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ISOLATION, PHYSICO-CHEMICAL CHARACTERIZATION AND *IN-VITRO* DRUG RELEASE STUDIES OF A NOVEL NATURAL POLYSACCHARIDE OF *ARAUCARIA HETEROPHYLLA* GUM

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ABSTRACT

Objective: The objective of the present research work for investigation of the physico-chemical, morphological and rheological properties of novel natural polymer, *Araucaria heterophylla* gum (AHG) and also investigate for its pharmaceutical applications as excipient. Hence, the present study was carried out to study its properties and applicability in the design of controlled release dosage forms. **Methods:** Diclofenac sodium matrix tablets prepared by wet granulation method. The tablets were compressed by using 10 mm punches. Drug-polymer compatibility studies were examined by Fourier transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction studies. *In vitro* dissolution studies for formulations were carried out in 0.1N HCl (pH 1.2) was for the first 2 h and pH 6.8 phosphate buffer was used for remaining 24 h as dissolution medium. **Results:** The obtained results confirmed that the absence of interactions between the drug and polymers. AHD 8 showed 99.52% drug release in 24 h. Stability studies showed no significant change of AHG sample. Tablets prepared with AHG matrix tablets showed zero order drug release and follows the erosion mechanism. The weight variation of the tablets was complied with the compendia standards for uniformity of weight. The hardness, drug content and friability values for all the formulations found to be in the range as per IP. **Conclusion:** The powder characteristics of the AHG showed good flowing properties and other physico-chemical properties were suitable to be used as excipient in the formulation. FTIR, DSC and XRD studies of AHG were carried for characterization of the gum. The bacterial and fungal counts were within limits and pathogenic microorganisms were absent in AHG. Rheological properties of AHG suggested that it could be used as an excipient in controlled release system in particular to hydrophilic matrix tablet formulations. Hence, concluded that AHG is novel polymer for controlled release of dosage form.

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INTRODUCTION

Some of the natural gums obtained from plants have been investigated for different applications in the development of pharmaceutical formulations. However, still many of the natural gums obtained from the plants and other sources are not fully explored for their pharmaceutical excipient activity. In now-a-days, gums and mucilages are used as natural excipients for conventional and novel drug delivery systems. These natural polymers have different advantages over synthetic ones due to they are chemically inert, nontoxic, less expensive, biodegradable, and widely available [1]. Natural gums are obtained as exudates by metabolic mechanism of plants from natural sources either absorb water to form a viscous solution or water soluble. Plant derived natural polymers are more suitable as pharmaceutical excipients due to non-toxicity, availability, stability, renewability and are, therefore, extensively used as a matrix forming agent in modified release dosage forms and controlled release dosage forms [2-4].

Araucaria heterophylla is a genus of evergreen coniferous tree belongs to the family of Araucariaceae. Fossil evidence indicated that the Araucaria family reached its maximum diversity during the Jurassic period[5]. The objective of the present research work for investigation of the physico-chemical, morphological and rheological properties of novel natural polymer, *Araucaria heterophylla* gum (AHG) and also investigate for its pharmaceutical applications as excipient.

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as a gift sample from Crips Laboratory Pvt. Ltd, Visakhapatnam. Microcrystalline cellulose (Prosolv SM, JRS Pharma, Germany), magnesium stearate, talc (Reachem Lab. Chemicals Pvt. Ltd, Chennai) were provided by Hetero Pharma, Hyderabad. All other chemicals used were of analytical grade.

Isolation of gum

Collection of exudates gum from trunk of the tree was done by tapping method. The plant was authenticated and botanically identified by Dr. S. B. Padal, Associate Professor, Department of Botany, Andhra University, Visakhapatnam with voucher specimen No. 22203. The gum was isolated by precipitation with acetone from aqueous dispersion of exudates. The exudates were cleaned by removing the bark and other extraneous materials by hand and dried in hot air oven at 50°C until it become sufficiently brittle. It was milled to powder using high speed mechanical blender (Butterfly, India) and sifted through the sieve No.100 (nominal mesh aperture size 75 µm and approximate %sieving area 36). It was dispersed in distilled water in the proportion of one part of plant material to ten parts of the water. The extraction continued for 24 h at room temperature with continuous stirring using rotary shaker (M/s. Remi Instruments Ltd, Mumbai, India). The supernatant was separated by muslin cloth. Residue was washed with water and washings were added to the supernatant. The procedure was repeated three times. Supernatant was treated with twice the volume of acetone to isolate the gum by continuous stirring and it was separated by centrifugation. Precipitate was washed with acetone and dried at 40-50°C in oven. The dried gum (AHG) was pulverized by laboratory blender and passed through sieve No.100. It was stored in tightly closed container and kept in a desiccators [6-7]. The %yield was calculated by the following equation.

$$\% \text{Yield} = \frac{W_1}{W_2} \times 100 \quad \text{Eq.1}$$

Where W_1 weight of crude exudates; W_2 weight of the isolated gum

Drug-excipient compatibility studies

Drug-excipient compatibility studies are employed in the present work to study the drug-polymer interactions by Fourier transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction studies. These studies were carried for pure drug diclofenac sodium, polymer (AHG) and optimised formulations.

Physico-chemical properties of isolated gum

Organoleptic evaluation and solubility behavior of gum

Organoleptic characters like colour, odour and taste were evaluated. Solubility studies were done in water and different solvents like methanol, ethanol, acetone and ether[8].

Determination of purity and identification tests for gums

Identification tests for isolated and purified gums were carried out as recommended by AOAC (1984) and FAO (1991) [9-10]. Phytochemical screening was carried to determine the purity of AHG powder. AHG was subjected to preliminary phytochemical screening for detection of different plant constituents like carbohydrates, gums, steroids, proteins, terpins, saponins, alkaloids, flavonoids, resins and tannins according to standard procedure[11].

Particle size distribution

Particle size was microscopically estimated by placing a small quantity of the powder uniformly dispersed in glycerin on a slide and covered with a cover slip and the eye piece micrometer was used to view the powder sample at the highest magnification of the microscope. Each division of the eye piece micrometer was calibrated using the stage micrometer. The sizes of 500 particles were measured and calculated by the following.

$$\text{Size of individual particle} = \frac{\text{No. of individual in eye piece}}{\text{X calibration factor}} \quad \text{Eq. 2}$$

Determination powder properties

Truedensity

True density was determined by liquid displacement method at 25°C. It was calculated from the volume of intrusion fluid (toluene) displayed in the density bottle by a given mass of a powder. The weight (W_1) of the clean, dry 25 ml density bottle was determined. The density bottle was filled with distilled water surface was dried with filter paper and weighted as (W_2). The procedure was repeated with using benzene to obtain weight (W_3). Benzene was used as displacement liquid. Specified weight of AHG powder was transferred into dried density bottle and weighted as (W_4). The bottle was filled with benzene and weight (W_5) was measured. True density was calculated by the following [12].

$$\text{Density of toluene} = \frac{(W_3 - W_1) 0.9971}{(W_2 - W_1)} \quad \text{Eq. 3}$$

(Density of water at 25°C = 0.9971 g/cc)

The true density of AHG was calculated from the following equation,

$$\text{Density of the sample} = \frac{W_4 - W_1}{\left[\frac{W_3 - W_1}{\rho} \right] - \left[\frac{W_5 - W_4}{\rho} \right]} \quad \text{Eq. 4}$$

Bulk density

The weighed quantity of dry powder (W) was transferred into 100 mL measuring cylinder. Carefully leveled the powder without compaction and initial volume (V_b) was measured. Bulk density was calculated by the following[13].

$$\text{Bulk density } (\rho_b) = \frac{\text{Weight of powder } (W)}{\text{Bulk volume } (V_b)} \quad \text{Eq. 5}$$

Bulkiness

Reciprocal of bulk density gives the bulkiness. Bulkiness was calculated by the following.

$$\text{Bulkiness} = \frac{1}{\text{Bulk density } (\rho_b)} \quad \text{Eq. 6}$$

Tappeddensity

The tapped density was obtained by mechanically tapping of graduated measuring cylinder containing the powder sample. After observing the initial powder volume, the measuring cylinder was placed on the tapped density tester (M/s. Electro lab, model: ETD-1020) and subjected to USP-II method i.e., 250 drops per minute and drop height is 3 mm±10%. The volume of powdered bed was measured after each increment of 250 drops until the difference of last two volume measurement is zero and the volume was recorded as tapped volume (V_t). Tapped density was calculated by the following.

$$\text{Tapped density } (\rho_t) = \frac{\text{Weight of powder } (W)}{\text{Tapped volume } (V_t)} \quad \text{Eq. 7}$$

Compressibility index (I) and Hausner ratio

Compressibility index or Carr's index and Hausner ratio are used as indicators for flowability and compressibility of the powder. They were calculated by the following.

$$\text{Compressibility index (I)} = \frac{V_b - V_t}{V_t} \times 100 \quad \text{Eq. 8}$$

$$\text{Hausner index} = \frac{\text{Bulk volume } (V_b)}{\text{Tapped volume } (V_t)} \quad \text{Eq. 9}$$

