

# Gum Copal and Gum Damar: Novel Matrix Forming Materials for Sustained Drug Delivery

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This study concerns the evaluation of natural gum copal and gum damar as novel sustained release matrix forming materials in tablet formulation. Along with the physicochemical properties, gum copal and gum damar were characterized for molecular weight, polydispersity index and glass transition temperature. Matrix tablets were prepared by wet granulation technique using isopropyl alcohol as a granulating agent. Diclofenac sodium was used as a model drug. Tablet weight (250 mg) and diameter (9 mm) was kept constant. Tablets were evaluated for pharmacotechnical properties, drug content uniformity and in vitro drug release kinetics. Effect of gum concentration (10, 20 and 30% w/w with respect to total tablet weight) on in vitro drug release profile was examined. Both the gums produced matrix tablets with good strength and acceptable pharmacotechnical properties. Matrix tablets with 30% w/w gum copal and gum damar showed sustained drug delivery beyond 10 h. Drug release from gum copal matrix tablets followed zero order kinetics while gum damar (10 and 20% w/w) was found suitable to formulate the insoluble plastic matrix that releases the drug by diffusion. It is concluded that both gums possess substantial matrix forming property that could be used for sustained drug delivery.

Sustained drug delivery systems significantly improve therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems. Regarding this, researcher investigated various natural, semi-synthetic and synthetic polymeric materials. Most thoroughly investigated and used synthetic polymers for sustained drug delivery are ethyl cellulose<sup>1</sup>, hydroxypropyl methylcellulose<sup>2</sup> and eudragit<sup>3</sup>. But individually when they showed specific limitations, different combinations like ethyl cellulose and hydrogenated castor oil<sup>4</sup>, eudragit and ethyl cellulose<sup>5</sup>, hydroxypropyl methylcellulose and polyamide<sup>6</sup> were tried by the researchers to obtain desired drug release profiles. These combinations were ultimately found to make the process complicated and increase the cost of formulation. Purely some natural gums were also investigated as hydrophilic matrices for sustained drug delivery, but they were found to be unable to sustain the drug release for a longer period of time even at the higher concentrations<sup>4</sup>. So in an alternate approach, the combinations of hydrophilic and hydrophobic polymers

were tried by the scientists for optimized drug delivery, but numerous of them also failed to prolong the drug release beyond 12 h<sup>4</sup>. Since a wide range of polymers has certain advantages as well as own limitations, it is a prerequisite, often, to investigate new polymeric materials for sustained drug delivery. Therefore the study of new drug-release-retarding materials is the motive of research even after the advent of synthetic, semi-synthetic and natural polymers.

The natural materials have been extensively used in the field of drug delivery because they are readily available, cost-effective, eco-friendly, capable of multitude of chemical modifications, potentially degradable and compatible due to their natural origin<sup>7</sup>. Past research therefore studied and acknowledged various natural gums like agar, konjac, guar gum, chitosan, xanthan gum, sodium alginate and locust bean gum for potential pharmaceutical and biomedical applications<sup>8</sup>. These particulars explicate the rationale why proposed article concerns the evaluation of natural gums for sustained drug delivery.

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Gum copal (GC) is a natural resinous material of plant

*Bursera bipinnata* (family *Burseraceae*). It has been used as a raw material for varnish because it produces glossy films with good weather protection properties<sup>9</sup>. It has been used as pigment binder in varnishes due to the excellent binding properties<sup>10</sup>. It has been mainly used as an emulsifier and stabilizer for the production of colour, paints, printing inks, aromatic emulsions and meat preservatives<sup>11</sup>. Interestingly, GC was also used as medicine for several different ailments such as in the treatment of burns, headache, nosebleed, fever, stomachache, and in the preparation of dental products and as remedy for loose teeth and dysentery<sup>12</sup>.

