

Preparation and evaluation of pellets using acacia and tragacanth by extrusion-spheronization

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ABSTRACT

Background and the purpose of the study: Extrusion-spheronization is an established technique for the production of pellets for pharmaceutical applications. In this study, the feasibility and influence of the incorporation of acacia, by itself and in combination with tragacanth, on the ability of formulations containing 2 model of drugs (ibuprofen and theophylline) to form spherical pellets by extrusion-spheronization was investigated.

Material and Methods: Formulations containing different ratios of acacia and tragacanth (8:2, 9:1, and 10:0) and different drug concentrations (20%, 40%, and 60%) were prepared, on the basis of a 3² full factorial design. Pellet properties, such as aspect ratio, sphericity (image analysis), crushing strength and elastic modulus (mechanical tests), mean dissolution time, and dissolution profiles were evaluated. The effect of particular factors on responses was determined by linear regression analysis.

Results: The sphericity, drug release rate, and the mechanical properties of the pellets were affected by the amounts and types of the drugs, and the ratio of the gums. Acacia, relative to tragacanth, produced pellets with higher mechanical strength and a faster drug release rate. Addition of small amounts of tragacanth to ibuprofen formulations resulted in matrix pellets with slow drug release.

Conclusion: The results showed that acacia and tragacanth can be used successfully as 2 natural binders in the pellet formulations.

Keywords: Natural gums, Extrusion-spheronization, Pelletization aid.

INTRODUCTION

Pellets are defined as small spherical or semispherical particles made up of fine powders or granules of drugs and excipients, by a variety of processes (1, 2). Their multiparticulate natures offer some important pharmacological, as well as technological advantages over conventional single-unit solid dosages, including more stable plasma profiles, little risk of local side effects and dose dumping, improved bioavailability, good flow properties, and easy coating (3). Extrusion-spheronization is a well-established process that has been described for obtaining pellets of high density, narrow size distribution, and high drug loading (4). Most of the pellet formulations for extrusion/spheronization include microcrystalline cellulose (MCC) as the main excipient, which has the proper rheological properties, cohesiveness, and plasticity to produce spherical particles (5). However, MCC is not universally applicable because it has a number of limitations: a lack of disintegration, prolonged drug release of poorly soluble drugs, chemical incompatibility with

specific drugs, and drug adsorption onto MCC fibers (2, 6). Thus, in recent years, several products have been evaluated to explore their applications as an extrusion-spheronization aid, to avoid the disadvantages of MCC and provide a broad application platform for extrusion-spheronization. The use of alternative biopolymers such as chitosan (7, 8), starch (9), pectin (10, 11), dextrin (12) and carrageenan (13), for the manufacture of pellets by extrusion-spheronization has been described. However, there are no report for evaluation of acacia and tragacanth as suitable natural binders for extrusion-spheronization.

Acacia is the dried gummy exudate obtained from the stems and branches of *Acacia senegal* or other related species of Acacia. It is a complex, loose aggregate of sugars and hemicelluloses (14). Tragacanth is a naturally occurring dried gum obtained from *Astragalus gummifer* and other species of Astragalus. It consists of a mixture of water-insoluble and water-soluble polysaccharides (14). In the present study, the use of acacia and tragacanth as extrusion-

spheronization aids to produce pellets, and their abilities to reduce the amount of MCC in formulations was investigated.

MATERIAL AND METHODS

Materials

MCC (Avicel PH101) was provided by FMC Bio Polymer (Ireland). Acacia and corn starch were supplied by Merck (Germany). The source of tragacanth was Isfahan (Iran). Ibuprofen and theophylline were provided by Darupakhsh (Tehran, Iran). All materials were used as received, unless otherwise specified.

Experimental design

A 3² full factorial design was used for the preparation of pellets. The independent variables and their levels are shown in table 1. The chosen dependent variables or responses were the mean dissolution time (MDT), crushing strength (CS), and elastic modulus (EM) of pellets.

