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Investigation of Kondagogu Gum and Ghatti Gum as Binders in Formulating Metoprolol Tartrate Tablets

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ABSTRACT

In the present study, an attempt was made to investigate the binding efficiency of natural tree gums, kondagogu gum and ghatti gum, in formulating metoprolol tablets. Metoprolol tartrate is a selective β1 receptor blocker used in the treatment of several diseases of the cardiovascular system, especially hypertension. The tablet formulations were prepared by varying the concentrations of kondagogu gum and ghatti gum as binding agents. The metoprolol granules were prepared by wet granulation technique and evaluated for surface morphology, bulk density, particle size distribution, angle of repose, Haunser ratio, Carr's index and were found to be satisfactory for preparing compressed tablets. The prepared tablets were evaluated for properties such as hardness, thickness, friability, disintegration time, weight variation, drug content, compatibility using DSC and FTIR. Formulations containing ghatti gum and kondagogu gum as binders showed short disintegration, good hardness along with good physico-mechanical properties. From the study it was concluded that, kondagogu gum and ghatti gum can be used as alternate binders in formulating a particular therapeutic agent.

Keywords: Binder, metoprolol tartrate, kondagogu gum, ghatti gum, mechanical properties.

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INTRODUCTION

A tablet is a pharmaceutical dosage form which comprises of a mixture of active substance known as drug and excipients, usually in powder form, which is pressed or compacted into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting, disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste, and pigments to make the tablets visually attractive. The compressed tablet is by far the most widely used dosage form, having advantages for both producer and user [1, 2].

The properties of the tablet (e.g. mechanical strength, disintegration time and drug release characteristics) are affected by both the properties of the constituent materials and the manufacturing process. Excipients such as diluents, binders and lubricants are generally needed in a formulation in order to facilitate the manufacturing process, but also to ensure that the resulting tablets have the desired properties. For instance, tablets should be sufficiently strong to withstand handling during manufacturing and usage, but should also disintegrate and release the drug in a predictable and reproducible manner. It is hence important to choose the appropriate excipient and manufacturing process when developing a new tablet formulation [3-4].

A binder is a material that is added to a formulation in order to improve the mechanical strength of a tablet. The rational choice of a suitable binder in a formulation requires extensive knowledge of which properties of a binder are important for the strength enhancing effect. Only then would it be possible to predict the function of a binder in a formulation. Binder is a pharmaceutical excipient, commonly employed in tablet formulation to impact cohesion on the powder mix, thereby improving the flow property of granules, and also provides sufficient mechanical strength to the tablet [2-5].

In direct compression, the binder is added in its dry state, whereas a liquid is employed in wet granulation. Besides the common aim of enhancing the bonding properties between particles or granules, the binder in wet granulation also aims at improving the binding between powder particles during agglomeration. Addition of a binder in its liquid state facilitate its distribution in the powder mix which otherwise can be difficult with a dry binder. Therefore, binders added as dry powders are generally less effective than when added as solutions [6-8].

Some of the commonly used binders in pharmaceutical industries are starch, polyvinyl pyrrolidone (PVP), gelatin, glucose, sorbitol, methyl cellulose, hydroxy propyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC), microcrystalline cellulose (MCC), acacia, tragacanth, sodium alginate, starch and its derivatives, dibasic calcium phosphate dehydrate, polyethylene glycol (PEG), sucrose etc [3].

Research is carried out in exploring new binders for use and the outcome was fruitful. Several such studies involved use of novel materials like date syrup [9], *Mangifera indica* gum [10], khaya gum [11], okra gum [12], *Anacardium occidentale* (cashew tree) gum [13], honey

[14] etc. Gums are byproducts obtained as a result of metabolic mechanisms of plants and are either water soluble or water swellable. They are economic and easily available. Kondagugu gum and ghatti gum are naturally occurring tree gums.