Gum damar (GD) is a whitish to yellowish natural gum of plant *Shorea Wiesneri* (family *Dipterocarpaceae*). It contains about 40% alpha-resin (resin that dissolves in alcohol), 22% beta resin, 23% dammarol acid and 2.5% water<sup>13</sup>. It has been mainly used as an emulsifier and stabilizer for the production of colour, paints, inks and aromatic emulsions in food and cosmetic industries and also in the manufacture of paper, wood, varnishes, lacquers, polishes and additives for beverages<sup>14</sup>. It has been used for water-resistant coating and in pharmaceutical and dental industries for its strong binding properties<sup>15</sup>. In India, Sal damar has been widely utilized as an indigenous system of medicine<sup>16</sup>. These wide applications of GC and GD propose their strong hydrophobic nature, substantial binding property and compatibility with the physiologic environment. Since matrix tablet is the easiest approach to design the sustained drug delivery system, we were interested in investigating the matrix-forming ability of GC and GD in tablets for sustained drug delivery.

In case of multiple-dosing regimens of immediate-release formulations, diclofenac sodium has propensity of systemic accumulation leading to sever toxicity in central nervous system, gastrointestinal system and cardiovascular system when used for long-term treatments of various arthritic conditions<sup>17</sup>. Low oral bioavailability (60%), short biological half life (1.1- 4.0 h) and low therapeutic index suggest need for sustained release formulation of diclofenac sodium. Therefore, it was chosen as a model drug for the present study.

## MATERIALS AND METHODS

GC and GD were received as a gift sample from Innovative Marketing Services, Mumbai. Diclofenac sodium and dicalcium phosphate were procured from M/s.

Zim Laboratories Ltd., Nagpur. Magnesium stearate was purchased from M/s. S. D. Fine Chemicals Ltd., Mumbai. Acetone and potassium dihydrogen phosphate were obtained from M/s. Ranbaxy Fine Chemicals Ltd., New Delhi. Methanol, dichloromethane and hydrochloric acid were purchased from M/s. Central Scientific India Ltd., Nagpur. Potassium hydroxide, boric acid, ether and chloroform were purchased from M/s. Upper India Scientific Ltd., Nagpur.

### Physicochemical properties and characterization of gum copal and gum damar:

Colour of GC and GD was observed visually and noted. For acid value, 10 g sample of each was dissolved in 50 ml mixture of equal volume of ethanol (95%) and ether previously neutralized with 0.1 M potassium hydroxide solution to phenolphthalein. After addition of phenolphthalein (1 ml), sample solution was titrated with 0.1 M potassium hydroxide until it remained faintly pink after shaking for 30 min. Acid value was calculated by the formula, Acid Value =  $5.61 \frac{n}{W}$ , where, n = number of ml of 0.1 M potassium hydroxide required, and W = weight in grams of substance. Softening and melting points of GC and GD were determined by Hercules drop technique. For relative solubility, 6 g gum sample in 10 ml organic solvent and 3 g gum sample in 10 ml of different pH buffer was placed in a test tube mounted on a water-bath shaker for 24 h. Then 2 ml of each was transferred to a porcelain dish and the solvent was evaporated. Half of the weight gain of porcelain dish after complete solvent evaporation was taken as solubility per ml of GC and GD in that particular solvent/solution. Molecular weight of GC and GD was determined by Gel Permeation Chromatography system (Perkin-Elmer) equipped with refractive index detector (La Chrom Detector L-7490). Samples were eluted through PL gel 3 Micron mixed column at the flow rate of 1 ml/min using chloroform as a solvent. Molecular weights were calculated relative to polystyrene standards (Polysciences, USA). Differential Scanning Calorimetry (DSC-Shimadzu 50) was employed for the determination of glass transition temperature (T<sub>g</sub>). About 2 mg of sample was placed in aluminium pan and scanned over a temperature range of 25-250° at the rate of 5°/min. Each sample was subjected to three consecutive DSC scans. T<sub>g</sub> was determined by the midpoint of endothermic changes associated with the glass transition.