Flow properties

Angle of repose was determined by the fixed funnel method by following[14-17].

$$\theta = \tan^{-1} \left(\frac{h}{r} \right) \quad \text{Eq. 10}$$

Determination of loss on drying

The accurately weighed 1.0 g gum (W_i) was transferred into bottle and dried in an oven at 105°C and the weight was checked at intervals of 10 min. It was cooled in desiccators before weighing. The procedure was repeated until a constant weight (W_f) was obtained. The percentage of weight lost was calculated by the following[18].

$$\% \text{Loss on drying} = \frac{\text{Initial weight } (W_i) - \text{Final weight } (W_f)}{\text{Initial weight } (W_i)} \quad \text{Eq. 11}$$

Determination of ash values**Total ash**

2 g of the powdered sample was accurately weighed in a tarred silica crucible. Then it was incinerated at a temperature not exceeding 450°C for 1 hr, until free from carbon, cooled and weighed. The percentage of total ash was calculated with reference to air dried sample by the following[19].

$$\% \text{Total ash value} = \frac{\text{Weight of total ash}}{\text{Weight of the sample taken}} \times 100 \quad \text{Eq. 12}$$

Acid insoluble ash

The ash obtained from the above step was boiled for 5 min with 25 mL of 2M HCl. Filtered and collected the insoluble matter on an ashless filter paper, washed with hot water and ignited in a tarred crucible at a temperature not exceeding 450°C for 1 hr. Cooled in a desiccator and weighed. Calculated the percentage of acid insoluble ash with reference to the air dried drug using following.

$$\% \text{Acid insoluble ash value} = \frac{\text{Weight of acid insoluble ash}}{\text{Weight of the sample taken}} \times 100 \quad \text{Eq. 13}$$

Water soluble ash

The ash obtained from the above step was boiled with 25 ml of water. It was filtered and collected the insoluble matter on an ashless filter paper, washed with hot water and ignited in a tarred crucible at a temperature not exceeding 450°C for 1 h. Cooled in a desiccator and weighed. The weight of insoluble matter was subtracted from the total weight of the ash. The difference in weight represents the weight of water soluble ash. The percentage of water soluble ash was calculated with reference to the air-dried powder using the following.

$$\% \text{Water soluble ash value} = \frac{\text{Weight of total ash} - \text{Weight of water insoluble ash}}{\text{Weight of the sample taken}} \times 100 \quad \text{Eq. 14}$$

Determination of melting point

The AHG powder was transferred into a melting point capillary tube and melting point was determined by using melting point apparatus (M/s. Shiv Scientific, Mumbai, India).

Determination of moisture content

Moisture content was determined by using Karl Fisher titrator (M/s. Lab India, KAFI⁺). Accurately weighed amount of AHG powder was transferred in dried titrating flask. The powder was dispersed in anhydrous methanol and stirred to extract water. It was titrated with standard Karl Fisher reagent (KF) free of pyridine until end point reached. Blank titration was carried out by omitting the sample. 15mL of the reagent is equivalent to 75 mg of water and the water equivalent is 5.2. Moisture content was determined by the following .

$$\% \text{Moisture content} = \frac{\text{Volume of the KF reagent} \times \text{Water equivalent}}{\text{Sample weight (mg)}} \times 100 \quad \text{Eq. 15}$$

Determination of pH

The pH of 1% w/v aqueous solution of AHG was determined by calibrated pH meter (M/s. Systronics, Model No: 361) at room temperature 25-27°C.

Determination of swelling index and water retention capacity

Swelling index and water retention capacity of AHG were determined by modified method reported by Gauthami and Bhat. 10 g of powder was accurately weighed and transferred to a 100mL stoppered measuring cylinder. The initial volume or height (X_0) of the powder in the measuring cylinder was noted. With distilled water the volume was made up to 100 mL and stoppered. It was shaken gently so that the all powder gets wet and the volume or height (X_t) occupied by the gum sediment was noted after 24 hrs. Swelling index (SI) was expressed as a percentage and calculated by the following[20].

$$\text{Swelling index (SI)} = \frac{X_t - X_0}{X_0} \times 100 \quad \text{Eq. 16}$$

The contents of the measuring cylinder from above test were filtered through a muslin cloth and water was allowed to drain completely into a dry 100 ml graduated cylinder. The volume of water was noted and the difference between the original volume of the mucilage and the volume drained was taken as water retained by the gum. It was referred as water retention capacity or water absorption capacity.

Determination of volatile acidity

Accurately weighed 1 g of AHG powder was transferred in to long necked round bottom flask. To this 100 ml of water and 5 ml of orthophosphoric acid were added and allowed to stand until the gum was completely swollen for 24 h. It was boiled for 3hrs under a reflux condenser and then steam distilled until 30 mL of distillate was obtained. The distillate was titrated with 0.1N sodium hydroxide using phenolphthalein as indicator. Blank titration was carried out by omitting the sample. The difference between two titration values gives the amount of alkali required to neutralize the volatile acid[21]. Each mL of 0.1N NaOH $\equiv$ 0.006005 g of $C_2H_4O_2$

Scanning electron microscopic studies

The morphological properties of AHG powder was characterized by scanning electron microscopy (Hitachi S3700N) with 15kV accelerating voltage.

Fourier transform infrared spectroscopy

The IR spectral analysis of AHG powder was done using press pellet technique using potassium bromide and it was recorded by using ALPHA Bruker, IR spectrometer (Eco-ATR) in the region between 4,000 and 400 cm^{-1} .

Differential scanning calorimetry (DSC)

Thermal properties of AHG powder was characterized using a differential scanning calorimeter (Hitachi Exstar DSC 7020). Sample was sealed in aluminium pan and heated from 25 to 725°C at a heating rate of 10°C/min in nitrogen atmosphere.

Powder X-ray diffractometry

Powder X-ray diffractometry (XRD) studies of the AHG was performed with the Rigaku X-ray diffractometer (D/MAX-B) using Ni-filtered Cu-K(α) radiation, a voltage of 40 kV and current of 30 mA. The width of receiving slit is 0.3 mm. The sample was analyzed over the 2θ range of 10-80°, scan speed of 4.0°/min with scan step and scan time of 0.020° and 0.3sec respectively.

Determination of rheological properties

Rheological properties of AHG were determined using Brookfield cone and plate viscometer (Model LV DV-III+ Rheometer). Gum concentrations of 3, 5 and 7% (w/v) were prepared by distilled water and allowed to stand undisturbed for 24 hrs for complete hydration. 0.5 mL of sample was placed in the plate of viscometer and analyzed for its viscosity, percent torque, shear stress, shear rate at different speeds and also tested for its thixotropic phenomena at 25°C using CP 52 spindle and Rheocalc software of the instrument[22].

Microbiological studies

Microbial count was performed as outlined in Indian Pharmacopeia for aerobic, fungal and pathogenic microorganisms. The plate count method used to estimate the number of viable bacteria and fungi cells in the sample. The media used are sterilized liquefied agar and potato dextrose agar medium for bacteria and fungi respectively. Solution of 1 g/ml of AHG was placed into each liquefied sterilized agar medium and the medium was poured into Petri plate and allowed to solidify. The plates were kept at 5–10°C for 1 hr and were incubated at 37°C for 18 hrs. The number of bacterial colonies formed in each plate after the incubation period was counted. Fungal count was determined in similar procedure using potato dextrose agar medium and the plates were incubated at room temperature (20–25°C) for a period of 5 d. The presence of pathogenic microorganisms in the gum sample was estimated using specific individual media like mannitol salt agar medium (*Staphalococcus aureus*), cetrimide agar (*Pseudomonas aeruginosa*), MacConkey agar medium (*Escherichia coli*) and deoxycholate citrate agar medium (*Salmonella* sp.). Culture mediums were prepared according to the procedure given in the IP. In each media AHG sample (1 g/ml) was placed and incubated at 37°C for 48 hours and growth of specific organisms depending on the selective media were observed[23].

Stability studies

Stability studies were carried out according to ICH guidelines (30±2°C/65±5%RH and 40±2°C/75±5%RH). The samples were securely packed in high density polyethylene (HDPE) bottles and kept in stability chambers (M/s. Remi Instruments Ltd, Mumbai, India). The sample was analyzed at regular intervals (0, 1, 2, 3 and 6 months) for appearance, pH, moisture content, microbiological studies and FTIR as per stability protocol[24].

Preparation of matrix tablets of diclofenac sodium

Diclofenac sodium matrix tablets were prepared by mixing the ingredients previously passed through sieve No. 100 sufficient for a batch of 200 tablets weighed according to the formulas shown in **Table 1**. The drug was geometrically mixed with polymer (AHG) until a homogenous blend was achieved. 5% w/v of AHG dispersion was used as granulating agent for preparation of AHG matrix tablets respectively. Granules were prepared by passing mass initially through sieve No. 12 (nominal mesh aperture size 1.4 mm and approximate %sieving area 44) and dried at 50°C in hot air oven. Dried granules passed through sieve No. 22 (nominal mesh aperture size 710 µm and approximate %sieving area 37). Hence, the final blend was compressed into tablets on a 16-station rotary punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India) using 10 mm round flat punches with compression force sufficient to obtain hardness of 4 to 5 kg/cm².

