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Studies on disintegrant action of *Leucaena leucocephala* seed gum in ibuprofen tablet and its mechanism

P R P Verma* and Balkishen Razdan

Department of Pharmaceutical Sciences, Birla Institute of Technology (BIT), Mesra, Ranchi 835 215

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Leucaena (*Leucaena leucocephala*) seed gum (LSG) was evaluated for disintegrant action in lactose (soluble) based tablets containing ibuprofen, a relatively insoluble drug. The properties of tablets evaluated include weight uniformity, hardness, friability, disintegration time and *in vitro* dissolution (k, T_{50}, A_{30}). LSG, at low concentration level (2% w/w), can be used as a disintegrant in tablet dosage form containing water-insoluble drug. In contrast to maize starch, LSG swells rapidly when brought in the contact with water, while preventing the liquid uptake in cylindrical column of powder. This presumably suggests that initial swelling of LSG particles generates enough pressure to elicit disintegration action in the tablet before further liquid uptake results in formation of mucilaginous, gel like coherent mass, which hinders further movement of water into the tablet matrix.

Keywords: Disintegrant action, Ibuprofen, *Leucaena leucocephala*, Seed gum

Introduction

In pharmaceutical sciences, disintegration usually means the process by which a solid dosage form breaks up when it comes in contact with aqueous medium and thus promotes rapid release of drug for faster absorption[1,2]. A rapid disintegration process is the prerequisite for a good bioavailability[3]. Polysaccharide gum, derived from seeds of *Leucaena leucocephala*[4,5], has been investigated for its potential as a pharmaceutical adjuvant. Purified *Leucaena* seed gum (LSG) is non-toxic and its oral administration indicated a high LD_{50} (1850.23 mg/kg) in mice[6]. LSG has been reported as a suspending agent[6], and as binding agent in granules and tablets[7]. LSG has been further evaluated for its disintegrant properties[8] in tablets of soluble base containing soluble drug (sodium salicylate). Rheological properties[9] and emulsifying properties[10] of gum has also been studied.

In present work, mechanism of disintegration and disintegrant profile of LSG in tablets of soluble base (lactose) containing a relatively insoluble drug (ibuprofen) has been studied. Maize starch (MS) was used for comparison of disintegrant profile. Minimum concentration, which can initiate and finally lead to break-up of the tablet, was also explored along with the mechanism of disintegrant action of LSG.

*Author for correspondence
Fax: 91-651-2275401
E-mail: prpverma275730@yahoo.com

Materials and Methods

Materials

Ibuprofen (Lark labs, New Delhi, India), potassium dihydrogen phosphate, sodium hydroxide (E. Merch India Ltd, Mumbai, India), lactose, magnesium stearate (Loba Chemic, Mumbai, India), acacia, maize starch (S.D. Fines Chem. Ltd, Mumbai, India) were used. All solvents and reagents were of AnalaR grade. *Leucaena* seeds were obtained from medicinal garden (BIT, Mesra, India) and processed. Various batches of LSG, prepared and stored in vacuum desiccators after isolation and purification in BIT's laboratory, was used in the study.

Preparation of Granules and Tablets

Granules were prepared by the wet granulation technique using lactose (45 g), ibuprofen (15 g) and aqueous solution of acacia gum (20% w/v) as binder (Table 1). Moist mass obtained during granulation was forced through a stainless steel sieve (1.7 mm). Granules

Table 1 — Composition of formulated tablets of ibuprofen

Ingredient	Quantity per tablet				
	Batch				
	I	II	III	IV	V
Ibuprofen, mg	100	100	100	100	100
Lactose, mg	300	300	300	300	300
Acacia, 20% w/v	q.s	q.s.	q.s.	q.s.	q.s.
Disintegrants*, mg (% w/w)	4.0 (1%)	8 (2%)	20 (5%)	30 (7.5%)	40 (10.0%)
Magnesium stearate, mg (1% w/w)	4	4	4	4	4
Talc, mg (1% w/w)	4	4	4	4	4

*Disintegrants used were leucaena seed gum and maize starch

were dried in a tray in a hot-air oven at 60±1°C for 1 h. Dried granules were rescreened through a 1 mm mesh and stored in desiccators. Ten such batches of granules of ibuprofen were made. Disintegrants (1, 2, 5, 7.5 and 10% w/w) were incorporated extra granularly and shaken thoroughly for 5 min. Magnesium stearate and talc as lubricants (1% w/w each), were also added and mixed for another 5 min. All granule batches were compressed on a Cadmach single stroke, single punch tablet machine at a constant pressure using standard flat faced punches and die. The first 10 and last 10 tablets were rejected. Only mid stream tablets were allowed to equilibrate for 48 h, before evaluation.

