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Formulation and Evaluation of Diclofenac Sodium Sustained Release Matrix Tablets Using *Aegle Marmelos* Gum

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Abstract
The aim of the study was undertaken to find out the potential of gum from the fruits of *Aegle marmelos* to act as a release modifier in the formulation of diclofenac sodium sustained release matrix tablets. Purified isolated gum was subjected to physicochemical characterization. Four formulations containing *Aegle marmelos* gum with each containing 100mg of Diclofenac sodium were prepared by wet granulation method using different drug: gum ratios viz. 1:0.25, 1:0.5, 1:1 and 1:2. Microcrystalline cellulose was used as diluent while magnesium stearate and talc were employed as lubricant and glidant respectively. The prepared formulations were evaluated for pre-compression parameters relevant to granules like angle of repose, bulk density, tapped density, hausner's index and carr's index while tablets were evaluated for various post-compression parameters like tablet thickness, hardness, weight variation, friability, content uniformity, disintegration time, swelling behaviour and in-vitro drug release study. All the formulations showed compliance with pharmacopoeial standards and found to be within the limits as per the standards. Among all the formulations, AM-4 showed a slow and complete drug release of 98.86% over a period of 12 hr and thereby exhibited a satisfactory sustained drug release phenomenon.
Key words: Diclofenac sodium, *Aegle marmelos*, Sustained release

Introduction
Oral route of drug administration is the most appealing, convenient, significant and popular route for the delivery of drugs owing to ease of swallowing, self medication, and most economic. Tablets are the most popular and preferred oral formulation available in the market because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids and because it is more tamperproof than capsules[1-4]. The primary benefits of a sustained release dosage forms compared to a conventional dosage forms, is maintenance of constant plasma drug concentration and therefore maintains uniform therapeutic effect.

Over the past two decades, sustained release drug delivery systems have made significant progress in terms of clinical efficacy and patient compliance. Drug-release-retarding polymers are the key performers in such systems. Regarding this, researchers investigated various natural, semi-synthetic and synthetic polymeric materials[5-7]. Matrix system is most commonly used method for modulating the drug release in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug[5, 8, 9].

Number of natural, semi synthetic and synthetic polymer materials are used in the sustained or controlled delivery of drugs. Natural polymers have gained the attention for their use in drug delivery systems due to their easy availability, non-toxic, cost effectiveness, ecofriendliness, biocompatible, capable of chemical modifications, potentially biodegradable and degradation under natural and physiological conditions[7, 10, 11]. *Aegle marmelos* gum is obtained from fruits of *Aegle marmelos* belonging to family Rutaceae is indigenous to India. The ripen fruit pulp is red in colour with mucilaginous and astringent taste. The pulp contains carbohydrates, proteins, vitamin C, vitamin A, angelenine, marmeline, dictamine, O-methyl fordinol and isopentyl halfordinol[12]. The study was undertaken to find out the potential of gum from the fruits of *Aegle marmelos* to act as a release modifier in the formulation of diclofenac sodium sustained release matrix tablets.

Materials and Methods

Materials:

Diclofenac sodium was purchased from Yarrow Chem Products, Mumbai, India. Microcrystalline cellulose, magnesium stearate and talc were procured from Central Drug House, New Delhi, India. *Aegle marmelos* fruits were collected from nearby locality of Dehradun, Uttarakhand. Plant sample was authenticated from Botanical Survey of India, Dehradun (Uttarakhand). One set of the sample was deposited in the herbarium of Botanical Survey of India, Northern regional Centre, Dehradun (Uttarakhand). All the other chemicals used were of analytical grade and were also purchased from Central Drug House, New Delhi, India.

Isolation and Purification of *Aegle marmelos* gum:[12, 13]

Fresh pulpy parts of edible fruits of *Aegle marmelos* were soaked in distilled water and boiled for 2-3 hours in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight so that most of the undissolved portion was settled out. The upper clear supernatant solution was decanted off and concentrated at 60ºC on a water bath until the volume reduced to its one third. Solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50ºC. The dried gum was powdered and stored in tightly closed container for further use.

