

## Evaluation of a drug with wax-like properties as a melt binder

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The study investigates ibuprofen with wax-like properties as a multifunctional agent (as an active component and as a melt binder). Binding efficiency was compared with granules prepared by wet granulation using polyvinylpyrrolidone (PVP K-30) as a binder for micromeritic, physical and mechanical properties such as angle of repose, particle size distribution Carr's index, Hausner's ratio, crushing strength, percentage fines, Heckel plot study and tensile strength. To check the binder distribution during melt granulation, the content uniformity was determined. To check changes in the physical state of ibuprofen, XRPD, DSC and FTIR studies were carried out. The present study underlines the fact that ibuprofen may be adopted as a binder in ibuprofen formulations using the melt granulation technique.

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Particle size enlargement or granulation is one of the most important unit operations in tablet manufacturing and is performed to impart some degree of functionality to particles, such as improved flowability, compressibility, and compactability. Though conventional granulation enjoys wider acceptability, various novel techniques such as extrusion-spheronization (1), spherical crystallization (2–4), melt extrusion (5) and melt granulation/solidification (6) are being developed. Binder is an essential component in this process, since it imparts strength to granules and tablets during processing, handling and packaging.

In recent years, melt granulation (MG) has become a popular technique due to its advantages over traditional wet granulation. MG is a well-known process whereby fine powders are agglomerated by means of a molten binder and are processed into spherical or nearly spherical granules of homogeneous size. The MG process is economical in terms of time and energy as compared to conventional wet granulation. Examples of melt binders used in the pharmaceutical literature include polyethylene glycol (PEG), microcrystalline wax, stearic acid, glyceryl stearate (7).

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Waxy binders have been used in the preparation of conventional and sustained release tablets (8), and more recently in the preparation of fast-release tablets (9). Yanze *et al.* (10) reported preparation of effervescent granules using PEG 6000 as melt binder using the fluidized bed melt granulation. The melt solidification technique for the preparation of sustained release ibuprofen beads with cetyl alcohol has been studied in our laboratory (11). Similarly, other waxy carriers like bee wax, carnauba wax, ceresine, microcrystalline wax, Precirol ATO5, Gelucire 64/02 have been studied (12, 13) in the preparation of microspheres. Sustained release ibuprofen mini-tablets have been prepared by the melt extrusion technique using microcrystalline wax and starch derivatives (14).

Recently, the use of the drug as a multifunctional agent has been documented. Crowley *et al.* (15) have investigated the drug-fatty acid salt (propranolol oleate) as binder in melt granulation with improved processing properties. Many researchers have shown that ibuprofen (IBU) functions as a plasticizer for acrylic films, *e.g.*, ibuprofen and methylparaben were demonstrated to have a significant plasticization effect on Eudragit RS 30 D (16). Wu and McGinity (17) have recently studied the influence of ibuprofen as a solid-state plasticizer in Eudragit RS 30 D on the physicochemical properties of coated beads. With its low melting point (80 °C), ibuprofen meets the preliminary requirement as a potential binder for melt granulation. The objective of the study was to investigate ibuprofen as a multifunctional agent (as an active component and as melt binder) and to study its binding ability.

## EXPERIMENTAL

### *Materials*

Ibuprofen, lactose monohydrate IP, polyvinylpyrrolidone K30 (PVP, BASF, Germany), were obtained as gift samples from Get-Rid Pharmaceuticals Pvt. Ltd., India. All other reagents were of analytical grade and were used as purchased.

### *Preparation of granules*

Melt granules (50 g each) were prepared with varying ratios of lactose: IBU (2:1, 4:1, *m/m*) using the melt granulation technique. Lactose was sieved through a 40 mesh (420  $\mu\text{m}$ ) sieve. IBU was melted in a beaker and added to the sieved lactose in the laboratory scale planetary mixer (Seema Enterprises, India) with the agitation speed at medium setting. Agitation was continued till uniform granules resulted due to IBU solidification.

Wet granules with varying percentage of PVP (2.5%, 5%, *m/V*) were prepared by wet granulation. The PVP was dissolved in distilled water and granulation was carried out in the laboratory scale planetary mixer. The granulation mass was subsequently wet milled through an 8 mesh (2000  $\mu\text{m}$ ) sieve and dried (loss on drying not more than 2%). Finally, the granules obtained both by melt and wet granulations were passed through a 20 mesh (800  $\mu\text{m}$ ) sieve and subjected to micromeritic and mechanical characterization.