Evaluation of Tablets

Uniformity of Weight and Hardness (Crushing Strength)

Randomly selected 20 tablets were weighed individually and together. Average weight was noted and standard deviation calculated. Hardness of tablets was determined using 5 tablets on the Monsanto Hardness Tester (IEC, Bombay). The mean and standard deviation were calculated.

Friability Test

Randomly selected 10 tablets from each batch were introduced into a friabilator (IEC, Bombay) set to rotate 100 times in 4 min. After test run, tablets were dedusted by directing a stream of air onto them. Weight loss (%) was determined by weighing tablets after the test.

Thickness and Surface Area

Randomly selected 10 tablets from each batch were tested for their thickness using a thickness gauge. The surface area (SA) was computed as

$$SA = 2\pi\, r\, (h+r) \qquad \ldots(1)$$

where, r is radius (mm) and h is thickness (mm) of the tablet.

Disintegration Time

Disintegration time (DT) was measured on Disintegration Test Apparatus IP/BP/USP (IEC, Bombay). Disintegration medium was distilled water at 37±1°C. Tablet holder was oscillating (30 times / min). Tablets (5) from each batch were employed and mean DT and standard deviation were calculated.

Assay

Ten formulated tablets were powdered and a content equivalent to 100 mg of ibuprofen was accurately weighed. The weighed powder was transferred to a 250 ml beaker, treated with 5 ml of ethanol and 40 ml of phosphate buffer (pH 7.2). The solution was filtered through G-4 sintered glass funnel. Residue was washed with phosphate buffer (pH 7.2; 2 x 25 ml). Combined filtrates were taken in a 100 ml volumetric flask and volume made up to 100 ml with phosphate buffer (pH 7.2). Accurately measured volume (1 ml) of this solution was further diluted to 100 ml in a volumetric flask and the absorbance of resulting solution measured at 220 nm spectrophotometrically (Systronics

spectro-photometer 108). Ibuprofen content (3 determinations for each formulation) was calculated from standard curve (r = 0.9998; p<0.001, slope = 0.0124, intercept = 0.0014) using pre-programmed Casio fx-3600 P, scientific calculator.

In vitro Dissolution

In vitro dissolution profile of each formulation was determined on Dissolution Test Apparatus IP/BP/USP. Dissolution vessel contained 1000 ml of phosphate buffer (pH 7.2) at 37±0.5°C. The speed of basket was set to 100 rpm. Samples (5 ml) were withdrawn at 5, 10, 15, 30, 45, 60, 75, and 90 min and analyzed at 220 nm. The volume so withdrawn was replenished with fresh medium maintained at 37±0.5°C. Five such runs were carried out for each formulated tablets and, mean and standard deviation calculated. Dissolution rate constant (k) min^{-1}, $t_{50\%}$ (time required for 50% dissolution in min), and A_{30} (% drug dissolved in 30 min) were calculated[11] by statistical treatment of pooled data.

Mechanism of Disintegrant Action

Bulk Swelling Capacity

Bulk swelling capacity (BSC) studies[12] were carried out on LSG and MS. Each of powdered gum (150 ¼m) was carefully introduced into a 100 ml graduated cylinder. Bulk volume was measured by three tap method. Then, distilled water (80 ml) was added, and the powder was well dispersed by shaking. Suspension volume was adjusted to 100 ml. The sediment volume of swollen mass was read after 24 h. BSC was calculated by determining the ratio of swollen volume to the bulk volume[12].

Water Sorption Investigation

LSG and MS (approx 1g each) were exposed to an atmosphere of 98% relative humidity (saturated solution of lead nitrate) at 30±1°C [13], and weighed at 1, 2, 3, 4, 5, 6 and 24 h.