Gum kondagogu is a dried gum exudates obtained from the tree *Cochlospermum gossypium* and other species of *Cochlospermum* belonging to the family Bixaceae [15]. Basically it is a polymer of rhamnose, galacturonic acid, glucuronic acid, b-D-galactopyranose, a-D-glucose, b-D-glucose, galactose, arabinose, mannose and fructose with sugar linkage of (1 →2) β -D-Gal *p*, (1→6)- β -D-Gal *p*, (1 → 4) β-D-Glc *p* A, 4-0-Me- α -D-Glc *p* A, (1 → 2) α-L-Rha*p*, with average molecular weight of 7.23 $X10^{-6}$ g/mol [16, 17].

Gum ghatti is a complex non-starch polysaccharide obtained as amorphous transluscent mucilage from wounds in the bark of *Anogeissus latifolia* tree which is found in the deciduous forests of India and Sri Lanka [18]. It has been widely employed in food, pharmaceuticals, paper industries primarly because of its emulsification and thickening property. It is a high molecular weight complex polysaccharide that occurs in nature as a mixed calcium, magnesium, potassium, and sodium salt; upon hydrolysis, it yields L-arabinose, D-galactose, D-mannose, D-xylose, L-rhamnose, and D-glucuronic acid [19, 20].

Both ghatti and kondagogu gums were assigned “generally regarded as safe” (GRAS) status in the US FDA [17, 21]. Even though, kondagogu and ghatti gums are important forest products, its commercial exploitation was limited due to non-availability of scientific information, especially in relation to its application in the pharmaceutical preparations. The overall objective of the present investigation was to investigate the utility of these natural and biodegradable gums in the pharmaceutical preparation as tablet binder. Metoprolol tartrate, which is a β_1-selective adrenergic blocking agent, is prescribed widely in diverse cardiovascular diseases such as hypertension, angina and post myocardial infarction was selected as model drug [22].

MATERIALS AND METHODS

Materials

Metoprolol tartrate was received as gift sample from Dr. Reddy’s Laboratories, Hyderabad, India. It is a white, odourless, crystalline powder, freely soluble in sodium hydroxide solution, n-butylamine, and in dimethylformamide; sparingly soluble in methanol; slightly soluble in water; and insoluble in ether, in chloroform, and in dilute mineral acids. Kondagogu gum and ghatti gums were purchased from girijan co-operative society, Govt. of Andhra Pradesh, Hyderabad, India. All other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Purification of Gum [17]

Foreign extraneous matter like bark etc was separated from the gums at the beginning, then powdered and passed through sieve # 80. The powdered gums were dispersed in distilled

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water to get 1% solution, homogenised at 20,000 rpm (Polytron-PT 1600E homogeniser) for 20 min and added to equimolar mixture of acetone and ethanol (1:2 v/v) to give precipitation of gum. Precipitated polymer was kept in an oven for drying, powdered, passed through sieve no. 100 and used for further studies.

Characterization of Gums [9, 13]

The gums were characterized for ash content, moisture content, pH and viscosity. The pH of the gum solution (1%, w/v) was determined using digital pH meter (pH system 335, Systronics, Mumbai). The viscosity of the gum dispersion was determined using LVDV II+ viscometer (Brookefield Engineering, USA). Viscosity was determined using spindle S28, at 50 rpm in a constant temperature bath maintained at 20 °C. Weight loss on drying was determined using a Shimadzu moisture balance (Shimadzu MOC 120H, Japan).

Preparation and Evaluation of Granules [9, 13]

The different batches F1-F10 (100 g) of metoprolol tartrate granules were prepared using different concentration of gums. Kondagogu and ghatti gum concentrations were used in the granule formulations (viz., 0.5, 1, 1.5, 2 and 3 % w/w) and the granules were prepared by wet granulation technique as shown in Table 1. The desired quantities of metoprolol, corn starch and lactose were dry mixed for 5 min using mortar and pestle, then moistened with appropriate amount of binder solution, which was prepared with different concentration of gum and with the selected binders massed separately with sufficient amount of water. Massing was continued for 5 min and the wet mass was granulated by passing it manually through a mesh 16 sieve and dried in a hot air oven at 100 ºC. Dried granules were sieved through a mesh 22 sieve and were collected for further studies. The granules were evaluated for surface analysis (SEM), bulk density, tapped density, particle size distribution, angle of repose, Hausner ratio and Carr's index.