### Characterization of granules

All the samples were analyzed in triplicate.

*Micromeritic properties.* – The flowability of granules was assessed by determining the angle of repose ( $\theta$ ) using the fixed funnel method (18). The bulk and tapped densities of granules were determined on a tap density tester USP (Electrolab, India) and data was further processed to obtain Hausner's ratio and compressibility index. Particle size distribution of granules was determined by sieve analysis. The granules (10 g) were passed through a series of sieves with pore size 850, 420, 250, 200 and 150  $\mu\text{m}$  by agitation. The graph of the percent mass retained on each sieve was plotted against the mean particle size (Fig. 1).

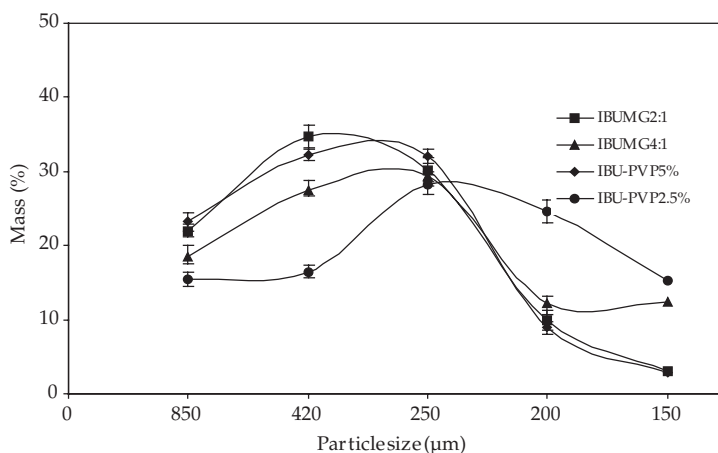


Fig. 1. Mass fraction of granules *vs.* mean particle size (mean  $\pm$  SD,  $n = 3$ ).

*Crushing strength.* – Crushing strength of granules passed through 16 (aperture size 1019  $\mu\text{m}$ ) and retained on 22 (aperture size 707  $\mu\text{m}$ ) was determined using the mercury load cell method as described by Jarosz and Parrott (19) on a specially fabricated crushing strength apparatus (Seema Enterprises, India).

### Physicochemical properties

*X-ray powder diffractometry (XRPD).* – The XRPD patterns of samples were recorded using a Philips PW 1729 X-ray diffractometer (PW 1729, Philips, The Netherlands). Samples were irradiated with monochromatized Cu  $K\alpha$  radiation (1.542  $\text{\AA}$ ) and analyzed between 2 and 50°  $2\theta$ . The voltage and current used were 30 kV and 30 mA, respectively.

*Differential scanning calorimetry (DSC).* – Thermograms of granules and pure IBU were obtained using a Mettler-Toledo DSC 821e (Mettler Toledo, Switzerland) instrument equipped with an intracooler. Indium/zinc standards were used to calibrate the

DSC temperature and enthalpy scale. Granules were hermetically sealed in an aluminum pan and heated at a constant rate of 10 °C min<sup>-1</sup> over a temperature range of 25–100 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL min<sup>-1</sup>.

*Surface topography.* – The surface of the drug and granules was coated with a thin gold-palladium layer by a sputter coater unit (VG-Microtech, UK) and the surface topography was analyzed with a scanning electron microscope (Cambridge Stereoscan S120, UK).

*Fourier transformed infrared spectroscopy.* – Fourier-transformed infrared (FT-IR) spectra of the pure crystalline drug and granules were obtained on JASCO V5300 FT-IR (JASCO, Japan). The samples were diluted with pure crystalline KBr. The pellets were prepared on a KBr-press (Spectra Lab, India). The spectra were scanned over the wave number range of 4000 to 400 cm<sup>-1</sup>.

#### *Measurement of binder distribution*

Samples (5 mg) of the different size granule fractions were dissolved in 100 mL phosphate buffer, pH 7.2. (0.05 mol L<sup>-1</sup> KH<sub>2</sub>PO<sub>4</sub>, 0.04 mol L<sup>-1</sup> NaOH) IBU content was determined using UV spectrophotometer (JASCO V530, Japan) with suitable dilutions at 222 nm.

