

## EVALUATION OF BINDING EFFECT OF *GLEDITSIA TRIACANTHOS* GALACTOMANNAN IN TABLETS

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### Abstract

*Binding effect of Gleditsia triacanthos Linn. (honey locust) endosperm containing galactomannan was investigated in the tablets prepared by direct compression method. For this aim, ground honey locust endosperm (GHLE) was obtained in 0.300 mm - 0.420 mm particle size. Polyvinylpyrrolidone K-30 (PVP) and dibasic calcium phosphate anhydrous (DCP) were chosen as commonly used binders for comparison. The tablets without active agent were prepared by using GHLE, PVP and DCP at various concentrations (1, 2.5 and 5 (w/w) %) and physical tests were performed on these tablets and their powder mixtures. According to the data, the best formulation was established by considering the other additives (i.e. lubricants and disintegrants) and their concentrations which would impart in desirable tablet formation. Model tablets containing ranitidine hydrochloride were then compressed. On these tablets and their powder mixtures, the same physical tests were carried out. The tablets obtained were found to meet the reported requirements. It was also found that the results of dissolution study met the requirement for ranitidine hydrochloride tablets reported in USP 27 as not less than 80 % of the labeled amount of ranitidine hydrochloride should be dissolved in 45 minutes. The results indicate that honey locust galactomannan as a binder is as effective as PVP and DCP.*

**Key words:** *Gleditsia triacanthos, Honey locust, Galactomannan, Ranitidine hydrochloride, Tablets, Tablet binder*

### Gleditsia Triacanthos Galactomannanının Tabletlerde Bağlayıcı Etkisinin Değerlendirilmesi

*Galaktomannan içeren Gleditsia triacanthos Linn. (yabani keçi boynuzu) endospermasının doğrudan basım yöntemi ile basılan tabletlerde bağlayıcı etkisi araştırıldı. Bu amaçla 0.300 mm - 0.420 mm partikül büyüklüğünde öğütülmüş yabani keçi boynuzu endosperması (GHLE) elde edildi. Yaygın olarak kullanılan polivinilpirolidon K-30 (PVP) ve susuz dibazik kalsiyum fosfat (DCP) mukayese için seçildi. Değişik konsantrasyonlarda (% 1, 2.5 ve 5 (a/a)) GHLE, PVP ve DCP kullanılarak etken madde içermeyen tabletler hazırlandı, bu tabletler ve toz karışımlarında fiziksel testler yapıldı. Verilere göre arzulanan tablet oluşumunda rol oynayan diğer katkı maddeleri (kaydırıcılar ve dağıtıcılar) ve konsantrasyonları da dikkate alınarak en iyi formülasyon oluşturuldu. Ranitidin hidroklorür içeren model tabletler basıldı. Bu tabletler ve toz karışımları üzerinde de aynı fiziksel testler yapıldı. Elde edilen verilerin daha önce bildirilen kriterlere uyduğu tespit edildi. Dissolüsyon çalışmasının sonuçlarının da ranitidin hidroklorür tabletler için Amerikan Farmakopesi 27’de rapor edilen ranitidin hidroklorürün bildirilen miktarının % 80’inden daha az olmamak koşuluyla 45 dakika içerisinde çözünmesi şartına uyduğu bulundu. Sonuçlar bir bağlayıcı olarak yabani keçi boynuzu galaktomannanının PVP ve DCP kadar etkin olduğunu göstermektedir.*

**Anahtar kelimeler:** *Gleditsia triacanthos, Yabani keçi boynuzu, Galaktomannan, Ranitidin hidroklorür, Tabletler, Tablet bağlayıcısı*

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## INTRODUCTION

Tablets are the most commonly used pharmaceutical dosage forms in therapy. Binders, one of the excipient groups in tablets which impart in tablet formation through compression, also affect other properties of tablets. They are natural, synthetic or semi-synthetic substances.

