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CORDIA MYXA POLYSACCHARIDE-G-POLY(ACRYLONITRILE) CO-POLYMER BASED MUCOADHESIVE GASTRORETENTIVE DELIVERY OF CAPTOPRIL

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Central Composite Design, *Cordia myxa*, Gastroretentive, Grafting, Mucoadhesion.

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ABSTRACT: The objective of the present study was to prepare gum *Cordia myxa*-g-polyacrylonitrile using microwave irradiation and to evaluate its mucoadhesive applications. The graft co-polymerization of poly(acrylonitrile) on gum *Cordia myxa* was carried out employing 3- level 4-factor central composite experimental design. It was observed that the concentrations of ammonium persulphate and concentrations of acrylonitrile exerted a significant synergistic and antagonistic influence on grafting efficiency and percent swelling respectively. Graft co-polymer was characterized by fourier transform infrared spectroscopy, X-ray diffraction and differential scanning calorimeter. Mucoadhesive properties of the graft-copolymer were evaluated by formulating tablets employing captopril as the model drug. On comparative evaluation the gastroretentive tablets of captopril formulated using graft co-polymer (20%) showed ex vivo mucoadhesive time of 12 h whereas the tablets formulated using native *Cordia myxa* gum and carbopol 934 showed ex vivo mucoadhesive time of 6 h and 8 h respectively. According to the results obtained it was concluded that grafting of poly(acrylonitrile) on gum *Cordia myxa* enhances its mucoadhesion and thus, the grafted *Cordia myxa* gum seems to be promising excipient for the development of mucoadhesive drug delivery systems.

INTRODUCTION: Drugs with poor stability in alkaline media could pose problems when exposed to intestinal pH. Gastroretentive controlled release system can address such issues of drugs which show short biological half life and are unstable at alkaline pH. Captopril is first line drug treatment for patients suffering with hypertension and congestive heart failure. This drug has to be administered thrice in form of a tablet because of its instability at alkaline pH as well as relatively short elimination half life. Thus, there is a strong clinical and commercial rationale for selection of gastroretentive dosage form that can deliver captopril in a controlled manner resulting in increased compliance and therapeutic potential [1, 2].

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The selection of novel polymers for improving mucoadhesive formulation design would be of interest in the scientific field. Biocompatibility of synthetic polymers pose a variety of issues while developing any drug delivery systems, in present work polymer from natural source was

characterized profoundly for the purpose. Biodegradability and easy availability are one of the factors that natural polysaccharides such as pectin, guar gum, chitosan, sodium alginate and xanthan gum are being widely used in controlled drug delivery.

The viscosity and swelling property of any polymer play key role in controlling the release of drug from the dosage form. It has been reported that synthetic polymers exhibit compromised viscous and swelling behaviour. However, the viscosity and swelling property of a polysaccharide from a natural origin play a greater role in their selection as release retardants, since the former properties are responsible for controlled behaviour of the delivery system in question [3]. Our previous reports suggest that natural polysaccharides containing galactouronic acid moieties exhibit greater swelling index and are more amenable for modification [4]. *Cordia myxa* gum is one such natural polysaccharide and in present work its acrylonitrile graft were evaluated to identify its potential role in designing and development of mucoadhesive gastroretentive dosage forms.

The fruits of *Cordia myxa* (Family Boraginaceae), commonly known as Lasora or gonda in Indian (Hindi) language are edible, round to ovoid shaped drupes, 1.75 cm in diameter, 2.92 g in weight, 2.88 ml in volume, light yellow to slightly greenish in colour; with mucilaginous mesocarp and hard endocarp. The seeds and fruit extracts of *Cordia myxa* is known for its analgesic, anti-inflammatory and antioxidants properties [5]. The published research acknowledged the use of *Cordia myxa* as potential non-toxic and safe pharmaceutical excipient with various successful applications [6-8].

Grafting is one of the preferred pathways for modification of polysaccharide gums. Grafting leads to formation of hybrid polymers by attaching a monomer to the backbone of natural polysaccharides [9, 10]. Various polysaccharides such as Artemisia seed gum, cassia seed gum, konjac glucomannan, carageenan and xyloglucan have been extensively graft modified to obtain macromolecular materials superior to the naive source polysaccharides for exhibiting higher mechanical strength, displaying desirable viscous nature, acceptable thermo- and degradation-resistant properties [11].

The present investigation was undertaken to demonstrate utility of *Cordia myxa* gum and to explore its grafted modification to serve as sustained release and mucoadhesive tablet excipient using captopril as the model drug.

MATERIALS AND METHODS:

Materials:

Cordia myxa fruits, partially ripe were procured locally from Punjab (India) and were authenticated by taxonomists of Herbarium, Punjabi University, Patiala, Punjab, India (Authentication voucher No: 59109). *Cordia myxa* polysaccharide (CMP) was used in the experimental analysis. Gum samples collected were stored in airtight polypropylene jars in desiccated condition. De-ionized (Milli-Q) water was used for all experiments. Acrylonitrile (ACLN) was procured from Loba chemie (Mumbai, India). Ammonium persulphate (AMPS) GR (99% pure) was obtained from Loba chemie (Mumbai, India). Captopril was received from Yarrow Chem, Mumbai. All other chemicals used were of analytical grade.

Extraction of CMP:

Cordia myxa gum was extracted from the fruits by modifying the method reported earlier [12]. Briefly, the fruits, washed under running water, were wiped dry and stored in plastic zipped bags at -20˚C until used. The outer thin skin (pulp) was removed manually and rest of the gummy part was mashed in glacial acetic acid solution (2% v/v). The slurry was stirred for 30 min. with heating and was kept aside overnight. To remove debris, the slurry was filtered through muslin cloth and added to acetone to precipitate the gum. Finally, the precipitates were dried in an oven at temperature not exceeding 50˚C. The dried gum was grounded to obtain fine powder. The gum was dialyzed and freeze dried to obtain pure CMP.