Preparation of pellets

The solid parts of each formulation (25 g) (Tables 2 and 3) were dry mixed using a kitchen mixer (AEG, Germany) for 5 min. Formulations which consisted of 10 % dry gums was added slowly in the form of mucilage (20% w/v) and mixed for 15 min. The required quantity of water was slowly added to the mixture to make a wet mass with a suitable consistency. The wet mass was passed through an axial screw extruder (Dorsa, Iran) with a 1 mm screen at 100 rpm. The extruded mass was rounded in a spheronizer (Dorsa, Iran) with a cross-hatched plate at 1000 rpm for 3 min (15). The obtained pellets were dried at 40°C for 15 hrs in a conventional oven (Memmert, Germany) and then kept in tightly closed containers.

Sieve analysis and yield of pellets

The pellets were sieved using a nest of standard sieves (1700, 1400, 1180, 1000, 710, 500, and 335 µm) shaken for 10 min on a sieve shaker (Erweka, Germany). The pellets retained on each sieve were weighed, and the resulting data were used to construct a frequency distribution. The size range of 710-1400 µm was considered appropriate, and the weight of pellets in this range is reported as yield of pelletization.

Image analysis

The shape and area of pellets were investigated by optical microscopic image analysis. Thirty pellets from each formulation were placed on black backgrounds, and a top cold light source was used to reduce the influence of shadows on image processing. The image analyzer consisted of a computer system linked to a color video camera

Table 1. Independent variables: factors and levels for full factorial design

Factors	Levels		
	-1	0	1
X ₁ : amount of drug (%)	20	40	80
X ₂ :ratio of acacia:tragacanth	8:2	9:1	10:0

(Sony, Japan) and a stereomicroscope (ZSM-1001-3E, Iran) (magnification 8.5×). Digitized images were analyzed by Scion image analyzing software (Scion Image for Windows, Release Beta 4.0.2). The area (A), perimeter (P_m), and Feret diameters of the pellets were measured, and 2 shape factors were calculated as follows (16):

$$\text{Aspect ratio (AR)} = d_{\max} / d_{\min} \quad (1)$$

$$\text{Sphericity} = 4\pi A / P_m^2 \quad (2)$$

where d_{\max} and d_{\min} were the longest and shortest Feret diameters measured, respectively.

Scanning electron microscopy (SEM)

The morphology of the surface of pellets was characterized using SEM. The pellets were mounted on an aluminum stub, sputter-coated with a thin layer of silver by using a sputter coater (Polaron, UK) in an argon atmosphere, and then examined using SEM (LEO1455 VP, UK).

Mechanical tests

The crushing strength (CS; load needed to break the pellets) and elastic modulus (EM) of 15 pellets (710–1000 µm size fraction) were determined using a universal testing machine fitted with a 1 kN load cell (WDW, China). The speed of the upper mobile plate was set at 1 mm/min. CS, EM, and force–displacement graphs were obtained by a computer system attached to the apparatus (17).

Dissolution studies

Samples (n=3) containing 500 mg of pellets were accurately weighed. In vitro drug release was performed in a dissolution testing equipment (Erweka, Germany), using USP apparatus I, at 100 rpm and 37°C, in phosphate buffer solutions of pH 7.2 and 6.0 for ibuprofen and theophylline, respectively. Samples were withdrawn at predetermined time intervals and replaced with an equal volume of the medium. The amount of drug released from the pellets was measured by UV absorption spectroscopy (Biochrom WPA, UK) at 265 nm for ibuprofen and 272 nm for theophylline.

A model independent approach was used to compare the dissolution data. For this purpose, the MDT was calculated for each formulation,

Table 2. Composition of different formulations of ibuprofen and their pelletization yields.

Test run	Ibuprofen (%)	Avicel (%)	Starch (%)	Ratio of acacia:tragacanth	710-1400 μm pellet yield (%)
1	20	10	60	8:2	89.05
2	20	10	60	9:1	82.32
3	20	10	60	10:0	90.30
4	40	10	40	8:2	93.67
5	40	10	40	9:1	82.85
6	40	10	40	10:0	80.49
7	60	10	20	8:2	80.94
8	60	10	20	9:1	76.86
9	60	10	20	10:0	86.70

Table 3. Composition of different formulations of theophylline and their pelletization yields.

