Purification and modification of *Cordia myxa* gum to enhance its nutraceutical attribute as binding agent

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Abstract: The aim of the present study was to purify, hydrolyze and modify the *Cordia myxa* gum to document its binder potential in pharmaceutical tablets formulation. The hydrolysis and modification was carried out to remove impurities, roughness, increase thermal stability and to improve the functional properties of biopolymers. Physiochemical properties such as pH, solubility, viscosity, swelling index, bulk and tapped density was performed prior to investigate binder potential. The binder potential of *Cordia myxa* gum was studied in its different forms such as crude, purified, modified and hydrolyzed in paracetamol tablets and was compared with standard hydroxypropyl methylcellulose (HPMC) being used as synthetic binder. Tablets were prepared by direct compression method and evaluated for weight uniformity, hardness, friability, disintegration time and dissolution analysis. Prepared tablets with selected gums exhibit faster and slower dissolution profile in the same dissolution system. The crude gum has high dissolution rate whereas the hydrolyzed and modified gums showed less dissolution rate. The hydrolyzed and modified gums having faster release rate and it could be helpful in conventional tablet formulations efficiently as compared to synthetic HPMC binder.

Keywords: *Cordia myxa*, hydroxypropyl methylcellulose (HPMC), binder, drug release, paracetamol.

INTRODUCTION

Pharmaceutical products are commonly administrated in to human body in the form of liquids (injections or syrups) or solids (powder or tablets). Tablets are the most popular and effective form of medication because of its easy manufacturing and self- administration (Rowe *et al*., 2006). It consist of one or more than one active ingredients and other substances in its formulation that mainly act as binding or additive agents to make body compatible administration and release in biological environment. The release of active ingredients mainly depending on solubility factors (Shah *et al*., 2009). However, the favorite binding agents are those that have fruitful general role or not at all in biological system but efficiently release the active ingredients in blood stream or at target site.

Recently plants have been the medium of attraction due to its promising potential to stand against number of disease. Natural products are the safe and active biological compounds that are being exercised as medicine in clinical setups and as functional food in food industry. About 80% of the world's population still depending on the auyredic medication (Ranjbar *et al*., 2013). The gums obtained from natural resources, due to lack of advanced medical resources, have attracted high attention due to its varied applications in the field of cosmetics, food and pharmaceutics due to their non-toxicity, high water solubility, swelling ability, stability at wide range of pH and biodegradable behavior (Cui *et al*., 2007). Further due to its resinous nature, high molecular weight polysaccharides, good dispersion or solubility in water and lack of toxicity more favorable for human administration as binding agent of pharmaceutical granular materials (Dinda and Mukharjee, 2009).

In pharmaceutical industry this molecules mainly act as binding agent for active ingredients to prepare tablets. A verity of natural, semi-synthetic and synthetic are being utilized in the formation of tablets as binders. Variety of plant gums are used as binding agents in tablet formulation viz. acacia, guar gum, and tragacanth gum in its raw form (Narkhede Sachin *et al*., 2010, Shahid *et al*., 2013). However, most of them, particularly synthetic and semisynthetic binding agents are significantly expensive and impart destructive effect on the stability of product (Goswami and Naik, 2014). The purity of natural gums is one of major issues to use as binding agent. They are prone to degradation due to microbes or oxidation. In this study we are reporting the purification and modification of natural gum extracted form of *Cordia myxa* followed by investigating its binder effects on the

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mechanical properties of tablets and to compare it with standard tablets with HPMC as binding agent.

MATERIALS AND METHODS

The *Cordia myxa* gum was purchased from the local market, Badha Dawakhana, Railbazar, Faisalabad. The gum that is polymer in nature, exuded by tree by disrupting the stem bark. All the chemicals of analytical grade were used in this study. Trifluoroacetic acid (TFA), sulfuric acid, ammonium chloride and potassium per sulphat were purchased from E. Merk (Germany). Silver nitrate, barium hydroxide, citric acid and acrylamide were from Sigma-Alderic (USA) unless otherwise noted. Lactose and cellulose was purchased from JRS pharma, Germany. Hydroxypropyle methylcellulose (HPMC) and paracetamol were obtained from saffron pharmaceuticals, Pakistan.