Modification of CMP to CMP-g-polyacrylonitrile (CMP-g-PAN) by Grafting:

Microwave-assisted grafting of ACLN on CMP was done by modifying the method reported earlier [13]. Powdered CMP (10-30mg) was dispersed in aqueous solution of acrylonitrile (0.05–0.15% w/v)

in a conical flask and mixed well using stirrer. Specified amount of AMPS (20–60 mmol/l) was added to the above mixture and the conical flask was placed on the turntable of a microwave oven (Samsung Electronics, India). The dispersion was irradiated at various level of microwave power (160–480 W) for specified time periods (30–90 s). After microwave irradiation, the mixture was cooled down by placing it under cold water.

The irradiated sample was then left overnight at ambient temperature and then precipitated using acetone. Further washing with acetone was done to remove unreacted residue samples. The grafted precipitates obtained were vacuum dried at 40ºC to a constant weight and converted to fines. The grafting efficiency was calculated using the following formula.

$$\%GE = \frac{w_1 - w_0}{w_2} \times 100$$

Where, % GE is grafting efficiency, w_1 is weight of graft co-polymer; w_0 is weight of polysaccharide and w_2 is weight of monomer.

Optimization using Experimental Design:

Optimization of CMP-g-PAN synthesis was done by using 3-level, 4-factor central composite experimental design [14]. Effects of various independent variables selected such as, Amount of CMP (A), Concentrations of ACLN (B), AMPS (C) and Microwave exposure time, MET (D), were studied on dependent variables, Grafting efficiency (% G) and percent swelling (% swelling) using 3 levels designated as low (−1), middle (0) and high (+1). The statistical analysis of data was done using the Design Expert software (Version 9.0.3.1, Stat-Ease, Inc. Minneapolis, MN). The composition of various grafting batches for graft co-polymerization using the central composite design are shown in **Table 1**.

TABLE 1: EXPERIMENTAL PLAN OF CENTRAL COMPOSITE DESIGN USING LEVELS AND CODED SYMBOL OF FACTORS TO BE STUDIED FOR GRAFTING OF *CORDIA MYXA* GUM (CMP-G-PAN)

Experimental Runs For Grafting	Factors with normalized levels			
	A:Amount of CMP	B:Concentration of ACLN	C:Concentration of AMPS	D:MET
	(mg)	(% w/v)	(mmol/l)	(s)
G1	30	0.15	20	30
G2	30	0.1	40	60
G3	20	0.1	40	60
G4	30	0.05	20	90
G5	10	0.15	20	90
G6	20	0.1	40	60
G7	30	0.05	60	90
G8	10	0.15	20	30
G9	30	0.15	60	90
G10	10	0.05	20	30
G11	30	0.05	20	30
G12	10	0.05	60	30
G13	10	0.05	20	90
G14	20	0.1	40	90
G15	20	0.1	40	60
G16	20	0.1	40	60
G17	20	0.1	40	30
G18	20	0.15	40	60
G19	30	0.15	60	30
G20	10	0.05	60	90
G21	20	0.1	20	60
G22	20	0.1	40	60
G23	20	0.1	40	60
G24	30	0.15	20	90
G25	20	0.1	60	60
G26	30	0.05	60	30
G27	10	0.15	60	30
G28	10	0.15	60	90

G29	20	0.05	40	60
G30	10	0.1	40	60

Factors	Coded Symbol	Levels		
		-1	0	+1
Amount of CMP	A	10	20	30
Concentration of ACLN	B	0.05	0.1	0.15
Concentration of AMPS	C	20	40	60
MET	D	30	60	90

Characterization of CMP-g-PAN:

Swelling Behaviour Study:

The percent swelling of CMP-g-PAN was carried out in buffer pH 1.2 (0.1 N HCl). The sample of CMP-g-PAN (10 mg) was soaked in 100 ml. of 0.1 N HCl for 24 h. The swollen material was then removed and weighed after superficial drying using a blotting paper [4]. The percent swelling (% swelling) was calculated as:

$$\text{Percent Swelling} = \frac{w_f - w_i}{w_i} \times 100$$

where, w_f is the weight of swollen material and w_i is the initial weight of the dry material.

Fourier Transform Infrared (FTIR) Studies:

FTIR spectra of CMP-g-PAN and CMP samples were recorded in KBr pellets using Fourier transform infrared spectrophotometer (Shimadzu, Japan) in the frequency region of 400-4000 cm^{-1} wave numbers [15].

X-ray Diffraction:

X-ray diffraction measurement of CMP-g-PAN and CMP were recorded using X-ray diffractometer (Bruker AXS D8 Advance, Bruker, Germany). Samples were scanned from 0° to 60° diffraction angle (2θ) range, X-ray source was Cu with voltage, 45 kV; current, 40mA and scan speed 1°C/min [15].

Thermogravimetric Analysis:

Thermal characteristics of CMP-g-PAN and CMP was recorded using differential scanning calorimeter (DSC-131 EVO, Setaram, France) under constant nitrogen purge of 1 ml/min over a temperature range of 30–330 °C raising temperature at a constant rate of 10 °C/min [16].

Formulation of Captopril Mucoadhesive Tablets:

The optimized CMP-g-PAN grafted batch and CMP were taken as the polymers for the preparation of Captopril mucoadhesive tablets using a direct compression method. Various formulation batches (F1-F4) were prepared by varying the concentration of polymers (10% and 20% w/w). The polymer was homogeneously mixed with the drug in a blender for 15 minutes. The mixture was lubricated with talc and magnesium stearate (after sieving through 60 mesh sieve) and then compressed using an 8-mm diameter die in a tablet punching machine (AK Industries, Nakodar, Punjab, India) weighing 200 mg of each tablet.