#### *Compressional properties*

*Heckel plot.*– Compressibility of granules was evaluated by the Heckel equation (20) in triplicate. Granules were lubricated with magnesium stearate and were compressed (average mass 300 mg ± 2%), at different pressures, up to constant density of compacts using the 8 mm flat faced punch and die set on a hydraulic press (Spectralab, India). The range of different pressures applied to get constant density was 20–100 kg cm<sup>-2</sup>. The tablets were stored in airtight moisture-proof containers for 24 hours to enable elastic recovery and hardening. The tablet actual mass was taken. Diametrical hardness tester (Pharmatest Ltd., India) was used to determine the diameter and thickness of prepared compacts. The compressibility behavior was studied using the Heckel equation and the mean yield pressure ( $P_y$ ) was obtained.

$$\ln[1(1-RD)] = kP_y + A$$

where RD is relative density and  $k$  and  $A$  are constants.

*Tensile strength.* – Hardness of the compact was determined using a diametrical hardness tester and the values were converted to tensile strength ( $T$ ) by the following equation:

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

where  $D$  and  $T$  are the diameter and thickness of the compacts, respectively, and  $P$  is the breaking force.

### Dissolution studies

Dissolution studies were performed in triplicate using a USP 24 type II dissolution test apparatus (21) (Electrolab TDT-06P, Mumbai, India). Phosphate buffer, (pH 7.4) 900 mL (250 mL 0.2 M potassium dihydrogen phosphate mixed with 196.5 mL 0.2 M sodium hydroxide solution and volume made up to 1000 mL with water) was used as dissolution medium the stirring speed was 100 rpm, temperature was maintained at  $37 \pm 2$  °C. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41, IBU concentration was determined spectrophotometrically at 222 nm. Analysis of data was done using the S'PCP Disso V3' software (PCP, India).

## RESULTS AND DISCUSSION

Granules obtained with IBU (2:1, 4:1) and PVP (5%) revealed no significant differences in Hausner's ratio, compressibility index, angle of repose and percent of fines. However, at lower concentrations, PVP (2.5%) granules showed significantly lower values of all the micromeritic parameters, indicating a significant proportion of fines (Table I). According to literature, powders with Carr's index (CI) between 5 and 15% and Hausner's ratio below 1.25 are suitable for producing tablets (21). This was also supported by the particle size distribution analysis (Fig. 1), indicating a maximum portion of the fraction under 250  $\mu\text{m}$  for PVP (2.5%) granules.

The resistance of a granule to crushing is a necessary attribute of any granulation technique. It provides uniform granule size irrespective of the extent and type of normal handling during processing. The crushing strength for IBU MG in both concentrations and PVP (5%) showed no significant differences. In the case of PVP (2.5%), the crushing strength showed lower values due to insufficient binder concentration (Table I). The IBU concentration in the different granule fractions was in the range of 95–105% which clearly indicated that the binder was well distributed in the granules.

The compressional properties of lubricated granules were expressed as compressibility and compactability and evaluated by mathematical treatment of the compressional study data by Heckel plot studies. The Heckel equation analyzes the ability of granules

Table I. Micromeritic properties<sup>b</sup>

	Binder	Hausner's ratio	Carr's index	Angle of repose ( $\theta$ )	Crushing strength (g)	Fines (%)
IBU	2:1 <sup>a</sup>	$1.22 \pm 0.05$	$13.18 \pm 1.25$	$22.6 \pm 1.3$	$130.6 \pm 20.5$	$13.0 \pm 2.00$
	4:1 <sup>a</sup>	$1.18 \pm 0.05$	$16.43 \pm 1.25$	$20.4 \pm 2.4$	$122.4 \pm 16.2$	$24.6 \pm 1.50$
PVP	5% (m/m)	$1.17 \pm 0.05$	$15.65 \pm 1.25$	$25.0 \pm 2.1$	$125.3 \pm 18.5$	$11.1 \pm 2.5$
	2.5% (m/m)	$1.12 \pm 0.05$	$19.65 \pm 1.25$	$23.5 \pm 1.9$	$105.4 \pm 20.5$	$39.8 \pm 1.50$

<sup>a</sup> Lactose/IBU ratio.

<sup>b</sup> Mean  $\pm$  SD,  $n = 3$ .

to undergo volume reduction, *i.e.*, compressibility. It describes the relationship of the compact, density to the applied pressure. The compressional force with relative density and tensile strength of the compact analyzes the ability of granules to be compressed into compacts of specified strength. The rate of density decrease with applied pressure is proportional to the volume fraction of pores. The reciprocal value of the slope ( $k$ ) represents the mean yield pressure ( $P_y$ ) by which a substance resists the deformation process. The value of the intercept ( $A$ ) describes the movement of granules or particles at the beginning of compression.