Purification of gum

The crude cordia gum (5g) was purified using soxhlet apparatus in ethanol. The product obtained was hydrated with deionized water (400ml) and stirred for mixing using magnetic stirrer for 3h. The solution was centrifuged at 1500 rpm for 10 minutes. Acetone was used to precipitate the supernatant, it was filtered and washed successively with ethanol. The final product was again dialyzed against deionized water for 6h and lyophilized (Dodi *et al*., 2011).

Determination of Physiochemical properties

The purified gum (PG) was subjected to test physiochemical properties including pH, fluorescence potential, viscosity and swelling behavior by dissolving the PG in distilled water following the protocol reported in literature (Akpabio *et al*., 2011, Chase Jr and Pratt, 1949, Dinda and Mukharjee, 2009, Jahan *et al*., 2008, Singh *et al*., 2010)

Hydrolysis of PG

Acidic hydrolysis of PG was performed using the protocol described by Größl *et al*. (Großl *et al*., 2005). Briefly, filtered PG samples in the range of 2-4 mg were taken in 2 M triflouroacatic acid solution (100uL/0.2 mg sample) and hydrolyzed in capped glass vials for 2h at 110ºC. The hydrolyzed samples were then collected through ethanol precipitation process and dried in hot air oven. Basic hydrolysis of PG was carried out following the method described by (Beltrán *et al*., 2008). Briefly, 5g PG sample was hydrolyzed with saturated solution of $Ba(OH)_2$ at 110ºC for 6h, followed by H_2SO_4 (1 M) neutralization process. The obtained product was precipitated using ethanol, filtered and dried.

Polyacrylamide grafting

PG has been chemically modified using a previously reported polyacrylamide grafting methodology (Singh *et al*., 2009). Briefly, 1g of PG was dissolved in 25 mL water. To the solution, subsequently added acrylamide (16×10^{-2} M), $AgNO_3$ (8.0×10^{-5} M) and citric acid (22×10^{-3} M). The obtained solution was then incubated in water bath at 35 °C, followed by, after an interval of 30 min, further 10 min incubation in $K_2S_2O_8$ (8.0×10^{-3} M) was performed and the reaction mixture was left to stand for 60 min. Finally, the polyacrylamide modified (PMG) gel was separated using ethanol precipitation. The PMG precipitate was then washed with ethanol and dried in an oven.

Pharmaceutical potential

To evaluate the binding potential of purified and hydrolyzed gum (PHG) in pharmaceutical tablet formulation, paracetamol were used as raw powder material and compared its potential with hydroxypropyl methylcellulose (HPMC); a synthetic routinely used binder in pharmaceutical industry. Tablet formulation using PHG binder was performed by following the wet granulation methodology (Singh *et al*., 2010). The binder (either PHG or HPMC) concentration 1.5% w/w per tablet in solution form was added to dry mixture of 33.02mg of paracetamol, 163 mg of lactose and 44.03mg of micro crystalline cellulose. The wet mass calculation was carried out by filtering the whole mixture through mesh sieve No.30. The granules were dried at 50°C in oven for 30 min, again filtered through mesh sieve No.30, and to filtered granules added 1% magnesium stearate.

Analysis of granules

Bulk and tapped densities

Granules (10g) were added to 50 mL graduated cylinder and noted the occupied volume (Vs) followed by calculating the apparent density ($P_{B)}$ using the expression; $P_B = W/V_B$ (g/mL). The stroke volume was recorded by mechanically applying the stress on cylinder at a fix height, until note-able decrease in volume (V_t). The captured density (P_t) was calculated using the equation; $P_t = W/V_t$ (g/mL). All these calculations was carried out by following the reported methods (Onunkwo, 2010).