Comparative study:

To evaluate the mucoadhesive potential of the CMP-g-PAN, comparative study was carried out by formulating a batch with Carbopol 934 as standard mucoadhesive polymer. Two formulation batches (F5 & F6) of Carbopol 934 in mucoadhesive tablets were prepared using 10% and 20% w/w concentration. Composition of different formulation batches of Captopril mucoadhesive tablets employing three different polymers are shown in **Table 2**.

TABLE 2: COMPOSITION OF FORMULATION BATCHES OF CAPTOPRIL MUCOADHESIVE TABLETS USING DIFFERENT POLYMERS.

Ingredients (mg)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Drug	25	25	25	25	25	25
CMP	20	40	-	-	-	-
CMP-g-PAN	-	-	20	40	-	-
Carbopol 934	-	-	-	-	20	40
Microcrystalline	50	50	50	50	50	50

Cellulose (Avicel pH 101)						
Magnesium Stearate VG	2	2	2	2	2	2
Talc	4	4	4	4	4	4
Lactose Monohydrate	99	79	99	79	99	79
Tablet Weight	200	200	200	200	200	200

'-' = Not incorporated

Evaluation of Captopril Mucoadhesive Tablets:
The tablets from each formulation batch (F1 to F6) were evaluated for weight variation, hardness, drug content, friability, *ex vivo* mucoadhesive strength, force of adhesion, *ex vivo* mucoadhesion time and *in vitro* drug release study.

Hardness and Friability:
The formulated tablets were evaluated for hardness and friability parameters using Monsanto hardness tester (Perfit, India) and Roche friabilator (Model 902, EI, India) respectively.

Drug Content:
Twenty tablets were finely powdered. A quantity equivalent to 25 mg of the drug was transferred to a volumetric flask and the volume was made upto 50 ml with 0.1N HCl. The mixture was allowed to stand for 12 h with an intermittent shaking. The mixture was filtered and after suitable dilution was analyzed for captopril content at 205 nm using a UV–Visible spectrophotometer (Shimadzu, Japan).

***Ex vivo* Mucoadhesive Strength:**
The mucoadhesive strength of each formulation was determined by measuring the force required to detach the formulation from freshly cut goat's gastric mucosa tissue using texture analyzer. In brief, goat's gastric mucosa tissues were obtained from the local slaughter house. Tissues were immediately used after separation. The tablet was attached to the probe (stainless steel cylindrical probe with 10 mm diameter) using cyanoacrylate adhesive. The probe was lowered at a speed of 0.5 mm/s until the tablet made contact with mucosal tissue. A constant force of 1 N was applied for 60 s, after which the probe was withdrawn at a speed of 0.5 mm/s to the distance of 15 mm. The maximum detachment force or bioadhesive strength, i.e. the force required for separating the sample from the tissue surface was obtained [17]. Each measurement was repeated three times.

Force of Adhesion:
Force of adhesion can be calculated by using the formula [18].

$$\text{Force of adhesion} = \frac{\text{Mucoadhesive strength} \times 9.81}{100}$$

***Ex vivo* Mucoadhesion Time:**
The *ex vivo* mucoadhesion time was examined after adhering the tablet on goat's gastric mucosa, that was procured from the slaughter house. Gastric mucosa was pasted on a glass slide using a double sided tape, and the tablet was wetted with a drop of pH 1.2 buffer and adhered to mucosa by applying a light force with fingertip for 30 seconds. The glass slide was then placed in a beaker, which was filled with 200 ml of buffer pH 1.2 and kept at 37±0.5ºC. After 2 min, a slow stirring rate (50 rpm) was applied to simulate the gastric environment, and the tablet mucoadhesion period was monitored [19]. The time of tablet's detachment from goat's gastric mucosa was recorded as the mucoadhesion time.

***In vitro* Dissolution Studies:**
In vitro dissolution rate study of the formulations was performed using USP paddle apparatus by maintaining 37°C temperature at 50 rpm using 900 ml of 0.1 N HCL solution. At various time intervals 5 ml sample was withdrawn and replaced with same amount of buffer (0.1N HCl). The samples were filtered through 0.2-µm Whatman filter paper and analyzed using U.V spectrophotometer (Shimadzu, Japan) at wavelength of 205 nm. The cumulative percent drug release was plotted against time to determine the release profile [16].

RESULTS AND DISCUSSIONS:
Preparation of CMP-g-PAN:
Modification of CMP by microwave-assisted grafting was achieved using acrylonitrile as a vinyl monomer. Rapidly changing electric field component of microwaves restricts the migration of large size polysaccharides; however, the increased

rate of reaction is a direct result of dielectric heating caused by localized rotation of pendent hydroxyl groups [11]. Microwave radiations are also reported to lower the Gibbs energy of activation of reactions enhancing the reaction rates [20]. The ammonium persulphate used in the synthesis works as free radical initiator which provides the free radicals that abstract hydrogen atom from CMP molecule yielding CMP macroradicals. These macroradicals initiate the chain reaction and further propagate the reaction by reacting with acrylonitrile monomer providing acrylonitrile free radicals which results in a series of free radical chain reactions yielding CMP-g-PAN and polyacrylonitrile homopolymer.

General flowchart depicting steps involved in the present study:

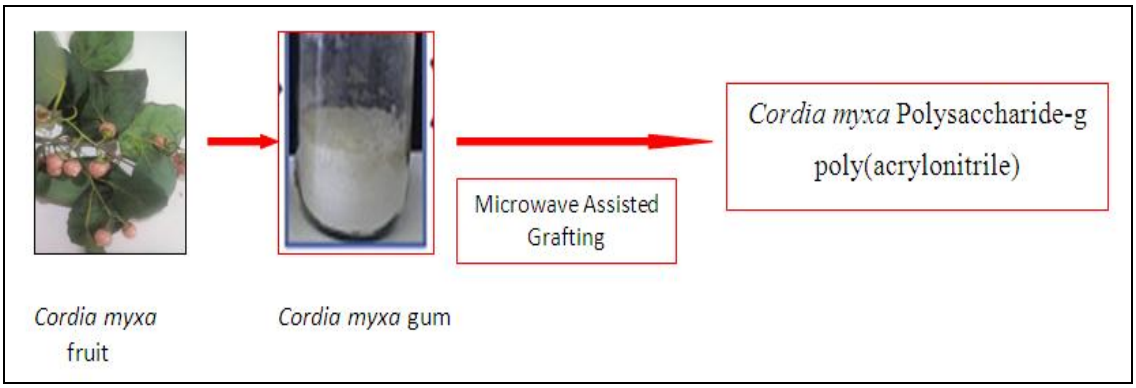

FIG. ?????????