### Preparation of matrix tablets:

All the concepts and the assumptions of biopharmaceutics,

i.e., absorption, distribution, metabolism and excretion, are the important factors for mathematical design of the sustained release dosage forms. Pharmacokinetic studies showed that a dose of 25 mg of diclofenac sodium produces an effective blood level concentration of 0.7-1.5 µg/ml within 1.5-2.5 h with the half life of 1.1-4.0 h<sup>18</sup>. Thus the elimination rate constant  $k = 0.693/t_{1/2} = 0.693/4 = 0.1732$  mg/h. Hence the availability rate  $R = k \times D = 0.1732 \times 25 = 4.3$  mg/h, where  $D$  is the usual dose of the drug. The maintenance dose  $D_m = R \times h = 4.3 \times 20 = 86$  mg, where  $h$  is the number of hours for which sustained action is desired. Thus, Total dose =  $D + D_m = 25 + 86 = 111$  mg.  $D_{corrected} = D - Rtp = 25 - (4.3 \times 2) = 16.4$  mg, where  $tp$  is the time period required to achieve a peak plasma level. Therefore, Total dose<sub>corrected</sub> =  $D_{corrected} + D_m = 16.4 + 86 = 102.4$  mg.

The preliminary formulation and dissolution studies showed that a 100:50 diclofenac sodium:gum ratio prolongs the drug release beyond 12 h. Therefore, in all cases, drug content was maintained at 100 mg, and gum concentrations 25, 50 and 75% w/w with respect to total drug content were utilized to examine the effect of gum:drug ratios on drug release profile of the tablets. The composition of different gum matrix tablets is given in Table 1. Several batches of the matrix tablets with almost constant theoretical weight of 250 mg and diameter 9 mm were produced. In all the formulations, ingredients were passed through Hicom test sieve No. 120. Then the ingredients were accurately weighed and granulated using isopropyl alcohol. Granules were allowed to dry at room temperature (27±2°). Dried granules after lubricating with magnesium stearate (2% w/w) were compressed between 9 mm round flat-faced punches on a hand-operated single-punch tablet machine (Kilburn and Co. Ltd., Kolkata).

#### Controlled tests for matrix tablets:

The diameter and thickness of matrix tablet were measured by Vernier calipers, and the hardness was

**TABLE 1: COMPOSITION OF MATRIX TABLETS**

Ingredients	Product Code					
	M1	M2	M3	D1	D2	D3
Diclofenac sodium	100	100	100	100	100	100
Gum copal	25	50	75	-	-	-
Gum damar	-	-	-	25	50	75
Dicalcium phosphate	120	95	70	120	95	70
Magnesium stearate	5	5	5	5	5	5

M1-D3 are various formulations of diclofenac sodium matrix tablets. In each formulation 100 mg diclofenac sodium was used. Quantities of gum copal or gum damar and dicalcium phosphate were varied and mixed with 5 mg of magnesium stearate to have each tablet of 250 mg.

determined by Stokes-Monsanto hardness tester. The friability test was conducted using Roche friabilator. For each batch, 20 randomly drawn tablets were checked for weight uniformity using a Mettler-AE 200 balance (Mettler Toledo GMBH, Greifensee, Switzerland).

#### Drug content determination<sup>19</sup>:

For drug content, 20 tablets were weighed accurately and powdered. Powder equivalent to 50 mg of diclofenac sodium was shaken with 60 ml of methanol in 200 ml volumetric flask, and volume was further adjusted with methanol. Finally, 5 ml of this was diluted to 100 ml with methanol, and drug content was determined by UV-spectrophotometer (UV-1601, Shimadzu, Japan) at 276 nm using calibration curve based on standard solutions.

#### In vitro drug release study:

Drug release study was carried out in USP paddle-type dissolution test apparatus. Dissolution medium was 0.1 N HCL buffer (pH 1.2) for initial 2 h and phosphate buffer pH 6.8 for remaining 8 h. Volume of dissolution medium was 900 ml, and bath temperature was maintained at 37±1° throughout the study. Paddle speed was adjusted to 100 rpm. After each hour, 5 ml of sample was withdrawn and analysed for diclofenac sodium content by UV-spectrophotometer at 276 nm.