Heckel plots for IBU and PVP as binders are shown in Fig. 2. The granules prepared with IBU MG showed a low  $P_y$  value, indicating that less force might possibly be needed to deform them. The relatively higher  $P_y$  value for granules made with PVP 2.5% indicates that the granules are softer, more plastic and hence could deform readily. With increasing the binder concentration from 2.5 to 5%, *m/m*, the  $P_y$  values decreased, implying that the onset of plastic deformation in the formulation occurred at lower pressures. In general, the compressibility of granules was in the order IBU-MG 2:1 > PVP 5% > IBU-MG 4:1 > PVP 2.5%. The mean yield pressure for IBU-MG (2:1), IBU-MG (4:1), IBU-PVP 2.5%, IBU-PVP 5% was 26.7, 26.9, 45.5 and 29.0, respectively.

XRPD patterns of the crystalline drug and granule samples are shown in Fig. 3. Melt granulation samples have shown significant differences in the XRPD pattern compared to the crystalline drug and the granules with PVP. Decreased intensities of peaks for melt granulation samples can be noted compared to the crystalline drug. This may be due to the change in the crystal habit that might have taken place during the processing of ibuprofen melt. Decrease in intensity indicates the presence of amorphous fractions generated during processing. IR spectra of the crystalline drug and granule samples are shown in Fig. 4. The IR spectra showed characteristic ibuprofen peaks at  $1720\text{ cm}^{-1}$  (C=O stretching) and  $2955\text{ cm}^{-1}$  (bonded stretching) for both the crystalline drug as well as granule samples. This clearly indicates the absence of any physical interaction of the drug with the excipients. The SEM microphotographs (Fig. 5a,b) of IBU-PVP (5%) showed a porous structure, which might be due to evaporation of the binder solvent,

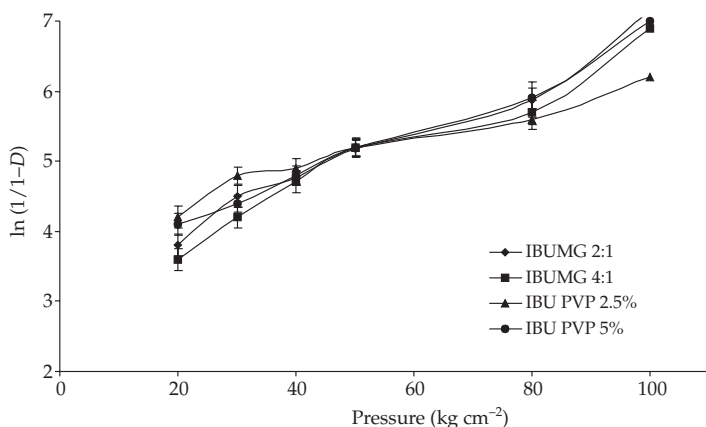


Fig. 2. Heckel plot for IBU and PVP as binders (mean  $\pm$  SD,  $n = 3$ ).

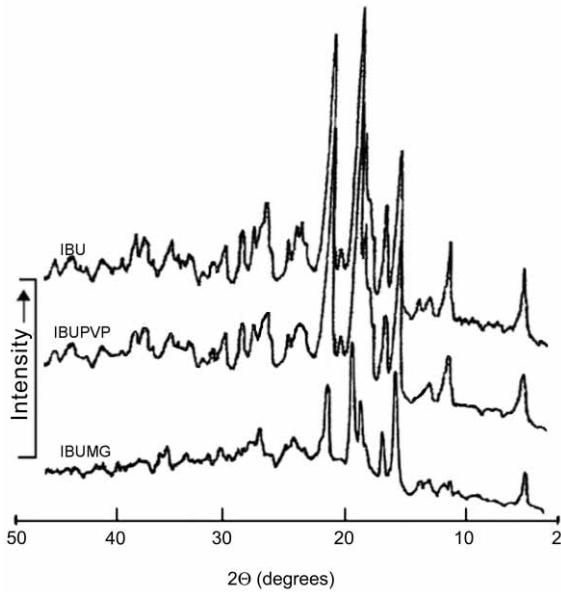


Fig. 3. XRPD pattern of pure IBU, IBU-MG (4:1) and IBU-PVP (5%).