Table 1: Formulation chart of metoprolol tartrate tablets prepared using kondagogu gum and ghatti gum as binders

Ingredients	Formulation code and weight in mg									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metoprolol tartrate	100	100	100	100	100	100	100	100	100	100
Kondagogu gum	1.5	3	4.5	6	9	--	--	--	--	--
Ghatti gum	--	--	--	--	--	1.5	3	4.5	6	9
Corn starch	50	50	50	50	50	50	50	50	50	50
Lactose	139.5	138	136.5	135	132	139.5	138	136.5	135	132
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3	3
Total weight of tablet (mg)	300	300	300	300	300	300	300	300	300	300

The bulk density of the sample was calculated by mass of powder/bulk volume of powder. A given quantity of the sample was transferred to a measuring cylinder and was tapped mechanically, using a bulk density apparatus (Electrolab, Mumbai, India) until a

constant volume was obtained, which was referred as bulk volume (Vb). Samples were tapped until no further reduction in volume of the sample was observed. Carr's index was calculated by ((initial volume−tapped volume)/tapped volume)×100. The Hausner ratio was determined by bulk tapped density/bulk loose density.

The angle of repose was measured using a fixed funnel method. A funnel that was secured with its tip at a given height above the graph paper was placed on a flat horizontal surface. Powder was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius and height of the pile were then determined. The angle of repose (θ) for samples were calculated using the formula, $\tan(\theta) = \text{height} / \text{radius}$.

Particle size distribution of each was determined by sieve analysis using 100 g of the test material and series of US standard sieves range in screen opening from 1000 µm to 180 µm. The test material was placed on the top sieve and mechanically shaken for 10 min on a shaker (Rota C 30, Germany). The fraction retained on each screen was weighed and the average particle size was calculated accordingly

Scanning Electronic Microscopy [23]

The granules morphology was further examined under the scanning electron microscope (Jeol, JSM-6360LV scanning microscope, Tokyo, Japan). Before microscopy, the samples were mounted on carbon tape and were sputter-coated using gold (Jeol, JFC-1100 fine coat ion sputter, Tokyo, Japan). The photomicrographs were taken at an acceleration voltage of 20 kV.

Preparation of Tablets

The prepared granules were mixed with required quantity of lubricants (magnesium stearate, 2% w/w and talc 1% w/w) and were compressed to form tablets (Table 1) by rotary tablet machine (Rimek, Ahmedabad, India) at 10 rpm and using 9 mm round concave punches at an optimum pressure.

Tablet Evaluation

The prepared tablets were evaluated for tablet properties such as hardness (Inweka hardness tester, Ahmedabad, India), thickness (Mitotoya screw guage, Japan), weight variation (Shimadzu AW 120, Japan), percent friability (Electrolab EF-2 friabilator, Mumbai, India) and drug content (Shimadzu 1800 UV/Visible spectrophotometer, Japan).

UV/Visible Spectroscopy

The wavelength of maximum absorbance (λ_{max}) of the selected drug, metoprolol tartrate was determined by scanning a known concentration of sample solution in the wavelength

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region of 200-400 nm by using Shimadzu 1601 UV/ Visible spectrophotometer. The λ_{max} was found to be 222 nm and this wavelength was used for assay studies.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of the pure metoprolol tartrate and the optimized formulation were recorded using a Fourier transform infrared spectrophotometer (FTIR 8400, Shimadzu, Japan). Samples were prepared as KBr disks using a hydraulic pellet press and scanned from 4000 to 400 cm^{-1}.