Influence of formulation variables on various responses studied in synthesis of CMP-g-PAN: The results of various batches for graft co-polymerization studied using the central composite design are shown in **Table 3**.

TABLE 3: EFFECT OF VARIOUS FACTORS ON RESPONSES STUDIED FOR VARIOUS GRAFTING BATCHES PREPARED USING CENTRAL COMPOSITE EXPERIMENTAL DESIGN

Grafting Batch	Factors				Responses	
	A:Amount of CMP	B:Concentration of ACLN	C:Concentration of AMPS	D:MET	% GE	% Swelling
Code	(mg)	(% w/v)	(mmol/l)	(s)	%	%
G1	30	0.15	20	30	58.6	131.9
G2	30	0.1	40	60	94	208.7
G3	20	0.1	40	60	93.65	199.2
G4	30	0.05	20	90	26.2	109.3
G5	10	0.15	20	90	14.81	104.3
G6	20	0.1	40	60	55.8	125.3
G7	30	0.05	60	90	92.38	189.4
G8	10	0.15	20	30	14	102.1
G9	30	0.15	60	90	89.5	181.3
G10	10	0.05	20	30	28.9	110.7
G11	30	0.05	20	30	23.4	107.6
G12	10	0.05	60	30	65.6	148.6
G13	10	0.05	20	90	61.02	140.3
G14	20	0.1	40	90	84.6	168.1
G15	20	0.1	40	60	97.5	232.2
G16	20	0.1	40	60	94.68	213.7
G17	20	0.1	40	30	36.23	113.6
G18	20	0.15	40	60	73.26	155.5
G19	30	0.15	60	30	64.34	145.2
G20	10	0.05	60	90	89.4	180.1
G21	20	0.1	20	60	44.28	118.6
G22	20	0.1	40	60	95	220.3

G23	20	0.1	40	60	95.45	228.4
G24	30	0.15	20	90	25.4	108.2
G25	20	0.1	60	60	92.8	191.7
G26	30	0.05	60	30	86.7	173.8
G27	10	0.15	60	30	53.2	122.8
G28	10	0.15	60	90	84.68	169.9
G29	20	0.05	40	60	90.42	186.6
G30	10	0.1	40	60	72.88	154.9

According to the experimental design, the responses fitted best into the response surface quadratic model. The mathematical relationship between the independent variables and the dependent variables can be expressed by the following equations:

Mathematical modeling equations:

$$\%GE=84.79+4.22A-4.79B+23.44C+7.61D+5.46AB+1.57AC-5.49AD-0.98BC-2.51BD+5.22CD+2.29A^2+0.69B^2-12.61C^2-20.73D^2 \quad \text{Eq. (1)}$$

$$\%Swelling=189.18+6.76A-6.96B+26.10C+10.81D+4.19AB+4.29AC-5.04AD-3.21BC-1.04BD+7.53CD+6.63A^2-4.12B^2-20.02C^2-34.32D^2 \quad \text{Eq. (2)}$$

The highest value and positive sign in both mathematical modeling equations suggests that various concentrations of AMPS (C) exhibited a pronounced synergistic effect on grafting efficiency and percent swelling. A negative sign in both mathematical modeling equations indicated that the concentrations of ACLN (B) employed had a significant antagonistic influence on grafting efficiency and percent swelling. The increasing order of influence of various response parameters on grafting efficiency and percent swelling was found to be; A< D < B < C.

Significance of model was estimated by applying analysis of variance (ANOVA) in the experimental design. The model was found to be significant and adequate (P< 0.0008) with 'lack-of-fit' being non-significant. According to model summary statistics, higher values of R^2 (0.9632) indicates a high degree of correlation between the experimental and predicted responses. Further, good agreement between the values of 'predicted R^2' (0.9120) and 'adjusted R^2' (0.8832) indicated the design model to be reliable. **Fig. 1 (A & B)** depicts the combined effect of different independent variables on percent grafting and percent swelling of CMP-g-PAN through 3-dimensional response surface graphs.

It can be interpreted from the graphs that increasing the concentration of AMPS, while keeping the concentration of ACLN at lower level, resulted in increase in grafting efficiency **(Fig. 1.A.3.)** and percent swelling **(Fig. 1.B.3)**. The plot shows that increasing the concentration of ACLN reduced the grafting efficiency and swelling. This could be attributed to formation of more amount of homopolymer on increasing the concentration of ACLN, which decreased the grafting efficiency, which, in turn reduced swelling.

On the other hand, increasing AMPS concentration at lower concentration of ACLN resulted in formation of more ACLN macroradicals, which probably reacted with sufficient amount of CMP backbone to yield graft co-polymer. However, increasing the ACLN concentration resulted in formation of excess amount of ACLN macroradicals, which due to insufficient polysaccharide backbone reacted amongst them to give homopolymer, thereby decreasing the grafting efficiency.