Capillary Action

LSG powder (150 ¼m) was blended with ibuprofen powder (150 ¼m) to contain 1%, 2%, 5%, 7.5% and 10% w/w *leucaena* gum in ibuprofen powder. The powders were mixed geometrically. Powder blend was, respectively, filled into Perspex capillary tubes (diam, 0.304 cm each). Each tube was tapped 20 times[14] on tile in order to obtain a constant height of 7 cm of powder column. Bottom ends were plugged with an absorbent paper and stood-dipped in water by means of supports. Water uptake by column in the tube was observed and measured at 5, 10, 15, 30, 45 and 60 min after the start of experiment [14]. Relevance of difference in generated data was evaluated statistically. The data were tested by two-way analysis of variance.

Results and Discussion

Disintegrant Properties

LSG tablets (1, 2, 5, 7.5 and 10% w/w), compared with MS, showed minimal deviation from the average weight of each batch (Table 2). The deviation was within pharmacopoeial limit[15]. For each disintegrant, average weight, thickness and SR of tablet increased as disintegrant concentration increased (1 to10% w/w). Assay of tablets varied (Table 2) for LSG (99.54-100.84) and MS (100.19-101.79).

Hardness of the tablet decreased with the increasing concentration of MS, because starch in its native form induces softening effects on tablets specially when added extra granularly (Table 3). However, when LSG was incorporated as disintegrant, hardness increased with increase in concentration of disintegrant. At low concentration of disintegrants (1%, 2% w/w), tablet produced with LSG were less harder than those produced with MS. However, when two disintegrants were compared, highly significant difference (p<0.01) were observed only at 1%, 7.5% and 10% w/w levels (Table 3). When hardness values were compared at different concentration levels of individual disintegrants, highly significant difference (p<0.01) was observed.

At equivalent disintegrant concentration, tablets containing LSG exhibited lower friability than the tablets containing MS (Table 3). In both formulations, irrespective of the concentration of disintegrant used, friability index remained well within 1% w/w, an upper level of acceptability for pharmaceutical products. Comparison of friability values of tablets produced with LSG and MS as disintegrants showed highly significant difference (p<0.01) at 5.0% and 10.0% w/w level. When friability values were compared at different concentration levels of individual disintegrants, highly significant difference (p<0.01) was observed (Table 3).

A significant or highly significant difference at all concentration of disintegrant was observed when DT was compared at different concentration level of individual disintegrants (Table 3). DT decreased with increasing concentration of MS but this was not true in case of tablets produced with LSG (Fig. 1). At 1% and 2% w/w disintegrant concentration, tablets produced with LSG took less time to disintegrate than those produced with MS. At 5% w/w disintegrant

Table 2 — Characteristics of tablets of Ibuprofen prepared with different concentration of disintegrants

Disintegrant	Concentration % w/w	Average* weight, g	Thickness** mm	Surface area** mm^2	Assay*** %
Leucaena seed gum	1.0	0.402 (0.013)	3.168 (0.018)	308.38 (0.48)	99.78 (0.93)
	2.0	0.416 (0.014)	3.177 (0.022)	311.33 (0.74)	100.84 (0.34)
	5.0	0.422 (0.019)	3.193 (0.014)	312.86 (1.38)	99.54 (0.86)
	7.5	0.431 (0.020)	3.301 (0.021)	315.01 (1.21)	100.27 (0.37)
	10.0	0.448 (0.018)	3.387 (0.013)	317.82 (0.49)	99.95 (0.25)
Maize starch	1.0	0.404 (0.019)	3.149 (0.006)	308.38 (0.48)	100.19 (0.24)
	2.0	0.410 (0.021)	3.158 (0.011)	309.16 (0.01)	101.41 (0.73)
	5.0	0.424 (0.013)	3.245 (0.014)	313.49 (0.48)	100.69 (0.69)
	7.5	0.436 (0.016)	3.301 (0.009)	314.65 (0.61)	101.79 (0.52)
	10.0	0.442 (0.016)	3.382 (0.018)	318.06 (0.91)	101.01 (0.14)

Values in parentheses indicate standard deviation
* Mean of 20 readings; ** Mean of 10 readings; *** Mean of 3 determination

concentration, DT of tablets produced with LSG did show statistical difference ($p<0.05$) with the tablet produced with MS (Table 3). At 7.5% and 10% w/w concentration, DT for LSG produced tablets are higher, probably due to swellable nature of LSG in aqueous medium which upon hydration form a gel-like barrier around the granule and/or the tablet core, thereby retarding fast disintegration.

