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Fruit Gum of *Aegle marmelos* as Pharmaceutical Aid

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Abstract: In the present study have formulated the oral tablets of paracetamol by using *Aegle marmelos* fruit gum as a binder. The four different tablet formulations were prepared by wet granulation method. The binder concentrations used in the formulation were 2, 4, 6 and 8% w/v of *A. marmelos* fruit gum, tablets were subjected for evaluation of hardness, friability, drug content uniformity. Preliminary evaluation of granules showed that, 0.71 to 0.77 mm granule size, 29.20 to 30.10° angles of repose and 22.1 to 12.7% fines. Hardness was found in the range of 7.1 to 7.4 kg cm^{-2}, the percent friability was in the range of 1.50 to 0.75%. The tablet showed 97.46 to 98.96% of labeled amount of paracetamol indicating uniformity in drug content, 8 to 18 min disintegration time and more than 90% dissolution in 75 min. Tablets at 6% w/w binder concentration showed more optimum results as tablet binder. The *Aegle marmelos* gum was found to be useful for the preparation of uncoated tablet dosage form.

Key words: *Aegle marmelos* gum, binder, paracetamol, dissolution

INTRODUCTION

Gum is obtained from fruits of *Aegle marmelos* belonging to family Rutaceae. It was a native of Australia and is also reported in India and Ceylon. This plant is a small, deciduous, smooth tree. The spines are straight, strong, axillary and about 2.5 cm in length. The leaflets are 3 to 5 and ovate-lanceolate, the laterals one being sessile and the terminal ones long petiole. The flowers are 3 cm across and greenish-white. The fruit is nearly spherical about 10 to 14 cm in diameter. The rind is grey or yellow and the pulp sweet, thick, aromatic, gelatinous and orange-colored. The seeds are numerous, oblong and flat. Pulp contains carbohydrates, proteins, vitamin C, vitamin A, angelenine, marmeline, dictamine, O-methyl fordinol and isopentyl halfordinol. The neutral oligosaccharides were characterized as 3-0-beta-D-galactopyranosyl-L-arabinose, 5-0-beta-D-galactopyranosyl-L-arabinose and 3-0-beta-D-galactopyranosyl-D-galactose and the acidic oligosaccharides as 3-0-(beta-D-galactopyranosyluronic acid)-D-galactose and 3-0-(beta-D-galactopyranosyluronic acid)-3-0-beta-D-galactopyranosyl-D-galactose (Bhattacharya and Mukherjee, 1976). Small unripe fruit is consumed with fennel seeds and ginger in decoction for piles (Kamalakkannan and Prince, 2005). The unripe fruit poultice is applied to inflammation, edema, constipation and jaundice (Pattanayak and Mohapatra, 2008). It were used against multi-drug resistant *Salmonella typhi* (Phulan and Khullar, 2004), dengue vector (Samarasekera *et al*., 2004), cure scurvy (Hema and Lalithakumai, 1999) and also used as antihyperglycemic (Narendra and Sweta, 2007). The various gums were used as a tablet binder in pharmaceutical dosage forms (Antony and Sanghavi, 1997; Editorial, 1994). In this present investigation *A. marmelos* gum has been evaluated as a suitable binder for paracetamol tablet.

MATERIALS AND METHODS

Paracetamol IP and Microcrystalline cellulose was received as a gift sample from Kem Well House, Bangalore. All other materials used in this study were of A.R. grade purchased from s.d.fine chemicals Mumbai. Fresh white gum of *Aegle marmelos* was collected from authenticated plant fruits in local area of Gadag district of Karnataka. This research work was conducted in period between November 2008 to July 2009.

Purification of gum: The well dried gum was powdered in mortar, passed through sieve No. 80 and solublised in distilled water. The concentrated solution was precipitated in acetone. The precipitate was separated and dried at 60°C. The dried gum was powdered and stored in tightly closed container for further usages.

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Standardization of gum: The gum was standardized for following properties. Loss on drying: The 5 g gum was dried at 105±5°C till the constant weight of gum was obtained. The loss on drying was found to be less than 8% w/w. Ash value: 1g of gum was accurately weighed and evenly distributed it in the crucible. It was dried at 105°C for 1 h and ignited in muffle furnace at 600±25°C. Percentage of ash content was found to be less than 7% w/w and 2 to 8% w/v gum solutions have pH 6.0 to 6.5.