Table 1: Formulas of AHG matrix tablets of diclofenac sodium prepared with different channelling agents.

Ingredients (mg per tablet)	Formula code							
	AHD1	AHD2	AHD3	AHD4	AHD5	AHD6	AHD7	AHD8
Diclofenac sodium	100	100	100	100	100	100	100	100
AHG	20	20	20	20	20	20	20	20
Lactose	-	-	-	10	15	20	25	30
DCP	10	-	-	-	-	-	-	-
MCC	-	10	-	-	-	-	-	-
Mannitol	-	-	10	-	-	-	-	-
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Tablet weight (mg)	135	135	135	135	140	145	150	155

Drug-excipient compatibility studies

All the formulations clearly showed retention of characteristic peaks of the drug and hence there was no chemical interaction or complexation occurred between diclofenac sodium and polymers.

Evaluation of prepared matrix tablets

Uniformity of weight

According to Indian Pharmacopoeia, twenty tablets were selected at random and average weight was determined. Tablets were weighted individually and the percentage deviation of its weight from the average weight was determined. Prepared tablets complies the test if not more than two of the individual weights deviated from the average weight by more than the 7.5 percentage and none deviate more than twice the percentage 7.5 for tablets weighing in the range of >80-<250 mg.

Hardness and Thickness

Five tablets were selected at random and the hardness of each tablet was measured using Monsanto hardness tester. Five tablets were selected at random and thickness of the each tablet was evaluated by Vernier callipers. Mean and standard deviation was calculated.

Friability

The friability test was carried out in Roche friabilator. The tablets equivalent to a weight 6.5 g were selected randomly and initial weight (w_0) was noted and put in a rotating drum. Then, they were subjected to 100 falls of 6 inches height (25 rpm for four minutes). After completion of rotations, the tablets were dedusted and weighed them accurately (w). The test was run only once unless the results are difficult to interpret or if the weight loss was greater, in that case the test was repeated twice and the mean of the three tests was determined. The percent loss in weight should not be greater than 1.0% is acceptable. The percent loss in weight or friability (f) was calculated by:

$$f = \left(1 - \frac{w}{w_0}\right) \times 100 \quad \text{Eq.17}$$

Estimation of drug content

From each batch, 10 tablets were randomly collected, powdered in a glass mortar individually and the powder equivalent to 50 mg of diclofenac sodium was placed in a 50 ml volumetric flask. The drug was extracted with 25 ml of methanol with vigorous shaking on a mechanical shaker for 1 hour and filtered into a 50 ml volumetric flask through 0.45 μ m Millipore nylon filter disc and the filtrate was made up to mark with methanol. Further appropriate dilutions were made with pH 6.8 buffer and the absorbance was measured at 276 nm against blank prepared under same conditions without drug using UV visible spectrophotometer.

In vitro dissolution studies

Dissolution test was carried out using USP XXIV dissolution test apparatus (M/s. Lab India, Model: DISSO 2000) employing the paddle stirrer (Apparatus II) and the stirring rate was 50 rpm. 0.1N HCl (pH 1.2) was for the first 2 h and pH 6.8 phosphate buffer was used for remaining 24 hrs as dissolution medium (900 ml) and was maintained at temperature $37 \pm 0.5^\circ\text{C}$. Samples of 5 ml were withdrawn at predetermined time intervals with syringe fitted with a pre-filter and immediately replaced with 5 ml of fresh medium maintained at temperature $37 \pm 0.5^\circ\text{C}$. The collected samples were diluted suitably with dissolution medium, wherever necessary and were analyzed for the diclofenac sodium content spectrophotometric method at 276 nm. Each dissolution study was performed for three times. The mean of percentage of diclofenac released from tablets and standard deviation were calculated.

Drug release kinetics of the matrix tablets

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process. The dissolution data is fitted to popular release models such as zero order, first order, diffusion and erosion. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi and erosion equations.

RESULTS AND DISCUSSION

Isolation of gum

The %yield was calculated as 34.38%. The % yield, depends on solvent used for isolation.

Organoleptic evaluation and solubility behaviour

Organoleptic evaluations such as colour, odour and taste were carried by sensory organs. When gum was precipitated with acetone it was white in colour and turned to light brownish colourup on drying. AHG powder does not have characteristic taste and odour, so it can be used in pharmaceutical formulations. Low concentration (1% w/v) of AHG in water formed colloidal dispersion and at higher concentration (20% w/v) formed thick viscous mucilage. It was insoluble in organic solvents like methanol, ethanol, acetone and ether. The solubility behaviour of any excipient is an important parameter to determine its suitability in different formulations.

Determination of purity and identification tests for gums

The specifications of identification and purity for food additives or formulations established by AOAC and FAO are intended to ensure the safety to all. These specific reactions will help in characterizing natural product. To one gram of AHG powder was added in 5 ml of reagent approximately. The results indicate the presence of polysaccharide. Corallin soda test: In freshly prepared corallin solution (5 g of corallin in 100 ml of ethyl alcohol) the sample was mounted, covered with a cover slip and after a few seconds it was irrigated with 25% sodium carbonate solution³⁰. Pytochemical tests were carried on AHG, confirmed the absence of alkaloids, glycosides, steroids and tannins. When treated with ruthenium red, it showed red colour confirming the isolated product is gum. A violet ring was formed at the junction of two liquids on reaction with Molisch reagent indicating the presence of carbohydrates. When AHG treated with ninhydrin reagent did not give purple colouration indicating the absence of amino acids.

Determination of particle size distribution

When observed under a microscope, AHG powder was found to be in the form of irregular shape, which were in the range of 16-160 μ m and average particle size was determined as 44.56 μ m.

The true density of AHG powder was 2.176 g/cc. The bulk and tapped density were found to be 0.543 g/cc and 0.594g/cc respectively. Compressibility index values $\leq 10\%$ indicates excellent flow properties and desirable packing characteristics. Compressibility index of AHG powder was 8.59%, which indicated that the powder has excellent flow property. The Hausner ratio value in between 1.00-1.11 indicates excellent flow property of the powder.

The Hausner ratio for AHG found to be 1.09 which indicated that the powder has excellent flow. The angle of repose values in the range of 25-30° indicates excellent flow property of the powder. The angle of repose of the AHG powder was found to be 25.12°. The low value of angle of repose indicated excellent flow property of AHG powder.

Determination of loss on drying and ash values

The loss on drying was determined for AHG and it was 7.5%. The acid soluble ash and water soluble ashes were 0.57% and 2.96% respectively. The total ash content was designed to measure the total amount of residual material remaining after ignition. Ash values reflect the level of adulteration. The low ash values indicated low levels of contamination during gathering and handling of the exudates.

Determination of melting point

AHG powder started charring above 300°C temperature without melting.

Determination of moisture content

Karl Fisher reagent was used to determine the moisture content and it was 5.48% for AHG. Pharmacopoeial limit for moisture contents of natural gums has been set at ≤15.0. The moisture content of AHG was low, suggesting its suitability in formulations containing moisture sensitive drugs and allow free flowing of the powder. Moisture content influences the tableting and stability properties of formulations. The presence of moisture not only promotes hydrolysis, but also favours microbial growth and subsequent decomposition of the material, thereby affecting the shelf life of the formulations.

Determination of pH

The pH of 1% w/v AHG solution was found to be 4.5-4.7 at temperature 25-27°C indicating the gum is slightly acidic in nature.

Determination of swelling index and water retention capacity

Swelling index of AHG (10% w/v) was found to be 180%. The swelling ability of any polysaccharide depends upon its water retention capacity or water absorption capacity. The water absorption capacity of AHG was found to be 4mL.

Determination of volatile acidity

The volatile acidity was estimated as 2.42% in 1 g of sample. Acidic nature of AHG may be due to the presence of acetyl groups, which was confirmed by the volatile acidity.

Table 2: Organoleptic evaluation and solubility behaviour of AHG powder.

Parameter	Observation
Colour	Slightly brown
Odour	Odourless
Taste	No characteristic taste
Solubility in water	Soluble
Solubility in solvents (methanol, ethanol, acetone, ether)	Insoluble

Table 3: Identification tests for food hydrocolloids as per AOAC, 1984.

S. No.	Reagent	Results
1.	GP-I Reagent (iodine-potassium iodine in zinc chloride solution)	Negative
2.	GP-II Reagent (alcoholic iodine solution)	Negative
3.	GP-III Reagent (ruthenium red solution)	Positive, stained pink
Confirmatory tests:		
4.	HCl test	Yellow
5.	Aq. methylene blue stain	Lightly stained
6.	GP-IV reagent	Dark red

Group (GP) – I reagent: 2.6 g of iodine, 3 g of potassium iodide in 5% zinc chloride solution

Group (GP) – II reagent: 3% iodine in alcohol

Group (GP) – III reagent: 8 g of ruthenium red in 10 mL of solution of lead acetate

Group (GP) – IV reagent: concentrated sulphuric acid

Table 4: Identification tests as recommended by FAO, 1991.

