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Original Article

Microwave-Assisted Synthesis and Characterization of N-Vinyl-2-Pyrrolidone Grafted Almond Gum: A Natural Dietary Polysaccharide for Controlled Release of Diclofenac Sodium

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ABSTRACT

Background: Gums occurring in nature are widely used in pharmaceuticals for their unique properties and diversified applications. The natural gums are almost safely consumed as food additives as well as drug carriers, almond gum commonly known as 'Badam' gum. It is inexpensive and endowed with a variety of beneficial traits such as antibacterial, antioxidant and emulsifier properties. Polymers are important in every individual's life, advancement in polymer sciences are helpful to improve their use, modifications and grafting alteration of natural gums with polymers has gained more values. N-Vinyl-2-Pyrrolidone (NVP) is the biocompatible, hydrophilic, non-ionic and non-toxic monomer. Due to its great affinity to numerous polymers it has diversified uses in the fields of cosmetics, medicine, food tech. **Objectives:** However, use of polymers is associated with problems; to overcome all the drawbacks and to assess the hidden benefits of them, here a research experiment is carried out to graft this almond gum with NVP for assessment of its activity as release modifier. **Materials and Methods:** The grafting is done with the help of microwave irradiation technique through the mechanism of free radical generation. Ceric ammonium nitrate was used as free radical inducer. Grafted gum was characterized by FTIR, DSC, SEM, XRD, EDX and Swelling study. Further the grafted gum was subjected to mucoadhesion study by preparing the tablet with diclofenac as model drug. Tablet was evaluated for Precompression and post compression parameters and finally the *in vitro* release study was performed on it. **Results:** Surprisingly the almond gum had shown controlled release activity on release of diclofenac from tablet with 98.49% steady release over the 12 hr. **Conclusion:** These findings opened a window for further research application of almond gum as standard release modifier.

Keywords: Almond gum, Microwave assisted grafting, N-vinyl-2-pyrrolidone, Factorial design, Mucoadhesion, Diclofenac sustained release tablets.

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INTRODUCTION

Polymers are very important in every part of individual's life. Willingly or unwillingly, all the peoples at present depended on polymer for fulfilment of numerous requirements.[1] Similarly gums occurring in nature are widely used in pharmaceuticals for their unique properties and diversified applications. The natural gums are almost safely consumed as food additives or drug carriers.[2] Now days the advancement in polymer sciences and natural gum are important as they are helpful to improve their use. Modifications and grafting alteration of natural gums with polymers has gained more values.[1] Natural gums are preferable as compared to synthetics because of their less-toxicity, cost effectiveness and easy availability. However, use of gum is associated with problems. These issues include the risk of contamination, thickening, pH dependence of solubility, decrease in viscosity and rate of hydration during storage. Chemical modification of gums like grafting with polymer not only minimizes these drawbacks but also enables their use for specific drug delivery purposes.[2] To obtain specific attributes for the material that needs to be modified, such as improved stability, compatibility, flexibility and stiffness, modification is required. The processibility of the polymers is improved by adding natural gums, giving the impression that this is a new angled method to get around the problems with the original polymer. Since many years, grafting techniques have been proven

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to be revolutionary methods to change polymers as needed and research on the grafting of various types of polymers and natural gums is still ongoing.[1] Over the past few decades, numerous plant gum exudates have been found. Examples of this category's usual products include tragacanth gum, gum arabic, gum ghatti and gum karaya.[3] One of the organic polymer that naturally exudes from the trunk of the almond tree (*Purnis dulcis*) is almond gum.[4] The rosaceae family includes almonds, which are indigenous to central Asia (India, Iran and Pakistan). It is mostly grown as an ornamental shrub or for the production of its nuts in India. In India, it is referred to as "Badam" in everyday speech. It has been determined that almond gum is a unique gum that can be used extensively in the food and related industries. It is an exudate that is collected from the trunk, branches and fruits of the almond tree. This natural polysaccharide can be used as an additive in a wide range of food systems because it is practically colourless, odourless and non-toxic. On a dry weight basis, proteins make up 2.45% of almond gum, while fats make up 0.85% and carbs make up 92.36%.[3] It is inexpensive and endowed with a variety of beneficial traits, including the ability to bind water, biodegradable and biocompatible, be non-toxic, be active biologically, be able to absorb metals, bind fat and have antibacterial qualities.[4] It is a more effective emulsifier with an antioxidant source that has been demonstrated to improve biological and functional qualities in a variety of food formulations.

N-vinyl-2-pyrrolidone is the biocompatible, hydrophilic, non-ionic and non-toxic monomer its simple initiation of polymerization done by radicals, heat, or photo irradiation.[5] N-Vinyl-2-Pyrrolidone (NVP) was selected as the grafting polymer due to its excellent hydrophilicity, which enhances the swelling and water absorption capacity of the grafted material.[6] Furthermore, NVP is known for its biocompatibility and non-toxicity, making it a safer choice compared to other polymers, especially in pharmaceutical applications.[7] Its film-forming ability and potential to improve mucoadhesive properties make it ideal for formulations targeting mucosal surfaces.[8] Moreover, NVP provides controlled drug release capabilities, allowing for better modulation of drug release profiles.[9] Its copolymers, homopolymers all have been employed as antibacterial agents in temporary skin coverings or wound dressings and wrapping materials for Single-Walled carbon Nanotubes (SWNTs).[10] Due to its great affinity to numerous polymers as well as resins, compatibility, good solubility and biodegradability it has also been successfully utilised in the production of hydrogel, which has numerous uses in the fields of cosmetics, medicine, food, printing inks, textiles and many others.[5] In 2022, N-Vinyl Pyrrolidone (NVP) was utilized in graft copolymerization using Reversible Addition-Fragmentation chain Transfer (RAFT) polymerization to enhance drug delivery systems, biomedical materials and surface coatings by improving biocompatibility, water solubility and mechanical properties.[11] Also a cheng *et al.* in 2022 published that NVP was grafted onto Polylactic Acid (PLA) to accelerate degradation while maintaining biocompatibility, showing potential in tissue engineering and drug delivery applications these recent researches on NVP proves the potential of NVP.[12]

The goal of the current research was to use microwave irradiation to synthesise and evaluate a graft copolymer comprising Almond Gum (AG) and n-Vinyl-2-Pyrrolidone (NVP). Also evaluate whether it could be used to deliver drugs with sustained release. Rational behind selection of microwave irradiation method for grafting was microwave irradiation significantly accelerates the grafting process by uniformly and rapidly heating the reaction mixture, which enhances reaction rates and improves grafting efficiency. This method ensures better interaction between N-Vinyl Pyrrolidone (NVP) and almond gum, leading to more consistent and effective grafting outcomes compared to conventional heating methods.[13,14] Additionally, microwave irradiation is both energy-efficient and environmentally friendly. It reduces overall energy consumption by directly heating the reactants and minimizes solvent use, lowering the environmental impact of the synthesis process.[15,16] The preparation of graft co-polymer was carried out by OFAT Design i.e. varying the amount of NVP and keeping the concentrations of AG, ceric ammonium nitrate and irradiation time constant and vice versa for each component. The Differential Scanning Colorimetry (DSC), X-ray Diffraction analysis (XRD), fourier-transform infrared spectroscopy (FT-IR), mucoadhesion study, Scanning Electron Microscopy (SEM), Elemental analysis (EDX) and swelling evaluations were used to characterise the optimised batch of NVP grafted almond gum. Matrix tablets of diclofenac with grafted gum were prepared to evaluate sustained release behaviour of copolymer. Sustained release behaviour was validated by performing *in vitro* release study.

Experimental

Materials

Almond gum was taken as gift sample by Girijan co-operative corporation, Hyderabad, India. Ammonium ceric nitrate AR (purity 99%) and dicalcium phosphate was obtained from Loba Chemie Pvt. Ltd., n-vinyl-2-pyrrolidone was procured from Sigma Aldrich Ltd., India. Diclofenac sodium was procured as gift sample from Coral Laboratory, Daman, India. All the other chemicals and reagents used were of required standard grade and were used as it is.

