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ASSESSMENT OF *FERULA GUMMOSA* GUM AS A BINDING AGENT IN TABLET FORMULATIONS

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Abstract: *Ferula gummosa* Boiss. (*Apiaceae*) is one of the natural plants of Iran. The whole plant, but especially the root, contains the gum resin "galbanum". A study of the comparative effects of galbanum gum and two standard binding agents – polyvinylpyrolidone and acacia – on characteristics of acetaminophen and calcium carbonate compacts was made. The *Ferula gummosa* gum was extracted and its swelling index was determined. Acetaminophen and calcium carbonate granules were prepared using the wet granulation method and were evaluated for their micromeritics and flow properties, while the compacts were evaluated for mechanical properties using the hardness, tensile strength and friability. The drug release from acetaminophen compacts were assessed using dissolution studies. The dry powder of *Ferula gummosa* gum resin (galbanum) yielded 14% w/w of gum using distilled water as extraction solvent. The swelling index indicates that galbanum gum swelled to about 190% of initial volume in distilled water. Thus galbanum gum has the ability to hydrate and swells in cold water. The bulk and tapped densities and the interspace porosity (void porosity) percent of the granules prepared with different binders showed significant difference. The hardness and tensile strength of acetaminophen and calcium carbonate compacts containing various binders was of the rank order PVP > acacia > galbanum gum ($p < 0.05$) and the friability percent was of the reverse order ($p < 0.05$). The ranking for the dissolution rate of tablets containing the different binders was PVP > galbanum gum > acacia. The results of mechanical properties of acetaminophen and calcium carbonate compacts indicate that galbanum gum could be useful to produce tablets with desired mechanical characteristics for specific purposes, and could be used as an alternative substitute binder in pharmaceutical industries.

Keywords: assessment, *Ferula gummosa*, galbanum, binder, tablet formulation

The role of excipients in determining the quality of a formulation and in many cases the bioavailability of drug from tablets has received considerable attention. Binders are added to tablet formulation to impart plasticity and thus increase the interparticulate bonding strength within the tablet (1).The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose. In recent times, increasing attention has been given to the application of gums of various sources as pharmaceutical excipients. Gums generally are polysaccharides which are polymeric in nature of natural substances obtained from woody and non-woody plant parts such as bark, seeds, sap, roots, rhizomes, fruits and leaves. Plant gums are widely used in diverse applications for the formulation of pharmaceutical dosage forms. The major application of gums is in tablets as binding agent (2–6). *Ferula gummosa* Boiss. (*Apiaceae*) is a perennial plant native to central Asia, growing in the northern and western parts of Iran (7). The whole plant, but especially the root, contains the gum resin "galbanum". Several medicinal actions such as anticonvulsant (8), expectorant, antispasmodic and anticatarrah have been reported for *F. gummosa* plant and its gum (9). Externally, it is used as a plaster for inflammatory swelling, ulcers, boils, wounds and skin complaints. Numbers of schizogenous ducts of *F. gummosa* are in the cortex containing the resinous gum. It is occasionally used in the making of modern perfume and special glue abroad of Iran (10). The aromatic gum resin "galbanum" is obtained from wounds made in the stem. Galbanum occurs usually in hard or soft, irregular, more or less translucent and shining lumps, or

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occasionally in separate tears, of a light-brown, yellowish or greenish-yellow color and a specific gravity of 1.212. It contains about 8% of terpene, 67–69% of a resin which contains sulfur, 17–19% of gum, 3–6% of volatile oils and a very small quantity of the colorless crystalline substance – umbelliferone (11, 12). Thus, in this work water soluble fraction of *Ferula gummosa* gum has been evaluated as a binding agent in acetaminophen and calcium carbonate tablet formulation in comparison with polyvinylpyrrolidone and acacia.

EXPERIMENTAL

Materials

Ferula gummosa gum resin was prepared from an herbal drug store in Sari, Iran. The gum resin was identified at the Pharmacognosy Department, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

Acetaminophen, calcium carbonate, polyvinylpyrolidone (PVP, Povidone 25), magnesium stearate and hydrochloric acid were purchased from Merck (Darmstadt, Germany). Acacia was purchased from Sigma-Aldrich, Inc., USA.