S. No.	Reagent	Results
1.	Swelling by ethanol solution	Negative
2.	Colour reaction with conc. HCl	Yellow
3.	Colour reaction with 5N NaOH	Yellow
Confirmatory tests:		
4.	Corallin soda test	Stained pink

Table 5: Determination of purity of gum.

S. No.	Tests	Results
1.	Test for carbohydrates: Molisch test	Present
2.	Test for gums: Ruthenium red	Present
3.	Test for proteins Ninhydrin test	Absent
4.	Test for steroids: Salkowski test, Libermann-burchard test	Absent
5.	Test for glycosides: Keller-Killaini test	Absent
6.	Test for alkaloids: Mayer's test, Hager's test, Dragendroff's test	Absent
7.	Test for flavonoids test: Shinoda test, Zinc/HCl reduction test	Absent
8.	Test for resins: Acetic anhydride and conc H ₂ SO ₄ , boiling with ethanol and precipitated with water	Absent
9.	Test for phenolic nucleus and Tannins: Ferric chloride test, Gelatin test	Absent

Table 6: Physico-chemical properties of AHG.

Property	Mean $\pm$ s.d., n=3
True density (g/cc) at 25°C	2.173 $\pm$ 0.04
Bulk density (g/cc)	0.543 $\pm$ 0.02
Bulkiness (cc/g)	1.845 $\pm$ 0.05
Tapped density (g/cc)	0.594 $\pm$ 0.08
Compressibility index (%)	8.59 $\pm$ 0.85
Hausner index	1.09 $\pm$ 0.01
Angle of repose(°)	25.12 $\pm$ 1.24
Loss on drying (%)	7.5 $\pm$ 0.8
Total ash (%)	12.9 $\pm$ 0.51
Acid insoluble ash (%)	0.57 $\pm$ 0.02
Water soluble ash (%)	2.96 $\pm$ 0.15
Melting point (°C)	Charring above 300
Moisture content (%)	5.48 $\pm$ 0.07
pH at 25-27°C	4.5 – 4.7
Swelling index (%)	180 $\pm$ 1.98
Water retention capacity (mL)	4 $\pm$ 1.46
Volatile acidity (%)	2.42 $\pm$ 1.24

All values(mean $\pm$ s.d., n=3).

Table 7: Analysis of rheological properties of different concentrations of AHG.

	Concentration of AHG (%)		
	3	5	7
Bingham			
η (cP)	2.03	12.9	70.5
τ_0 (dynes/cm ²)	23.1	32.5	53.0
Cof (%)	87.5	87.0	92.7
Casson			
η (cP)	0.89	3.07	31.8
τ_0 (dynes/cm ²)	15.4	24.5	50.3
Cof (%)	95.3	87.6	93.0
Power law			
CI (cP)	667.7	1695	4557
FI, n	0.26	0.21	0.07
Cof (%)	91.2	97.7	93.4
NCA/CMA casson			
η (cP)	0.89	3.07	4.03
τ_0 (dynes/cm ²)	14.5	23.2	47.6
Cof (%)	95.3	97.6	93.0
IPC Paste			
10 rpm.v (cP)	78.9	341.9	408.1
S.S	0.74	0.79	0.97
Cof (%)	91.2	97.7	93.4

η – plastic viscosity, τ_0 – yield stress, Cof – Confidence of fit, CI – consistency index, FI – flow index, 10 rpm.v – 10 rpm viscosity and S.S – shear sensitivity.

Table 8 : Tableting characteristics of diclofenac matrix tablets.

Formulation	*Uniformity of weight (mg)	Hardness (kg/cm ²)	*Thickness (mm)	Friability (%)	*Drug content (%)
AHD1	135.84±1.1037	4 – 5	3.52±0.13	0.28	99.58±0.71
AHD2	135.48±0.4786	4 – 5	3.51±0.08	0.31	99.34±0.42
AHD3	136.39±1.1379	4 – 5	3.50±0.14	0.45	99.68±0.83
AHD4	134.91±0.9067	4 – 5	3.49±0.09	0.36	100.26±0.54
AHD5	140.05±0.4774	4 – 5	3.52±0.11	0.27	99.79±0.56
AHD6	145.36±0.9562	4 – 5	3.56±0.06	0.42	99.81±0.64
AHD7	150.74±1.3000	4 – 5	3.59±0.07	0.34	99.72±0.93
AHD8	155.53±0.3215	4 – 5	3.63±0.12	0.35	100.42±0.36

*All values(mean±s.d., n=3).

Table 9: Microbiological studies of AHG.

Parameter	Fresh Sample	Specified microbial limit as per I.P.
Total aerobic microbial count	22 CFU/g	NMT 100 CFU/g
Total fungal count	11 CFU/g	NMT 100 CFU/g
Pathogenic microorganisms		
<i>S. aureous</i>	Absent/g	Should be absent/g
<i>P. aeruginosa</i>	Absent/g	Should be absent/g
<i>E. coli</i>	Absent/g	Should be absent/g
<i>Salmonella</i> sp.	Absent/g	Should be absent/g

Scanning electron microscopic studies on gum

The SEM photograph of AHG is shown at 500 μ m resolution. SEM photographs also revealed that the different sizes of particles with irregular shape.

Fourier transform infrared spectroscopy on gum

The FTIR spectra of the AHG has broad absorption band of -OH stretching at 3420.45 cm^{-1} , asymmetric stretching of -CH at 2969.08 cm^{-1} , aldehyde C=O stretching in between 1734.40 cm^{-1} - 1717.49 cm^{-1} , -CO stretching in between 1699.44 cm^{-1} - 1685.10 cm^{-1} , -C=C- stretch in between 1625.79 cm^{-1} - 1560.12 cm^{-1} , -CH₃ stretching at 1456.84 cm^{-1} and -CH₂ stretching at 1475.25 cm^{-1} . The characteristic peaks observed in between 893.31 cm^{-1} - 868.83 cm^{-1} and 766.74 cm^{-1} - 746.26 cm^{-1} were assigned to the pyranose ring of polysaccharide.

Differential scanning calorimetry on gum

DSC measures the exothermic or endothermic processes resulting from physical or chemical changes within a sample as a function of temperature. Broad, asymmetric curve suggests impurities or more than one thermal process. The major intense peak recorded in the DSC thermogram was endothermic transition at 133°C followed by weaker exotherms and endothermic peak at 334°C . The continuous (broad) endothermic transition was the glass transition temperature. A small endothermic peak at 334°C was observed, at this AHG gets charred without melting because the same observation was made in melting point determination of AHG powder with melting point apparatus. DSC thermogram and melting point value of AHG indicated the stability of the gum up to 300°C explained the thermal stability of the gum.

Powder X-Ray diffraction study

In PXRD of AHG no characteristic peaks were observed in the spectrum, indicating that the AHG was completely amorphous in nature. The compounds can be arranged in a regular repeating three-dimensional array (a crystal lattice), which results in crystalline solid or more or less randomly to produce an amorphous solid. Solids are characterised by an extended three-dimensional arrangement of atoms, ions or molecules in which the components are generally locked into their positions. Crystalline solids have well defined edges and faces, diffract X-rays and tend to have sharp melting points. In contrast, amorphous solids have irregular or curved surfaces and do not give well-resolved X-ray diffraction patterns.

Determination of rheological properties

To determine the rheological properties of AHG, different concentrations were prepared and evaluated by using Brookfield cone and plate viscometer. As the concentration of AHG was increased the shear rate necessity for the flow also increased. The AHG concentrations were subjected for increase in the shear stress at constant intervals and again it was reduced, after a particular maximum value. In Newtonian flow shear stress is proportional to shear rate (a linear relationship). Non-Newtonian fluids will exhibit a nonlinear stress/rate relationship. The Newtonian equation for viscosity has been modified many times to attempt to characterize non-Newtonian behaviour. Some of the widely used equations are summarized below.

$$\text{Bingham equation: } \tau = \tau_0 + \eta D \quad \text{Eq. 18}$$

$$\text{Casson : } \sqrt{\tau} = \sqrt{\tau_0} + \sqrt{\eta D} \quad \text{Eq. 19}$$

$$\text{Power law: } \tau = k D^p \quad \text{Eq. 20}$$

$$\text{NCA/CMA Casson: } (1+a)\sqrt{\tau} = 2\sqrt{\tau_0} + (1+a)\sqrt{\eta D} \quad \text{Eq. 21}$$

$$\text{IPC Paste: } \eta = k R^n \quad \text{Eq. 22}$$

Whereas τ denotes the shear stress, τ_0 denote the yield stress, D denotes the shear rate, η denotes the plastic viscosity, k denotes the consistency index, p denotes the flow index, n denotes the shear sensitivity, a denotes the gap ratio and R denotes rotations per minute. A power law index of $p = 1$ represents Newtonian flow behaviour, $p < 1$ represents shear thinning (pseudoplastic) behaviour and $p > 1$ represents shear thickening (dilatants) behaviour. Rheogram was plotted between shear rate and shear stress and it was observed that there was no difference between the upward and downward curve indicating the absence of thixotropy. The viscosity data was analyzed by using Bingham, Casson, Power law, NCA/CMA Casson and IPC Paste equations. The analysis of the AHG at different concentrations (3, 5 and 7%) obeys Power law with %confidence of fit values ranging 91-98. The AHG was exhibiting non-Newtonian plastic flow which was indication for the gelling behaviour and confirmed its suitability in the development of controlled release delivery systems.