Formulation of grafted co-polymer of Almond gum and N-vinyl-2-pyrrolidone

The copolymer by grafting was derived from N-Vinyl-2-Pyrrolidone (NVP) and Almond Gum (AG), it was prepared by polymerization method with microwave assistance and mechanism involved was free radical induction.[17,18] The polymerization reaction with the help of microwave assistance was carried out in microwave oven. (LG electronics: 800 W

output power and 2,450 MHz frequency). Table 1 shows the components and compositions required to synthesize a grafted polymer as per One Factor at a Time (OFAT) design. Briefly, specified amount of NVP (1.5-7.5 mL) was stirred with to previously ready aqueous dispersion (3 g AG in 30 mL) of AG for 2 hr. at room temperature. A previously decided amount of CAN (from Table 1) was solubilized in water and then poured to the above dispersion of NVP. The final dispersion was placed in microwave oven for irradiation over the 5 min at 800 W of power. During microwave assisted irradiation, additional 1 min heating and 1 min cooling cycle were applied.[19] Then sample that had been microwave-irradiated was kept untreated for 24 hr at room temperature afterwards it is precipitated with acetone. The unreacted homopolymer, unreacted NVP and other components were removed through further washings with ethanol (30%v/v). After vacuum drying at 40°C to constant weight, the NVP grafted gum was kept in a desiccator for further use.[19] The following equation applied to calculate the grafting efficiency (%):

$$(\%\ GE)=\left(\frac{w2-w1}{w1}\right)\times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, W_1 denotes weight of AG and W_2 denotes the weight of grafted copolymer.

Characterization of Almond Gum and Grafted Gum

Characterization of Grafted copolymer of AG and NVP is done by FT-IR spectroscopy, energy dispersive X-ray spectroscopy, differential scanning colorimetry, X-ray diffraction study, swelling study and scanning electron microscopy.

FT-IR spectroscopy

The grafted gum of NVP and Almond gum was confirmed by subjecting the samples to Fourier-Transform infrared spectrophotometer (FTIR Alpha II Brucker, Berlin Germany) within a range of 8000-400 cm^{-1}.

Differential Scanning Colorimetry

Differential Scanning Calorimeter (DSC 60 Plus, Shimadzu) is utilized to record thermograms of almond gum and grafted almond gum. A standard aluminium pan containing about 2 mg of the powder sample was heated within range of 40-350°C with a rate of 10°C/min. In an inert atmosphere of N_2 (nitrogen) (rate 50 mL/min), analysis was performed.[20]

Scanning electron microscopy

SEM (Quanta FEG 250, FEI, USA) is utilized to examine the morphology of the surface of almond gum and grafted almond gum. The processed sample attached on carbon tape with double adhesion, set on a sampling holder and thinly coated in gold while operating in high vacuum. A selection of magnifications was used to take the photomicrographs with a 20 kV accelerating voltage.[20]

X-ray diffraction study

The pattern of powder X-ray diffraction of grafted gum and almond gum was observed in X-ray diffractometer (D2 Phase II generation, Bruker). The experimental conditions for XRD analysis includes the radiations generated by copper at 40 kV and 35 mA and differential angle range of 0-80°.[19]

Swelling study

Swelling behaviour of gum was studied by determining their intensity of swelling. Study of swelling on grafted gum and AG were performed as sample were placed in the petri dishes in pH 1.2 and pH 6.8 phosphate buffer solutions as swelling media and weighed (w_0). At predetermined intervals, immersed baskets were removed from the media and promptly weighed (wt), following a thorough blotting of the surface with blotting paper. The index of swelling was calculated as;

$$Swelling\ (\%) = \frac{Wt-Wo}{Wo}\times 100 \ldots\ldots\ldots\ldots\ldots (2)$$

Where, w_0 denotes weight of sample in initial stage and w_t denotes weight after time 't'.

Energy dispersive X-ray spectroscopy

EDX study is an important investigative instrument for the detection of elemental composition present in the materials. In the present investigation, Quanta FEG 250, FEI, USA with voltage of 20 kV in acceleration mode was used to obtain the EDX spectrums of almond gum and grafted AG-NVP gum. Samples were prepared by placing a droplet onto an aluminium specimen stub, which was coated with gold before imaging and then dried overnight before analysis.[21]

Table 1: Batches for Preparation of NVP grafted Almond Gum.

Batch code	AG (g)	CAN (mg)	Irradiation Time (min)	NVP (mL)	%GE
F1	3	1000	5	1.5	34.6±1.41
F2	3	1000	5	3.0	58.2±2.37
F3	3	1000	5	4.5	75.0±3.06
F4	3	1000	5	6.0	88.3±3.60
F5	3	1000	5	7.5	80.9±3.30

AG: Almond gum, CAN: Ceric ammonium nitrate, NVP: N-vinyl-2-pyrrolidone.

Preparation of Tablets

To test the controlled release property, graft copolymer was used to make diclofenac sodium matrix tablets. Almond gum or grafted almond gum (100 mg) was mixed with the needed amount of diclofenac sodium (100 mg), calcium phosphate (48 mg) employed as diluent and the magnesium stearate (2 mg) as lubricant. The polymer, drug, diluent and lubricants were combined in tumbling in a polybag before being directly compressed, the dry blend was thus obtained and directly compacted in a single station manually controlled tableting machine employing 8 mm biconvex punches and dies (Karnavati Rimek Mini Press-'B' tooling) The hardness was kept between 4-6 kg /cm^2.[22]

Evaluation of grafted AG-NVP gum as mucoadhesive polymer

A comparative evaluation of grafted gum was done for pharmaceutical applications by preparing tablets and subjecting them to the texture analyser. Tablets were prepared of almond gum and grafted almond gum (optimized batch). *Ex vivo* mucoadhesion study is done to evaluate the mucoadhesive properties.

Ex vivo mucoadhesion study

The *ex vivo* mucoadhesive studies were conducted under the approval of the Institutional Animal Ethics Committee (Ref. no.: IAEC/RCPIPER/2021-22/ 31). *Ex vivo* mucoadhesive properties of the grafted AG-NVP gum were examined with the help of texture analyzer (CT3 Brookfield texture analyzer). For this study stomach mucosa of goat was used. The simulated gastric media was maintained at temperature of 37±0.5ºC. The stomach mucosa of goat was allowed to spread on tissue holder by removing lid. Afterwards lid was covered again and screwing the screw was used to fix it. Now for 10 to15 min the tissue holder was kept in simulated gastric media and allowed to stand in same beaker. After that, two-sided tape was taken and one side of that properly fixed on the probe and on another side tablet was attached to the tape. The probe then was stuck to the probe shaft of the texture analyser. The 50 g of probing force was applied for 5 s at the surface of membrane by keeping the shaft lowered towards membrane and removing it. Finally, the tablet gets detached from mucous membrane that force was measured.[23]

Evaluation

Pre-compressional studies of blend

Angle of repose, Bulk density, Carr's index, particle size, tapped density and hausner's ratio are all determined as part of the study.

Bulk Density

It is the proportion of the powder's bulk volume to its whole mass. The following formula is used to determine it:

$$\text{Bulk density} = \text{Weight of powder as bulk} / \text{Bulk volume (without tapping)} \quad \ldots\ldots\ldots (3)$$

Tapped Density

It is the proportion of the weight of the mixture to the minimal volume that the powder occupies in the measuring cylinder. The final volume was measured after tapping the porous powder mass to the minimal volume with the help of tap density apparatus.[20]

$$\text{Tapped density} = \text{weight of powder mixture} / \text{final volume after tapping} \quad \ldots\ldots\ldots (4)$$

Carr's index

Utilising tapped density and bulk density, the following formula was applied to calculate the% compressibility of the powder mixture.

$$\text{Carr's index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad \ldots\ldots\ldots\ldots (5)$$

Particle size

The particle size of the preformulation blend was analyzed using a mechanical sieve shaker. A series of stainless-steel sieves were arranged in decreasing order of their mesh size. Approximately 15 g of the blend was placed on the top sieve and the stack was subjected to vibration for 10 min. The mass of the material retained on each sieve was weighed and the particle size distribution was calculated based on the cumulative mass percentage retained on each sieve.