Plant gums which are natural polysaccharides, and their derivatives have been used in various fields for years, since they are distributed with a wide structural variety in nature and are easy to obtain from many species all over the world with low cost (1).

Galactomannans are plant polysaccharides usually found as reserve carbohydrates in endosperm of numerous plants, particularly the Leguminosae e.g. locust bean gum, guar gum and tara gum (2-4). They are built up of a  $\beta$ -(1-4) mannan backbone with galactose branches linked  $\alpha$ -(1-6). Different species have different proportions of D-galactose and D-mannose (5,6). They are hydrocolloids which form highly viscous and stable aqueous solutions. Due to this property, they are commonly used in various fields including pharmaceutical and cosmetic (7-10). Most galactomannans used in pharmaceutical technology and cosmetics are usually unpurified gums, i.e. they are ground endosperm of the Leguminosae seeds to different particle sizes depending upon applications (1,11).

*Gleditsia triacanthos* Linn. (Leguminosae) grows up in the United States, South America, Middle Europe and Mediterranean countries including Turkey. Its endosperm contains high level of gum (12-14). In a relevant study, galactomannan content was found as 68.22 % in GHLE (12,13). Its fruits get ripened and fall until the end of winter. The highest gum yield is obtained from the seeds when the fruits are ripened (14).

In this study, the binding effect of endosperm in honey locust seeds containing galactomannan was evaluated in tablets. Binding performance of GHLE was compared with PVP and DCP as commonly used binders in tableting technology. Powder mixtures containing various ingredients and their tablets were prepared by direct compression method. Various concentrations (1, 2.5 and 5 (w/w) %) of GHLE, PVP and DCP were studied. Physical tests were performed on the powder mixtures and the tablets. In general, formulations displayed problems due to their very poor flowability properties which lead to undesirable tablets. Therefore, results of the physical tests on them were not given in a table or a diagram. According to the results obtained, suitable additions were made at certain concentrations and new powder mixtures were prepared. Same tests were repeated on them and their tablets: Bulk density, packed bulk density and compressibility % (Carr's Index) on the powder mixtures and weight variation, diameter, thickness, hardness, friability and disintegration time on the tablets. According to the data, the most suitable binder concentration (2 (w/w) %) was found for the model tablets. The model tablets containing ranitidine hydrochloride were compressed by the same method. Dissolution of drug from the tablets was determined in addition to the physical tests. In this paper, studies were given on the last improved formulations without active agent where suitable additions were made at certain concentrations, and the model tablets.

## EXPERIMENTAL

### *Materials*

Legumens of *Gleditsia triacanthos* (honey locust) were collected in Fatih, Istanbul. A voucher specimen was deposited in the Herbarium of Faculty of Pharmacy, Istanbul University (ISTE No: 79425). Ranitidine hydrochloride (HCH Uquifa, Spain), polyvinylpyrrolidone (Kollidon® K-30, BASF, Germany), dibasic calcium phosphate anhydrous (Budenheim, Germany), lactose

anhydrous 200 mesh (DMV International, The Netherlands), maize starch (Nişkoz, Turkey), talc (Merck, Germany), magnesium stearate (Prever, Italy) and colloidal silicon dioxide (Aerosil® 200, Degussa AG, Germany) were used in this study. The other chemicals were of analytical grade.