Stability Studies

Stability studies of the optimized formulation was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40 ºC/75% RH for 3 months (Thermolab, Mumbai, India). Formulation was analyzed every 15 days for its hardness and % drug content.

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded for pure metoprolol tartrate and the optimized formulation using a differential scanning calorimeter (Shimadzu DSC-60, Japan). Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids, and heated at a constant rate of 5 °C/min over a temperature range of 0-300 °C.

RESULTS AND DISCUSSION

The pH and viscosity of 5% ghatti gum was found to be 5.6 and 287 cP respectively. On the other hand, 2% kongagogu gum showed a pH of 4.9 and viscosity of 396 cP. This change in viscosity may be attributed to the molecular structural complexity of kondagogu gum over ghatti gum.

Table 2: Evaluation data for the prepared granules

Parameter	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Mean particle size (mm)	0.439 ±0.016	0.522 ±0.011	0.546 ±0.014	0.551 ±0.013	0.558 ±0.012	0.417 ±0.015	0.518 ±0.012	0.539 ±0.013	0.542 ±0.012	0.551 ±0.011
Angle of repose (°)	37.34 ±0.12	32.18 ±0.14	30.74 ±0.13	27.51 ±0.14	26.46 ±0.13	36.37 ±0.11	31.72 ±0.12	29.46 ±0.12	27.24 ±0.14	26.38 ±0.13
Bulk density (g/ml)	0.344 ±0.016	0.370 ±0.021	0.395 ±0.018	0.417 ±0.012	0.424 ±0.018	0.358 ±0.021	0.384 ±0.019	0.403 ±0.017	0.418 ±0.018	0.427 ±0.019
Carr's index (I)	17.6 ±0.12	13.8 ±0.11	10.4 ±0.11	9.8 ±0.12	9.6 ±0.10	17.5 ±0.12	13.6 ±0.11	10.3 ±0.11	9.8 ±0.12	9.5 ±0.10
Hausner ratio	1.2 ±0.04	1.14 ±0.03	1.11 ±0.03	1.04 ±0.04	1.03 ±0.04	1.19 ±0.03	1.13 ±0.04	1.11 ±0.03	1.03 ±0.03	1.02 ±0.04
Moisture content (%)	0.12 ±0.04	0.54 ±0.07	1.12 ±0.14	2.33 ±0.18	3.11 ±0.16	0.12 ±0.06	0.54 ±0.11	1.12 ±0.14	2.33 ±0.21	3.11 ±0.24

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The characterized gums were used as a excipient for preparing tablets to find out the binding efficiency of the gums. The natural gums were selected for evaluation of binding property because of their low cost, abundant availability, ease of isolation and optimum viscosity. The prepared granules were evaluated for bulk density, tapped density, particle size distribution, angle of repose, Carr's index, Hausner ratio and the obtained results are shown in Table 2.

From the table, it was clear that mean particle size for granules prepared using kondagogu gum and ghatti gum lies in range 0.439-0.558 mm and 0.417-0.551 mm respectively. The angle of repose (θ) values were 37.34° and 36.37° for granules prepared with 0.5% w/w of kondagogu and ghatti gums respectively. This result indicated that the granule flow property is fair, but not adequate. The values obtained for 1, 1.5, 2 and 3% w/w of gums were below 35° indicating good to excellent flow property of prepared granules. From the table, it was also clear that bulk density of the prepared granules lies in the range 0.344-0.427 g/ml. The data obtained from Carr's index and Hausner ratio indicated good to excellent compressibility for the prepared granules. The formulations F1 and F6 containing 0.5%w/w of kondagogu and ghatti gum possessed fair compressible property.

The surface of the prepared granules was observed by SEM microphotograph as shown in Fig. 1 and 2. From the figures, it was clear that the granules were irregular in shape and the granules prepared with kondagogu gum as binder were porous in nature.

The percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) standards and the data obtained is given in Table 3. The tablets prepared with kondagogu gum as binder showed hardness in the range 1.8-9.1 Kg. It was clear that as the gum concentration in the tablet increased, the hardness of the tablets also increased. On the other hand, tablets prepared with ghatti gum as binder showed hardness in the range 2.2-10.1 Kg. This result clearly indicates that ghatti gum proved to be effective in increasing the hardness of the tablets. However, the difference in hardness shown by the selected binders was minimal.

Table 3: Evaluation data obtained for prepared tablets

Formulation code	% weight variation*	Thickness* (mm)	Hardness* (kg/ cm2)	Friability* (%)	Disintegration time (min)	% Drug content*
F1	301±2.1	5.1±0.11	1.8±0.44	1.22±0.16	1.02±0.11	100.5±1.7
F2	300±1.5	5.2±0.11	3.9±0.56	0.81±0.14	4.36±0.16	99.8±2.3
F3	298±2.0	5.1±0.12	5.6±0.42	0.47±0.12	10.21±0.21	101.3±1.8
F4	302±1.7	5.0±0.11	8.6±0.34	0.36±0.11	15.54±0.19	98.9±2.1
F5	299±2.2	5.1±0.11	9.1±0.41	0.28±0.09	19.39±0.26	99.4±1.3
F6	303±1.6	5.1±0.13	2.2±0.52	1.01±0.09	1.35±0.15	101.2±2.8
F7	302±2.1	5.2±0.12	4.3±0.48	0.74±0.21	5.48±0.13	100.7±2.4
F8	298±1.8	5.0±0.11	6.5±0.53	0.38±0.15	12.18±0.14	99.2±1.8
F9	301±1.5	5.1±0.12	9.6±0.47	0.24±0.16	14.42±0.21	98.6±2.2
F10	297±1.9	5.2±0.11	10.1±0.43	0.21±0.15	18.38±0.28	99.2±1.8

*mean ± SD, n = 3

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From the table, it was noticed that the percent drug content and thickness lies in the range 98.6-101.3 % and 5.0-5.2 mm respectively. Friability values of the prepared formulations indicated that the tablets prepared with 0.5% w/w of gums (F1 and F6) were friable and showed friability of more than 1%. Tablets prepared with higher concentration of kondagogu gum (F2-F5) and ghatti gum (F7-F10) showed less % friability indicating that the gums were effective in higher concentration. From the table, it was also clear that as the gum concentration in the tablet formulation increased, the friability values decreased. The tablets prepared with kondagogu gum as binder showed disintegration time in the range 1.02-19.39 min. On the other hand, tablets prepared with ghatti gum as binder disintegrated within 1.35-18.38 min. From this result, it was clear that as the gum concentration in the tablet increased, the disintegration time increased. Tablets prepared with 0.5 and 3% w/w (F1, F4 and F5, F10) concentrations showed least and highest disintegration time. From the results of disintegration time, friability and hardness, formulations containing 1.5% w/w of gums (F3 and F8) were selected as optimized formulations for tablets prepared with kondagogu gum and ghatti gum respectively.

The IR spectra of pure metoprolol tartrate and optimized formulations (F3 and F8) are shown in Fig. 3. The FTIR spectra obtained indicated that no chemical interaction occurred between the drug, polymers and the excipients used in formulating the tablet. But, a slight shift in absorption peaks position was noticed which indicated that physical interaction might have occurred between drug and the polymer. The optimized formulations F3 and F8 were subjected for 3 months stability studies. Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any degradation during its shelf life. The data obtained from the stability studies is tabulated in Table 4. From the tablet hardness and drug content data, it was clear that the drug was stable in the optimized formulation for the study period.