Carr's compressibility index and Hausner's ratio

While performing the Carr's compressibility index and Hausner's ratio study, the data obtained was used in calculating the Carr's index (CI) and Hausner's ration (HR) by following expression; CI = 100(TD-BD) and HR = TD/BD where TD is tapped density and BD is bulk density (Basawaraj *et al*., 2010).

Preparation of tables and evaluation

The tablets were prepared by compressing the granules using tablet machine (F3-Manesty, UK) equipped with convex shaped puncher to prepare 8mm-250 g tablets.

Determination of weight uniformity: Twenty tablets were picked randomly for each batch and weighed individually and collectively to calculate the mean weight as reported in literature (Ahuja *et al*., 2013).

Hardness test: The hardness test was performed by picking 10 tablets of each batch – for this the TBH-200 hardness test was followed to calculated average hardness (Ahuja *et al*., 2013).

Friability: Twenty tablets were picked randomly from each batch and their weight was recorded collectively as initial weight. After that, tablets were placed in friability tester (Copley FR-1000) at the rate of 25 rpm for 4 min followed by dusting and weighing (Ahuja *et al*., 2013). Finally, the friability was calculated using the following formula;

F = (initial weight – final weight)/ initial weight x 100

Disintegration time determination

The disintegration time of tablets was studied by following the method described earlier in British Pharmacopoeia, 2010. Following the protocol, six tablets randomly picked from each formulations batch were placed in disintegrate equipment (Copley, ZT-34, UK). The 0.1M NH_4Cl solution (maintained at 37ºC ± 5ºC) was used disintegration medium and then calculated the disintegration time using protocol reported in literature (Ahuja *et al*., 2013).

Dissolution rate determination

The dissolution bath equipment (USP-II, PTS3C, drug testing company Hainburg, Germany) was used to determine the drug release/dissolution from tablets following the protocol described in British Pharmacopoeia, 2010. One tablet was placed in equipment and subjected to 100 revolutions/min for predefined time period. The 0.1 N HCl was used as the medium of dissolution at 37ºC ± 5ºC, then after each five min interval, 1 mL sample was taken from dissolution medium and analyzed at 243 nm using UV/VIS spectrophotometer. From the spectrophotometric data the rate of drug release into solution was calculated.

RESULTS

Extraction, purification and physiochemical properties of gum cordia myxa

The extraction of gum from crude gum was carried out by using Soxhlet apparatus in methanol which showed more than 80% yield. The physiochemical properties such as swelling potential, pH, and viscosity and fluorescence color were studied. While dissolving the PG in water and phosphate buffer, the PG showed 3.92g and 2.32g swelling index in water and phosphate buffer, respectively. The pH of 1% water solution was noted 6.7 that was slightly acidic. The viscosity of PG gum was assessed about 411 cp or 4.11 poise. The fluorescence study under UV light showed brown color of the PG.

Hydrolysis and polyacrylamide grafting of gum

The acidic and basic hydrolysis showed successful precipitation with 99.9% ethanol. The modification of PG was also carried out successfully using polyacrylamide grafting method. This chemical modification polymerizes the PG to become more stable. The hydrolysis and grafting process was assessed by scanning electron microscope as shown in fig. 1. PHG of *Cordia myxa* was tested as tablet binders in paracetamol tablets and the binding potential was compared with synthetic HPMC binder. The gum solution was used as granulating fluid which has the function of binding.