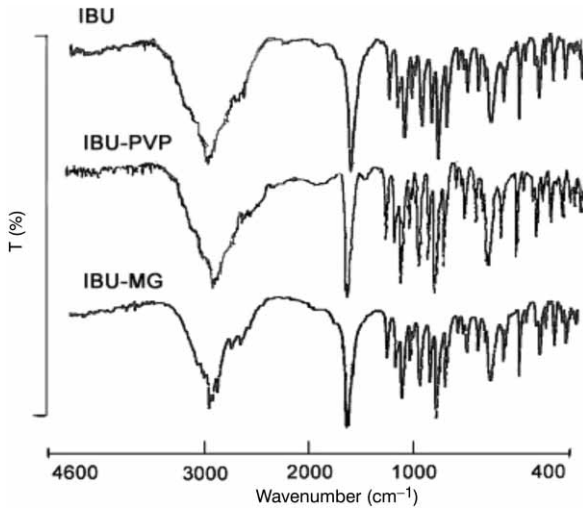


Fig. 4. IR spectra of pure IBU, IBU-MG (4:1) and IBU-PVP (5%).

whereas the IBU-MG (1:2) granules have micro pores (Fig. 5c,d). At higher magnification, the microphotograph showed the presence of crystalline IBU in IBU-PVP granules; this was confirmed by the XRD data. Crystalline drug could not be compressed due to its capping and sticking to the tools. Fig. 6 shows the DSC thermographs for pure IBU and for granules. DSC of pure IBU showed a sharp melting peak at 79.4 °C whereas the

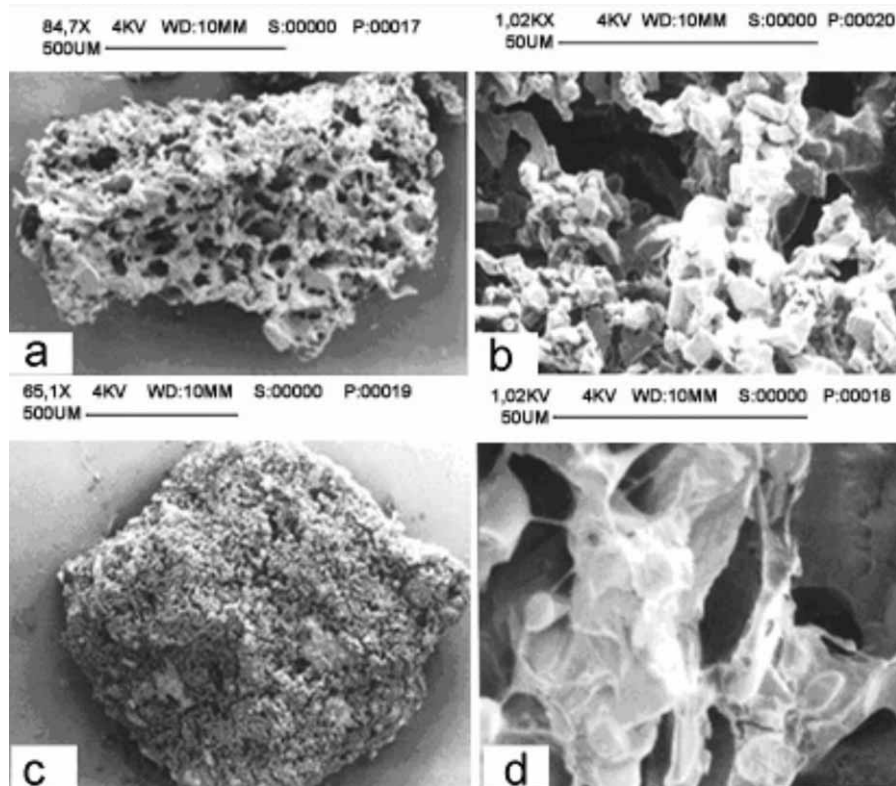


Fig. 5. SEM microphotograph of: a) IBU-PVP granules, and b) magnified image, c) IBU-MG granules, d) and its magnified image.

melting peaks of IBU-MG and IBU-PVP granules were shifted to 79.9 °C and 80.8 °C, respectively. There was a very slight decrease in the heat of fusion ( $\Delta H_f$ ) of IBU-MG compared to crystalline IBU. This decrease in the heat of fusion might be due to the presence of high melting components like lactose and PVP or the presence of amorphous fractions generated during the cooling of molten IBU, which is in accord with the XRD data.