#### *Obtaining honey locust endosperms*

Honey locust legumens were collected at 24<sup>th</sup> week after anthesis when pods and seeds had dried fully with the highest galactomannan content at that ripeness as reported earlier (14). The seeds were taken out from the pods. The husks were peeled by using 98 % sulphuric acid (1:1) on a boiling water bath for 1.5 hour. The seeds were washed three times with water, three times with ethanol (10<sup>o</sup> (w/w)) and then repeatedly with ethanol (96<sup>o</sup> (v/v)) until husks and acid were totally removed. They were dried in open air over 1 night and were coarsely powdered using a Siebtechnik Typ T 100 mill (Germany), then sieved for removing embryo/cotyledone parts (germ). The endosperm containing galactomannan were ground in the same mill and passed through 40 mesh (0.420 mm) and 50 mesh (0.300 mm) sieves (VEB Metallweberei, Germany). Particle size fraction of 0.300 mm - 0.420 mm endosperm was defatted by Soxhlet extraction using petroleum ether (40-60<sup>o</sup>) for 10 hours. The powder gained (GHLE) was stored in a desiccator and used for the determination of loss on drying and tablet compression for evaluation of its binding effect.

#### *IR spectrum of honey locust galactomannan*

For this aim, 1 % (w/v) solution of defatted GHLE under 50 mesh sieve was prepared in water. Mucilaginous solution was centrifuged using a Janetzki K23 centrifuge (Germany) at 4000 rpm for 20 minutes. After the residue was diluted and the same procedure was repeated twice, supernatants were collected together. Honey locust galactomannan was precipitated with alcohol (96<sup>o</sup> (v/v)) and dried at 50<sup>o</sup>C. 1 % (w/v) galactomannan solution was prepared in water. 0.2 ml solution and 150 mg KBr were mixed in an agat mortar. After the mixture was dried at 105<sup>o</sup>C, it was powdered in the same mortar. A pellet was compressed and IR spectrum was obtained by using a Perkin Elmer-1600 Series FTIR Spectrophotometer (USA).

#### *Loss on drying*

0.5 g sample was dried to constant weight in a Mettler LP16 PM100 IR balance (Germany) at 105 °C as reported for guar gum in USP 27.

#### *Preparation of the tablets*

##### *Preparation of the PVP and DCP granules*

PVP and DCP were individually granulated to equalize their particle size to that of GHLE for comparison of the binding effect. For this aim, PVP and DCP were compressed into tablets using a Manesty type rotary tablet machine (UK) equipped with 18 mm flat punch. Tablets were passed through an Erweka Type SM granulator (Germany) and sieved using the same sieves. The same particle size fraction (0.300 mm - 0.420 mm) was handled in this study.

#### *Tablet compression*

Powder mixtures without active agent containing GHLE, PVP and DCP as binders, lactose as diluent and magnesium stearate as lubricant were prepared. Their tablets were compressed using

an eccentric tablet machine (Dühning, Germany) equipped with a 11.0 mm flat punch at 8 pressure units. Loading depth was adjusted to obtain 330 mg tablets. After evaluating the data obtained from the physical controls on both of the powder mixtures and their tablets, magnesium stearate:talc (1:9) mixture as lubricant and aerosil as glidant were decided to be added into these formulations instead of magnesium stearate, alone (Formulations A-I) (Table 1). Maize starch as disintegrant was added into the powder mixtures due to increase of lubricant concentrations. It was reported that talc might require concentrations as high as 5 % when used alone and excessive amounts of hydrophobic material in a tablet formulation could result in “waterproofing” the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance (17).

**Table 1.** Composition (w/w %) of the tablet formulations

Formulation	Ranitidine HCl	Lactose	Maize Starch	Binder			Magnesium Stearate:Talc (1:9)	Aerosil
				GHLE	PVP	DCP		
A	-	86	5	1	-	-	7	1
B	-	86	5	-	1	-	7	1
C	-	86	5	-	-	1	7	1
D	-	84.5	5	2.5	-	-	7	1
E	-	84.5	5	-	2.5	-	7	1
F	-	84.5	5	-	-	2.5	7	1
G	-	82	5	5	-	-	7	1
H	-	82	5	-	5	-	7	1
I	-	82	5	-	-	5	7	1
J	55	30	5	2	-	-	7	1
K	55	30	5	-	2	-	7	1
L	55	30	5	-	-	2	7	1

Model tablets containing 180 mg ranitidine hydrochloride were compressed by the same method (Formulations J-L). The same physical tests were performed to reveal conformity of the tablets to reported requirements.