Test run	Theophylline (%)	Avicel (%)	Starch (%)	Ratio of acacia:tragacanth	710-1400 μm pellet yield (%)
1	20	10	60	8:2	95.08
2	20	10	60	9:1	90.73
3	20	10	60	10:0	92.97
4	40	10	40	8:2	95.96
5	40	10	40	9:1	90.91
6	40	10	40	10:0	76.57
7	60	10	20	8:2	95.56
8	60	10	20	9:1	86.57
9	60	10	20	10:0	85.27

using the following equations (18):

$$MDT = \frac{\sum \bar{t}_i \Delta M_i}{\sum \Delta M_i} \quad (3)$$

$$\bar{t}_i = (t_i + t_{i+1}) / 2 \quad (4)$$

$$\Delta M_i = (M_{i+1} - M_i) \quad (5)$$

Where \bar{t}_i is the midpoint of the time period during which the fraction ΔM_i of the drug has been released from the dosage form. A high MDT value for a drug delivery system means that it has a slow in vitro drug release.

Statistical analysis of data

The effects of the independent variables on each experimental response, Y, were modeled using a second-order polynomial equation:

$$Y = C + b_1 X_1 + b_2 X_2 + b_3 X_1^2 + b_4 X_2^2 + b_5 X_1 X_2 \quad (6)$$

Models were simplified with a backward, stepwise linear regression technique. Only significant terms ($P < 0.05$) were chosen for the final model. Modeling was performed using SPSS (version 15.0), and related surface plots were obtained by STATGRAPHICS (version 5.1 plus).

RESULTS AND DISCUSSION

The results of this study showed the feasibility of incorporation of acacia and tragacanth in pellet formulation to produce spherical and uniform pellets in a desired size range, i.e., more than 80% of the pellets were in the size range of 710–1400 μm (Tables 2 and 3). All formulations in this study contained only 10% MCC; while it is often necessary to use at least 30% MCC to achieve desirable pellet properties (19). Figure 1 shows the scanning electron micrograph of pellets containing 20% ibuprofen (Formulation 1) as an example. The results of image analysis indicate that almost all ibuprofen pellets had an acceptable aspect ratio ($AR < 1.2$) (Table 4). The results revealed that among pellets with the same drug loading and different ratios of acacia/tragacanth, formulations with a 9:1 of the gums had better sphericity and aspect ratio.

Table 4 shows that in the case of theophylline pellets, a few formulations had AR lower than 1.2. It seems that theophylline formulations (especially those containing 40% and 60% of the drug) are more affected by gum compositions, i.e., formulations without tragacanth (acacia/tragacanth ratios of 10:0) had an acceptable AR. An increase in the percentage of tragacanth led to an increase in the number of dumbbell-shaped particles (Fig. 2). Overall results of image analysis demonstrated that ibuprofen pellets had better sphericity than those of theophylline.

Table 4. Results of image analysis of ibuprofen and theophylline pellets

Run	Ibuprofen pellets		Theophylline pellets	
	Aspect ratio	Sphericity	Aspect ratio	Sphericity
1	0.08 ± 1.124	0.14 ± 0.724	0.14 ± 1.331	0.12 ± 0.574
2	0.06 ± 1.114	0.12 ± 0.761	0.06 ± 1.128	0.16 ± 0.628
3	0.11 ± 1.187	0.19 ± 0.568	0.18 ± 1.275	0.16 ± 0.588
4	0.14 ± 1.266	0.18 ± 0.566	0.29 ± 1.434	0.10 ± 0.595
5	0.09 ± 1.159	0.14 ± 0.645	0.14 ± 1.275	0.14 ± 0.623
6	0.06 ± 1.165	0.14 ± 0.610	0.08 ± 1.169	0.13 ± 0.650
7	0.10 ± 1.182	0.13 ± 0.567	0.23 ± 1.335	0.14 ± 0.537
8	0.13 ± 1.161	0.10 ± 0.672	0.16 ± 1.279	0.12 ± 0.648
9	0.10 ± 1.138	0.10 ± 0.645	0.14 ± 1.194	0.10 ± 0.651