Physicochemical Properties of *Aegle marmelos* gum:[12, 13, 14, 15]

Macroscopic properties of the gum were evaluated by observation of the colour, taste and odour of the powdered gum. The gum was evaluated for solubility in water, ethanol, acetone and chloroform in accordance with the standards. Other physicochemical properties were also determined for the gum like loss on drying, total ash, pH, angle of repose, bulk density, tapped density, hauser's ratio and carr's index.

Preparation of Diclofenac Sodium Sustained Release Matrix Tablets:[13, 16]

Oral sustained release matrix tablets each containing 100mg of Diclofenac sodium were prepared by wet granulation method using different drug: gum ratios viz. 1:0.25, 1:0.5, 1:1 and 1:2 for various formulations containing *Aegle marmelos* gum. Microcrystalline cellulose was used as filler to maintain the tablet weight. The compressed tablets were stored in a closed container for 15 days, no significant evidence of chemical change was observed.

Evaluation:

The prepared formulations were evaluated for the following parameters:

1. **Pre-compression evaluation**[13, 15, 16]

   i. **Angle of Repose:**

   The angle of repose of granules was determined by the funnel method. The accurately weight granules were taken in the funnel. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation:

   $$\tan \theta = h/ r \quad \text{or} \quad \theta = \tan^{-1} (h/ r)$$

   Where, θ = angle of repose,
   h = height of the cone, and
   r = radius of the cone base

   ii. **Bulk Density:**

   Bulk density (D_b) was determined by measuring the volume (V_b) of known weighed quantity (W) of granules using bulk density apparatus and can be calculated by using the formula:

   $$D_b = W/ V_b$$

   iii. **Tapped Density:**

   Tapped density (D_t) was determined by measuring the volume (V_t) of known weighed quantity (W) of granules using bulk density apparatus and can be calculated by using the formula:

   $$D_t = W/ V_t$$

   iv. **Hausner's Index:**

   The Hausner's index was calculated by dividing the tapped density by the bulk density of the granules.

   $$\text{Hausner's index} = \frac{D_t}{D_b}$$

   Where, D_t is the tapped density and D_b is the bulk density.

   v. **Carr's Index:**

   The Carr's index (% compressibility) of the granules was calculated from the difference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage.

   $$\text{Carr's Index (\%)} = \frac{D_t - D_b}{D_t} \times 100$$

   Where, D_t is the tapped density and D_b is the bulk density.

2. Post-compression evaluation[14, 15]

i. Tablet Thickness:

The thickness of the tablets was determined by using vernier caliper. Five tablets were used, and average values were calculated.

ii. Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

iii. Weight Variation:

To study weight variation twenty tablets of the formulation were weighed using a digital balance and the test was performed according to the official method. The specification for weight variation of tablets as per USP was mentioned in Table 1. Twenty tablets were selected randomly and weighed individually to check for weight variation.

Table 1: Specification for weight variation of tablets as per USP

Average weight of tablets (mg)	% difference
130 or less	10
From 130 to 324	7.5
More than 324	5

iv. Friability:

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again. The % friability was then calculated by:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

% Friability of tablets less than 1% are considered acceptable.

v. Content Uniformity:

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in acetone, the drug content was determined measuring the absorbance at 276 nm after suitable dilution using Elico SL210 UV-Visible double beam spectrophotometer. The drug content was estimated from the standard curve of diclofenac sodium.

vi. Disintegration Time:

Disintegration time test was carried out according to USP specification. 6 tablets were placed in a disintegration tester filled with distilled water at 37±0.20C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh. Disintegration times recorded are mean of two determinations.

vii. Swelling Behaviour of Formulations:

The swelling index of all the tablet formulations was studied. The extent of swelling was measured in terms of percent weight gain by the tablet. To study the swelling behavior, one tablet from each formulation was kept in a petri dish containing 20 ml phosphate buffer pH 7.4. At the end of 1 hr, the tablet was withdrawn, kept on tissue paper and weighed. The process was continued for every 2 hr, till the end of 12 hr.