Table 2: Composition of Batches for the Tablet Formulation.

Batch code	Diclofenac sodium (mg)	Polymer (mg)	Calcium phosphate (mg)	Magnesium stearate (mg)	Total (mg)
AG Tablet	100	100	48	2	250
F1	100	100	48	2	250
F2	100	100	48	2	250
F3	100	100	48	2	250
F4	100	100	48	2	250
DS Tablet	100	00	148	2	250

AG: Almond gum, DS: Diclofenac sodium.

Hausner's ratio

It indirectly indicates how simply powder flow can be measured. Hausner's ratio is lower than by a higher one then it indicates the better flow properties (>1.25).[24]

Hausner's ratio=Dt. / Do ..... (6)

Where,

Dt.=tapped density; Do=bulk density ..... (7)

Angle of repose

It is described as the angle made by the heap to the horizontal. Angle of repose can be calculated by keeping the funnel constant on tripod stand i.e. fixed funnel method. The aperture of funnel was blocked by thumb and then predefined amount of powder blend was poured into the funnel. After that thumb was removed and allowed powder to flow freely to form a pile. Then the height of pile with respect to radius of pile was measured to get the angle of repose.[25]

Angle of repose $\theta = \ldots\ldots\ldots\ldots\ldots$ (8)

Where, h denotes the height of the powder pile and r denotes the radius of the pile.

Post compression studies

The matrix tablets appearance, hardness, thickness, friability, weight variation and drug content were assessed.

Appearance

General appearance of tablet was studied visually.

Thickness

The diameter and thickness of the tablet was measured with the help of vernier calliper (calibrated). The average thicknesses of 20 tablets were taken which were randomly selected from every batch.[26]

Weight variation

20 tablets were weighed and the average weight was determined. To ascertain the variation, the weight of every tablet was taken individually. Weight variation was calculated by comparing the weight of each tablet to the average weight.[24,27]

Hardness

To determine the force required to tablets could be to crush the Monsanto hardness tester were used. The average hardness was determined after evaluating three tablets at random from each batch.

Friability

Before use, a tablet is put through a friability test to see how well it will withstand handling, storage and transportation without chipping or breaking. The term "friability" describes the decrease in tablet weight that occurs when the surface of the tablet undergoes removal of particles. The Roche friabilator, which was set to run at 25 revolutions per minute (for 100 revoulutions) for 4 min with a fall height of 6 inches, was used to assess the friability of tablets. The difference between the weight of the tablet prior to and following the friability test was noted.[28]

Drug content

The tablets were crushed into a powder and 100 mg of Diclofenac sodium as powder of was precisely measured and transferred into the volumetric flask of 100 mL. Then phosphate buffer (pH 6.8) 10 mL was added initially and shaken for 10 min. Afterwards

Figure 1: FTIR overlay spectra of (A) AG and (B) NVP grafted Almond gum.

Figure 2: FTIR overlay spectra of formulation of AG (A) and NVP grafted AG tablet formulation (F4 batch) (B).

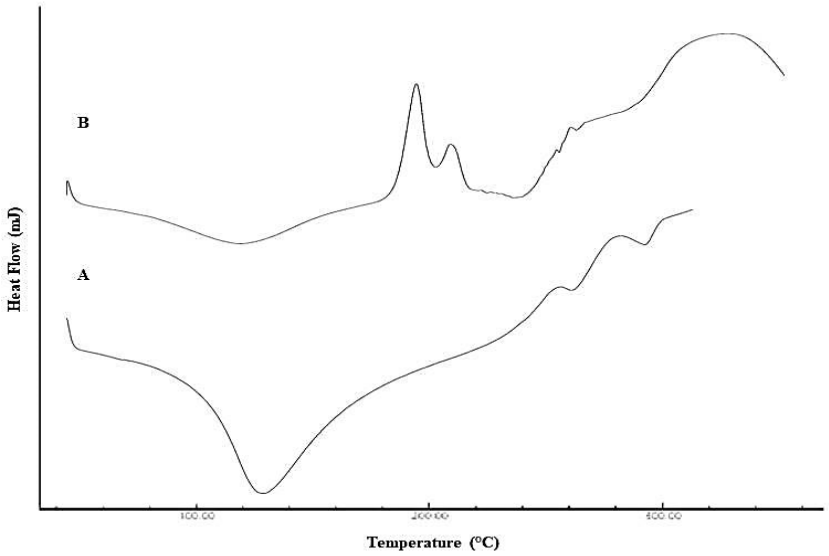

Figure 3: DSC of AG (A), NVP grafted Almond gum (B).

total volume to 100 mL was made with phosphate buffer solution. The volumetric flask's solution was then filtered; from that filtrate 1 mL of the filtrate was taken and diluted before being measured at 276 nm with a UV-visible spectrophotometer (Shimadzu UV-1800, Japan). Every sample's drug content was calculated based on its standard curve.[29]

In vitro drug release study

A USP Type-II dissolution test device was used to conduct an *in vitro* dissolution rate analysis of the formulations (n=6). For 2 hr and for a total of 12 hr, respectively, a dissolution rate investigation was conducted in phosphate buffer pH 1.2 and in simulated intestinal fluid (PBS pH 6.8). Throughout the investigation, the temperature of each dissolving media (900 mL) was kept constant at 37±0.5ºC. At predefined intervals (2, 3, 4, 6, 10 and 12 hr), the samples (5 mL) were taken out and replaced with a similar quantity of new medium. The samples were filtered using a membrane filter (0.45 m) before being examined at a maximum UV-visible wavelength of 276 nm. To calculate the release profile, the cumulative percentage drug release was plotted versus time.[30]

RESULTS

Synthesis of NVP grafted Almond Gum

Free radical graft copolymerization of NVP on almond gum utilized to make the grafted almond gum. Copolymerization was initiated using Ceric Ammonium Nitrate (CAN). Generation of free radical needs a critical quantity of redox initiator. The first stage in this process is the formation of the AG-ceric complex, which is initiated by the action of ceric ions on AG macrochains. By oxidising a hydrogen atom and producing a free radical on the backbone of AG, the complex ceric (IV) ions are then degraded to ceric (III) ions. Covalent bonds are used to bind the AG free radical to the NVP monomer unit. The reaction time is shortened by the rapid energy transfer caused by microwave irradiation. Almond gum is a large molecule with pendant -OH groups. Almond gum macroradicals get created by the breakage of pendant O-H bonds caused by microwave irradiation. These macroradicals can be created by the ceric ion free radicals by taking hydrogen from the almond gum molecule. Following a series of chain reactions that are started by free radicals and lead to the synthesis of the homopolymer and graft copolymer shown below; these free radicals subsequently react with NVP monomer to create NVP free radicals.[31]

$$S_2O_{82}\text{-}\rightarrow{}_2SO_4\text{*-}$$

$$AGOH+R^*\rightarrow AGO^*+RH$$

Where;

R^* is SO_4^{*-} and AGOH is Almond gum.

$$AGO^*+N\rightarrow AGON^*$$

$$R^*+N\rightarrow RN^*$$

Where;

N is N-vinyl-2-pyrrolidone.

Chain propagation

$$AGON^*+N\rightarrow AGON^*1$$

$$AGON1^*+N\rightarrow AGON^*2$$

$$AGON^*n\text{-}1+N\rightarrow AGON^*n$$

$$RN^*+N\rightarrow RN^*1$$

$$RN^*1+N\rightarrow RN^*2$$

$$RN^*n\text{-}1+N\rightarrow RN^*n$$

Chain termination

$$AGON^*n+AGON^*n\rightarrow \text{graft co-polymer}$$

$$AGON^*n+RN^*n\rightarrow \text{graft co-polymer}$$

$$RN^*n+RN^*m\rightarrow \text{Homopolymer}$$

Table 3: Swelling intensities in pH 1.2 and pH 6.8.