Table 5. Experimental responses for different formulations of ibuprofen

Test run	MDT (min)	CS (N)	EM (GPa)
1	46.927 ± 18.77	14.933 ± 1.486	17.814 ± 7.437
2	40.771 ± 1.03	12.933 ± 2.374	16.050 ± 5.321
3	48.473 ± 4.62	17.933 ± 4.185	1.415 ± 1.970
4	58.707 ± 6.87	11.133 ± 2.325	0.539 ± 0.135
5	56.675 ± 9.83	10.933 ± 2.737	0.676 ± 0.136
6	28.130 ± 2.68	11.733 ± 2.914	0.764 ± 0.215
7	55.585 ± 1.66	8.333 ± 1.914	0.627 ± 0.115
8	57.793 ± 0.82	8.133 ± 1.407	0.575 ± 0.120
9	49.218 ± 1.64	11.866 ± 2.642	0.780 ± 0.167

Table 6. Experimental responses for different formulations of theophylline

Test run	MDT (min)	CS (N)	EM (GPa)
1	20.977 ± 1.57	37.333 ± 8.747	1.114 ± 0.383
2	12.377 ± 0.78	33.600 ± 6.511	0.971 ± 0.217
3	15.574 ± 0.89	42.600 ± 10.959	0.958 ± 0.267
4	29.823 ± 1.28	35.133 ± 9.364	1.192 ± 0.358
5	35.371 ± 1.84	33.600 ± 5.973	0.921 ± 0.217
6	41.477 ± 1.82	41.266 ± 14.916	1.403 ± 0.595
7	43.795 ± 2.71	36.600 ± 7.356	1.220 ± 0.283
8	59.360 ± 0.95	33.333 ± 6.354	1.196 ± 0.339
9	50.895 ± 3.64	36.200 ± 9.405	1.399 ± 0.485

These results may be attributed to the plastic nature of ibuprofen (20), which enhance the formation and promote plasticity of the wet mass required for production of spherical particles (21).

The results of dissolution studies are shown in tables 5 and 6 as MDT. Equations 7 and 8 are mathematical models obtained by regression analysis of the results. The effects of variables on MDT of ibuprofen and theophylline pellets are demonstrated as surface plots in figures 3 and 4, respectively.

$$\text{MDT}_{\text{ibuprofen}} = 604.859 + 2.204 X_1 + 13.927 X_2 - 0.075 X_2^2 - 0.021 X_1 X_2 \quad R^2 = 0.735 \quad (7)$$

$$\text{MDT}_{\text{theophylline}} = 166.885 - 0.146 X_1 - 3.461 X_2 + 0.020 X_2^2 \quad R^2 = 0.947 \quad (8)$$

The results showed that by increase in the amount of drug, MDT increased in both ibuprofen and theophylline formulations; which may be attributed to the decrease in the percentage of starch as a disintegrating agent in pellet formulation. It has been reported that the use of starch as the main excipient leads to enhanced pellet disintegration,

and hence rapid dissolution of poorly soluble drugs (22). Figure 3 shows that at lower ratios of acacia, the amount of ibuprofen had a significant effect on MDT, while in the presence of 100% acacia, the effect of drug content on drug release rate was suppressed which may be related to the hydrophilic nature of acacia. The ratio of acacia/tragacanth had no significant effect on the MDT of theophylline pellets (Fig. 4); however, ibuprofen pellets had the highest MDT in formulations containing a 9:1 ratio of acacia/tragacanth. One disadvantage of MCC in pellet formulations has been related to the lack of pellet disintegration, which could be the reason for the decrease in dissolution rate of poorly soluble drugs (2, 11). Results of this study showed that all formulations containing 100% acacia disintegrated after a short time, but pellets containing tragacanth remained intact during dissolution. It means that the tragacanth has more binding effect than acacia and ensures the integrity of pellets during dissolution. Acacia was dissolved in water gradually, where the major part of tragacanth is water insoluble polysaccharides (14). Figure 5 shows the SEM of a pellet matrix after dissolution. A similar study on pellets containing a poorly soluble drug using pectinic acid has shown the disintegration of pellets