#### In vitro drug release kinetics:

In order to study the exact mechanism of drug release from the matrix tablets, drug release data was analysed according to Zero order, First order, Higuchi square root, Hixon-Crowell and Baker-Lonsdale kinetic equations<sup>20,21</sup>. The criterion for selecting the most appropriate model was chosen on the basis of goodness-of-fit test.

## RESULTS AND DISCUSSION

Results of the characterization and physicochemical evaluation of GC and GD are summarized in Table 2. Average molecular weight of GC and GD was found to be 150 and 180 respectively. GD has a narrow range of molecular weight distribution as indicated by the polydispersity index of 1.7 compared to GC, for which it is 2.3. Though the stability of GC and GD was not investigated, very low acid value of GD compared to GC may indicate its better chemical stability. Glass transition temperature of GC and GD was found to be 38.79°. Softening points of GC and GD were observed in the range of 79-82° and 90-93° respectively. Low Tg and softening point values indicate soft nature, while absence of sharp melting point indicates amorphous nature of the

**TABLE 2: PHYSICO-CHEMICAL PROPERTIES AND CHATACETRIZATION OF GUM COPAL AND GUM DAMAR**

Characteristics	Gum Copal	Gum Damar
Colour	Brown	Yellow
Acid Value (mg of KOH)*	140	27.08
Softening point (°)*	79-82	90-93
Melting point (°)*	123-125	141-143
Average molecular weight (Mw)	150	180
Polydispersity index (Mw/Mn)	2.3	1.7
Glass transition temperature (°)	38.79	38.79

\*Represents mean of five determinations.

gums (Table 2). Both gums exhibited good solubility in almost all the organic solvents and greater solubility in alkaline compared to acidic pH, as can be seen from Table 3.

Composition of GC and GD matrix tablets is given in Table 1. It is well acknowledged that magnesium stearate in high concentrations interferes with the bindings between the particles in the mix; that can seriously affect the technological properties of the tablets<sup>2</sup>. Therefore, the low percentage of magnesium stearate was initially tried in the formulations. But concentration below 2% w/w exhibited poor granule flow, and thus 2% w/w magnesium stearate was employed for lubricating the granules throughout the study. Dicalcium phosphate was a diluent in all produced tablets. Explanation for using specified amounts of drug and gums is given earlier in the text. Pharmacotechnical properties of the matrix tablets are summarized in Table 4. All examined tablets showed reproducible technological properties and good weight,

thickness and diameter uniformity. Due to low T<sub>g</sub> values of both the gums, low pressures were employed to compress the granules into tablet to avoid any changes in the gum structure and properties. This may be the reason why GC and GD matrix tablets exhibited the breaking strength in the range of 5-5.2 kg/cm<sup>2</sup>. Hardness of all tested tablets was found always within the limits to give good handling properties without breakage or excessive friability problems.

Diclofenac sodium release profile of GC and GD matrix tablets is shown in Fig. 1 and Fig. 2 respectively. As regards the effect of gum concentration, decrease in drug release rate was observed when GC and GD content in the matrix was increased. This may be due to the reason that the gums in higher concentrations in the tablets might have produced dense matrix around the drug particles, providing more barriers for them to escape and dissolve<sup>22</sup>. Further, such dense matrix, specifically when it is hydrophobic in nature, may be expected to favour less penetration of the dissolution medium in the tablets. This may also be the auxiliary reason for obtaining slow drug release profiles through GC and GD matrix tablets. Moreover, it is reported that the varying drug release profile may also occur due to the difference in T<sub>g</sub> and crystallinity that depends on polymer molecular weight<sup>23</sup>. Particularly, matrix of low-molecular-weight polymer was found to degrade and release drug rapidly<sup>24</sup>. But GC and GD, in spite of low average molecular weights of 150 and 180 respectively, showed significant sustained drug delivery through matrix