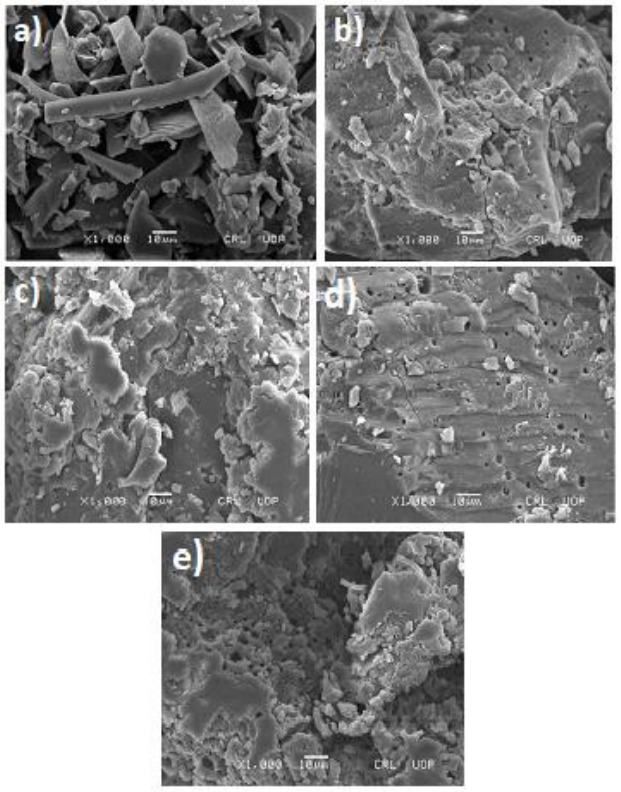

Fig. 1: Scanning electron microscope analysis of a) Crude, b) purified, c) acidic hydrolyzed, d) basic hydrolyzed and e) polyacrylamide grafted gum

Granules analysis

Granules were prepared using raw gum, purified, modified and hydrolyzed gum and HPMC. Pre-compression parameters such as bulk density and tapped density were studied and the results were tabulated in table 1.

Preparation of tablets

The paracetamol tablets were prepared in 15 batches using different gum samples and HPMC (fig. 2). After the preparation of tablets the parameters like weight

uniformity, hardness, friability, disintegration time, dissolution analysis was studied and the results were computed in table 2.

Rate of releasing of active ingredients

The rate of releasing of paracetamol ingredients from tablets prepared by using different samples of *Cordia myxa* gum is shown in figure 3. The 75% of tablets were dissolved within 30 min; however, tablets prepared from crude gum was not dissolve within 30 min. It showed delay in release due to comparatively high viscosity of crude gum. The PG and PHG gums showed promising releasing rate within 30 min which almost similar to HPMC releasing profile.

Fig. 2: Tablet prepared using gum cordia as binder in the form of a): Crude, b): Pure, c) acidic hydrolyze, d) basic hydrolyze, e): acrylamide grafting and f) using HPMC as control binder agent

DISCUSSION

The extraction from raw gum through soxhlet apparatus produced highly quality purified gum for using as binder and further modification to explore the binder properties. The step-by-step scanning electron microscope characterization of treated and modified crude, purified, hydrolyzed and grafted gum indicate successful resulted product. As a binder in tablet formulation the pH of the gum is an important parameter to determine its suitability in acidic, basic or neutral drugs and in formulation process. Because the physico-chemical properties and the stability of the preparation depend on the pH (Singh *et al*., 2010). Another function of pH is that it has an influence on the active molecular surface (proteins and polysaccharides) and the interactions between them (Mahfoudhi *et al*., 2012). The viscosity of the PG gum was measured about 4.11 poise which indicates that the gum is colloidal in nature, which do not settle down quickly and favorable for utilization in tablet formulation (Dinda and Mukharjee, 2009). The swelling rate of gum was noted high in water, mainly due to polysaccharides present in gum as compared to buffer solution which is more favorable property for tablet formulation and dispensing orally in patient's body(Kumar and Ahuja, 2012, Pawar and Jadhav, 2015) (Dodi *et al*., 2011, Mayor *et al*., 2007). Further, swelling of binding agents is a prime parameter for diffusion controlled release of active ingredients into physiological environment which is preferably considered while formulating the tablet preparations (Akpabio *et al*., 2011, Sujitha *et al*., 2012).