#### *Physical tests on the powder mixtures*

##### *Bulk density, packed bulk density and compressibility % (Carr's Index)*

This study was replicated 3 times for each formulation. 10 g powder (W) was poured into a 50 ml measuring cylinder and bulk volume ( $V_B$ ) was found. Bulk density ( $D_B$ ) was calculated with Equation 1.

$$D_B = W/V_B \quad \text{Eq. 1}$$

The cylinder was then assembled to a packed density apparatus (J. Engelsman, Germany) and powder was tapped 1250 times. Packed volume ( $V_p$ ) of the powder was determined. Packed density ( $D_p$ ) and Carr's Index (CI) were calculated with Equations 2 and 3, respectively:

$$D_p = W/V_p \quad \text{Eq. 2}$$

$$CI = [(D_p - D_B)/D_p] \cdot 100 \quad \text{Eq. 3}$$

### Physical tests on the tablets

#### Weight variation, diameter, thickness and hardness

These controls were replicated 10 times for each tablet formulation. Weight uniformity of the tablets was examined according to the method in USP 27. Diameter and thickness of the tablets were determined using a micrometer (Mitutoyo, Japan). Hardness of the tablets were determined using a Monsanto hardness tester.

#### Friability test

Twenty tablets were weighed ( $W_1$ ) and rotated for 4 minutes at 25 rpm in a friabilator (Aymes, Turkey). The tablets were reweighed ( $W_2$ ) and friability % (F %) was calculated with Equation 4.

$$F \% = [(W_1 - W_2)/W_1] \cdot 100 \quad \text{EQ. 4}$$

#### Disintegration time

This test was made on six tablets of each formulation according to the method reported in USP 27 using 900 ml water as disintegration medium at  $37 \pm 0.5^\circ\text{C}$ .

#### Dissolution studies

Dissolution of ranitidine hydrochloride from the model tablets (Formulations J-L) was studied in 900 ml distilled water at  $37 \pm 0.5^\circ\text{C}$  according to USP 27 Method II (paddle). Rotation speed was 50 rpm. 2 ml samples were taken at predetermined time intervals, diluted to 50 ml with water and filtered through S&S<sup>5893</sup> type blue ribbon filter paper. Cumulative percentage of dissolved drug was assayed spectrophotometrically (Varian 6345 UV-Visible Spectrophotometer) at 314 nm.

## Results and Discussion

### IR spectrum of honey locust galactomannan

IR spectrum obtained from honey locust galactomannan is shown in Figure 1 (15).