Water mass uptake in %	Swelling time in hr											
	0.5 hr (30 min)		1 hr (60 min)		2 hr (120 min)		4 hr (240 min)		6 hr (360 min)		8 hr (480 min)	
	pH 1.2	pH 6.8	pH 1.2	pH 6.8	pH 1.2	pH 6.8	pH 1.2	pH 6.8	pH 1.2	pH 6.8	pH 1.2	pH 6.8
AG	878	864	845	852	752	764	220	621	154	547	87.4	514
F1	124	377	176	488	192	602	264	641	308	698	336	725
F2	145	228	269	316	302	337	352	379	390	412	427	448
F3	228	302	268	312	277	320	289	336	312	348	329	362
F4	112	164	119	183	130	198	192	218	225	238	262	260

Table 4: **Precompression studies: evaluation of flow properties of blend.**

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index	Hausner's ratio	Angle of repose (θ)
AG	0.62±0.01	0.75±0.02	8.31±0.02	1.03±0.01	25.61±0.02
F1	0.54±0.02	0.62±0.01	9.42±0.02	1.01±0.03	32.48±0.02
F2	0.57±0.02	0.63±0.02	8.63±0.01	1.08±0.02	27.25±0.01
F3	0.56±0.01	0.64±0.01	9.85±0.01	1.02±0.01	34.72±0.01
F4	0.63±0.01	0.69±0.01	9.52±0.01	1.09±0.02	28.25±0.01
DS Tablet	0.53±0.02	0.63±0.01	8.26±0.01	1.04±0.02	32.05±0.02

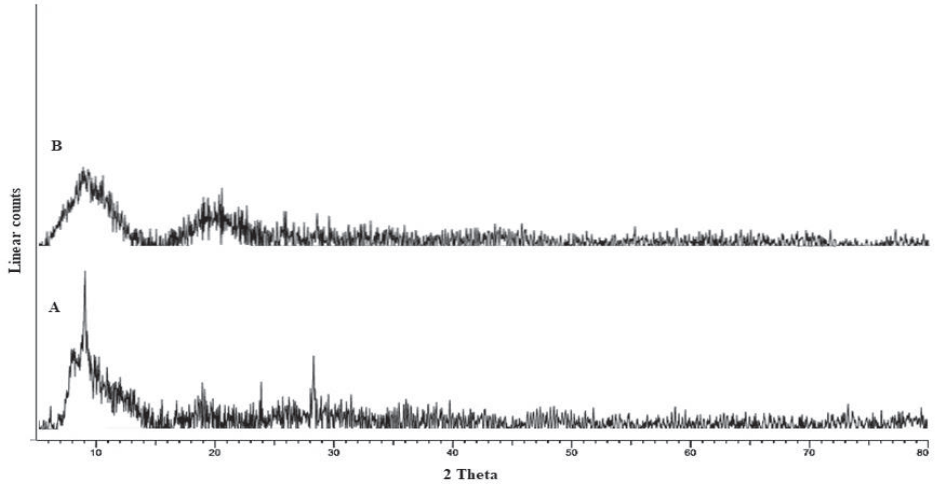

Figure 4: XRD of AG (A), NVP grafted Almond gum (B).

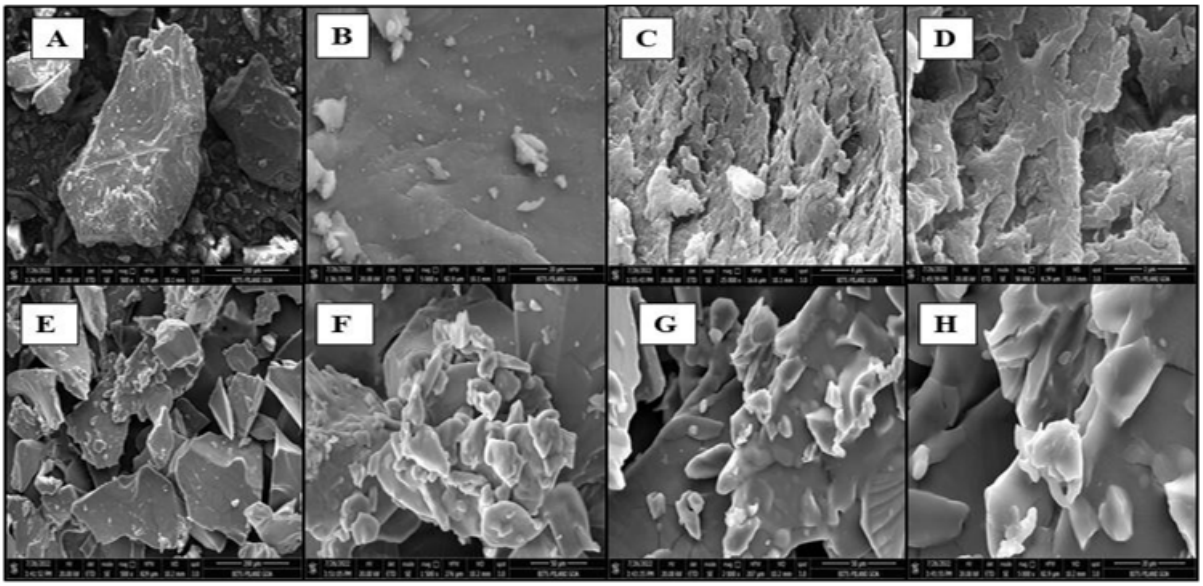

Figure 5: SEM image displaying the shape (A), (B) and surface morphology of almond gum (C), (D) and as well as the shape (E), (F) and surface morphology (G), (H) of NVP-grafted AG respectively.

Optimization of batch from OFAT design

OFAT design was applied for optimization and after considering the batches with different concentration of NVP from 1.5 mL to 7.5 mL for 5 batches, F4 batch is optimized batch due to higher grafting efficiency i.e 88.3±3.60% with 6.0 mL of NVP.

Characterization of grafted gum

Fourier transforms infrared spectroscopy (FT-IR Spectroscopy)

The O-H and C-H stretching modes are represented by the spectral bands between 3000 and 3600 cm^{-1} and 2800 and 3000 cm^{-1}, respectively (Figure 1). Spectra shows peaks of Pure almond gum and the grafting of gum with NVP is depicted with characteristic peaks in Figure 1. Afterwards the Figure 1 summarizes both spectra and shows the characteristic changes in peak due to grafting. Similar is case with Figure 2 which is comparing spectra of grafted gum with diclofenac tablet and batch 4 formulation of almond gum tablet. Detail confirmation is summarized in discussion section.

Differential Scanning Colorimetry

DSC was used for evaluation of thermal responses of AG and NVP grafted AG as depicted in Figure 3.

X-ray Diffraction (XRD) Analysis

Figure 4 signifies the X-ray diffraction of Almond Gum and NVP grafted Almond gum. The diffractogram of AG displays distinctive and sharper peaks occurring at 6.5°, 9.4° and 28.6° (2θ) compared to graft copolymer, shows that AG has crystalline nature.

Scanning Electron Microscopy (SEM)

Figure 5 shows the scanning electron micrographs for shape and surface morphology of AG and NVP grafted AG.

Swelling study

Figure 6 and Table 3 shows the swelling features of AG and AG-g-poly (NVP) batches on pH 1.2 and pH 6.8. Swelling was observed for total 8 hr (480 min) of time period. When samples were subjected to swelling it was observed that AG shown maximum swelling.

Elemental Analysis (EDX)

Figure 7 shows an EDX spectrum of AG shows intense strong peak of carbon with total 60.5% weight of sample, oxygen content observed was 39.5% of total with strong peak and absence of peak for nitrogen as it is 0.0% content in analysis.