Microbiological studies on isolated gum

Microbiological studies of AHG powder was carried out for samples immediately after collection and processing of the gum powder. Results proved that the AHG did not support bacterial and fungal growth. AHG did not contain any pathogenic microorganisms like *E.coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Salmonella* sp. Microbial quality of AHG was satisfactory and met the Indian Pharmacopoeia requirements of microbiological quality of pharmaceutical preparations.

Stability studies on isolated gum

The sample was stored at different temperatures and humidity ($30\pm 2^\circ\text{C}/65\pm 5\%\text{RH}$ and $40\pm 2^\circ\text{C}/75\pm 5\%\text{RH}$) according to the ICH guidelines. The samples were withdrawn in regular intervals (1, 2, 3 and 6 months) and physico-chemical properties like colour, moisture content, pH and viscosity were studied. The total aerobic microbial and fungal count of AHG was done according to the procedure for six months old sample. The FTIR spectra of six months old sample showed similar peaks of AHG. There was no significant difference was observed in initial and 6 months old sample in physico-chemical, microbiological and FTIR studies indicating the polymer was stable according to ICH guidelines. Matrix tablets were formulated according to formulae and evaluated the suitability for controlled release systems for 24 h. Diclofenac sodium matrix tablets were prepared by AHG by wet granulation method. The angle of repose values of granules were found to be AHG which indicated that all the granules were free flowing and good enough for punching. The tablets were compressed using 8 mm punches depending on the total weight of the tablet. The prepared tablets were evaluated for their tableting characters and drug release.

Uniformity of weight, hardness, thickness, friability and drug content

The results of uniformity of weight, hardness, thickness, friability and drug content for all formulations were calculated. The weight variation of the tablets was complied with the compendia standards for uniformity of weight. The hardness for all the formulations found to be in the range of 4-5 kg/cm². The friability values of all formulations were found to be less than 1%. The drug content of each individual preparation was found to be within the specified limits of 90 to 110% of the stated amount of diclofenac sodium, indicating that the test complies with the official compendia test for tablets as per IP.

In vitro dissolution studies

Diclofenac sodium is more soluble in the alkaline media and it is slightly soluble in acid media. Therefore, in pH 1.2 percent diclofenac sodium released from the matrix tablets was less than 7% due to its low solubility in acidic media. Even though there was no significant difference in the release among the channelling agents, there was a recognizable enhanced release with lactose in order of lactose > MCC > mannitol > DCP. Among them lactose was selected and different concentrations lactose was used at 1.5:2, 2:2, 2.5:2 and 3:2 ratios (lactose-AHG) in formulations AHD5, AHD6, AHD7 and AHD8 respectively. Lactose is water soluble and enhances drug release by forming pores for the entry of solvent molecules thereby increasing the porosity of the matrix. It was observed that as the concentration of the lactose was increasing the gradual drug release also increasing. The formulation AHD7 showed 100.94% drug release in 24 h. Formulations AHD5, AHD7 and AHD8 showed drug release 98.2, 99.48 and 99.52% drug release in 24 h respectively. This may be due to the presence of high concentration of lactose, which dissolved in dissolution fluid and for channels in the matrix for faster drug release for poorly soluble drugs.

Drug release kinetics

The values are higher than first order release suggests the zero order drug release kinetics. Tablets prepared with AHG matrix tablets showed zero order drug release.

Table 10: Cumulative percent of drug released from matrix tablets diclofenac sodium containing different channelling agents (AHD1 to AHD4).

	Time (hrs)	Cumulative percent (mean $\pm$ s.d., n=3) diclofenac sodium released			
		AHD1	AHD2	AHD3	AHD4
pH 1.2	0.5	0.85 $\pm$ 0.24	0.93 $\pm$ 0.36	0.89 $\pm$ 0.23	1.85 $\pm$ 0.33
	1	1.35 $\pm$ 0.15	1.67 $\pm$ 0.24	1.53 $\pm$ 0.11	2.74 $\pm$ 0.23
	1.5	1.99 $\pm$ 0.29	2.31 $\pm$ 0.73	2.14 $\pm$ 0.17	3.32 $\pm$ 0.14
	2	2.24 $\pm$ 0.63	2.82 $\pm$ 0.13	2.32 $\pm$ 0.93	5.06 $\pm$ 0.29
pH 6.8	3	16.53 $\pm$ 1.29	17.36 $\pm$ 0.89	16.78 $\pm$ 1.20	20.93 $\pm$ 1.46
	4	22.07 $\pm$ 1.25	26.87 $\pm$ 0.97	24.15 $\pm$ 1.14	27.04 $\pm$ 0.57
	6	38.05 $\pm$ 1.71	39.11 $\pm$ 1.15	38.75 $\pm$ 1.52	39.50 $\pm$ 1.86
	8	46.57 $\pm$ 0.81	48.18 $\pm$ 1.64	47.64 $\pm$ 1.72	49.42 $\pm$ 1.38
	10	55.74 $\pm$ 1.27	58.35 $\pm$ 1.02	56.34 $\pm$ 1.05	57.18 $\pm$ 0.78
	12	63.96 $\pm$ 1.70	67.76 $\pm$ 0.98	65.80 $\pm$ 1.68	68.66 $\pm$ 1.25
	16	77.35 $\pm$ 1.75	79.71 $\pm$ 1.34	78.87 $\pm$ 2.07	78.24 $\pm$ 1.40
	20	89.86 $\pm$ 1.96	92.95 $\pm$ 2.14	91.42 $\pm$ 0.93	92.48 $\pm$ 1.14
	24	94.57 $\pm$ 1.32	95.87 $\pm$ 1.33	95.46 $\pm$ 1.40	96.87 $\pm$ 1.06

All values(mean $\pm$ s.d., n=3).

Table 11: Cumulative percent of drug released from matrix tablets diclofenac sodium containing different concentrations of lactose (AHD5to AHD8).

	Time (hrs)	Cumulative percent (mean±s.d., n=3) diclofenac sodium released			
		AHD5	AHD6	AHD7	AHD8
pH 1.2	0.5	2.54±0.25	2.68±0.22	2.92±0.52	3.06±0.47
	1	3.14±0.43	3.71±0.50	4.59±0.25	4.89±0.25
	1.5	4.26±0.28	5.05±0.64	5.44±0.13	5.65±0.86
	2	4.59±0.26	5.34±0.29	6.25±0.18	6.33±0.26
pH 6.8	3	24.3±1.01	25.67±1.52	25.49±1.60	28.21±1.44
	4	30.14±0.97	33.69±1.39	35.59±1.29	44.17±1.51
	6	44.77±1.83	46.69±1.43	49.85±1.36	61.6±1.84
	8	53.83±0.84	57.47±1.15	59.09±1.63	69.19±1.54
	10	61.61±0.82	64.33±0.66	68.46±1.32	81.14±1.35
	12	69.14±1.37	74.68±1.96	80.5±1.68	93.98±0.71
	16	80.54±1.17	85.41±1.65	94.17±0.89	99.52±0.75
	20	95.25±1.27	97.46±0.73	100.48±1.21	
	24	98.2±0.92	100.94±1.11		

All values(mean±s.d., n=3).

Table 12: Correlation coefficients (r) values of drug release kinetics of matrix tablets of diclofenac sodium.

Formulation	Zero order		First order	
	k ₀ (mg.hr ⁻¹)	r	k ₁ (hr ⁻¹)	R
AHD1	4.586	0.9757	0.094	0.9747
AHD2	4.739	0.9711	0.106	0.9664
AHD3	4.665	0.9742	0.101	0.9711
AHD4	4.752	0.9706	0.104	0.9695
AHD5	4.918	0.9781	0.128	0.9561
AHD6	5.132	0.9513	0.138	0.9482
AHD7	5.969	0.9649	0.188	0.9225
AHD8	7.506	0.9633	0.244	0.9223

Table 13: Correlation coefficients (r) values of drug release mechanism of matrix tablets of diclofenac sodium.

Formulation	Higuchi r	Erosion r
AHD1	0.9375	0.9920
AHD2	0.9407	0.9914
AHD3	0.9381	0.9915
AHD4	0.9482	0.9925
AHD5	0.9545	0.9899
AHD6	0.9556	0.9905
AHD7	0.9466	0.9889
AHD8	0.9322	0.9859

Drug release mechanism

The drug release mechanism was determined by fitting dissolution data to the linear regression plots for dissolution profiles. This release mechanism can be explained as a result of the hydration of the polymer molecule on the surface of the tablet, due to low porosity restrict the penetration water in to the centre and slowly drug release from the matrix surface. The tablet did not disintegrate during the course of dissolution but it decreased its size at the end of the dissolution. Another factor that may be responsible for the controlled drug release from dosage form is the poor solubility nature of diclofenac sodium.