Methods

Extraction of gum from galbanum

The powdered dried galbanum (200 g) was macerated in distilled water (100 mL) at 50°C and shaked for 30 min, and then the mixture was stirred for 24 h. The mixture was filtered and the filtrate was concentrated to dryness and weighed.

Swelling index of gum

Swelling characteristics of the separated gum was determined by the British Pharmacopoeia method (13). Swelling index was calculated from mean reading of three determinations.

Preparation of granules

Acetaminophen and calcium carbonate were used as a model drug and galbanum gum, acacia and PVP were used as binders to formulate granules. Acetaminophen and calcium carbonate individually mixed with different concentration of binders (Table 1) which dissolved in warm distilled water. Wet massing was performed for 5 min, and then the wet mass was passed through a mesh 12 sieve (1400 μm) and dried in a hot air oven for 18 h at 50°C. Dried granules were sieved through a mesh 16 sieve (1000 μm) and then stored in air tight containers. The mean moisture content was determined to be 1.2 ± 0.3% (w/w). The degree of mixing of the acetamin-

Table 1. Characteristics of acetaminophen granules prepared with different concentrations of binders.

Binder	Concentration of binder (% w/w)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Compressibility index	Interspace porosity (%)	Angle of repose (°)	Mean particle size (μm)
Acacia	4	0.48 ± 0.01	0.56 ± 0.01	1.16	14.28	63.6	28.5 ± 0.34	526
	5	0.45 ± 0.03	0.52 ± 0.02	1.15	13.46	63.8	28.2 ± 0.55	535
	6	0.43 ± 0.01	0.48 ± 0.02	1.11	10.41	64.2	27.8 ± 0.61	540
PVP	4	0.44 ± 0.02	0.49 ± 0.01	1.11	10.20	66.8	28.6 ± 0.85	537
	5	0.41 ± 0.01	0.48 ± 0.01	1.17	14.58	67.2	28.4 ± 0.62	539
	6	0.39 ± 0.01	0.44 ± 0.01	1.12	11.36	67.4	27.9 ± 0.42	543
Galbanum gum	4	0.51 ± 0.01	0.57 ± 0.01	1.11	10.52	61.51	28.2 ± 0.58	520
	5	0.49 ± 0.01	0.54 ± 0.01	1.10	9.25	61.92	28.3 ± 0.63	529
	6	0.46 ± 0.01	0.51 ± 0.01	1.10	9.80	62.3	28.1 ± 0.73	536

Table 2. Characteristics of calcium carbonate granules prepared with different concentrations of binders.

Binder	Concentration of binder (% w/w)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Compressibility index	Interspace porosity (%)	Angle of repose (°)	Mean particle size (µm)
Acacia	3	0.69 + 0.01	0.74 + 0.01	1.07	6.75	43.9	28.5 + 0.51	425
	4	0.67 + 0.01	0.72 + 0.01	1.07	6.94	44.3	28.7 + 0.39	431
	5	0.64 + 0.01	0.69 + 0.01	1.08	7.24	44.5	28.9 + 0.47	437
PVP	3	0.66 + 0.01	0.70 + 0.01	1.06	5.71	46.31	28.5 + 0.35	430
	4	0.64 + 0.01	0.69 + 0.01	1.08	7.24	46.54	28.6 + 0.43	436
	5	0.61 + 0.01	0.66 + 0.01	1.08	7.57	46.93	28.8 + 0.68	440
Galbanum gum	3	0.70+ 0.02	0.76 + 0.01	1.08	7.89	43.11	28.4 + 0.43	418
	4	0.68+ 0.01	0.73 + 0.01	1.07	6.84	43.34	28.7 + 0.72	422
	5	0.65+ 0.01	0.70 + 0.01	1.07	7.14	43.71	28.9 + 0.89	42

ophen granules was determined by spectrophotometric assay of acetaminophen at 257 nm and was found to be > 0.96.

Granule evaluation tests

Granule size distribution

The size distribution analysis was carried out using a 100 g sample of granules and a set of standard sieves (British standard 410, 1962). The cumulative weight percent retained was plotted against the sieve aperture. The mean granule size was taken as the size corresponding to 50% of cumulative weight oversize.

Bulk and tapped densities

The bulk and tapped densities of the granules were assessed in accordance with the USP 25 using a tapped volumeter apparatus (Erweka, SVM101, Germany).