At the disintegration range up to 5% w/w, DT data of the tablets produced with LSG are comparable with tablets made with MS, thereby indicating that LSG could be used as disintegrant at low concentration (up to 5% w/w level). Drug release was hindered as LSG concentration was increased (2-10% w/w), whereas reverse was true in case of MS (Fig. 2).

Dissolution results[11] can be plotted as log percent drug undissolved vs. time.

$$\text{Log}\ (w^{\alpha} - w) = \log M - kt \qquad ...(2)$$

Log $(w^{\alpha} - w)$ is the amount of drug undissolved after time 't', 'k' is first order release rate constant and 'M' is another constant, which depends on SR available for dissolution and solubility of the drug.

Goodness and linearity of the plots are supported by the values of co-efficient of correlation (r) for tablets made with LSG (0.989-0.996) and that of MS (0.980-0.994). In both the cases, a significant linear correlation $p < 0.001$ was found. As a result, the slope of such plot (dissolution rate constant, determined from log % undissolved vs. time) will quantitatively affect the drug release profile.

Dissolution rate constant (k), time taken to dissolve 50% of drug (T_{50}), and percent drug dissolved in 30 min (A_{30}) are given in Table 4. As the disintegrant

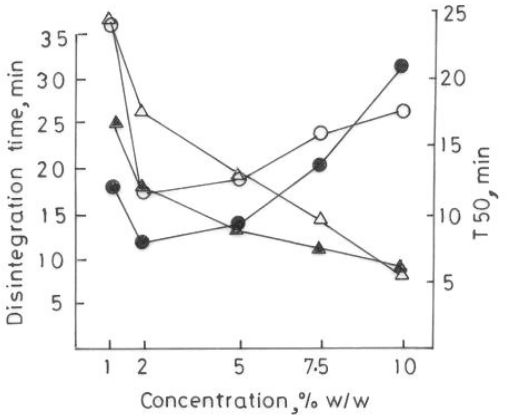

Fig. 1 — Disintegration time & concentrations of leucaena seed gum (•) and maize starch (▲), and T_{50} & concentrations of leucaena seed gum (o) and maize starch (Δ) as disintegrants

concentration increased, in case of LSG, k increased up to 2% level and then decreased, whereas in case of MS, k experienced the progressive increase. At 1% and 5% w/w disintegrant concentration, 'k' value of tablets involving LSG has shown statistically no significant difference ($p>0.05$) with the tablets with MS, whereas at 2%, 7.5% and 10% w/w levels, highly significant difference ($p<0.01$) were observed. When k was compared at different concentration levels of individual disintegrant, highly significant differences ($p<0.01$) were observed.

No significant difference ($p>0.05$) were observed at 1% and 5% level, while highly significant difference were found at 2%, 7.5% and 10% level when T_{50} values generated from tablets with LSG and MS were compared (Table 4). When T_{50} was compared at different concentration level of individual disintegrants, highly significant difference ($p<0.01$) were observed (Table 4).

At the concentration range up to 5% w/w, T_{50} value of the tablets with LSG are comparable with tablets made with MS, thereby indicating that LSG could be used as tablet disintegrant at low concentration. With increase in concentration, DT and T_{50}, values decrease in case of tablets made with MS, whereas in case of LSG produced tablets, DT and T_{50}, values decrease up to 2% level and then increase with increase of disintegrant concentration (Fig. 1). This indicates that disintegrant property of MS acts independent of its concentration; but LSG has a potential as disintegrant for tablet dosage form at up to 5% w/w concentration levels.