It can be inferred from **Fig. 1.A.4.** and **Fig. 1.B.4.** that concentration of AMPS had more pronounced effect on dependent variables (GE and swelling) than MET. AMPS is a free radical initiator. Increasing its concentration resulted in formation of greater amount of free radicals, which resulted in enhanced formation of graft co-polymer. Response surface graphs showing the combined effect of concentration of ACLN and MET on percent GE and percent swelling are depicted in **Fig. 1.A.5.** and **Fig. 1.B.5.** The effect of MET is less pronounced than the effect of concentration of ACLN on

dependent variables. The lower concentration of acrylonitrile and exposure for higher duration favours the formation of graft co-polymer with higher percentage grafting. The optimal parameters were obtained using numerical optimization approach by setting the goals and the constraints i.e., maximizing the percent grafting efficiency and percent swelling, keeping concentrations of CMP (A), ACLN (B), AMPS (C), and MET (D) within the range. A set of solutions were provided by the optimization tool of the central composite design. The optimal batch (G15) with concentrations of CMP (A)—20 mg, ACLN (B)—0.1% (w/v), AMPS (C)—40 (mmol/l), MET (D)—60 s, provided a graft co-polymer (CMP-g-PAN) with grafting efficiency of 97.5% and percent swelling of 232.2%.

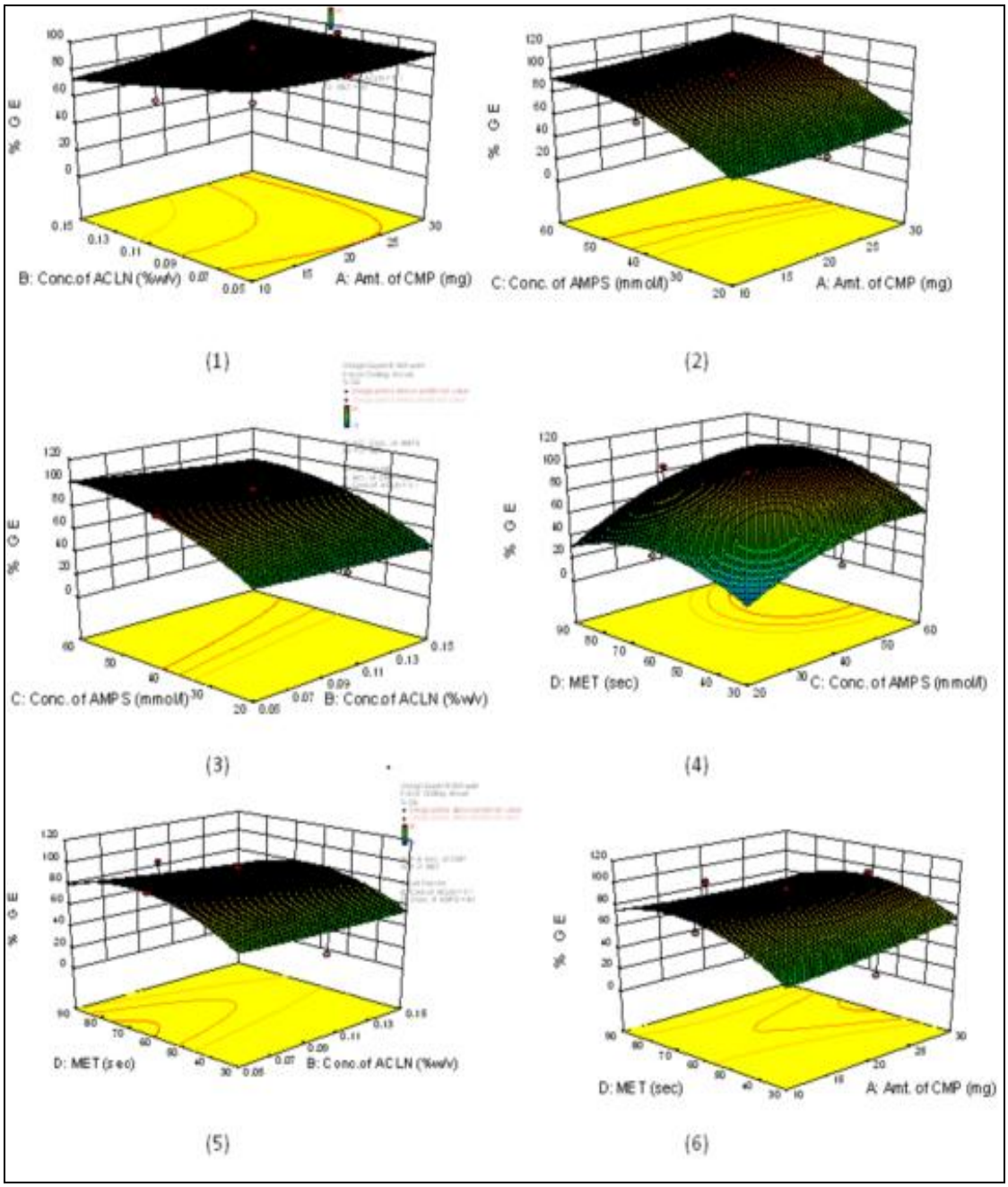

FIG. (1).A: Response surface plots showing the combined effect of (1) concentrations of CMP and acrylonitrile (ACLN) on percent grafting, (2) concentration of CMP and ammonium persulphate (AMPS) on percent grafting (3) concentrations of ACLN and AMPS on percent grafting (4) concentration of AMPS and Microwave exposure time (MET) on percent grafting, (5) concentration of ACLN and MET on percent grafting and (6) concentration of CMP and MET on percent grafting.