Acute toxicity study: This study was designed to elucidate the toxicity of the widely used fruit gum of *Aegle marmelos* in rats. We have taken total whole aqueous solution from the gum of *A. marmelos* and studied their toxic effects. Acute, sub-acute and LD_{50} values were determined in experimental rats. The dead animals were obtained from primary screening studies, LD_{50} value determination experiments and acute studies subjected to postmortem studies. The external appearance of the dead animals, the appearance of the viscera, heart, lungs, stomach, intestine, liver, kidney, spleen and brain were carefully noted and any apparent and significant features or differences from the norm were recorded. Following the chronic administration of *A. marmelos* for 14 days, the vital organs such as heart, liver, kidney, testis, spleen and brain were carefully evaluated by histopathological studies and any apparent and significant changes or differences from the norm were studied. From the acute administration of *A. marmelos*, the LD_{50} values were determined using graphical method. The hearts stopped in systolic stand-still in the acute experiments. There were no remarkable changes noticed in the histopathological studies after 40 mg kg^{-1} b.wt. of the gum solution of *A. marmelos* when administered intraperitoneally for 14 days successively. Pathologically, neither gross abnormalities nor histopathological changes were observed. After calculation of LD_{50} values using graphical methods, we found a broad therapeutic window and a high therapeutic index value for *A. marmelos* extracts. Intraperitoneal administration of gum solution of *A. marmelos* at doses of 40, 80, 120 and 140 mg kg^{-1} b.wt. for 14 consecutive days to male and female Wistar rats did not induce any short-term toxicity. Collectively, these data demonstrate that the gum solution of *A. marmelos* have a high margin of drug safety.

Preparation and evaluation of granules: The formulation was developed with Paracetamol IP as model drug by wet granulation method. Binder solution of gum in the concentration 2, 4, 6 and 8% w/v were prepared in distilled water (Table 1). Binder level was adjusted by lowering the level of MCC in the formula. All ingredients were dry mixed manually in mortar. Binder solution was slowly added into mixture. The wet mass was granulated by passing them manually through a number 12 mesh sieve. Granules were dried at 60°C in oven and again received through number 16 mesh sieve. The granules were evaluated for percentage of particle size, angle of repose and fines. Granules were mixed with 4% talc and evaluated for flow property (Bankar and Neal, 1987; Gorden and Fonner, 1999). The tablet formulations were developed for 600 mg, by using fixed dose of 400 mg paracetamol as a drug, talc powder (24 mg) as a lubricant and microcrystalline cellulose (164-128 mg) as a diluent and *A. marmelos* gum (2-8% w/v) as a binder. In the above formulations, 6% w/v of binder concentration was shown satisfactory tablets.

Preparation and evaluation of tablets: The tablets were compressed by using single punch tablet machine fitted with flat faced punches. The batch size prepared was of 100 tablets. The prepared tablets were stored in closed container for 30 days. No evidence of chemical change was observed. The tablets were evaluated for content uniformity, hardness, friability, disintegration time and dissolution study (Chukwu and Okpalaezinne, 1989; Odeku and Iiolia, 2005). Dissolution study was carried out in 900 mL 0.1 N HCL medium using paddle type Dissolution Test Apparatus. The dissolution was carried out at 37±1°C and 60 rpm paddle speed. The 10 mL samples were withdrawn at 10 min intervals. Ten milliliter dissolution medium was added into dissolution chamber as a replacement for sampling after each interva (Table 2). Absorbance was measured at 243 nm using UV spectrometer Simadzu (Indian Pharmacopoeia, 1996; Kulkarni and Suresh, 2002).

Table 1: Formulation of tablet containing *Aegle marmelos* gum as binder

	Variation of binder concentration by lowering the level of MCC			
Ingredients	Batch I	Batch II	Batch III	Batch IV
Paracetamol (mg)	400	400	400	400
Microcrystalline cellulose (mg)	164	152	140	128
Binder (*A. marmelos* gum) (% w/v)	2	4	*6	8
Talc (mg)	24	24	24	24

*Indicates good concentration of binding agent. In the formula, weight of one tablet (600 mg) is mentioned, but each batch was calculated and taken for 100 tablets.

Table 2: Evaluation of granules prepared from *Aegle marmelos* gum

	Binder concentration (% w/w)			
Characteristic	2	4	6	8
Fines (%)	22.1	19.5	16.2	12.7
Particle size (mm)	0.710	0.722	0.750	0.772
Angle of repose	29.20°	29.40°	29.65°	30.10°

RESULTS

Four batches of granules were prepared with binder solution of *A. marmelos* fruit gum in the concentration 2, 4, 6 and 8% w/v and have pH 6.0-6.5. The flow property of granules was determined by angle of repose and was found 29.20°, 29.40°, 29.65° and 30.10° for batch I to IV, respectively. The increased percentage of fines (22.1, 19.5, 16.2 and 12.7% for batch I to IV, respectively) reduces particle interlocking and friction, thus decreasing angle of repose. Found average granule size distribution 0.710, 0.722, 0.750 and 0.772 mm for batch I to IV, respectively. The tablets exhibited a good uniformity in content like batch-I 97.46%, batch-II 98.96%, batch-III 98.96% and batch-IV 98.94%. The hardness of tablet increased with increase in percentage of binding agent like batch-I 7.1 kg cm^{-2}, batch-II 7.3 kg cm^{-2}, batch-III 7.00 kg cm^{-2} and batch-IV 7.4 kg cm^{-2}. The friability values decreased with increase in binder concentration from batch-I 1.50%, batch-II 1.30%, batch-III 1.00% to batch-IV 0.75%. The disintegration time also increased with increase in binder concentration from 8 to 18 min 10 sec (Table 3). All the evaluation parameters were found within the pharmacopoeial limits at binder concentration 6 to 8% w/v. Dissolution study showed that drug release from the tablets containing 2 to 8% w/v of binder was more than 90% in 75 min (Fig. 1).