DSC thermograms of the pure drug and its formulations before and after stability studies were recorded to evaluate whether the drug has undergone any degradation during the study period. From the DSC data obtained (Fig. 4), it was evident that the melting point of metoprolol tartrate has not changed after placing the tablets for stability studies. Hence, it may be inferred that there was no interaction between galantamine HBr and polymers used. From DSC results, it may be concluded that the drug maintained its chemical identity throughout the process.

Table 4: Stability study data for the optimized formulations

Time in days	Hardness* (kg/ cm^2)		% Drug content *	
	F3	F8	F3	F8
0 (Initial)	5.6±0.42	6.5±0.53	101.3±1.8	99.2±1.8
15	5.7±0.26	6.6±0.44	101.8±1.4	99.6±2.3
30	5.5±0.25	6.5±0.37	102.5±2.1	100.5±1.7
45	5.6±0.31	6.6±0.29	99.8±1.5	101.2±2.1
60	5.7±0.39	6.4±0.42	101.5±1.6	99.8±1.4
75	5.5±0.41	6.5±0.51	99.2±2.3	101.1±2.2
90	5.6±0.28	6.6±0.35	99.8±1.5	100.8±2.3

*Standard deviation n=3

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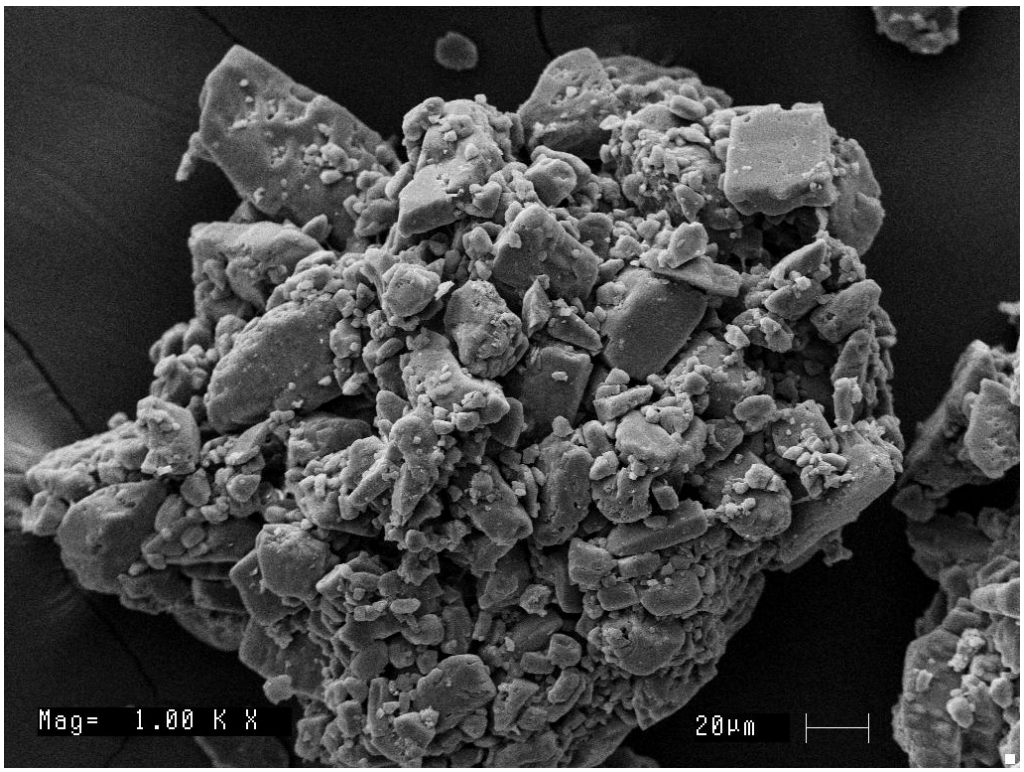

Figure 1: SEMmicrophotoraph of formulation F3 (granules prepared with kondagogu gum as binder)