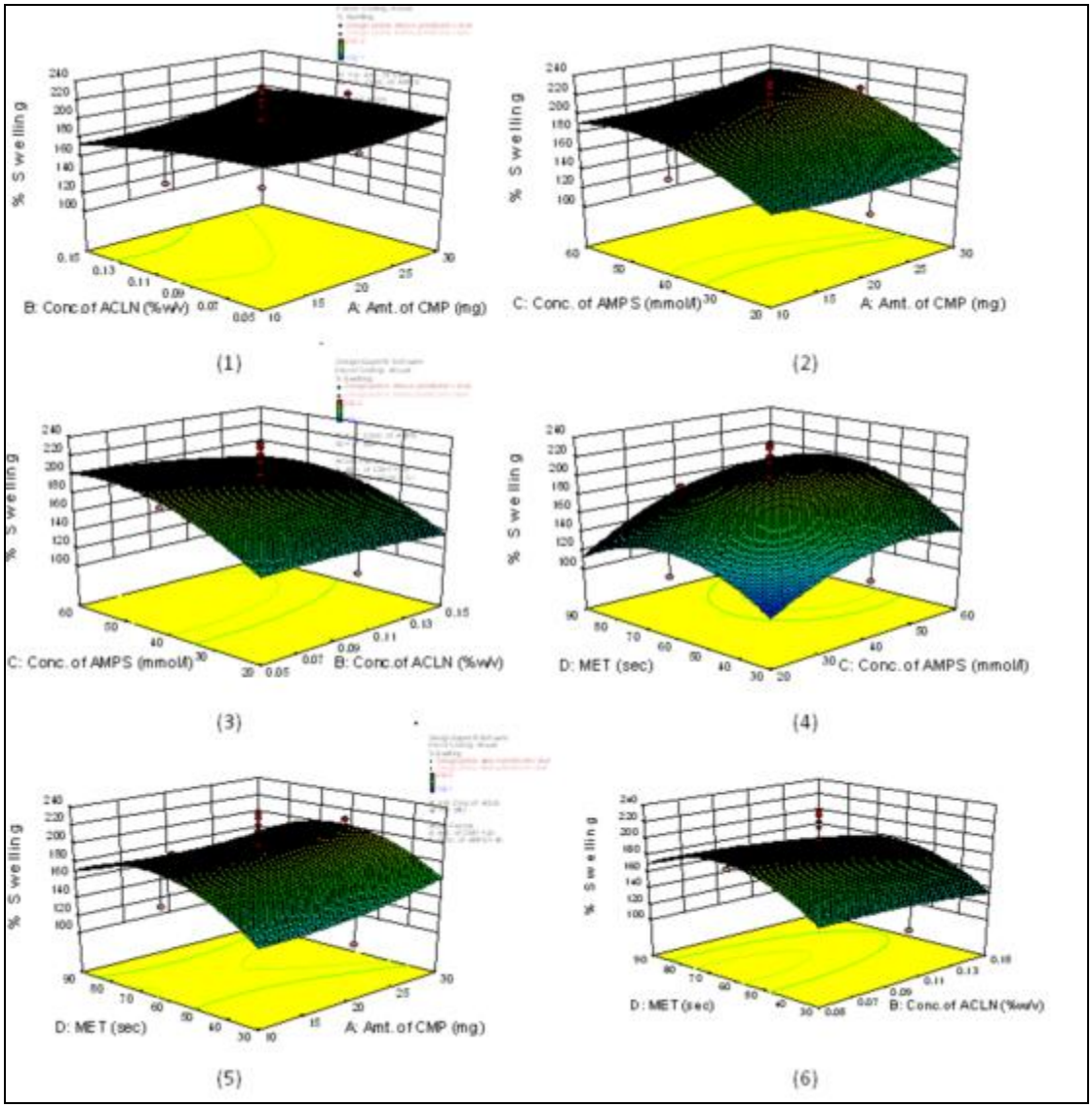

FIG. (1).B: Response surface plots showing the combined effect of (1) concentrations of CMP and acrylonitrile (ACLN) on percent swelling, (2) concentration of CMP and ammonium persulphate (AMPS) on percent swelling (3) concentrations of ACLN and AMPS on percent swelling (4) concentration of AMPS and microwave exposure time (MET) on percent swelling, (5) concentration of CMP and MET on percent swelling and (6) concentration of ACLN and MET on percent swelling.

Characterization of CMP-g-PAN:

Swelling Behaviour Study:

The swelling characteristics of all the grafting batches for CMP-g-PAN investigated in buffer pH 1.2 (0.1 N HCl) are shown in **Table 3**. The results revealed increased swelling of matrices with enhanced percent grafting. The optimized formulation batch (G15) with highest percent grafting (97.5%) showed maximum swelling (232.2%). Therefore, higher magnitude of swelling of CMP-g-PAN can be expected to be useful for modulating the drug release from dosage forms.

FTIR spectra:

In the spectra of CMP-g-PAN **(Fig. 2A)**, a peak at 3250 cm^{-1} was assigned to the –OH stretching in alcohol group while the peak appearing at 3010 cm^{-1} is due to symmetric stretching of methylene group. Peak at 1720 cm^{-1} confirms the presence of C=C of monomer.

Grafting of acrylonitrile was confirmed by the presence of peak at 2250 cm^{-1} which is due to nitrile stretching. The spectrum of CMP-g-PAN was compared with the spectra of CMP **(Fig. 2B)**. A broad absorption band at 3380 cm^{-1} was observed, which, can be attributed to –OH stretching. A peak appearing at 1380 cm^{-1} was due to C-O stretching, while peaks at 1190cm^{-1} and 1100 cm^{-1} can be ascribed to C-O-C stretch of ether.

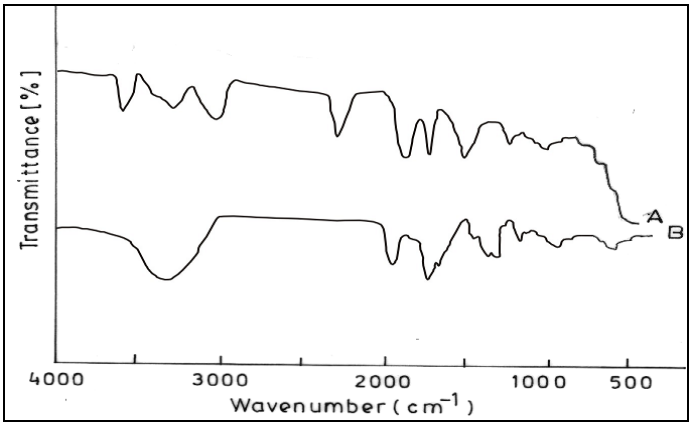

FIG. 2: FT-IR SPECTRA OF (A) CMP-G-PAN (B) CMP.