**TABLE 3: RELATIVE SOLUBILITY OF GUM COPAL AND GUM DAMAR**

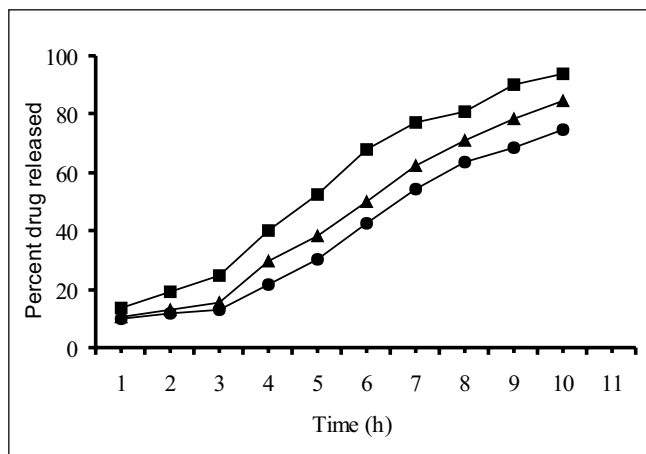
Solvent*	Solubility in different solvents		pH	Solubility in different pH solutions	
	Solubility (g/ml) <sup>a</sup>			Solubility (g/ml) <sup>a</sup>	
	Gum Damar	Gum Copal		Gum Damar	Gum Copal
1	0.68±0.032	0.56±0.029	1.2	6.4±0.9 × 10 <sup>-3</sup>	4.7±0.4 × 10 <sup>-3</sup>
2	0.50±0.012	0.42±0.042	4.0	8.8±0.8 × 10 <sup>-3</sup>	6.1±0.8 × 10 <sup>-3</sup>
3	0.45±0.036	0.36±0.017	6.8	10.7±1.4 × 10 <sup>-3</sup>	7.6±0.4 × 10 <sup>-3</sup>
4	0.36±0.027	0.31±0.024	8.0	13.0±1.6 × 10 <sup>-3</sup>	9.8±0.6 × 10 <sup>-3</sup>
5	0.32±0.021	0.29±0.032			
6	Insoluble	Insoluble			

\*Solvents used were 1-Chloroform, 2-Dichloromethane, 3-Acetone, 4-Isopropyl alcohol, 5-Ethanol, 6-Water. 2 g each gum sample was placed in 10 ml each solvent and buffer solutions for solubility determinations. <sup>a</sup>Mean ± S.D.

**TABLE 4: PHARMACOTECHNICAL PROPERTIES OF MATRIX TABLETS**

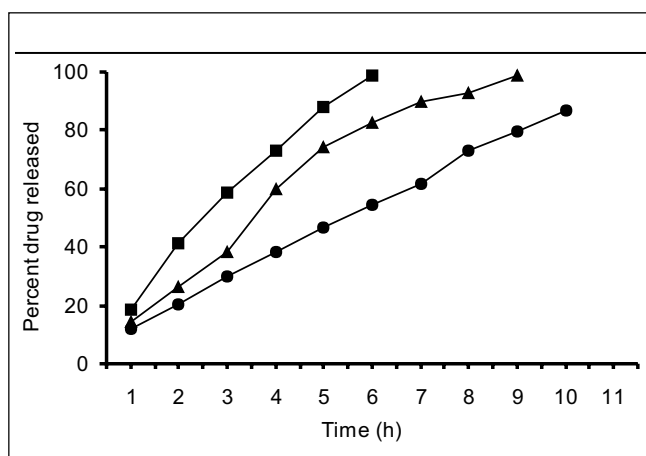
Product code	Diameter (mm)*	Thickness (mm)*	Weight (mg) <sup>a</sup>	Hardness (kg/cm <sup>2</sup> )*	% Friability	% Drug content
M1	9.13±0.009	6.10±0.012	249.0±1.5	5.0±0.16	> 0.5	99.6
M2	9.09±0.010	6.09±0.014	250.0±1.3	5.1±0.22	> 0.5	99.8
M3	9.10±0.007	6.03±0.017	249.0±0.9	5.1±0.26	> 0.5	100.1
D1	9.07±0.008	6.11±0.011	250.0±1.4	5.0±0.19	> 0.5	100.0
D2	9.08±0.011	6.10±0.016	248.0±1.7	5.0±0.21	> 0.5	99.5
D3	9.11±0.005	6.08±0.013	250.0±1.3	5.1±0.20	> 0.5	100.0

M1-D3 are various formulations of matrix tablets. \*Mean for 10 tablets±SD <sup>a</sup>Mean for 20 tablets±SD.