Ex vivo Mucoadhesion study

The *ex vivo* mucoadhesion properties of formulations were described in Figure 8. The mucoadhesion test was performed by using a texture analyzer. The force required to separate the tablet from tissue was noted down as final load (Figure 8 a) and Work of adhesion (W_{ad}) (Figure 8b). Here the final load is the maximum load required for deformation while the work of adhesion is the total weight required to separate the tablet from tissue.

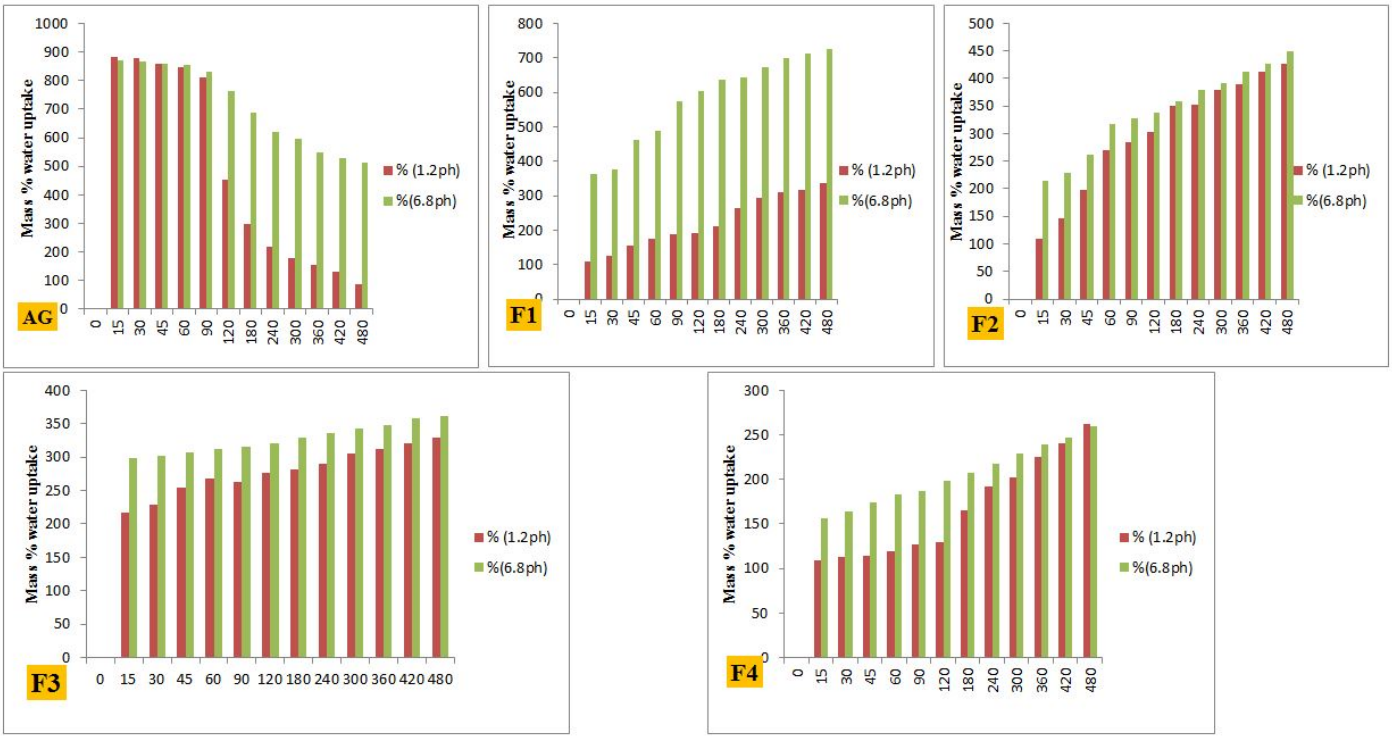

Figure 6: Swelling study of AG and grafted batches.

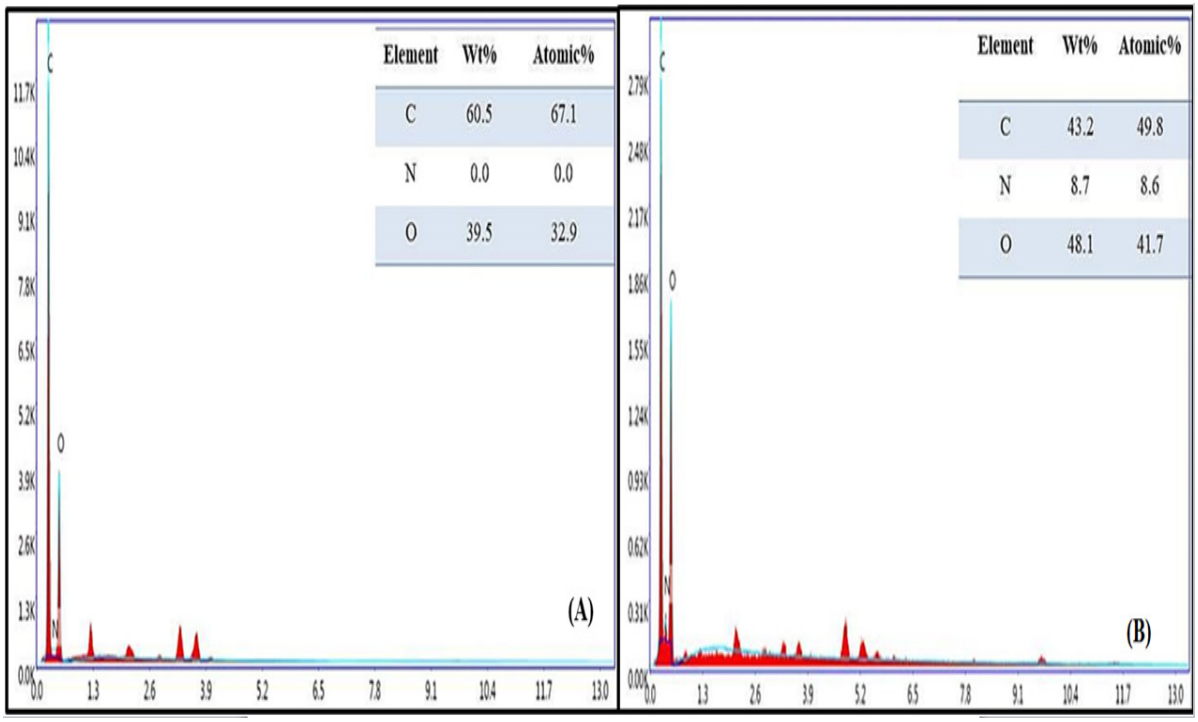

Figure 7: (A)EDX spectra of AG (B) EDX spectra of NVP grafted AG.

Table 5: Post compression studies: In-process checks.

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug content (%)	Drug release (%)
AG Tablet	248±1.52	13.33±0.01	4.5±0.20	0.46±0.02	93.2±0.10	83.14±0.80
F1	244±1.52	13.13±0.02	4.3±0.15	0.40±0.01	92.5±0.15	92.85±1.18
F2	245±2.51	13.47±0.01	4.7±0.26	0.63±0.01	97.3±0.15	94.63±1.23
F3	247±1.52	13.64±0.01	4.8±0.15	0.64±0.01	96.6±0.10	95.21±1.38
F4	249±1.00	13.67±0.01	4.9±0.10	0.65±0.02	98.4±0.10	98.49±0.12
DS Tablet	246±1.00	12.29±0.02	4.6±0.15	0.62±0.01	91.2±0.10	80.23±0.23

Evaluation of Tablets

Tablets were evaluated before compression i.e. Precompression study of blend and post compression evaluation of tablets.

