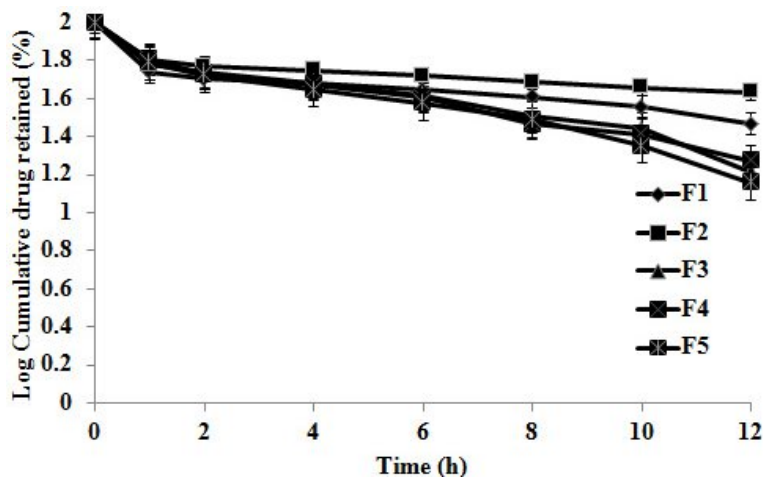


Fig. 7: First order plots of matrix tablets

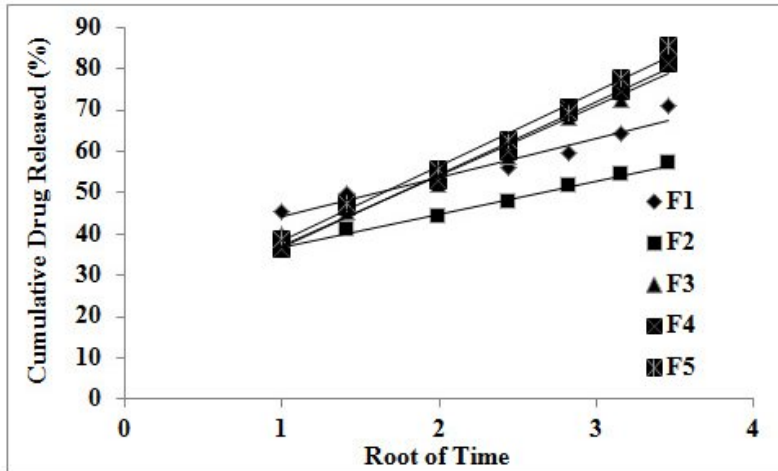


Fig. 8: Higuchi plots of matrix tablets

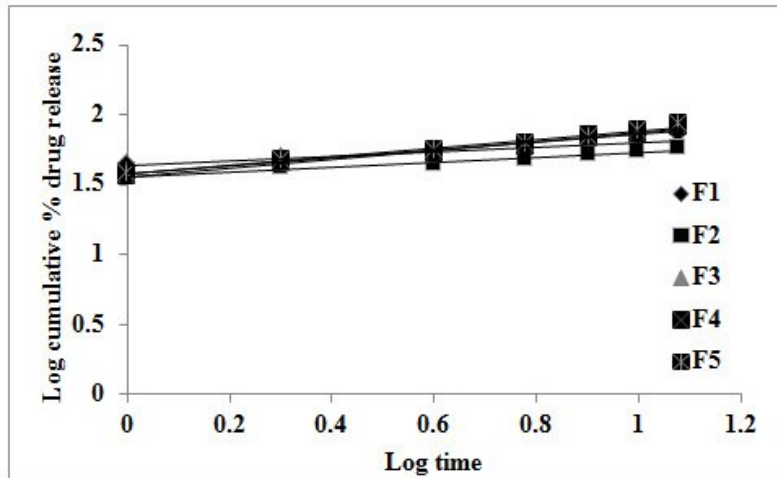


Fig. 9: Korsmeyer Peppas plots of matrix tablets

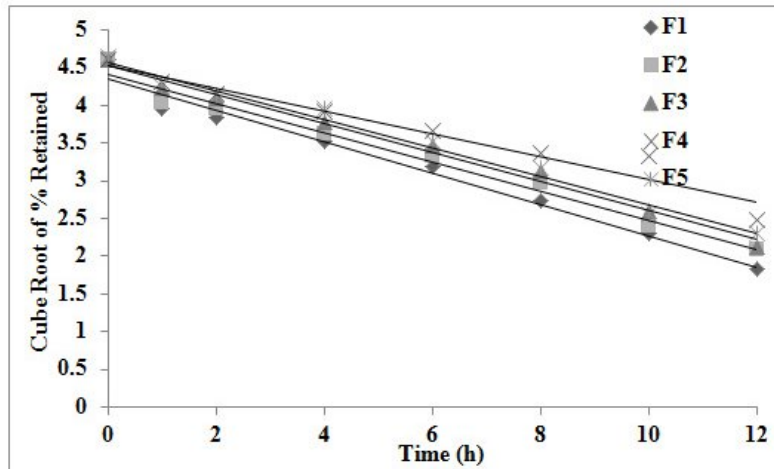


Fig. 10: Hixon Crowell plots of matrix tablets

CONCLUSION

The present study revealed that *P. cumanensis* fruits mucilage and Povidone combination appears to be suitable combination for use as a release retardant in the formulating sustained release matrix tablets because of its compatibility, good swelling, good flow properties and drug release characteristics.

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