X-ray Diffraction:

Fig. 3 shows the results of XRD analysis for CMP-g-PAN and CMP samples. From the XRD diffractogram it is possible to understand that the CMP **(Fig. 3B)** gave a more intense peak than that of CMP-g-PAN **(Fig. 3A)**. This suggested that amorphous nature of the CMP increased after grafting. The amorphous materials generally had higher water solubility. Successful grafting led to an increase in amorphous nature of modified gum and this was reflected by changes in swelling index as shown in **Table 3**.

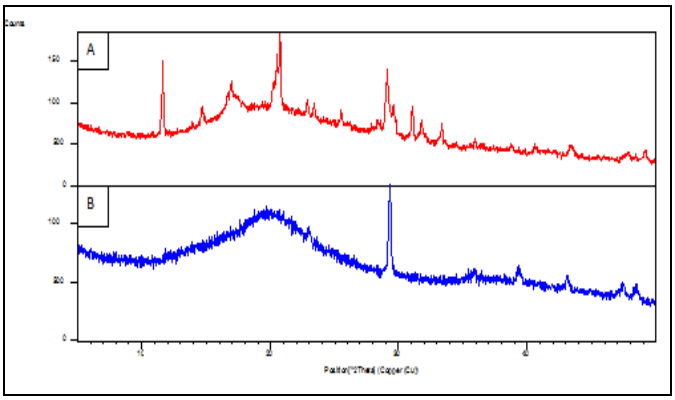

FIG. 3: XRD DIFFRACTOGRAM OF (A) CMP-G-PAN (B) CMP.

Thermo gravimetric analysis:

Fig. 4 shows the thermogram of CMP-g-PAN **(Fig. 4A)** and CMP **(Fig. 4B)**. CMP-g-PAN thermogram showed a sharp endothermic peak at 194°C **(Fig. 4A)**, whereas, the endothermic transition of CMP exhibited a sharp peak at 79°C followed by an exothermic peak at 275°C **(Fig. 4B)**. Thus, shifting of endothermic peak and disappearance of an exothermic peak in CMP-g-PAN indicated that modification of CMP has taken place. The shifting of endotherm to higher temperature also indicates enhanced thermal stability of graft co-polymer over native gum.

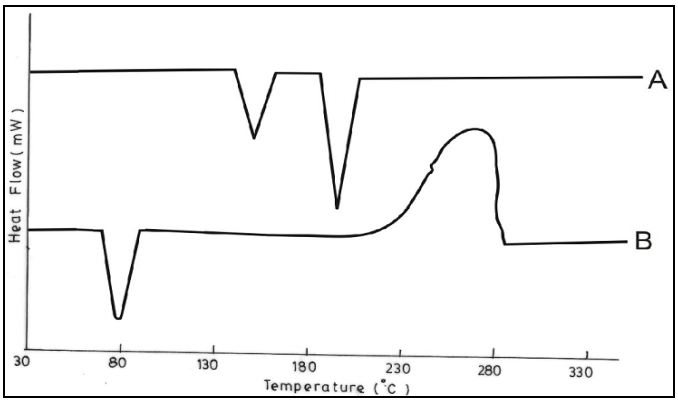

FIG. 4: DSC CURVES OF (A) CMP-G-PAN (B) CMP.

Evaluation of Captopril Mucoadhesive Tablets:

Weight variation:

The average weight of 20 tablets along with standard deviation of entire formulations has been presented in **Table 4**. The percentage of weight variation of individual tablets from the average weight was found to be within ±5% w/w which proved that the entire tablets have passed the USP weight variation test.

Drug content:

The drug content of all the tablets in formulation batches were found to be in the range of 98.29 ± 1.0% to 102.10 ± 1.4% as shown in **Table 4**. The results indicated that tablets of entire batches have passed the USP criteria for the drug content of tablets.

Hardness:

The hardness of tablets of all formulation batches were found to be in the range of 6.0 ± 0.5 kg/cm^2 to 6.5 ± 0.7 kg/cm^2. The friability results revealed that the tablets of entire batches had passed USP criteria of friability testing (<1.00% w/w) showing good mechanical strength. The results are shown in **Table 4**.

Ex vivo Mucoadhesive Strength:

Mucoadhesive strength describes the mucoadhesive property of the polymer i.e. affinity of the polymer to attach with mucus layer in the mucus part of the body. The *ex vivo* mucoadhesion strength ranged from 12.52 ± 1.5 g to 55.15 ± 3.5 g. It was observed that mucoadhesive strength of the tablets increased with increase in concentration of the

grafted polymer. The maximum mucoadhesive strength was noted with F4 (55.15 ± 3.5 g). Uronic acid content present in the gum makes the molecule modification easy by grafting due to reaction of hydroxyl groups of gum with acrylonitrile polymer to form graft polymer where radical stripped down the H atom of the –OH group of the gum to generate macro radicals [21]. The introduction of new functional group by grafting resulted in enhanced charge density on CMP-g-PAN, making it easy to bind to opposite charge present on mucin layer thus increasing the mucoadhesion strength [19]. The mucoadhesion strength and force of adhesion for all the formulation batches are evident in **Table 4**.

Force of Adhesion: Force of adhesion of CMP-g-PAN was found to be 5.44 ± 0.48 N. The enhanced mucoadhesive force is believed to be due to attraction forces across the electrical double layer, formed between CMP-g-PAN and the mucosal surface.

***Ex vivo* Mucoadhesion Time:**

The mucoadhesion time for the various batches is depicted in **Table 4**. The formulations containing CMP-g-PAN took more time (12 h) for complete detachment when compared to the tablets containing CMP (6h) and carbopol 934 (8h).