Table 14: Microbiological studies of AHG for six months old sample.

Parameter	Six months old sample	Specified microbial limit as per I.P.
Total aerobic microbial count	25 CFU/g	NMT 100 CFU/g
Total fungal count	14 CFU/g	NMT 100 CFU/g
Pathogenic microorganisms		
<i>S. aureus</i>	Absent/g	Should be absent/g
<i>P. aeruginosa</i>	Absent/g	Should be absent/g
<i>E. coli</i>	Absent/g	Should be absent/g
<i>Salmonella</i> sp.	Absent/g	Should be absent/g

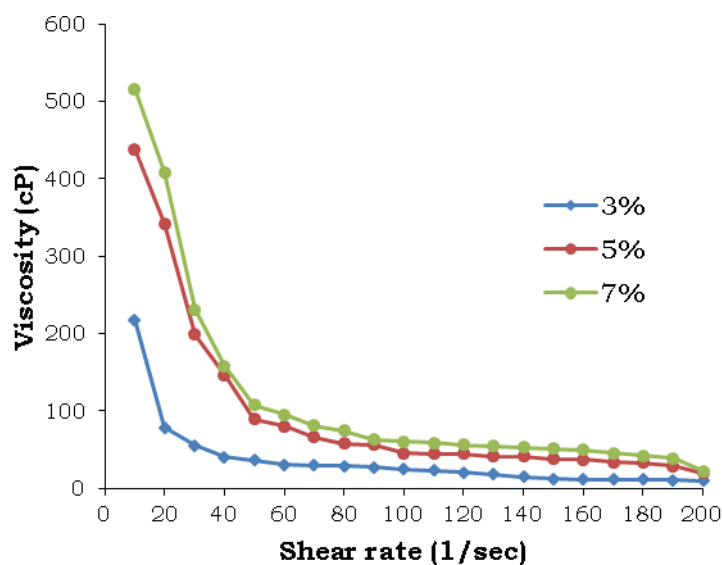


Fig. 1: Shear rate vs. viscosity profiles of 3, 5 and 7% (w/v) AHG.

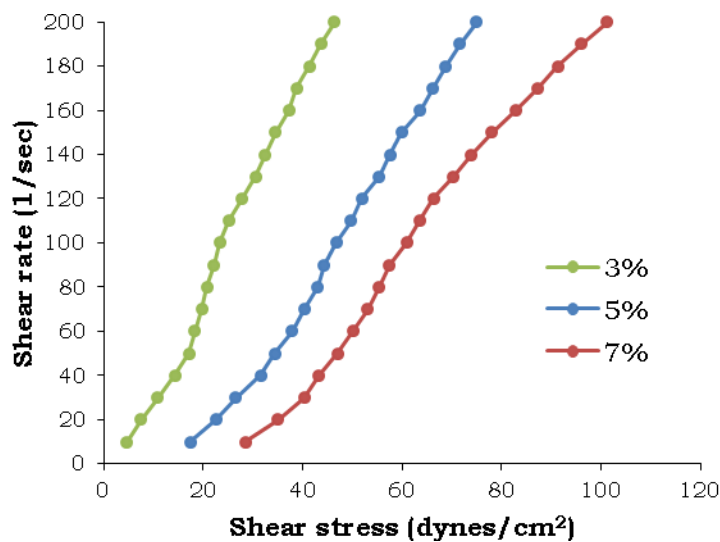


Fig. 2: Shear stress vs. shear rate profiles of 3, 5 and 7% (w/v) AHG.

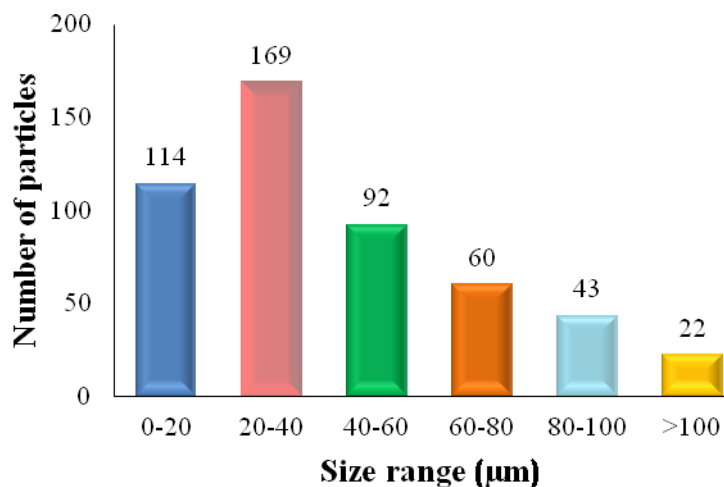
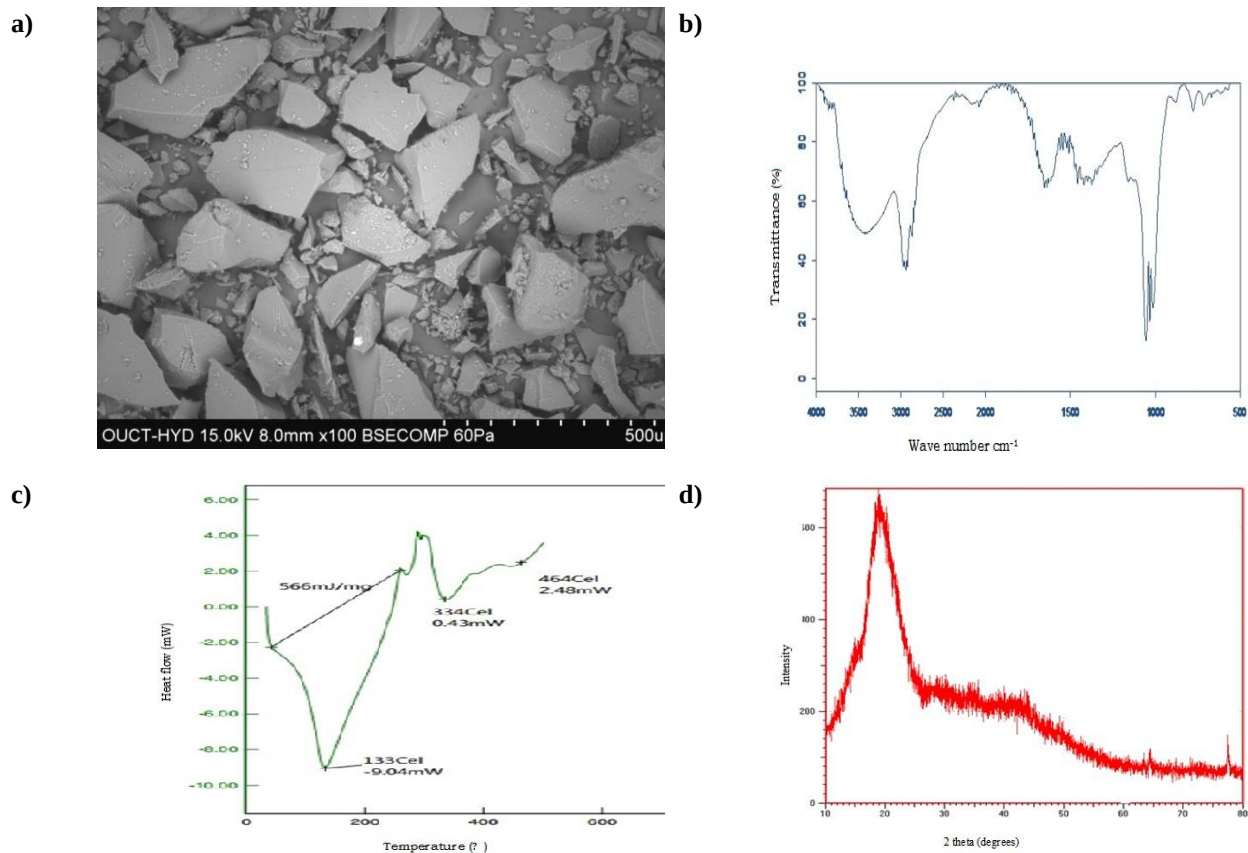


Fig. 3: Microscopic particle size distribution of AHG powder Determination of powder properties.



e)