Precompression studies

Precompression study on blend was performed to ensure the good flow properties of blend for better compression characteristics; results of that are summarized in Table 4. The sample powder mixture was assessed for particle size was and a number of parameters including bulk density, angle of repose, tapped density, Hausner's ratio and Carr's index.

Post compression studies

Diclofenac-containing matrix tablets were subjected to weight variation test.

In vitro Release study

Figure 9 displays the diclofenac tablets *in vitro* release profile prepared using AG and AG-g-poly (N-vinyl-2-pyrrolidone). Both tablets released diclofenac at a consistent rate. The drug released from the DS tablets is 65.29% after 2 hr. in a 1.2 pH buffer and 80.23% in 4 hr. The drug released from AG tablet after 2 hr. In pH 1.2 buffer was 31.82%. In case of formulations, the % drug release from F1, F2, F3 and F4 batches were 26.86%, 23.23%, 19.74% and 14.80%, respectively after first 2 hr. While % drug release from AG tablet and F1, F2, F3, F4 was shown 83.14%, 92.85%, 94.63%, 95.21% and 98.49% release respectively after 12 hr in simulated colonic fluid media.

Release Kinetics

For studying the drug release mechanism by formulations, data of drug release of *in vitro* study were fitted to the several kinetic models.

DISCUSSION

Based on preliminary studies, five batches for optimization of NVP concentration were planned. It was found that concentration of NVP is directly proportional to the grafting efficiency, as the quantity of NVP increases in same proportion the grafting efficiency increases. But as at a certain point as the quantity of NVP increases in same proportion the grafting efficiency does not increases that seen in case of batch F5. There taken almost 5 batches; in all batches the quantity of almond gum and of CAN was kept constant. The quantity of NVP was gradually increased from 1.5 mL in F1 to 7.5 mL in F5. In response the grafting efficiency was found to increase from 34.6% in F1 to 88.3±3.60% in F4 but suddenly decreased in batch F5 to 60.9%. From this batch F4 was selected as optimized batch as it was with maximum grafting efficiency and batch F5 was not taken under consideration for further study as it show less grafting efficiency with increasing conc. of NVP.

Then formulation batch was subjected to IR spectroscopy for confirmation of grafting. Peaks observed in Figure 1. 3429.55 cm^{-1} and at 2931.90 cm^{-1} in the spectra are therefore due to the presence of O-H and C-H groups respectively. The presence of -COOH is confirmed by peaks in the spectra at 1608.69 cm^{-1} and 1423.51 cm^{-1}. The polymer backbone's C-O-H, C-H bending and C-O, C-C and C-O-C stretching modes were indicated by the peaks between range of 800 cm-1 to 1200 cm^{-1}. Bands found in the spectra at 783.13 cm^{-1} may correspond to 1-4 linkage of galactose.[7] The spectra of NVP grafted AG exhibited intensity change and peak shifting due to OH stretching, showing that hydroxyl groups were involved in the chemical reaction.[25] Its confirmation is by the characteristic peak for the C=O stretching vibration of the cyclic amide (lactam) at 1653 cm^{-1}, the stretching of the tertiary amine group produced another peak at 1294.28 cm^{-1}, which supports the grafting of N-vinyl-2-pyrrolidone. Figure 1. Spectrum demonstrates an absorption peak at 3410.26 cm^{-1} due to OH, a peak at 1074.39 cm^{-1} caused by the C-O

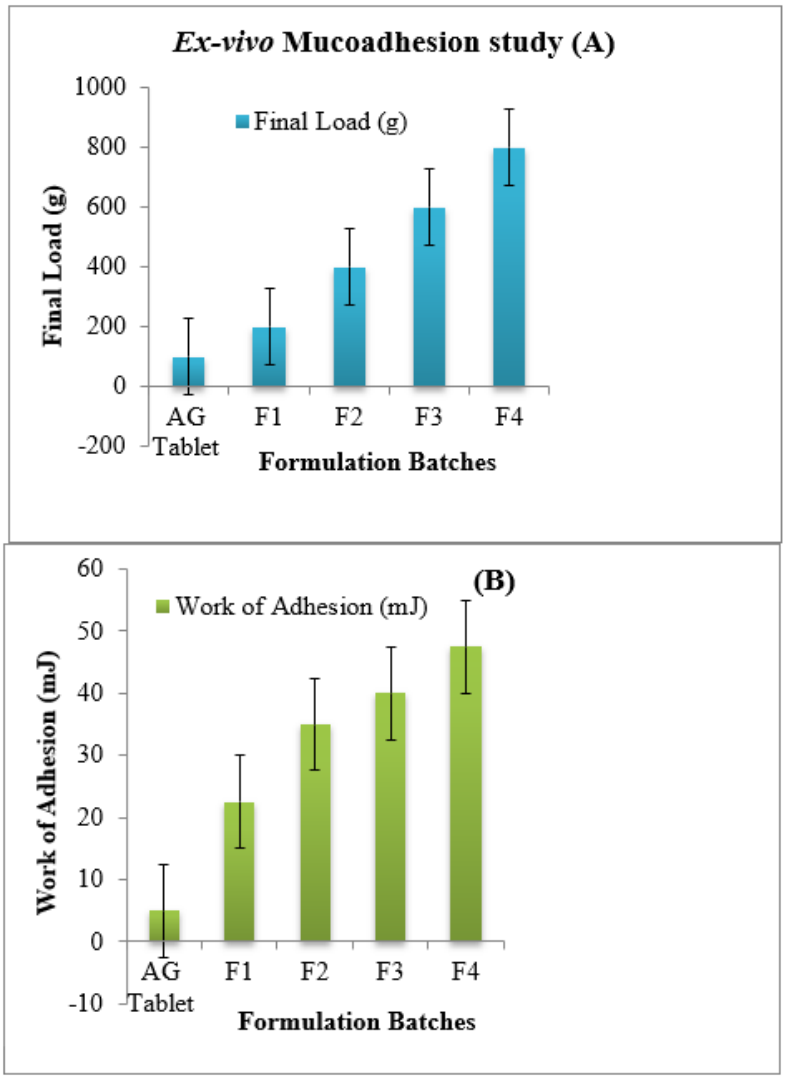

Figure 8: *Ex vivo* Mucoadhesion properties of different formulations: final load (a) and work of adhesion (b).

stretching of alcohol and a third peak at 2916.47 cm^{-1} caused by the CH stretching of the alkane group.[12] Figure 1 Shows the FTIR peaks at 3404.47 cm^{-1}, 2920.32 cm^{-1}, 2850.88 cm^{-1}, 2281.87 cm^{-1}, 1199.76 cm^{-1}, 1458.23 cm^{-1}. Figure 2 summarizes additional peaks and ultimate confirmation of grafting.The peaks observed in these ranges confirmed the compatibility of the polymer and the drug. FTIR spectra of NVP grafted AG show peaks at 3412.19 cm^{-1}, 2922.25 cm^{-1}, 2850.88 cm^{-1}, 1680.05 cm^{-1}, 1604.83 cm^{-1}, 1288.49 cm^{-1}, 1384.94cm^{-1} FTIR of the drug and polymer shows that the polymer and diclofenac sodium are functionally compatible.[32]

DSC thermogram of AG (Figure 3 A) shows a widespread endothermic peak at 119.99°C indicating the melting range of almond gum with crystalline nature, after which there is an exothermic peak at 283.56°C. A very wide endothermic peak at 122.73°C is shown on the thermogram of NVP-grafted AG (Figure 3 B) which indicates the successful grafting of almond gum to the NVP, which is followed by an exothermic peak at 196.65°C indicating the amorphous nature of grafted gum.[18] In a consequence, the thermal curve shows that AG is altered. The grafting was again confirmed with the help of X-ray diifraction studies. The X-ray diffractogram of NVP grafted AG shows that the peaks of AG are attenuated; indicating that grafting is successful and nature of graft copolymer is amorphous.[14] It reveals that its degree of crystallinity is reduced when NVP is grafted onto almond gum, making it more amorphous in nature.[20]

The surface morphology of formulation was studiesd using SEM. SEM pictures of AG revealed that the surface of the particles were uneven and rough. The SEM images of grafted AG show polyhedral-shaped particles and a surface of grafted gum is relatively smooth. As a result, it was observable that grafting NVP to almond gum makes the entire surface smooth.[18] Thus; the findings of the X-ray diffraction and DSC tests are supported by the findings of the SEM analysis. In swelling studies it was observed that AG shows 874% water mass uptake in pH 1.2 and pH 6.8 buffer media in initial time span of 30 min. After that swelling was somewhat stagnant and gradually decreased to 87% in pH 1.2 and 514% in pH 6.8 over period of 8 hr, but in case of optimised batch F4 of NVP-grafted gum it was observed that swelling was gradually increasing in slow manner over period of 8 hr. The % water mass uptake was only 262% at end of 8 hr, which

Table 6: *In vitro* drug release kinetic model data.