Fig. 2 — Dissolution profile of ibuprofen tablets: a) prepared with 1 % w/w (■), 2 % w/w (•) and 5 %w/w (▲) of leucaena seed gum, and 1% w/w (□), 2 % w/w (❍) and 5% w/w (Δ) of maize starch as disintegrants; b) prepared with 7.5 % w/w (•) and 10 %w/w (▲) of leucaena seed gum, and 7.5 % w/w (❍), and 10% w/w (Δ) of maize starch as disintegrants

For all samples investigated there was a direct correlation between DT and T_{50} to dissolve and observations are in good agreement with reported[16-17] work. Highly significant difference ($p<0.01$) was observed at 2-10% w/w level of disintegrant concentration and non-significant difference was found only at 1% w/w level, when A_{30} value generated from tablets with LSG and MS were compared (Table 4). When A_{30} was compared at different concentration levels

Table 3 — Characteristics of tablets of ibuprofen prepared with different concentrations of disintegrants

	Hardness*, kg/cm^2			Friability*, % w/w			Disintegration time*, min		
Disintegrant Concentration % w/w	LSG	MS	Anova	LSG	MS	Anova	LSG	MS	Anova
1.0	4.40(0.29)	5.45(0.57)	P<0.01HS	0.294(0.018)	0.358(0.011)	P<0.05S	18.28(0.98)	25.09(0.83)	P<0.01HS
2.0	4.65(0.34)	5.15(0.22)	P>0.05NS	0.379(0.008)	0.411(0.016)	P>0.05NS	11.96(0.27)	17.79(0.39)	P<0.01HS
5.0	5.10(0.29)	4.94(0.13)	P>0.05NS	0.416(0.015)	0.503(0.025)	P<0.01HS	14.06(0.42)	13.24(0.39)	P<0.05S
7.5	5.35(0.34)	4.65(0.14)	P<0.01HS	0.541(0.019)	0.686(0.023)	P<0.05S	20.23(1.04)	11.15(0.38)	P>0.01HS
10.0	5.80(0.27)	4.05(0.21)	P<0.01HS	0.631(0.013)	0.802(0.027)	P<0.01HS	31.60(0.91)	9.11(0.053)	P>0.01HS
Anova Two-way	P<0.01HS	P<0.01HS	—	P<0.01HS	P<0.01HS	—	P<0.01HS	P<0.01HS	—

Values in parentheses indicate standard deviation; *Mean of 5 readings
LSG - Leucaena seed gum , MS - Maize starch; HS - Highly significant, NS - Not significant, S - Significant

Table 4 — Dissolution characteristics of tablets of ibuprofen prepared with different concentrations of disintegrants

	Dissolution rate constant ,k* min^{-1}			Dissolution half life ,$t_{50\%}$*			Drug dissolve in 30 min A_{30}*,%		
Disintegrant Concentration % w/w	LSG	MS	Anova	LSG	MS	Anova	LSG	MS	Anova
1.0	0.0289(0.003)	0.0288(0.046)	P>0.05NS	24.252(2.693)	24.577(4.113)	P>0.05NS	55.498(4.623)	50.872(3.177)	P>0.05NS
2.0	0.0639(0.002)	0.0405(0.007)	P<0.01HS	10.862(0.371)	17.549(3.162)	P<0.01HS	85.149(0.871)	59.206(3.117)	P<0.01HS
5.0	0.0554(0.003)	0.0538(0.019)	P>0.05NS	12.544(0.735)	12.897(0.449)	P>0.05NS	77.749(1.996)	72.486(1.226)	P<0.01HS
7.5	0.0439(0.030)	0.0713(0.005)	P<0.01HS	15.863(1.147)	9.653(0.632)	P<0.01HS	71.531(3.159)	84.740(1.457)	P<0.01HS
10.0	0.0392(0.019)	0.1271(0.016)	P<0.01HS	17.726(0.852)	5.515(0.613)	P<0.01HS	65.574(1.091)	96.669(0.885)	P<0.01HS
Anova Two-way	P<0.01HS	P<0.01HS	—	P<0.01HS	P<0.01HS	—	P<0.05S	P<0.01HS	—

Values in parentheses indicate standard deviation; *Mean of 5 readings
LSG - Leucaena seed gum , MS - Maize starch; HS - Highly significant, NS - Not significant, S - Significant

Fig. 3 — Rate of water absorption of leucaena seed gum (•) and maize starch (o) powders at ambient temperature and 98% relative humidity