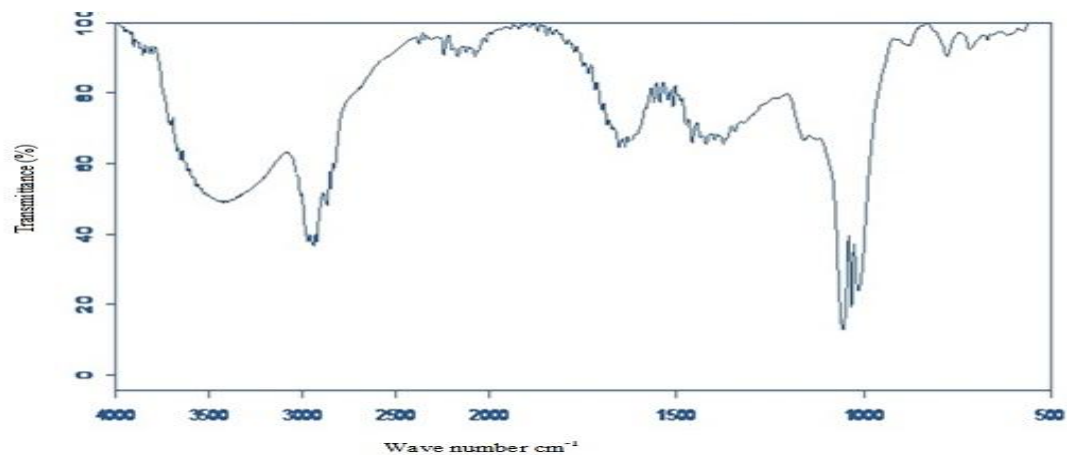


Fig. 4. a) SEM photographs of AHG powder; b) FTIR spectra of the AHG sample; c) DSC spectra of the AHG sample; d) XRD spectra of the AHG sample; e) FTIR spectra of the six months old AHG sample

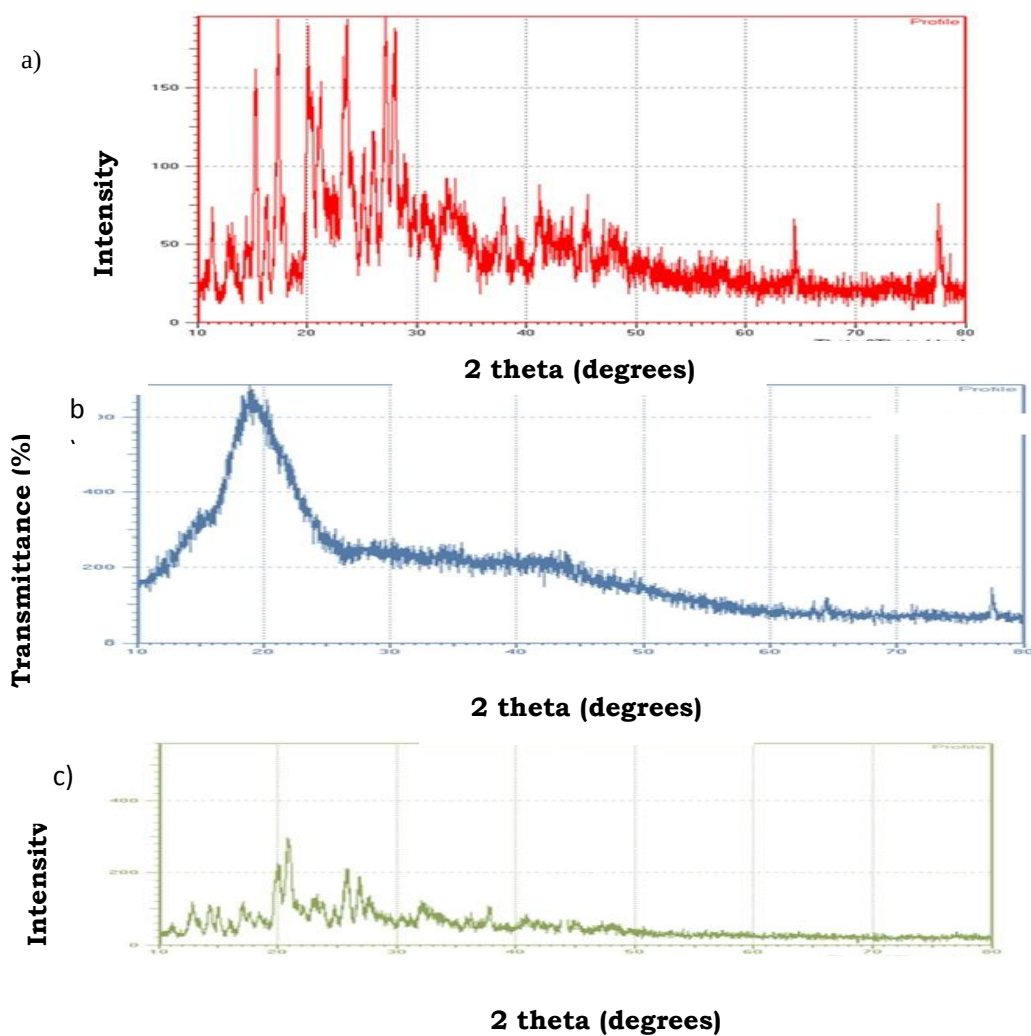
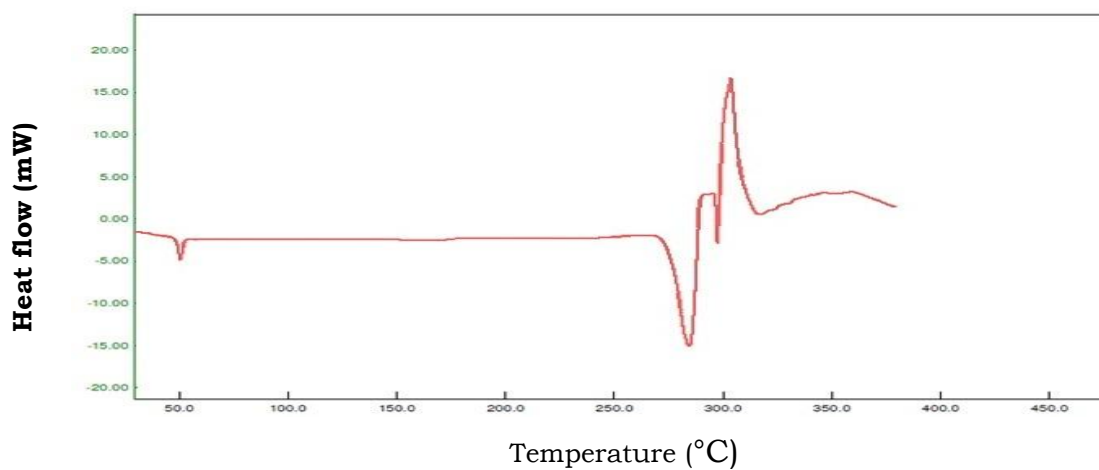
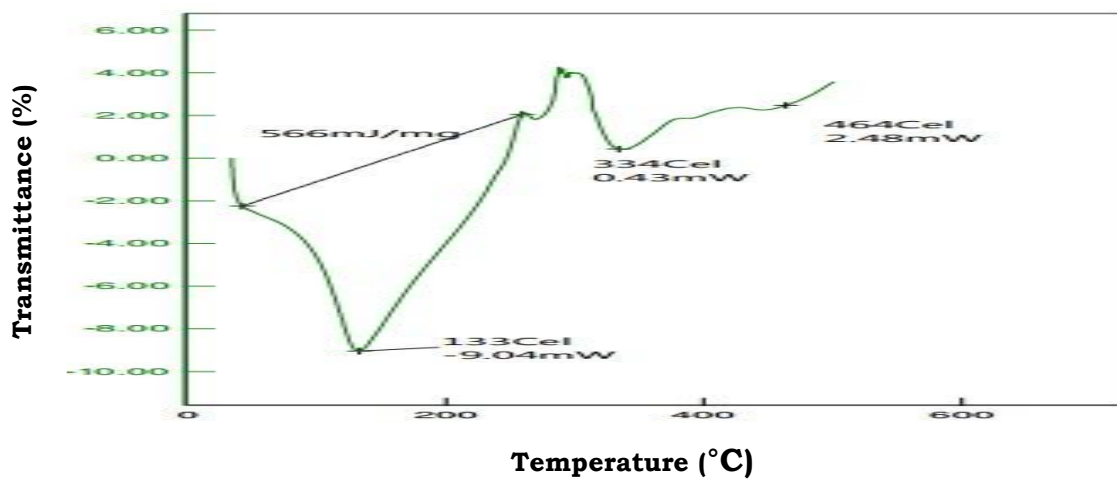


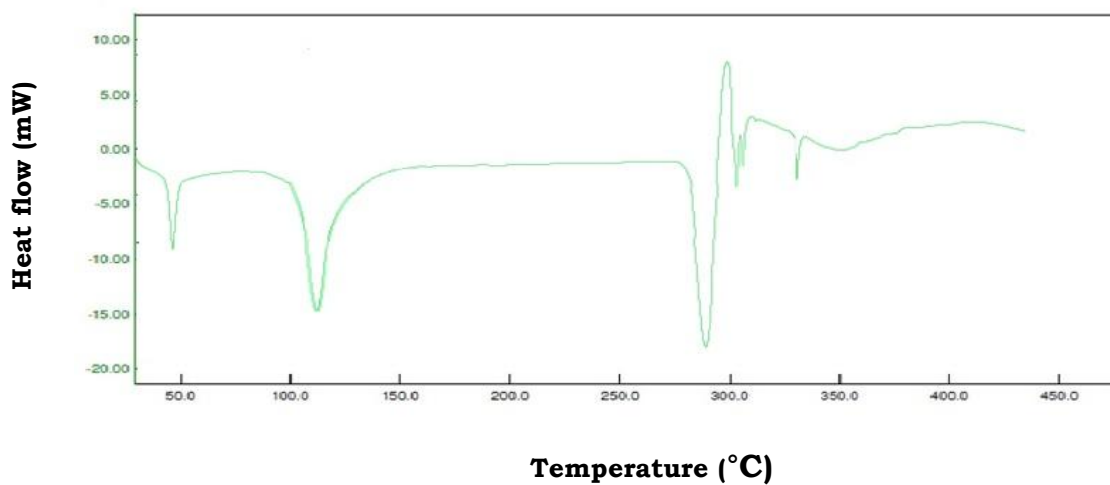
Fig. 5: XRD patterns of (a) diclofenac sodium (b) AHG (c) formulation AHD8.