Batches	Zero order	First order	Higuchi	Korsmeyer Peppas	Hixon Crowell
AG tablet	0.8955±0.04	0.8427±0.04	0.945±0.04	0.9539±0.04	0.862±0.04
F1	0.9911±0.01	0.9588±0.01	0.9958±0.01	0.9958±0.01	0.9728±0.01
F2	0.9981±0.01	0.9688±0.01	0.9923±0.01	0.9979±0.01	0.9842±0.01
F3	0.9971±0.01	0.9576±0.01	0.9949±0.01	0.9986±0.01	0.9774±0.01
F4	0.995±0.02	0.9412±0.02	0.9978±0.02	0.9964±0.02	0.9668±0.02
DS tablet	1	1	1	1	1

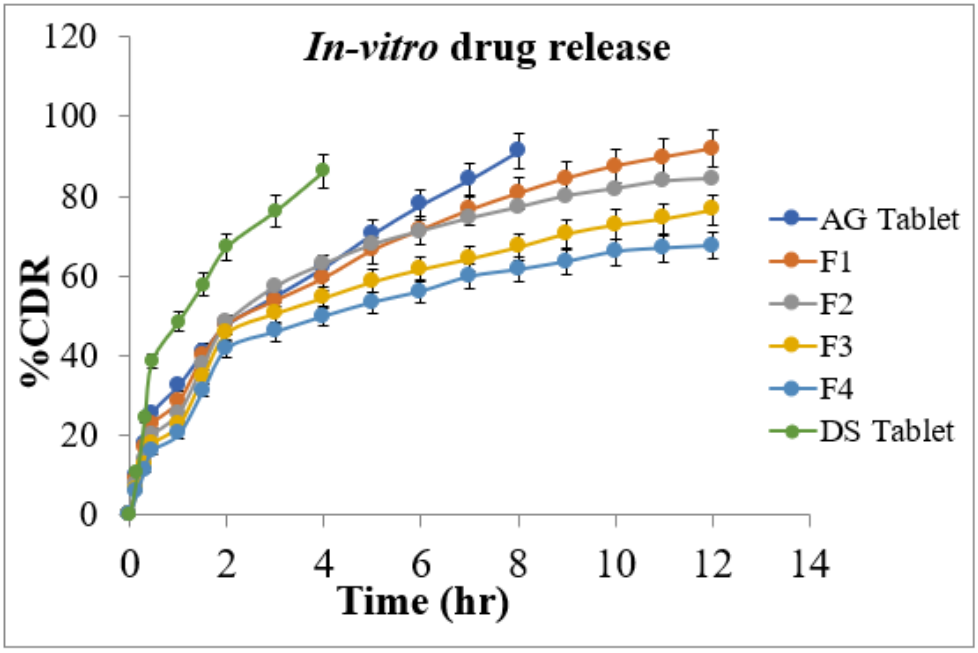

Figure 9: *In vitro* dissolution study.

indicates that grafted gum had modified the swelling behaviour and henceforth the release pattern will be like sustained release for releasing the active moiety.[18]

The elemental composition of the grafted gum was evaluated using EDX studies. Figure 7 shows the EDX spectrum of optimized batch F4 of NVP grafted AG, which shows a significant amount of nitrogen with strong peak, indicating incorporation of nitrogen during grafting so that the grafting was successful and graft was efficient. The highest Nitrogen (N) is (8.7%) was attributed to the maximum propensity for grafting, indicating that higher levels of NVP have a progressive effect on % grafting. Although the output of the grafted almond gum very less impacted by microwave radiation time. The impact of concentration of redox initiator i.e. CAN were minimal since NVP was the prominent source of nitrogen.[19]

The prominent study that is mucoadhesive property was evaluated using *in vivo* mucoadhesion test. All the grafted formulation batches showed excellent mucoadhesive properties, the final load, W_{ad} range from 70 to 778 g and 5.19 to 46.83 mJ**,** respectively. Mucoadesion property in grafted gum is due to multiple reasons, as almond gum has swelling properties as assessed in swelling study also the grafted batch F4 has maximum swelling property ultimately it has maximum mucoadhesion property because the swelling behaviour adds to mucoadhesion. From results it is seen that mucoadhesion property of the formulations is gradually increasing from AG tablet to F4 tablet, the pure almond gum shows mucoadhesion up to certain level but the F4 tablet shows maximum mucoadhesion. This indicates that the conc. of NVP also contributes towards the mucoadhesion; maximum the NVP conc., maximum will be mucoadhesion. Final we can conclude that grafted almond has mucoadhesive property which helps in modifying the release behaviour of active moiety when incorporated with grafted gum.[23] All sample formulations have an angle of repose value that ranges from 25.61±0.02 to 34.72±0.01 (θ), demonstrating good particle flow characteristics. Bulk density values ranges between 0.53±0.02 to 0.63±0.01 g/cm^3 and tapped density values ranges between 0.62±0.01 to 0.75±0.02 g/cm^3 respectively. Sieve analysis of the blend showed 20% of particles were larger than 250 µM, 20% were between 180 µM and 250 µM, 30% were between 125 µM and 180 µM, 20% were between 90 µM and 125 µM and 10% were smaller than 90 µM. The results indicate that the blend is composed predominantly of medium-sized particles, which are expected to contribute to good flow properties during tablet formulation. Compressibility indicators, such as Carr's index and Hausner's ratio, have values ranging from 8.26±0.01 to 9.85±0.01 and 1.01±0.03 to 1.09±0.02 respectively. Post compression test of weight variation for tablet reported to weigh between 244±1.52 mg to 249±1.00 mg. The thickness ranged from 12.29±0.02 mM to 13.67±0.01 mM and the range of % friability was found to be 0.40±0.01% to 0.65±0.02%. The hardness of the tablet was observed to be between 4.3±0.15 kg/cm^2 and 4.9±0.10 kg/cm^2.

From the statistical data of *in vitro* release study, The NVP grafted Almond gum demonstrated the grafting's impact by delaying the drug's release from the tablet formulation. In comparison to AG tablet, the tablets prepared with grafted gum showed better drug release control. Grafted almond gum in the optimum concentration is apparent from the drug release profiles could be used to enable the drug with sustained colonic absorption. The mechanism of drug release followed by formulations is non-fickian (anomalous). The release of the drug from the formulation could have been achieved by combining erosive, swollen and diffusion processes.