Dissolution of pure IBU and granules was carried out to study the effect of the method of granulation on the *in vitro* drug release performance (Fig. 7). Complete dissolution of the drug from pure IBU powder was observed within 30–45 min. Granules with varying proportions of PVP showed a slight increase in dissolution profiles. This may be due to the presence of a hydrophilic polymer in the microenvironment of the drug, which causes wetting and solubilization of the drug. Similarly, melt granules with lactose showed a slight increase in dissolution compared to IBU and granules with PVP. This might be partly due to wetting and solubilization of lactose and partly to the presence of amorphous fractions that might have been generated during the melt granulation of IBU. The presence of traces of amorphous fractions is also supported by the



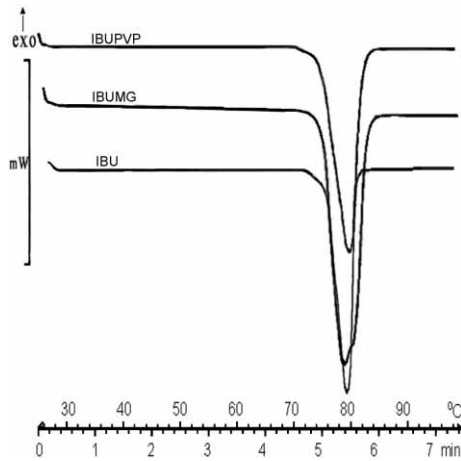


Fig. 6. DSC thermograms of pure IBU, IBU-MG (4:1) and IBU-PVP (5%).

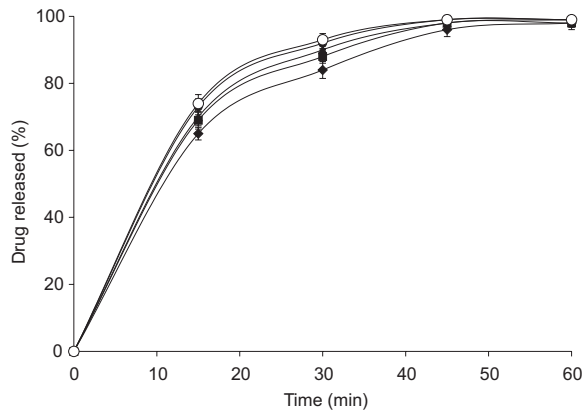


Fig. 7. Comparative dissolution profiles of IBU (◆); IBU-MG (2:1) (■), IBU-MG (4:1) (▲), IBU-PVP (2.5%) (●), IBU-PVP (5%) (○)(mean  $\pm$  SD,  $n = 3$ ).

XRPD and DSC data. The dissolution profiles of melt granules are comparable with the granules obtained by the wet granulation process. Hence it can be concluded that the method does not affect the *in vitro* performance of the granules except for a slight increase in the rate of dissolution.

### CONCLUSIONS

Granule properties of IBU-MG were comparable with the granules of the well-known binder PVP K-30. The physicochemical study showed no significant change in ibuprofen

properties due to melt granulation and granules were able to maintain the content uniformity. Ibuprofen as melt binder may be applicable to the systems having ibuprofen as one of their active components.

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## S A Ž E T A K

### Ispitivanje vosku sličnih svojstava ibuprofena kao veziva

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Svrha rada je ispitivanje vosku sličnih svojstava ibuprofena, tvari s višeznačnom funkcijom (ljeikovita tvar i vezivo pri granulaciji). Vezivna svojstva uspoređivana su s granulama pripremljenim vlažnom granulacijom s polivinilpirolidonom (PVP K-30) kao vezivom, ispitivanjem mikrometričkih, fizikalnih i mehaničkih svojstava kao što su sipkost materijala, Carrov indeks distribucije veličine čestica, Hausnerov parameter, otpornost na vlak. Da bi se ispitala distribucija veziva tijekom granulacije taljenjem određivana je ujednačenost sadržaja. Za praćenje promjena fizikalnih svojstava ibuprofena snimljeni su XRPD, DSC, FTIR spektri. Istraživanja ukazuju da se ibuprofen može koristiti kao vezivo u ljeikovitim pripravcima ibuprofena u kojima se primjenjuje granulacija taljenjem.

*Ključne riječi:* ibuprofen, vezivo, granulacija taljenjem

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