Table 3: Evaluation of tablets prepared from *Aegle marmelos* gum as binder

	Binder concentration (% w/w)			
Characteristic	2	4	6	8
Content uniformity (%)	97.46	98.96	98.96	98.94
Hardness (kg cm^{-2})	7.1	7.3	7.0	7.4
Friability (%)	1.50	1.30	1.00	0.75
Disintegration time	8 min	10 min 15 sec	13 min 20 sec	18 min 10 sec

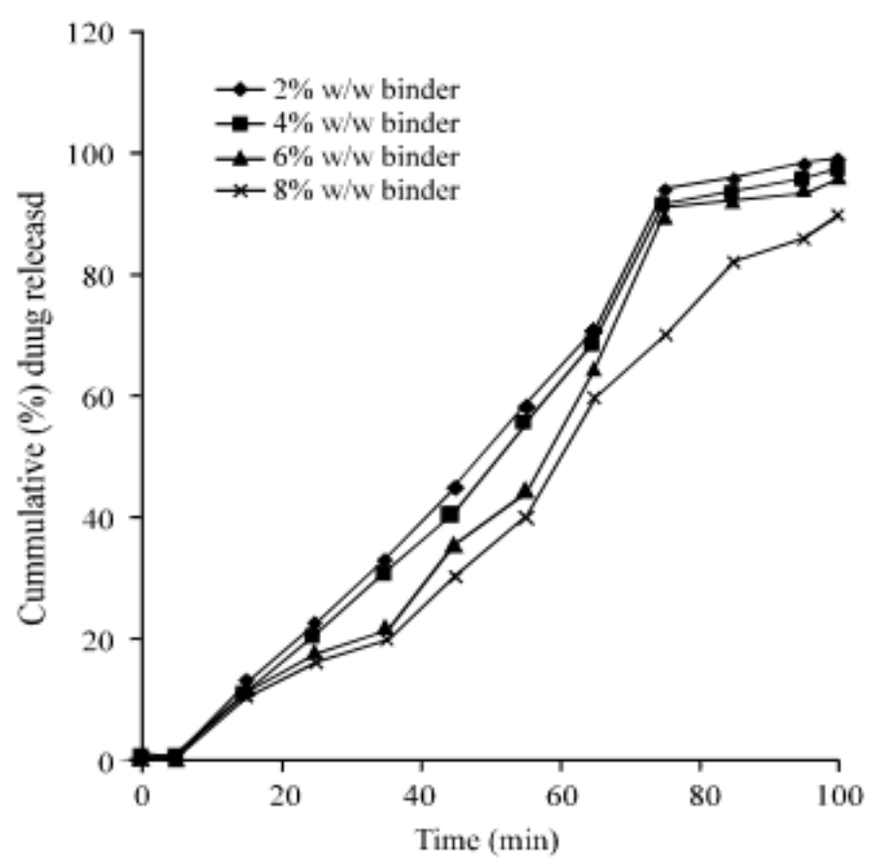

Fig. 1: Dissolution study of paracetmol

DISCUSSION

The prepared granules were evaluated for percentage of fines, particle size and flow properties. It was observed that the percentage of fines was reduced as the concentration of binder was increased (Ibezin *et al*., 2008; Javadzadeh *et al*., 2008). All batches of tablets with variation of binder concentration were prepared and evaluated for content uniformity, hardness, friability and disintegration time. They exhibited a good uniformity in content, hardness of tablet increased with increase in percentage of binding agent, friability values decreased with increase in binder concentration and disintegration time also increased with increase in binder concentration. The drug release from tablets decreased with increase in binder concentration. Tablet prepared with *A. marmelos* fruit gum in the concentration of 6% w/v shown more optimum results as tablet binder.

The animal experimental of gum with incorporation of medicament is required further study.

CONCLUSION

Binders as the name suggests help to bind the ingredients together-to achieve a desired bulk and form for manufacturing. Like glue that holds all the ingredients together. *Aegle marmelos* gum (6% w/v) exhibited good binding properties for uncoated tablets. The increased concentration of gum showed small retardation in drug release from tablet.

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