CONCLUSION

The method for NVP graft copolymerization on AG was optimized. FT-IR, DSC, XRD, SEM and EDX were utilized to further characterize the graft copolymer, confirming that AG-g-poly (NVP) was formed. Similar to this, the graft copolymer was assessed for alteration of rate of release using a diclofenac sodium tablet. The study showed that graft copolymer tablets released DS over an extended period of time than AG. Thus based on the results, it can be determined that NVP grafting on almond gum prolonged the time the drug was released. The development of modified drug release using the grafted gum was achieved by the *in vitro* drug release. The results of this study indicate that almond gum grafted with NVP has significant potential as a sustained-release drug delivery system. The promising outcomes of the mucoadhesive study further reinforce its potential, suggesting that this graft copolymer can enhance the retention time of drugs at the site of action, improving bioavailability. Future research could focus on optimizing the grafting ratio and exploring its application with a broader range of drugs to fully harness its capabilities. With continued development, this grafted polymer system could play a vital role in improving therapeutic outcomes for various drug formulations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NVP: N-vinyl-2-pyrrolidone; **DS:** Diclofenac sodium; **CAN:** Ceric ammonium nitrate; **PBS:** Phosphate buffer solution; **AG:** Almond gum; **OFAT:** One factor at a time; **DSC:** Differential

scanning colorimetry; **XRD:** X-ray diffraction analysis; **FT-IR:** Fourier-transform infrared spectroscopy; **SEM:** Scanning electron microscopy; **EDX:** Elemental analysis; **W_{ad}:** Work of adhesion.

SUMMARY

Microwave assisted grafting of almond gum on N-vinyl-2-pyrrolidone.

OFAT design applied for batch optimization.

Grafted gum formulated as tablet evaluated with texture analyser for mucoadhesion study.

Diclofenac tablet with grafted gum prepared to evaluate sustained release behaviour.

Grafted gum shown sustained release behaviour and higher *ex vivo* mucoadhesion time.

REFERENCES

1. Rohit, R., Gangadharappa, H., Afrasim, M., Gowda, D., and Riyaz Ali, M. Grafting technique with special emphasis on natural gums: applications and perspectives in drug delivery. Nat Prod J. 2015;5(2):124-39.
2. Rana, V., Rai, P., Tiwary, A. K., Singh, R. S., Kennedy, J. F., and Knill, C. J. Modified gums: Approaches and applications in drug delivery. Carbohydrate polymers, 2011;83(3):1031-47.
3. Bashir, M., and Haripriya, S. Assessment of physical and structural characteristics of almond gum. International journal of biological macromolecules, 2016;93:476-82.
4. Hussain IS, Jaisankar VJ. An eco-friendly synthesis, characterization and antibacterial applications of novel almond gum-poly (acrylamide) based hydrogel silver nanocomposite. Polymer Testing. 2017;62:154-61.
5. Yiğitoğlu M, Aydın G, Işıklan N. Microwave-assisted synthesis of alginate-g-polyvinylpyrrolidone copolymer and its application in controlled drug release. Polymer bulletin. 2014;71:385-414.
6. Muankaew C, Loftsson T. Cyclodextrin-based formulations: A non-invasive platform for targeted drug delivery. Basic Clin Pharmacol Toxicol. 2018;122(1):46-55.
7. Gupta AK, Shukla P, Ghosh A. Synthesis and characterization of N-vinyl-2-pyrrolidone grafted xanthan gum: A promising approach for drug delivery. Int J Biol Macromol. 2020;147:84-94.
8. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. J Control Release. 2011;153(2):106-16.
9. Li J, Zhang X, Zhao L. Polyvinylpyrrolidone: Versatile material for drug delivery systems. J Drug Deliv Sci Technol. 2019;51:521-30.
10. Ahuja M, Thakur K, Kumar A. Amylopectin-g-poly (N-vinyl-2-pyrrolidone): synthesis, characterization and *in vitro* release behavior. Carbohydrate polymers. 2014;108:127-34.
11. Asadi M, Hassan ZM, Jafari R, *et al.* Application of RAFT Polymerization in Developing Grafted N-vinyl pyrrolidone Copolymers for Drug Delivery. Macromolecular Chemistry and Physics. 2022;223(6):2301-10.
12. Cheng J, Li J, Wang S, *et al.* Grafting of N-vinyl pyrrolidone onto Polylactic Acid for Enhanced Degradation and Biomedical Applications. Journal of Polymer Research. 2022;29(3):59-70.
13. Mondal MIH, Mondal MH. Microwave-assisted polymer synthesis: An overview. J Mater Sci Res. 2020;9(1):45-57.
14. Mishra S, Malik A. Microwave irradiation in grafting of vinyl monomers onto polysaccharides: A rapid approach for polymer modification. Prog Polym Sci. 2018;77:41-60.
15. Kumar A, Sharma R. Microwave-induced synthesis: A sustainable approach for polymer grafting. Polym Chem. 2019;10(25):3420-30.
16. Clarke AJ. Green chemistry techniques in the synthesis of polymeric materials using microwave irradiation. Sustain Chem Pharm. 2021;19:100370.
17. Kaity S, Isaac J, Kumar PM, Bose A, Wong TW, Ghosh A. Microwave assisted synthesis of acrylamide grafted locust bean gum and its application in drug delivery. Carbohydrate polymers. 2013;98(1):1083-94.
18. Vijan V, Kaity S, Biswas S, Isaac J, Ghosh A. Microwave assisted synthesis and characterization of acrylamide grafted gellan, application in drug delivery. Carbohydrate polymers. 2012;90(1):496-506.
19. Rani P, Singh I. Microwave assisted synthesis and characterization of N-vinyl-2-pyrrolidone grafted locust bean gum for colonic delivery of budesonide. Drug Delivery Letters. 2016;6(2):98-103.
20. Ahuja M. Moringa gum-g-poly (N-vinyl-2-pyrrolidone)-a potential buccoadhesive polymer. International journal of biological macromolecules. 2018;109:732-9.
21. Rashmi, Rimpy, Ahuja M. Iodine impregnated poly (N-Vinylpyrrolidone) grafted antibacterial cotton gauze for wound dressing applications. Fibers and Polymers. 2020;21:1411-21.
22. Kumar A, Singh K, Ahuja M. Xanthan-g-poly (acrylamide): microwave-assisted synthesis, characterization and *in vitro* release behavior. Carbohydrate polymers. 2009;76(2):261-7.
23. Rajput K, Tawade S, Nangare S, Shirsath N, Bari S, Zawar L. Formulation, optimization and *in vitro-ex vivo* evaluation of dual-crosslinked zinc pectinate-neem gum-interpenetrating polymer network mediated lansoprazole loaded floating microbeads. International Journal of Biological Macromolecules. 2022;222:915-26.
24. Nagaich U, Bharti C, Pal AK, Gulati N. diclofenac sodium loaded sustained release matrix tablet possessing natural and synthetic polymers: Formulation and *in vitro* characterization. Indian J Pharm Edu Res. 2014;48:49-55.
25. Aulton ME. Pharmaceutics: The Science of Dosage Form Design; hurchill Livingstone: London.
26. Mitkare SS, Sakarkar DM. The effect of different grades polymer blends on release profiles of diclofenac sodium from hydrophilic matrices. Journal of Applied Pharmaceutical Science. 2015;5(10):142-6.
27. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Philadelphia: Lea and Febiger; 1976.
28. Yadav A, Chaudhari P, Khatri S, Thapa C. Formulation, *in vitro* Evaluation and Comparative Study of Itopride Hydrochloride Loaded Sustained Release Matrix Tablet Using Okra Mucilage as a Natural Binder. tablet. 2021;13:25.
29. Malviya R, Srivastava P, Bansal M, Sharma PK. Formulation and optimization of sustained release tablets of diclofenac sodium using guar gum as release modifier. Int J Pharm Sci Res. 2010;1(6):83.
30. Singh AV, Nath LK. Evaluation of microwave assisted grafted sago starch as controlled release polymeric carrier. International journal of biological macromolecules. 2013;60:62-8.
31. Malik S, Kumar A, Ahuja M. Synthesis of gum kondagogu-g-poly (N-vinyl-2-pyrrolidone) and its evaluation as a mucoadhesive polymer. International journal of biological macromolecules. 2012;51(5):756-62.
32. Madaan R, Bala R, Vasisht T, Sharma R, Garg S. Formulation and characterization of matrix tablets using mucilage of tinospora cordifolia as natural binder. International Journal of Pharmacy and Pharmaceutical Sciences. 2018;10(7):22-7.

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