The % weight gain by the tablet was calculated by formula:

$$S.I. = \{(Mt-M0) / M0\} \times 100$$

Where, S.I. = swelling index
Mt = weight of tablet at the time (t)
Mo = weight of tablet at time 0.

viii. In-Vitro Drug Release Profile Studies:

Release of Diclofenac sodium from the matrix tablets was studied using a six basket USP dissolution apparatus taking 900 mL of 0.1 N HCl (pH 1.2) solution for first 2 hrs and phosphate buffer (pH 7.4) for next 10 hrs. The dissolution media were maintained at a temperature of 37°± 0.5°C. The speed of rotation of basket was maintained at 50 rpm. Aliquot equal to 10 ml sample was withdrawn at specific time intervals and the dissolution media volume was complimented with fresh and equal volume of phosphate buffer. The samples were filtered and suitably scanned with appropriate dilution and amount of Diclofenac sodium released from the tablet samples was determined spectrophotometrically at a wavelength of 276 nm by comparing with the standard calibration curve.

Results and Discussion

Macroscopic properties showed that *Aegle marmelos* gum obtained after extraction from the fresh fruit pulp of plant was an amorphous free flowing powder with yellow colour, sweet in taste and characteristic sweetish odour. The gum was found to be soluble in water and gave viscous solution on standing but practically insoluble in ethanol, acetone and chloroform. It has pH around 6.4 with acceptable limit loss on drying (7.15%) and total ash (2.85%). Flow properties of gum was determined in terms of angle of repose (28.80º), bulk density (0.54g/cc), tapped density (0.69g/cc), hausner's index (1.28) and carr's index (21.74%). All these physicochemical properties were tabulated in Table 2.

Table 2: Physicochemical Properties of *Aegle marmelos* gum

S.No.	Parameters		Results
1.	Macroscopic Property	Colour	Yellowish
		Taste	Sweet
		Odour	Characteristic sweetish
2.	Solubility	Water	Soluble
		Ethanol	Insoluble
		Acetone	Insoluble
		Chloroform	Insoluble
3.	Loss on Drying (%)		7.15
4.	Total Ash (%)		2.85
5.	pH		6.4
6.	Angle of Repose (º)		28.80
7.	Bulk Density (g/cc)		0.54
8.	Tapped Density (g/cc)		0.69
9.	Hauser's Ratio		1.28
10.	Carr's Index (%)		21.74

Preformulation studies of model drug i.e. Diclofenac sodium was performed for determining the solubility, melting point and λmax. The results showed that the drug was found to freely soluble in ethanol, acetone and methanol, sparingly soluble in distilled water and glacial acetic acid while practically insoluble in ether. Melting point of Diclofenac sodium was found to be 170°C approx. The λmax of Diclofenac sodium was found to be 276 nm and standard calibration curve of Diclofenac sodium was prepared as showed in Figure 1. Diclofenac sodium matrix tablets were prepared by wet granulation method as per the formulae given in the Table 3. The granules of different formulations were evaluated for angle of repose, bulk density, tapped density, hausner's index and carr's index as pre-compression parameters and results were depicted in Table 4. Angle of repose values ranged from 20.61°-24.02º indicates good flow property of granules. The values of bulk density and tapped density ranged from 0.56-0.66 g/cc and 0.74-0.79 g/cc respectively were found to be within the limits as per standards. The free flowing properties of granules were then calculated by determining hausner's index and carr's index (%). The hausner's index values were ranged from 1.20-1.36 and carr's index values were ranged from 16.46-26.32%.