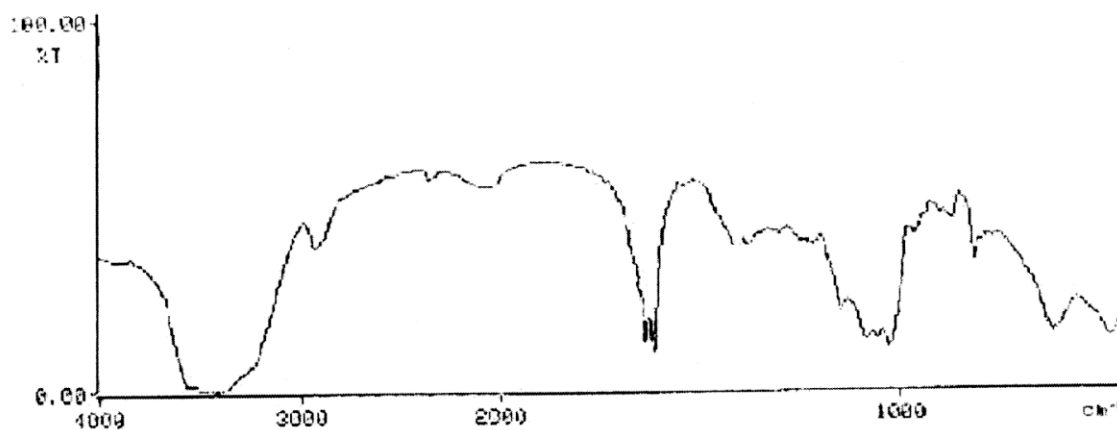


Figure 1. IR spectrum of honey locust galactomannan

IR spectroscopy showed a hydroxyl band at  $3628\text{ cm}^{-1}$ , aliphatic carbon hydrogen bands at  $2893\text{ cm}^{-1}$  and other aliphatic carbon hydrogen bands at  $1457\text{ cm}^{-1}$  and  $1374\text{ cm}^{-1}$ , primary and secondary alcohol bands at  $1394\text{ cm}^{-1}$  and ether bands at  $1027\text{ cm}^{-1}$ .

#### Loss on drying

Loss on drying was found as  $9.90\%$ .  $\leq 15\%$  is usually required for ground endosperm such as guar gum by compendia (13). It could be therefore accepted that  $9.90\%$  water content didn't affect the evaluation of the binding effect of GHLE.

#### Physical tests on the powder mixtures

For the powder mixtures of the tablets containing  $1\%$  magnesium stearate, CI values indicated poor flowability performance according to the classification reported by Carr (16). As  $1\%$  magnesium stearate was not sufficient for the flowability performance, desired flowability was improved by addition of talc and aerosil at suitable concentrations as seen in Tables 1 and 2 (Formulations A-I). Only flowability of Formulation I containing  $5\%$  DCP was poor with  $25.89$  CI value (Table 2). Tablets of GHLE and PVP were superior than those of DCP at each concentration. Increasing binder concentration displayed increasing CI values from fair flowability to passable flowability on borderline. Carr reported that material might hang up for passable flowability on borderline (16). In case of the model tablets (Formulations J-L), presence of drug slightly improved the flowability of the powder mixtures (Table 2).

**Table 2.** The mean values and standart deviations of the physical test results of the powder mixtures (n = 3)

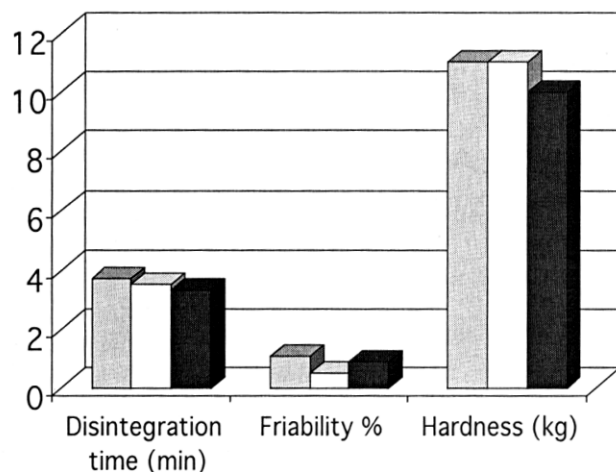
Formulations	$D_B$ (g/ml) $\pm$ SD	$D_p$ (g/ml) $\pm$ SD	CI $\pm$ SD
A	$0.58 \pm 0.01$	$0.72 \pm 0.01$	$19.81 \pm 1.52$
B	$0.57 \pm 0.02$	$0.73 \pm 0.02$	$20.00 \pm 0.83$
C	$0.59 \pm 0.01$	$0.77 \pm 0.02$	$23.47 \pm 0.85$
D	$0.58 \pm 0.01$	$0.72 \pm 0.01$	$20.27 \pm 1.99$
E	$0.57 \pm 0.01$	$0.73 \pm 0.01$	$20.63 \pm 0.17$
F	$0.58 \pm 0.01$	$0.77 \pm 0.01$	$23.79 \pm 0.18$
G	$0.57 \pm 0.02$	$0.73 \pm 0.01$	$21.56 \pm 2.13$
H	$0.57 \pm 0$	$0.72 \pm 0.02$	$20.79 \pm 2.20$
I	$0.59 \pm 0$	$0.80 \pm 0.03$	$25.89 \pm 2.35$
J	$0.56 \pm 0.02$	$0.69 \pm 0.01$	$18.84 \pm 1.15$
K	$0.56 \pm 0$	$0.70 \pm 0.01$	$19.66 \pm 1.53$
L	$0.57 \pm 0$	$0.69 \pm 0.01$	$17.99 \pm 1.01$