**Fig. 1: Diclofenac sodium release profile of Gum copal matrix tablets.**

Gum concentration used was (■) 10%, (▲) 20% and (●) 30% w/w with respect to total tablet weight. Each point represents a mean of three determinations.



**Fig. 2: Diclofenac sodium release profile of Gum damar matrix tablets.**

Gum concentration used was (■) 10%, (▲) 20% and (●) 30% w/w with respect to total tablet weight. Each point represents a mean of three determinations.

tablets. This may be attributed to their hydrophobicity, strong binding property and amorphous nature as well, because it has been documented that reduced polymer crystallinity is favourable when slow drug release is desired<sup>25</sup>. GD matrix with all concentrations showed rapid drug release compared to GC in first 2 h, which may be

due to the higher solubility of GD compared to GC at pH 1.2. In low concentrations (10% w/w), GC showed significant sustained drug delivery compared to GD. Tablets with 20% w/w GC and GD showed 84.84% and 94% total drug release at the end of 10 and 9 h respectively. This may be due to the low solubility of GC compared to GD at pH 1.2 and pH 6.8. However, tablets with 30% w/w GC as well as GD were found effective in sustaining the drug release beyond 10 h.

To describe the kinetics of drug release from matrix tablets, release data was analysed according to different kinetic equations. Table 5 indicates that drug release from the matrix tablets with 30% w/w GD obeys zero order kinetics while the release data from the matrix containing 10 and 20% w/w GD seems to fit the best to Higuchi square root kinetic, indicating that diffusion was the main factor controlling the drug release rate and that the release mechanism was not significantly influenced by formulation variables. On the other hand, all examined GC matrix tablets showed drug release by zero order kinetics. So it is possible to conclude that GC can be utilized to formulate the system in which drug release rate is independent of its concentration, whereas GD favours insoluble matrix formation that releases drug by diffusion.

The present study was carried out to investigate the matrix-forming ability of GC and GD in tablets for sustained drug delivery. Result of the physicochemical evaluation and characterization indicated the soft and amorphous nature of GC and GD. For GD, low acid value was observed; that can be the indication of its better chemical stability. Although low compression pressures were used during tablet formulations, all produced tablets showed good strength for handling. Pharmacotechnical properties of all examined tablets were within the acceptable limits. Both the gums in 30% w/w concentration retarded diclofenac sodium release beyond 10 h. GC was found more effective than GD at low concentration (10% w/w) in sustaining the drug release

**TABLE 5: CORRELATION COEFFICIENTS ACCORDING TO DIFFERENT KINETIC EQUATIONS FOR MATRIX TABLETS**

Kinetic Model	Gum Damar (%)			Gum Copal (%)		
	10	20	30	10	20	30
First order	0.8701	0.9208	0.9580	0.9577	0.9724	0.9780
Baker-Lonsdale	0.8611	0.9773	0.9516	0.9644	0.9423	0.9431
Hixon-Crowell	0.8927	0.9443	0.9803	0.9727	0.9849	0.9853
Zero order	0.9196	0.9742	0.9989	0.9884	0.9917	0.9854
Higuchi	0.9564	0.9881	0.9914	0.9832	0.9705	0.9577

Table values represents correlation coefficient (r) for linearity according to different kinetic equations used for describing the drug release from various matrix tablets.

rates. Drug release from GC and GD matrix followed zero order and Higuchi square root kinetics respectively. In conclusion, results of the present study suggest substantial matrix forming ability of GC and GD that could be used for sustained drug delivery.

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