Fig. 4 — Capillary uptake of water by drug/leucaena seed gum mix powder column: 1% w/w (•), 2% w/w (×), 5% w/w (▲), 7.5% w/w (o), and 10% w/w (Δ)

of individual disintegrants, highly significant difference ($p<0.01$) was observed in case of MS, whereas relatively less significant difference ($p<0.05$) was found in case of tablets made with LSG (Table 4). Best concentration for LSG as a disintegrant is up to 5% w/w when A_{30} values were higher than those for MS. The lower release at higher concentration in case of LSG could be attributed to gel forming tendency of this gum following increased hydration, which acts as an obstacle to the quick release of drug.

Mechanism of Disintegrant Action

LSG showed good swelling capacity [11.75 (0.25)], which is a usual characteristic of hydrophilic, swellable natural gum. MS showed least [0.925 (0.025)], which is in conformity with the earlier report[12]. A non-adhesive disintegrant with a higher water uptake and pronounced swelling properties should be quite effective. But neither LSG nor MS absorb water at a fairly rapid rate (Fig. 3). The result related MS is in conformity with the reported[13] work.

Rate and extent of water uptake by the densified column increases with the decrease in concentration of gum powder in the mixture (Fig. 4). In the column containing 10% and 7.5% w/w of gum, gelling occurred upon the initial contact of powder mix and water, hence, further liquid uptake was prevented. In the column containing 5% and 2% w/w of gum, an initial rapid liquid uptake was observed up to 30 and 45 min respectively, which then slowed down and finally stopped. In case of column containing 1% gum, liquid uptake was good (Fig. 4). In the column containing higher amount of gum, the uptake of liquid in these column is found to be entirely dependent on the non-gelling (ibuprofen) component while gelling component (gum) swelled rapidly to form a coherent gel through which liquid uptake occurred either very slowly or not at all.

Best concentration of LSG as a disintegrant was observed at 2%, whereas height of capillary uptake was maximum at 1% concentration, when swelling of gum was not enough to exert pressure so that tablet could disintegrate. At critical concentration (2% w/w) for DT, particle of polymer occupy minimum distance apart in tablet matrix, which permits rapids liquid penetration and does not allow formation of continuous gel network, as in case of higher concentration, which may hinder fluid diffusion.

Swelling substances[18] that tend to be mucilaginous or gel-forming in water are not able to act as disintegrating agent. Such materials develop a viscous coat around tablet, which hinder further movement of water into the tablet matrix. For a given tablet formulation[19], a critical amount of starch is required to cause the quickest disintegration of tablets. The same was observed with the LSG for ibuprofen tablet formulation. The shortest disintegration time was recorded in tablets containing 2% w/w of the gum, hence the critical concentration of the new gum for disintegration in ibuprofen tablets formulated by wet granulation may be assessed to be 2% w/w. It is believed that this concentration may represent a certain threshold value, in which the particles of the polymer occupy minimum distances apart in the tablet matrix, which permits rapid liquid penetration and does not allow the formation of continuous gel network and hinder fluid diffusion.

The studies revealed that the gum is likely to initiate disintegration action by swelling. It is possible

that upon an initial contact between LSG and water, particles swell thereby generating enough pressure to initiate disintegration well before the gel is formed. List & Muazzam[20] showed that a very slight increase in the volume of particles of disintegrant, which cannot be perceived by a visible increase in diameter of grains, could display sufficient force to activate disintegration. LSG normally forms gel during swelling, but its initial swelling could elicit disintegration action in the tablet before further liquid uptake results in more extensive swelling and gelling.

Conclusions

LSG is a potential disintegrant in tablet dosage form at low concentrations levels (2%). Increase in concentration of seed gum increases friability and decreases hardness and disintegration time. Dissolution rate constant and A_{30} were also increased while T_{50} decreased with the increase in disintegrant concentration (up to 2%). LSG swells in contact with water thereby generate enough pressure to initiate disintegration well before the gel is formed. Critical concentration (2%w/w) of LSG for disintegration in ibuprofen tablet represents a certain threshold value, in which the particles of the gum occupy minimum distances apart in the tablet matrix, which permits rapid liquid penetration and does not allow the formation of continuous gel.

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