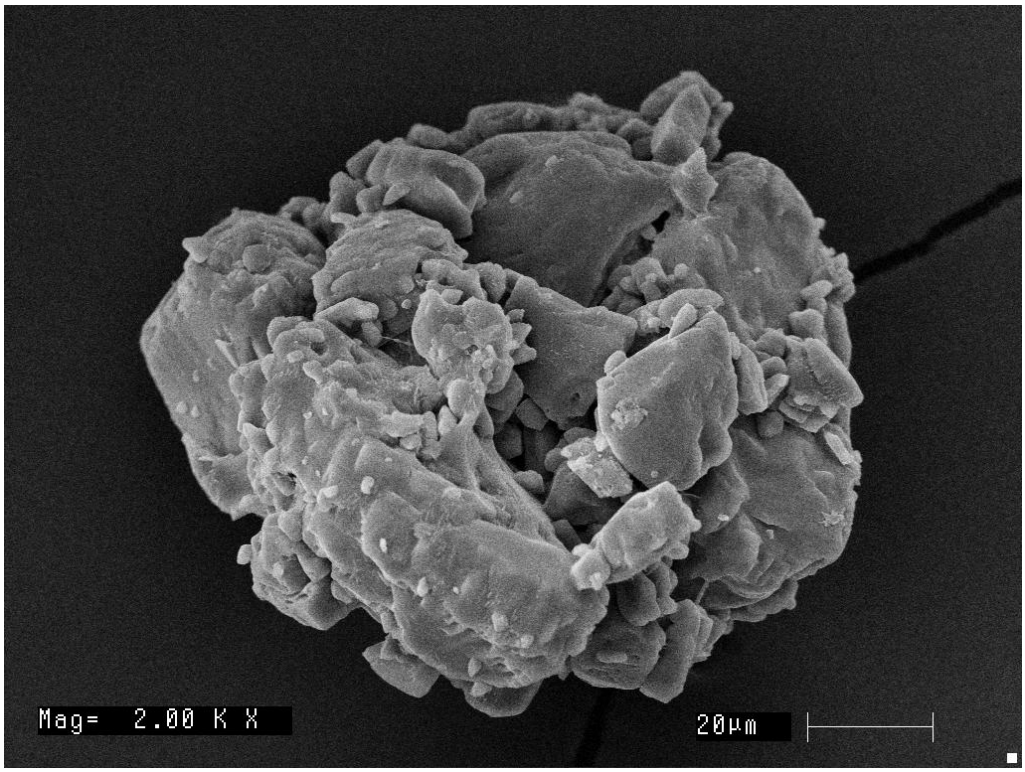

Figure 2: SEMmicrophotoraph of formulation F3 (granules prepared with ghatti gum as binder)

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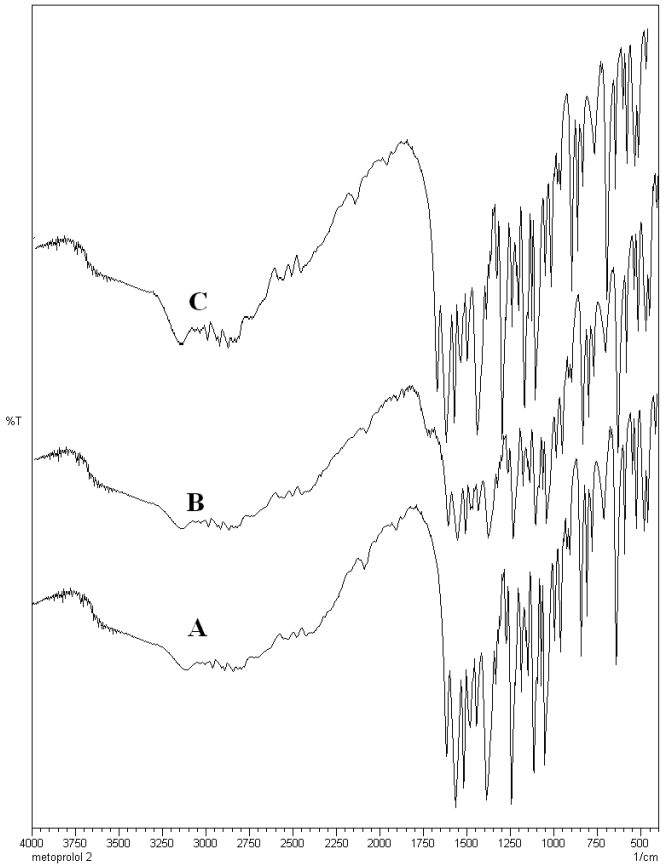