$D_B$  bulk density,  $D_p$  packed bulk density, CI Carr's Index of the powder, SD standart deviation

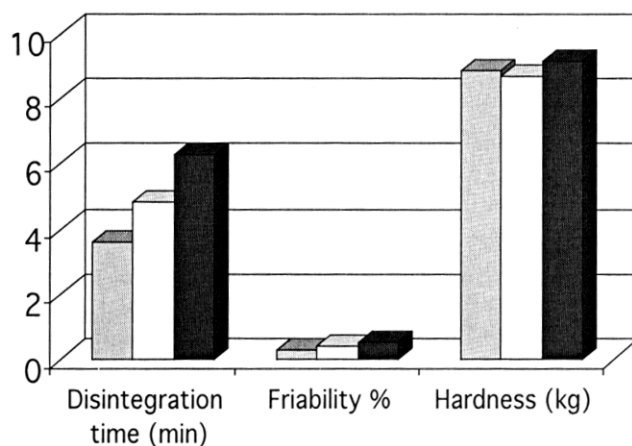
*Physical tests on the tablets*

*The tablets without active agent*

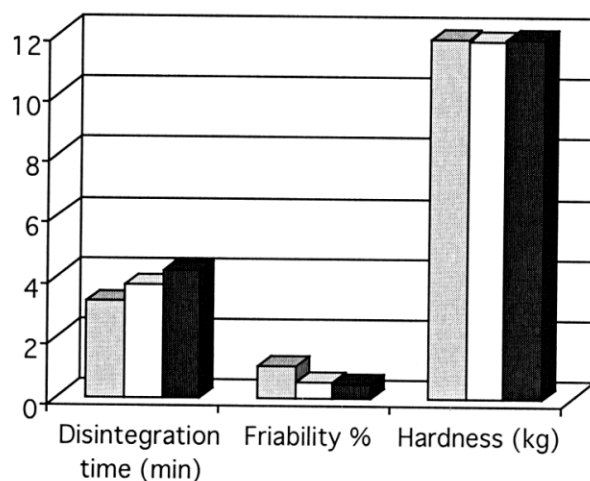
It was seen that friability of the tablets with 1 % GHLE concentration was higher than compendial requirement. 1 % concentration was not sufficient to bind the powder and to impart in mechanical resistance of the tablets, whereas, 2.5 and 5 % GHLE concentration in the tablets met the compendial requirement with 0.49 and 0.86 % friability values, respectively (Figure 2). While friability was consistent at each PVP concentration, the tablets with 1 % DCP exhibited much higher friability than compendial requirement (Figures 3 and 4).



**Figure 2.** Disintegration time, friability % and hardness data obtained from the tablets without active agent containing 1 % (■), 2.5 % (□) and 5 % (■) GHLE: Formulations A, D and G, respectively



**Figure 3.** Disintegration time, friability % and hardness data obtained from the tablets without active agent containing 1 % (■), 2.5 % (□) and 5 % (■) PVP: Formulations B, E and H, respectively



**Figure 4.** Disintegration time, friability % and hardness data obtained from the tablets without active agent containing 1 % (■), 2.5 % (□) and 5 % (■) DCP: Formulations C, F and I, respectively

Hardness and disintegration values for all the tablets were found satisfactory (Formulations J-L) (Figures 2-4).