Angle of repose, Hausner ratio and compressibility index

The angle of repose was calculated *via* fixed funnel method. Calculations were made from the cone height acc. to the equation: tangent $\alpha = h/r$.

To obtain Hausner ratio, the tapped density (D_T) is divided by bulk density (D_B). The compressibility index (CI) percent is obtained by the following formula:

$$CI\% = [(D_T - D_B) / D_T] \times 100$$

Granule density and interspace porosity (void porosity) percent

Granule densities (D_G) were determined three times for each formulation by the pycnometer method with xylene as the displacement fluid. The following equation was used for calculation of interspace porosity percent (P %):

$$P\% = [1 - (D_B / D_G)] \times 100$$

Preparation of compacts

Two hundred fifty and 300 mg of size fractions of acetaminophen and calcium carbonate were compressed for 10 s into compacts with predetermined load (1078 MNm^{-2} for acetaminophen and 462 MN^{-2} for calcium carbonate) using a hydraulic hand press (Specac®, UK). Before compression, the die (9 mm diameter) and the flat faces punches were lubricated with a 2% w/v dispersion of magnesium stearate in ethanol : ether (1:10). After ejection, compacts were properly stored over silica gel for 24 h to allow for hardening and elastic recovery.

Table 3. Characteristics of acetaminophen compacts prepared with different concentrations of binders.

Binder	Concentration of binder (% w/w)	Hardness (N)	Tensile strength (MNm^{-2})	Friability (%)
Acacia	4	49.00 ± 1.57	1.15 ± 0.03	1.97 ± 0.11
	5	68.00 ± 1.83	1.60 ± 0.04	1.67 ± 0.08
	6	77.25 ± 2.01	1.82 ± 0.04	1.41 ± 0.09
PVP	4	69.40 ± 2.84	1.63 ± 0.06	1.55 ± 0.06
	5	82.75 ± 2.48	1.95 ± 0.05	1.20 ± 0.05
	6	91.00 ± 1.96	2.14 ± 0.04	1.15 ± 0.07
Galbanum gum	4	34.00 ± 1.91	0.80 ± 0.04	3.30 ± 0.12
	5	48.75 ± 1.43	1.15 ± 0.03	2.05 ± 0.12
	6	61.25 ± 2.97	1.44 ± 0.07	2.12 ± 0.10

Table 4. Characteristics of calcium carbonate compacts prepared with different concentrations of binders.

Binder	Concentration of binder (% w/w)	Hardness (N)	Tensile strength (MNm^{-2})	Friability (%)
Acacia	3	66.25 ± 2.15	1.30 ± 0.04	1.68 ± 0.04
	4	90.25 ± 2.34	1.77 ± 0.04	1.19 ± 0.05
	5	119.00± 3.14	2.33 ± 0.06	1.11 ± 0.03
PVP	3	88.50 ± 3.21	1.73 ± 0.06	1.24 ± 0.06
	4	106.50 ± 2.45	2.09 ± 0.04	1.07 ± 0.05
	5	13.7.75 ± 3.52	2.70 ± 0.06	0.96 ± 0.04
Galbanum gum	3	42.34 ± 1.25	0.83 ± 0.02	2.66 ± 0.06
	4	51.25 ± 1.51	1.01 ± 0.02	2.13 ± 0.07
	5	78.00 ± 2.11	1.53 ± 0.4	1.10 ± 0.05