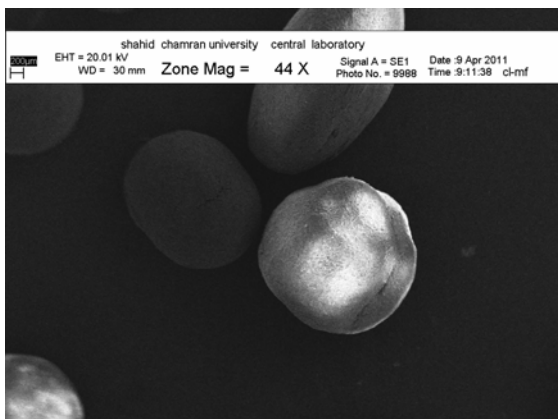


Figure 1. Scanning electron micrograph of the pellets containing 20% ibuprofen (formulation 1 of ibuprofen) (44×).



Figure 2. Stereomicroscopic image of dumbbell-shaped particles containing 60% theophylline (formulation 7 of theophylline) (8.5×).

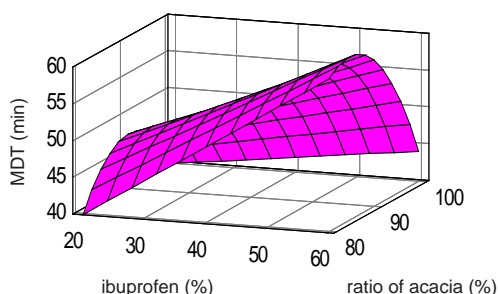


Figure 3. Influence of the amount of ibuprofen and the ratio of acacia on MDT of pellets.

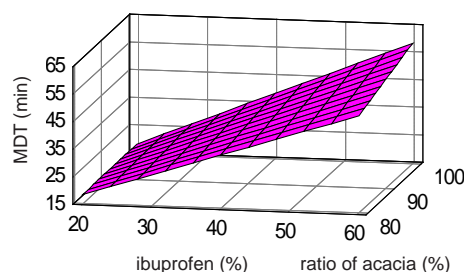


Figure 4. of the amount of theophylline and the ratio of acacia on MDT of pellets.

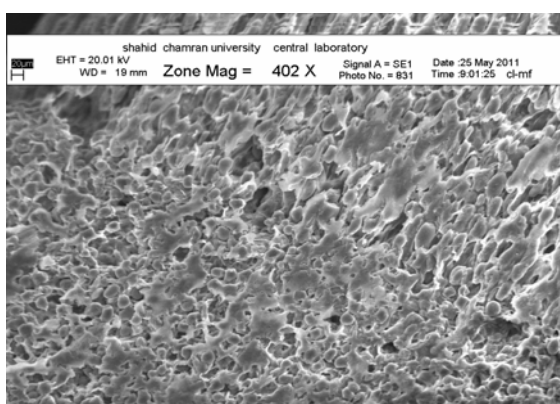


Figure 5. Scanning electron micrograph of a matrix pellets after dissolution test (formulation 5 ibuprofen) (400×).

and 30-60% drug release within 15 min (11). The results of mechanical tests, CS and EM, on pellets are shown in tables 5 and 6. The mathematical relation between variables and responses are described in equations 9 and 10. The results are also depicted as surface plots (Figs. 6–9).