The reason behind this can be the fact that the CMP-g-PAN contains $–COO^-$ groups due to the presence of uronic acid molecule and the mucosal mucin protein surface has $–NH_3^+$ groups, both carrying opposite electrical charges. When the polymers come in contact with the mucosal surface, electron transfer occurs in an attempt to balance Fermi levels, causing the formation of a double layer of electrical charge at the polymer–mucin interface, which enhances the time of contact of CMP-g-PAN with mucosal surface [22, 23].

TABLE 4: EVALUATION OF CAPTOPRIL MUCOADHESIVE TABLETS

Formulation Code	Hardness (kg/cm^2)	Weight Variation	Friability	Drug Content(%)	*Ex vivo* Mucoadhesion Strength (g)	Force of Adhesion (N)	*Ex vivo* Mucoadhesion Time (h)
F1	6.0 ± 0.5	201 ± 2.5	0.39 ±0.02	98.29 ± 1.0	12.52 ± 1.5	1.15 ± 0.20	2.5 ± 0.30
F2	6.3 ± 0.7	203 ± 1.6	0.36 ± 0.04	101.43± 2.8	22.76 ± 1.8	2.22 ± 0.25	6 ± 0.55
F3	6.3 ± 0.6	199 ± 1.4	0.47 ± 0.07	99.21 ± 1.8	29.44 ± 2.5	3.58 ± 0.40	9 ± 0.80
F4	6.5 ± 0.7	201 ± 2.6	0.38 ± 0.05	99.87 ± 2.0	55.15 ± 3.5	5.44 ± 0.48	12 ± 0.91
F5	6.2 ± 0.5	205 ± 1.8	0.45 ± 0.02	102.10± 1.4	16.98 ± 1.4	1.34 ± 0.14	4 ± 0.35
F6	6.2 ± 0.6	202 ± 2.3	0.37 ± 0.04	99.46 ± 2.4	28.45 ± 1.8	2.48 ± 0.20	8 ± 0.55

All values represent mean ± standard deviation (n=3).

***In vitro* Drug Release Study:**

The results of *in vitro* drug release study of all the formulation batches of captopril mucoadhesive tablets are presented in **Fig. 5**. From the drug release profile of the formulation batches, F1 & F2 it was seen that the release of drug from the matrix tablet was more rapid. This occurred due to the fact that the formulations were made up of native *Cordia myxa* gum which was having less branched network of the polymer leading to rapid swelling of the matrix. The F5 and F6 batch (with standard mucoadhesive polymer) showed a controlled release pattern but drug release was completed within 08 h. Release profile of batch F3 & F4 showed a superior fit to the required drug release profile among all the batches. The result of drug release profile of the batch F4 showed 28.12 % w/w of drug released during the first 2 h, while 68.76 % w/w drug was released within 6 h and the remaining amount of the drug was released in the next 6 h (99.56 % w/w). Hence, a controlled release pattern of drug was observed from the batch F4 throughout the 12 h of dissolution study. The reason might be the fact that the matrix is formed of comparatively greater branched grafted gum (grafting efficiency was high), which leads to retarded swelling.

The *in vitro* drug release studies F3 and F4 with different concentration of polymer (10% and 20%) showed that an increase in polymer concentration reduced the drug release throughout. This might be due to the higher concentration of the polymer which upon swelling reduces the diffusion of the drug from the matrix of mucoadhesive tablets. Comparative *in vitro* dissolution profile of CMP-g-

PAN and carbopol 934 indicated that mucoadhesive tablets prepared with CMP-g-PAN showed controlled release pattern of 12 h compared to carbopol 934 where drug release ended in 8 h. The batch prepared with 20% w/w of CMP-g-PAN (F4) was identified as an ideal batch based on its *in vitro* drug release profile, *ex vivo* mucoadhesive time and optimum mucoadhesive strength.

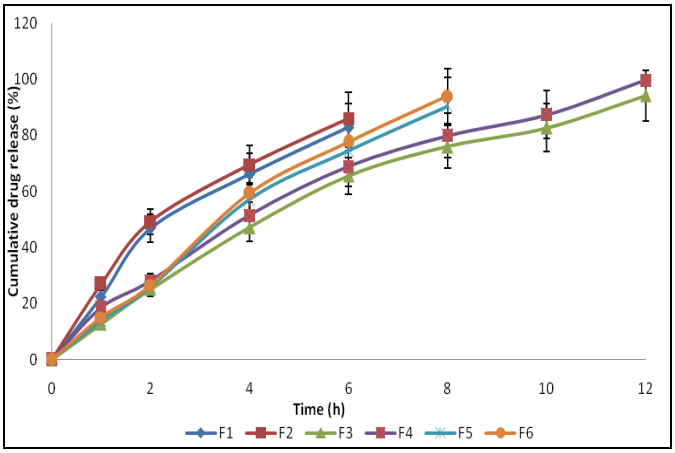

FIG.5: *IN-VITRO* DRUG RELEASE DATA OF VARIOUS FORMULATION BATCHES (F1-F6) PREPARED USING DIFFERENT CONCENTRATIONS OF CMP, CMP-G-PAN & CARBOPOL 934.

CONCLUSIONS: The modification of CMP was successfully accomplished by grafting technique and simultaneously optimized the process using central composite experimental design. The optimization parameters such as, concentrations of ammonium persulphate, acrylonitrile and microwave exposure time were observed to play a vital role in influencing the grafting efficiency and percent swelling. Sustained release tablet of Captopril was developed by using CMP-g-PAN as a drug release rate controlling and mucoadhesive polymer.

The grafted derivative (CMP-g-PAN) was found to be superior to the native gum (CMP) and carbopol 934 in terms of its controlled release effect carried upto a period of 12 h and its enhanced mucoadhesive potential in terms of time and strength. Furthermore, it was also inferred that the rate of release of the drug substance as well as the mucoadhesive strength of the formulation can be modulated by varying the amount of gum included in the tablet. In conclusion, the *Cordia myxa* polysaccharide modification (CMP-g-PAN) by microwave irradiation grafting technique exhibited acceptable and improved mucoadhesive properties.

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