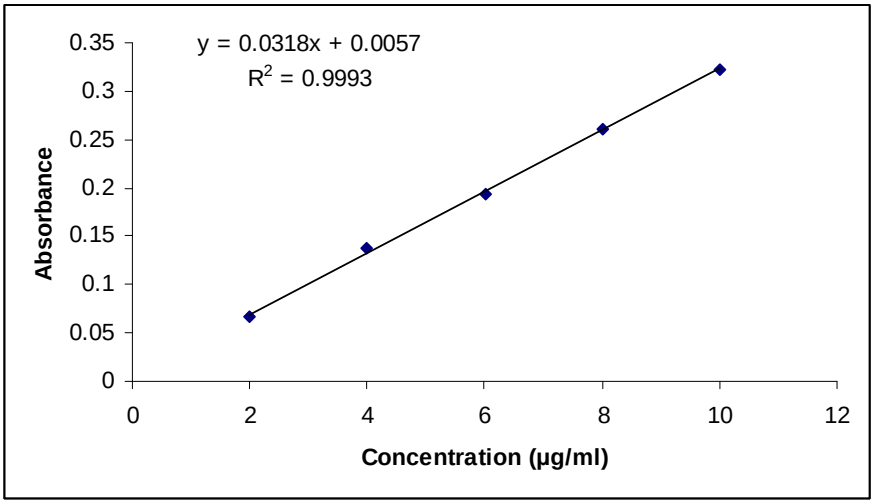

Figure 1: Standard calibration curve of Diclofenac sodium in distilled water

Table 3: Formulation of Diclofenac Sodium Sustained Release Matrix Tablets

Ingredients	Formulations (mg/tablet)			
	AM-1 D:G (1:0.25)	AM-2 D:G (1:0.5)	AM-3 D:G (1:1)	AM-4 D:G (1:2)
Diclofenac Sodium	100	100	100	100
Aegle marmelos Gum	25	50	100	200
Microcrystalline Cellulose	360	335	285	185
Magnesium Stearate	10	10	10	10
Talc	5	5	5	5
Total	**500**	**500**	**500**	**500**

* AM- *Aegle marmelos*, * D: G = Drug: Gum ratio

Table 4: Pre-compression evaluation of Diclofenac sodium granules

S.No.	Parameters	Formulations			
		AM-1	AM-2	AM-3	AM-4
1.	Angle of Repose (º)	20.61±0.46	21.50±0.34	24.02±0.21	22.62±0.31
2.	Bulk Density (g/cc)	0.64±0.03	0.60±0.02	0.56±0.08	0.66±0.02
3.	Tapped Density (g/cc)	0.78±0.04	0.74±0.01	0.76±0.02	0.79±0.01
4.	Hausner's Index	1.22	1.23	1.36	1.20
5.	Carr's Index (%)	17.95	18.92	26.32	16.46

*Values are in mean±s.d. (n=3) (s.d.= standard deviation)

The post-compression evaluation of tablet formulations were based on quality control parameters which include thickness, hardness, weight variation, friability, content uniformity and disintegration time. All the results relative to post-compression evaluation were tabulated in Table 5. Thickness of tablets in all formulations was found to be ranged from 3.92-4.04 mm. All the formulations showed reasonably good hardness values ranged from 6.18-7.40 kg/cm^3. The weight variation of 20 tablets from the average was remained within ±0.1% and thus revealed that the tablets were within the range of pharmacopoeial limit. The % friability of tablets was ranged between 0.42-0.84% and found to be within the pharmacopoeial limit. Content uniformity of all tablets was within the range of 99.6 to 100.4% indicating good uniformity among different formulations of the tablets. The disintegration time was found to be ranged from 9.45-23.54 min for all the formulations and could be a contributing factor in considering the role of this gum as a release modifier.

Table 5: Post-compression evaluation of Diclofenac sodium tablets

S.N.	Parameters	Formulations			
		AM-1	AM-2	AM-3	AM-4
1.	Tablet Thickness (mm)	3.96±0.02	4.04±0.08	3.88±0.06	3.92±0.05
2.	Hardness (Kg/cm^3)	6.18±0.02	6.50±0.04	6.44±0.12	7.40±0.26
3.	Weight Variation (mg)	498±0.02	501±0.04	499±0.02	496±0.01
4.	Friability (%)	0.42±0.03	0.56±0.02	0.66±0.01	0.84±0.04
5.	Content Uniformity (%)	99.8±1.01	99.6±0.93	99.7±0.64	100.4±0.85
6.	Disintegration Time (min)	9.45±0.22	15.22±0.37	18.42±0.52	23.54±0.24

*Values are in mean±s.d. (n=3) (s.d. = standard deviation)

The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to certain limit. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, and as gum concentration increases, swelling index was increased. The relationship was better interpreted by comparing the swelling behaviour of different formulations from Table 6.