Gum has positive physiological benefits. High viscosity makes it difficult to incorporate it into products and nutritional solutions. The hydrolyzed (acidic or basic) and polyacrylamide grafting (through copolymerization) of gum was carried out to lower the viscosity to use it easily into diet and pharmaceuticals products (Slavin and Greenberg, 2003) as guar hydrogel having low viscosity, low residual glutaraldehyde, and thermal stability was potentially applied as a biological material with certain rheological requirements (Cunha *et al*., 2005).

The tapped and bulk density of the gums used almost showed the same results as HPMC. According to literature, the granules containing the Carr's index range from 5-15% and the Hausners ratio less than 1.25, showing good flow properties (Reddy and Archana, 2018). Each tested composition has a Hausners ratio less than or equal to 1.25, while the Carr's index was up to 15% which was excellent. Thus, all granules possess good flow properties. Weight uniformity of tablets was noted in each batch using PHG binder and least variation was recorded in standard deviation which indicates the uniform behavior of PHG as a binding agent. The other binder properties for example hardness and friability (less than 1%) was comparable to standard binding agent, HMPC which indicates the PHG *Cordia myxa* is also favorable binding agent in tablet formulation. A large number of natural polymers have been used in pharmaceuticals. As a binder, natural materials such as starch, gum, mucilage and dried

Table 1: Evaluation of granules

Gum sample	Bulk density	Tapped density	Untapped density	Hausner's ratio	Carr's index (%)
Crude	0.58	0.71	0.39	1.22	13
Purified	0.58	0.70	0.40	1.20	12
Acidic Hydrolysis	0.55	0.71	0.39	1.29	16
Basic Hydrolysis	0.56	0.70	0.38	1.25	14
Polyacrylamide grafting	0.59	0.73	0.38	1.23	14
HPMC	0.48	0.59	0.28	1.22	11

Table 2: Tablet analysis of *Cordia myxa*

Tablets using	Weight uniformity (mg) n=20	Hardness (N) n=10	Friability (%)	Disintegration time (min)
Crude	254.46±1.03	100.06±0.32	0.79	17
Purified	251.77±1.21	96.74±0.67	0.8	11
Acidic hydrolysis	252.32±1.12	89.43±0.48	0.93	6
Basic hydrolysis	252.88±0.97	91.51±0.72	0.41	13
Polyacrylamide grafting	251.63±0.83	88.49±0.69	0.41	4
HPMC	251.18±1.17	90.88±0.89	0.88	3

fruits are being used. They have good potential as filers, disintegrating agent and sustain releasing agent (Bhosale *et al*., 2014). In consistent to current research outcomes, (Hussain *et al*., 2017) reported that okra gum has binding potential, it is a better binder than synthetic one and can be used as binding agent in tablet formulation.

Releasing time determines the impact of the binder on tablet to get a solution. According to this method the disk must be disintegrate within 15 min. Some of the prepared tablets were dissolved within 15 min and others were not. The dissolution rate of the tablets was carried out using 0.1 N hydrochloric acid for 90 min (fig. 2). Our results were found in consistent with the study of Reddy and Archana (2018) who used hydrophilic natural and synthetic polymers to prepare *repaglinide* tablets. Similarly, (Hussain *et al*., 2017) reported the binding properties of okra gum. The dissolution study showed that the use of 4% w/w concentration of binder showed maximum drug release that is up to 83.54% within 1h.

CONCLUSION

The utilization of natural extracts having binding properties may play more favorable role in safe administration of pharmaceutical products. Recently, the utilization of variety of natural products as binding agents in addition to nutraceutical use, has gained promising attention due to its healthy effects. In this study, the use of *cordia myxa* gum after purification and modification as binding agent showed promising results; which are comparable to commonly used synthetic binding agent HMPC. Based on the results, it is concluded that the PHG has strong potential to use as natural binding agent to prepare pharmaceutical tablets in place of synthetic agents; which, more or less, show side effects.

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