$$CS_{\text{ibuprofen}} = 84.501 - 3.287 X_1 + 0.014 X_1^2 - 0.006 X_2^2 \quad R^2 = 0.941 \quad (9)$$

$$CS_{\text{theophylline}} = 8.649 - 0.001 X_2^2 + 0.001 X_1 X_2$$

$$R^2 = 0.958 \quad (10)$$

$$EM_{\text{ibuprofen}} = 395.902 - 8.236 X_2 + 0.047 X_2^2 \quad R^2 = 0.847 \quad (11)$$

$$EM_{\text{theophylline}} = 15.663 - 0.332 X_2 + 0.002 X_2^2 + 0.000074 X_1 X_2 \quad R^2 = 0.850 \quad (12)$$

Figure 6 demonstrates that the CS of pellets decreased by increase in the amount of ibuprofen; the same result can be found in figure 7 for the EM of pellets, which might be related to the plastic nature of ibuprofen, which can lower the elasticity of pellets (20). It appears that ibuprofen pellets had lower mechanical strength than theophylline pellets, but the amount of theophylline had no effect on the mechanical strength of the pellets (Figs. 8 and 9). The results also revealed that by increase in the proportion of acacia, the CS and EM of both ibuprofen and theophylline pellets increased, which means that formulations containing only acacia as binder produce harder pellets; but disintegrate upon dissolution. It has been reported that tablets containing acacia as binder resulted in hard tablets that their in mechanical strengths increased during their shelf lives (23).

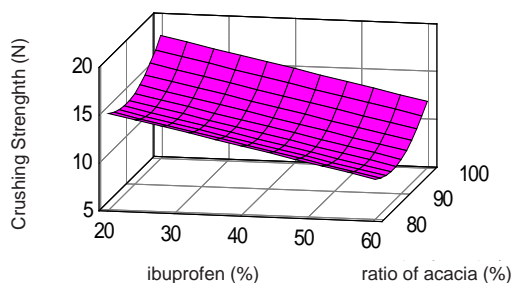


Figure 6. Influence of the amount of ibuprofen and the ratio of acacia on crushing strength of pellets

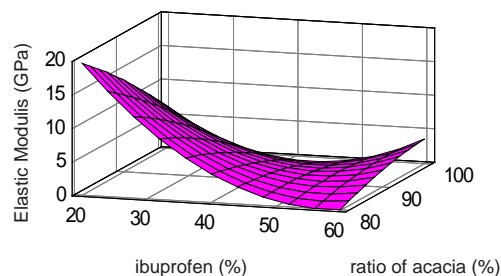


Figure 7. Influence of the amount of ibuprofen and the ratio of acacia on elastic modulus of pellets

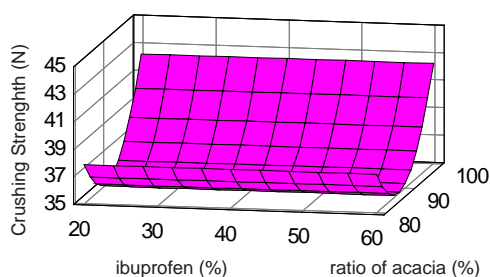


Figure 8. Influence of the amount of theophylline and the ratio of acacia on crushing strength of pellets.

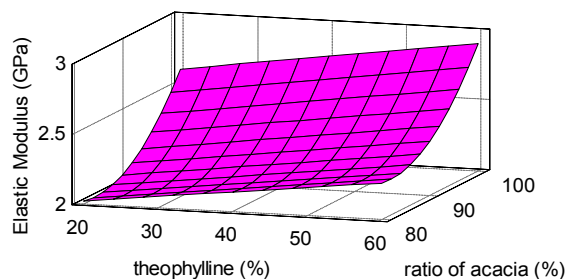


Figure 9. Influence of the amount of theophylline and the ratio of acacia on elastic modulus of pellets.

CONCLUSIONS

The results of this study show the capability of acacia and tragacanth as 2 natural binders in pellet formulation. The sphericity, drug release rate, and mechanical properties of pellets were affected by the amounts and types of drugs and the ratio of the gums. Acacia can produce pellets with higher mechanical strength, and faster drug release rate.

Addition of small amounts of tragacanth to ibuprofen formulations yields matrix pellets having slow drug release.

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