Figure 3: FTIR chromatogram for pure metoprolol tartrate (peak A), formulations F5 (peak B) and F8 (peak C)

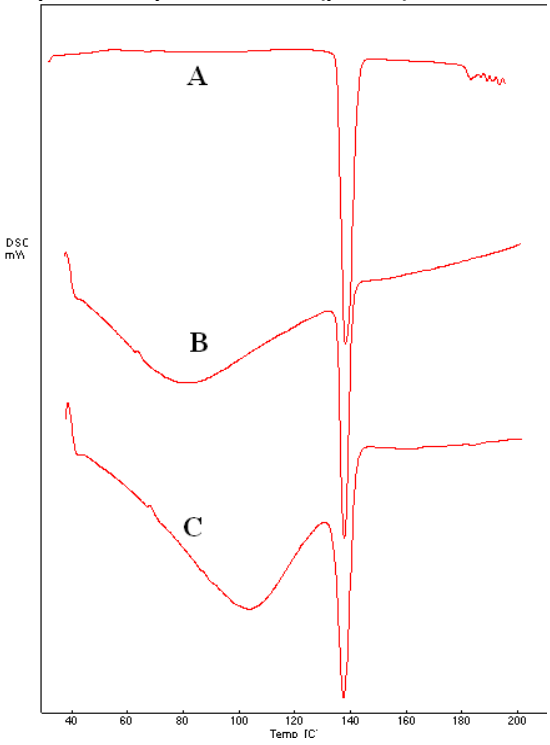

Figure 4: DSC chromatogram for pure metoprolol tartrate (peak A), formulations F5 (peak B) and F8 (peak C)

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CONCLUSION

The natural gums were selected for evaluation of binding property due to their distinguished characters such as low cost, abundant availability, ease of isolation and viscosity. Kondagogu gum powder after purification was pale yellow in colour, had ash content of 8.2% and the moisture content was 12.8%. Ghatti gum powder after purification was light yellow to brown colour powder, had ash content of 2.6% and a moisture content of 11.6%. The prepared granules were evaluated for bulk density, tapped density, particle size distribution, angle of repose, Carr's index, Hausner ratio and the obtained results indicated good to excellent flow property and compressibility index of prepared granules. From the SEM microphotographs it was clear that the granules were irregular in shape and the granules prepared with kondagogu gum as binder were porous in nature. The percentage weight variation, percent friability and content of active ingredient for the prepared tablets were found to be well within United States Pharmacopoeia (USP) standards. Tablets prepared with higher concentration of kondagogu gum (F2-F5) and ghatti gum (F7-F10) showed less friability, good hardness and good disintegration time indicating that the gums were effective in higher concentration (1, 1.5 and 2% w/w). Formulations containing 1.5% w/w of gums (F3 and F8) were selected as optimized formulations for tablets prepared with kondagogu gum and ghatti gum respectively. The FTIR and DSC spectra obtained indicated that no chemical interaction occurred between the drug, metoprolol tartrate, polymers and the excipients used in formulating the tablet. From the stability study data, it was clear that the drug was stable in the optimized formulation for the study period. From the results obtained, it can be concluded that natural and biodegradable tree gums like kondagogu gum and ghatti gum can be employed for use as a binder in developing drug delivery systems.

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