Where only 1 % percent magnesium stearate was used as a lubricant, weight variation values of all the tablets without active agent were not within reported limits for tablets weighing more than 324 mg. But use of magnesium stearate:talc mixture (1:9) and aerosil (Table 1) improved the flowability. The variation from the average weight in the weights of not more than two of the tablets did not differ by more than 5 %; no tablet differed by more than double that percentage (Formulations A-H). The highest variation was 2.22 % (Formulation I).

#### *The model tablets*

The mean values and standart deviations of all the physical test results on the model tablets are shown in Table 3. Weight variation results indicated that flow properties could be improved by adding magnesium stearate:talc mixture (1:9) and aerosil at 7 and 1 % concentrations, respectively. Weight variation of the tablets was within the limits reported for tablets more than 324 mg, according to these data.

Disintegration time and hardness value for each series was as suitable as not to affect desired dissolution time of drug. Friability values were lower than 1 %.



**Table 3.** The mean values and standart deviations of the physical test results of the model tablets

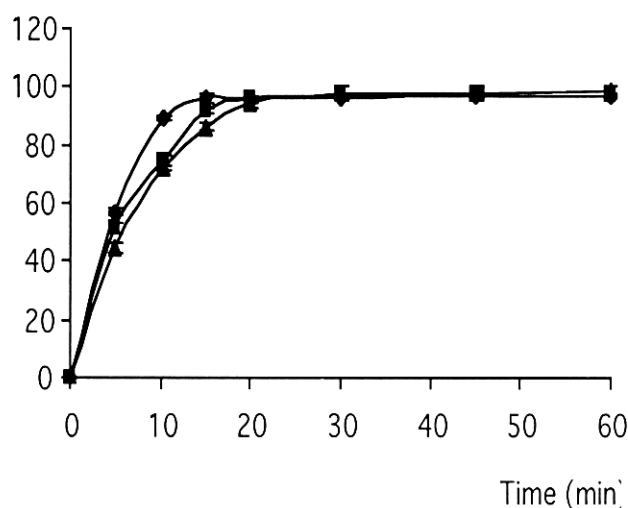
Formulations	W (mg) ± SD	h (cm) ± SD	D <sub>i</sub> (min) ± SD	F %	H (kg) ± SD
J	332 ± 4.94	0.263 ± 0.01	3.3 ± 0.26	0.59	10.70 ± 1.08
K	334 ± 2.54	0.296 ± 0.01	3.7 ± 0.27	0.27	8.95 ± 1.65
L	333 ± 2.15	0.302 ± 0.01	3.8 ± 0.27	0.26	12.50 ± 0

W weight, h height, D<sub>i</sub> disintegration time, F % friability %, H hardness of the tablets, SD standart deviation

Diameter of the tablets was found as 11.1 ± 0 mm

*Dissolution study*

According to the data obtained, no significant difference was observed among the dissolution profiles of the model tablets (Formulations J- L) (p>0.5). It was found that 96.93 ± 1.99, 96.99 ± 2.23 and 97.91 ± 1.99 % of drug was dissolved from the tablets after 45 minutes, respectively. These values meet the requirement reported for ranitidine hydrochloride tablets in USP 27 as not less than 80 % of labeled amount of ranitidine hydrochloride should be dissolved in 45 minutes (Figure 5).



**Figure 5.** Dissolution profiles of drug from the model tablets in distilled water. Formulations J (●), K (■) and L (▲) with GHLE, PVP and DCP as binder, respectively.

**CONCLUSION**

It was concluded that ground endosperm of honey locust seeds containing galactomannan exhibited a good binding effect at 2 % concentration in the tablets and was found to be as suitable as PVP and DCP which are commonly used binders. Therefore, it is suggested that this natural

gum in honey locust seeds might be used in tableting technology, since it can be obtained by convenient and well-known cost-effective methods.

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