(a)

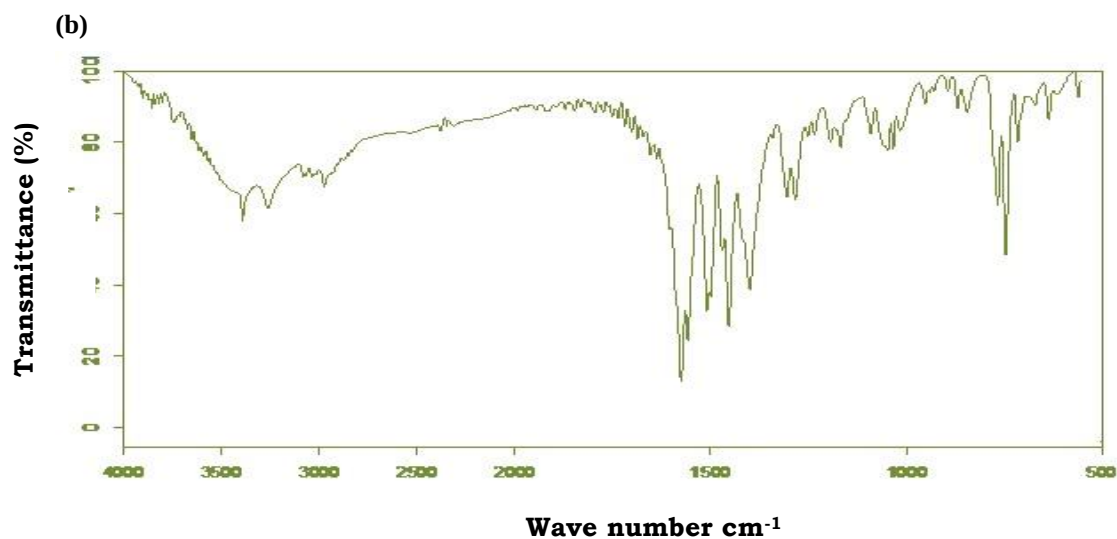
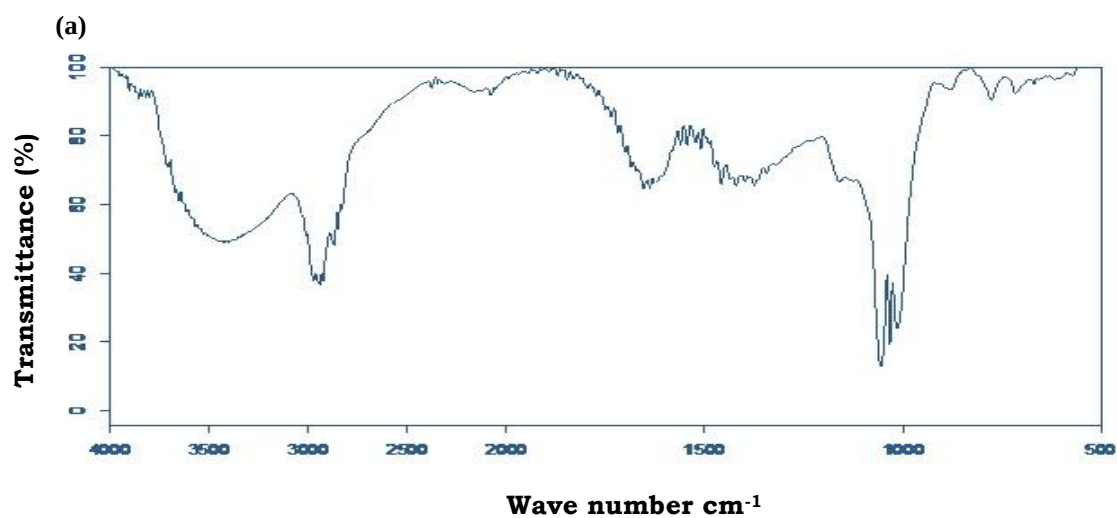
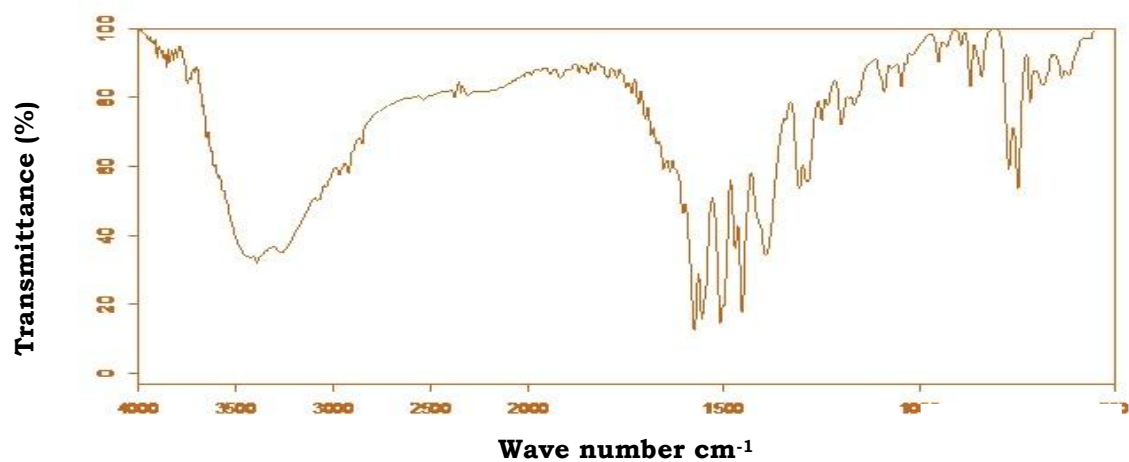


(b)



(c)

Fig. 6: DSC spectra of (a) diclofenac sodium (b) AHG (c) formulation AHD8.



(c)

Fig. 7: FTIR spectra of (a) diclofenac sodium (b) AHG (c) formulation AHD8.

Study protocol

Name of the material : AHG powder
 Date of starting : 07-12-2012
 Quantity loading : 20 g sample
 Quantity sampled : 2 g appox.

Table 15: Stability protocol and stability data of AHG powder

Test condition		Tests carried out							
Date	Period (Months)	Physical observation		Moisture content (%)		pH of 1% mucilage		Viscosity ^a (cP)	
		1	2	1	2	1	2	1	2
07-01-2012	Initial	Light brown colour		5.48		4.6		78.88	
07-02-2012	1	No change	No change	5.51	5.47	4.6	4.7	78.6	78.5
07-03-2012	2	No change	No change	5.55	5.56	4.5	4.6	78.6	78.4
07-04-2012	3	No change	No change	5.60	5.63	4.7	4.8	78.5	78.3
07-07-2012	6	No change	No change	5.61	5.67	4.8	4.8	78.4	78.3

1. 30±2°C/65±5%RH 2. 40±2°C/75±5%RH a. 3% w/v AHG solution at 10 rpm.

CONCLUSION

Chemical tests of AHG indicated the presence of polysaccharide. The powder characteristics of the AHG showed good flowing properties and other physico-chemical properties were suitable to be used as excipient in the formulation. FTIR, DSC and XRD studies of AHG were carried for characterization of the gum. The bacterial and fungal counts were within limits and pathogenic microorganisms were absent in AHG. The stability studies showed no significant differences between the initial and 6 months old sample. Rheological properties of AHG suggested that it could be used as an excipient in controlled release system in particular to hydrophilic matrix tablet formulations. Matrix tablets of AHG were prepared at different concentrations. All the formulations showed good tableting characteristics. AHG was able to control the diclofenac sodium release from matrix tablets for extended period of time. The drug release was enhanced by using channelling agents, in which lactose showed enhanced drug release than the other diluents like MCC, mannitol and DCP. Drug release kinetics and drug release mechanism were evaluated. FTIR, DSC and XRD studies indicated that there was no interaction between drug and polymers.

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Ethical Issues:

Not applicable

Conflict of Interest:

The authors report no conflicts of interest in this research work.

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