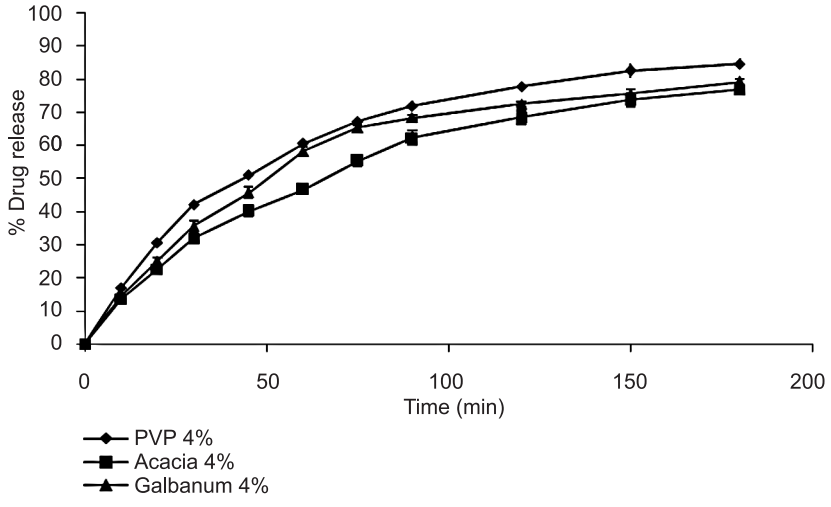

Figure 1. Dissolution profiles of acetaminophen tablets containing 4% w/w PVP, acacia and galbanum gum as binders in 0.1 M HCl

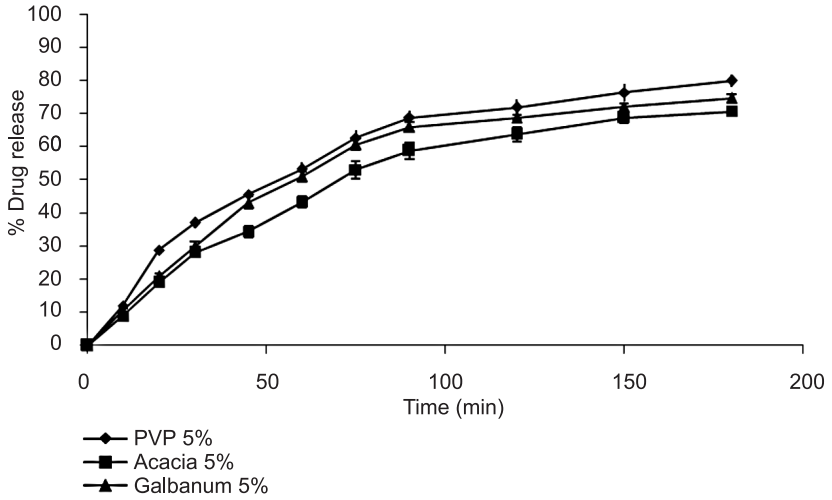

Figure 2. Dissolution profiles of acetaminophen tablets contaning 5% w/w PVP, acacia and galbanum gum as binders in 0.1 M HCl

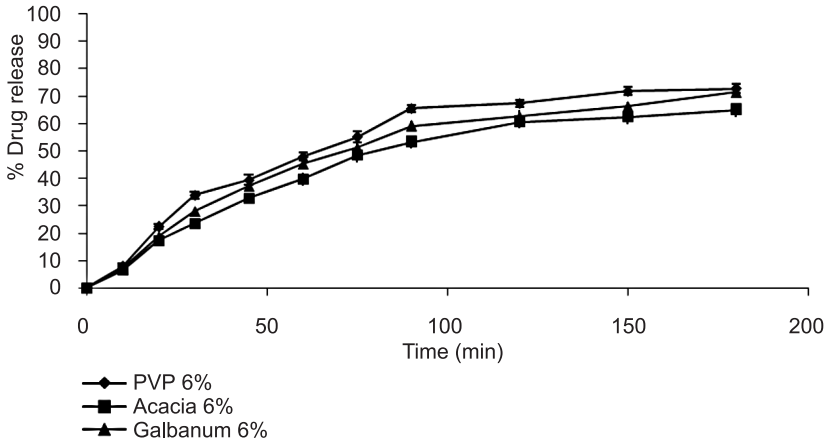

Figure 3. Dissolution profiles of acetaminophen tablets containing 6% w/w PVP, acacia and galbanum as binders in 0.1 M HCl

Compact dimensions

The thickness and diameter of acetaminophen and calcium carbonate compacts were determined using a micrometer gauge (Mitutoyo, Japan). The mean and standard deviation of 20 randomly selected compacts from each formulation was calculated.

Hardness and tensile strength

The Erweka (GmbH, Germany) hardness tester was used to determine the force required to diametrically break ten randomly selected compacts from each formulation. Tensile strength was calculated employing the following equation:

$$T = 2P / DH\pi$$

where T, P, D, H and π are the tensile strength (Nmm^{-2}), hardness (N), diameter (mm), thickness (mm) of the compacts and the ratio of the circumference of a circle to its diameter, respectively.