Table 6: Swelling behaviour of Diclofenac sodium tablets

S.No.	Time (hr)	Swelling Index (%)			
		AM-1	AM-2	AM-3	AM-4
1.	1	8.12	12.24	21.81	24.21
2.	2	25.06	28.65	32.61	47.32
3.	4	37.23	41.60	56.66	64.65
4.	6	27.22	64.21	69.51	87.43
5.	8	10.72	56.32	78.43	103.22
6.	10	0.00	49.30	81.11	102.87
7.	12	0.00	39.28	82.14	97.22

The in vitro release of different formulations of Diclofenac sodium tablets was showed in Table 7 and Figure 2. Among all the formulations, AM-4 showed a slow and complete drug release of 98.86% over a period of 12 hr. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix.

Table 7: In vitro release data of Diclofenac sodium tablets

S.No.	Time (hr)	% Cumulative Drug Release (Mean ± S.d., n=3)			
		AM-1	AM-2	AM-3	AM-4
1.	1	8.21±0.23	10.21±0.20	12.64±1.43	12.21±2.01
2.	2	21.64±1.24	17.32±0.93	16.08±0.63	12.67±2.42
3.	3	45.75±1.15	35.60±1.24	22.77±2.06	18.64±1.02
4.	4	75.21±1.65	67.62±1.58	47.44±1.54	28.88±1.65
5.	5	97.65±1.36	81.55±1.03	53.63±1.61	33.76±1.32
6.	6	-	98.22±1.15	62.45±1.23	45.66±0.23
7.	7	-	-	72.14±1.11	59.32±0.23
8.	8	-	-	79.17±1.51	67.75±0.23
9.	9	-	-	88.23±1.16	81.46±0.23
10.	10	-	-	97.45±1.02	89.64±0.23
11.	11	-	-	-	94.22±0.23
12.	12	-	-	-	98.86±0.23

*Values are in mean±s.d. (n=3) (s.d. = standard deviation)

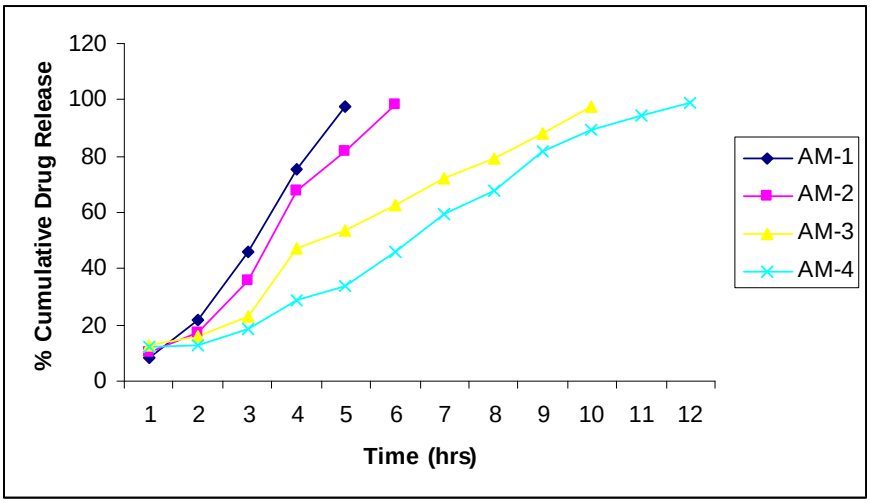

Figure 2: In vitro release profile of Diclofenac sodium tablets

Conclusion

The study revealed that *Aegle marmelos* gum appears to be suitable for use as a release modifier in the preparation of sustained release matrix tablets of diclofenac sodium because of its properties to give excellent and better results by evaluating the pre-compression and post-compression parameters for different formulations containing variable ratios of drug and gum. By observing the good swelling index and appropriate drug release pattern in tablet

formulations, it was revealed from the study that among all the formulations, AM-4 was found to release the drug in a slow, controlled manner with maximum drug release of 98.86% over a period of 12 hr. Hence it can be concluded that, the *Aegle marmelos* gum can be used as a promising drug release retardent in a particular concentration range.

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