Friability

Ten compacts selected randomly from each tablet formulation were deducted and weighed using analytical balance. These were introduced into a friabilator (Erweka, GmbH, Germany), which was set to rotate at 25 rpm for 4 min. At the end of the rotation time, compacts was dedusted, re-weighed and the percentage weight loss was calculated as the friability.

Dissolution profile studies

The dissolution test was carried out on the acetaminophen compacts using the USP XXXIII basket method (Erweka dissolution tester, DT 80,

GmbH, Germany) rotated at 50 rpm in 900 mL of 0.1 M HCl, maintained at 37 ± 0.5°C. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with equal volume of the fresh medium. The amount of acetaminophen released was determined using a UV spectrophotometer (Varian, Cary 50, USA) at 257 nm.

Statistical analysis

Statistical analysis was done to compare the effects of galbanum gum, PVP and acacia on the properties of acetaminophen and calcium carbonate compacts using one-way ANOVA with a Tukey's *post hoc* test. At 95% confidence interval, the p value lower than or equal to 0.05 was considered the limit of significance.

RESULTS

The dry powder of *Ferula gummosa* gum resin (galbanum) yielded 14% w/w of gum using distilled water as extraction solvent. The separated gum was evaluated for its swelling index and it was found to be about 2.1 mL.

The characteristics of acetaminophen and calcium carbonate granules prepared with different concentrations of binders are shown in Tables 1 and 2, respectively. Results show that the acetaminophen and calcium carbonate granules sizes were in the range of 520 to 540 μm and 418 to 441 μm, respectively. The bulk and tapped densities and the interspace porosity (void porosity) percent of the granules prepared with different binders showed significant difference ($p < 0.05$). Taking flow properties into account, satisfactory values for Hausner ratio (HR), Carr index (CI) and angle of repose (α) were obtained for all granule formulations (Tab. 1 and 2). The Hausner ratio values obtained were below 1.25, Carr indexes were below 15% and angles of repose were around 28°. The mechanical properties of the compact formulations were assessed by the hardness, tensile strength and friability percent. Table 3 and 4 show these characteristics of acetaminophen and calcium carbonate compacts containing different binders. The hardness, tensile strength and friability of the acetaminophen compacts prepared by using galbanum gum as a binder at the concentration of 5% w/w were close to those of acetaminophen compacts prepared using acacia at the concentration of 4% w/w as binder. The hardness, tensile strength and friability of calcium carbonate compacts prepared by using PVP K25 as a binder at the concentration of 3% w/w was close to those of calcium carbonate compacts prepared using acacia at the concentration of 4% w/w as binder. The hardness and tensile strength of acetaminophen and calcium carbonate compacts containing various binders was of the rank order PVP > acacia > galbanum gum ($p < 0.05$) and the friability percent was of the reverse order ($p < 0.05$). The comparative dissolution profiles of the acetaminophen compacts prepared with PVP, acacia and galbanum gum as binders in different concentrations is shown in Figures 1–3. In general, the amount of drug release decreased as the binder concentration increased. In equal binder concentration, PVP and acacia showed a faster and slower release rate than the other binders, respectively.

DISCUSSION

Natural gums are polysaccharides of natural origin, capable of causing a large viscosity increase in solution, even at low concentration. Hydrocolloids or water-soluble gums are highly functional ingredients that may typically be used as binders in tablet manufacture. A binder is defined as the ingredient that contributes mainly to the adhesiveness of the powder during the initial granulation and to the tablet after compression. The gums as binders also add cohesiveness to the tablet.

The swelling index indicates that galbanum gum swelled to about 190% of initial volume in distilled water. Thus galbanum gum has the ability to hydrate and swells in cold water.

Micromeritics properties of acetaminophen and calcium carbonate granules

Galbanum gum produced granules comparable to those of prepared using acacia. Granules containing PVP were larger in size than those of acacia and galbanum gum. This may probably be due to the relatively high adhesive property of PVP compared to acacia and galbanum gum. The mean particle size of granules granulated with different binders increased with increasing the binder concentration, implying that the initial packing of the formulation as a result of die filling increased with the increase in binder content. In all cases, the bulk and tapped densities and the interspace porosity (void porosity) percent decreased with increasing the binder concentration. Interspace porosity significantly controls densification and deformation during compression as well as compaction, which is measured by the tensile strength (14). On the other hand, the results showed that the calcium carbonate granules have the smaller mean particle size and greater bulk and tapped densities than the acetaminophen granules. This is

due to the mechanical properties (plastic) of calcium carbonate, which led to increased deformation and densification during granulation. Porosity has been shown to have a direct effect on the rate of drug dissolution. Calcium carbonate and acetaminophen granules containing 6% PVP showed the highest interspace porosity, thus this binder concentration yielded highly compressible granules. The Carr index provides an indirect measure of material fluidity and the higher its value, the more cohesive the substance. Generally, materials with CI up to 16% indicate good flow behavior while those above 28% indicate cohesive or poor flow. Hausner ratio measures the flowability of the granules. Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. The Hausner ratio, Carr index and angle of repose values of all granule formulations indicated that the granules have good flowability.

Mechanical properties of acetaminophen and calcium carbonate compacts

The acetaminophen and calcium carbonate compacts were prepared by wet granulation method using different concentrations of binders. Various factors, such as test conditions, deformation properties of the material, homogenity of the compacts, adhesion conditions between the compacts and its support and the compact shape may influence the hardness and the tensile strength measurement. In all cases, hardness and tensile strength increased and friability decreased with increasing the binder concentration. Increasing the binder concentration led to more solid bond formation between the substrate particles, and furthermore, the tensile strength of compacts was increased. This is probably due to the fact that binding agents being plastoelastic in nature undergo extensive plastic deformation under high compression forces to make stronger solid bonds between particles. The number of bonds formed depends considerably on the concentration of binder employed. The differences in compaction behavior of acetaminophen and calcium carbonate can be explained by their different deformation properties. Acetaminophen and calcium carbonate show mainly elastic and plastic deformation upon compaction, respectively. During the tabletting compression cycle, powders go through initial packing and rearrangement of particles, formation of temporary structures, elastic deformation, plastic deformation and breakage of particles, bond formation and consolidation, followed by elastic recovery during the decompression process. Various parameters that characterize the deformation characteristics of powders include young's modulus, poison's ratio, yield stress and fracture toughness. Calcium carbonate has good compression characteristics and it would be possible to postulate that the calcium carbonate compacts have higher contact area and higher ultimate bond strength, which our results confirmed. Acetaminophen is poorly compressible and deforms elastically. Elastic deformation is time independent, reversible deformation of a particle. The compactibility of a powder will be influenced mainly by the deformability of the particles. Our results showed that the acetaminophen compacts have lower bond strength than calcium carbonate compacts, which attribute to the lower number and the bonding force of interparticulate binds and elastic deformation behavior of acetaminophen. On the other hand, the physicochemical properties of the binders can affect the binder distribution, physical and compressional characteristics of the resulting granules, and on the physicochemical properties of tablets (15).

***In vitro* drug release study**

Drug libration from solid dosage forms results from a series of simultaneous and successive, primary and secondary processes (wetting, capillary penetration, swelling, disintegration, diffusion, dissolution etc.) which strongly depend on type, quantity and properties of the ingredients (drugs and additives) as well as on the results of unit operations of the manufacturing procedures(16). The difference in dissolution rate of acetaminophen compacts is related to the type and concentration of used binders. In all formulations, the drug release rate decreased when the proportion of binders increased. It was reasoned that, as the amount of binder in the compact increased, there would be a greater degree of binder hydration with simultaneous swelling. This would result in a corresponding lengthening of the drug diffusion pathway and reduction in drug release rate. The results showed that the release of acetaminophen from formulations containing acacia and galbanum gum as a binder at 4% w/w concentration was comparable as well as PVP and galbanum gum at 6% w/w concentration ($p > 0.05$). The ranking for the dissolution rate of tablets containing the different binders was PVP > galbanum gum > acacia. The higher dissolution rate of acetaminophen compacts which were prepared with PVP is probably attributed to acetaminophen ability to form a water-soluble complex with PVP. Our results suggest that galbanum gum is a good granulating agent in acetaminophen compacts and compared well with PVP and acacia. The low drug release in all formulation can be ascribed to the high compression force during compacts preparation.

CONCLUSION

The results of mechanical properties of acetaminophen and calcium carbonate compacts indicate that galbanum gum could be useful to produce tablets with desired mechanical characteristics for specific purposes, and could be used as an alternative substitute binder in pharmaceutical industries.

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