DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(16), 2383-2407 (1990)

AUTOHESION IN
PHARMACEUTICAL SOLIDS

G.P. Millili*, R.J. Wigent, J.B. Schwartz
Department of Pharmaceutics
Philadelphia College of Pharmacy & Science
Philadelphia PA. 19104

I. Abstract

Autohesion is a diffusion controlled mechanism that can be utilized to explain how high molecular weight polymers interact. This mechanism finds its origin in the rubber and plastics industries and has been briefly alluded to in the pharmaceutical literature only in the area concerning film coating of solid dosage forms[1]. Since many pharmaceutical dosage forms contain high molecular weight polymers in their formulations, this review will attempt to introduce the concept and the factors that affect it to the pharmaceutics area. An

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* American Foundation For Pharmaceutical Education Fellow

understanding of autohesion may assist the developer in producing solid dosage forms with desired strength and release characteristics.

II. Introduction

An understanding of the interactions occurring in solid dosage forms containing high molecular weight polymers is of increasing importance in pharmaceutical technology. A thorough understanding of the mechanisms and properties of the polymer or processing variables affecting the final state of the polymer may assist the formulator in developing a drug delivery system to its desired use.

Autohesion or other interchangeable terms such as self-adhesion, self-sticking, self-diffusion and conglomeration[2,3,4] is defined as the mutual interdiffusion of free polymer chain ends across the particle-particle interface of high molecular weight polymers resulting in a strong stable link[5,6]. Autohesion of high molecular weight polymers has been well documented in the latex paint[7,8,9,10], rubber[6,11,12,13,14,15,16,17], and plastics industries[18]. However, it should be recognized that autohesion may have an effect on compaction[19], and milling processes[6], and the strength of the dosage form when working with high molecular weight polymers of pharmaceutical interest. An excellent review of the essential back ground on autohesion has been authored by Voyutskii[20]. An understanding of autohesion will provide the formulator with a better appreciation of the factors that may influence the strength and durability of solid dosage forms, and the physical properties of the coatings containing high molecular weight polymers. Therefore, the purpose of this review is to present the concept of autohesion to the area of pharmaceutical technology.

The concept of autohesion was first discussed in 1935 by Zhukov and Talmud[21]. They were the first to separate the concept of self-sticking from other adhesive properties, and to study this property experimentally. Priklonskaya[22] as well as Maslovskii and Popova[23] were the first to study autohesion in rubber. Josefowitz and Mark[11] were the first to postulate that stickiness is connected with the movement of free chain ends of high molecular weight polymers such as rubber. They also were the first to mention factors that either inhibit or enhance autohesion such as temperature, degradation, and crystallization. Scott[24] suggested that the fusion of two particles of high molecular weight polymers probably occurs through the interdiffusion of polymer strands from one surface to the other. However, even with these proponents, the concept of autohesion was not widely accepted until the early 1950's.

Materials which autohere often start out as liquid dispersions which then are dried (i.e. rubber tires, latex paint, and aqueous film coats). Dillon, Matheson, and Bradford[25] worked with latex films of high molecular weight polymers formed by coalescence of particles upon evaporation of water. They suggested that particle-particle coalescence occurs in part as a result of the viscous flow of the polymer, which can be described by the equation of Frenkel[26].

$$\Theta = \left[\frac{3\gamma t}{2\pi\eta r}\right]^{1/2} \qquad \text{Equation 1}$$

where Θ is the half angle of contact (cf. figure 1), γ is the surface tension of the solvent, η is the viscosity of the polymer, t is the time of contact, and r the particle radius.

Brown[2] argued that two factors influence the ability of polymer dispersions to form films. One factor is the force of capillary pressure, F_c, produced by the angle of curvature of the droplet of solvent formed between the polymer material as it dries. The other factor is the resistance of the polymer to deformation ,F_g. Brown concluded that F_c must be greater than F_g during the drying process in order for film formation to occur.

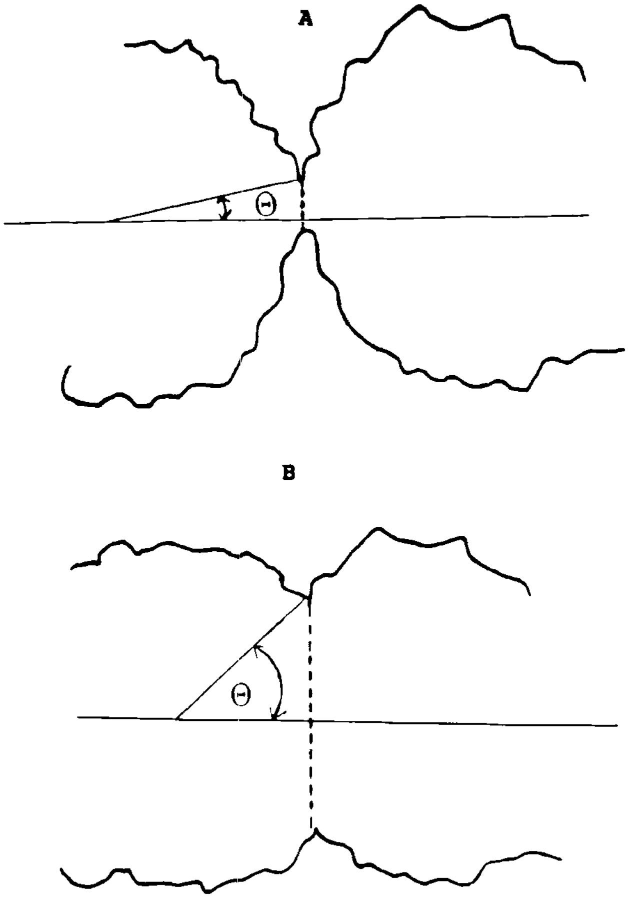

FIGURE 1

PARTICLE DEFORMATION

A) Initial particle approach with small half angle of contact. B) Greater extent of deformation showing an increased half angle of contact.

More recently, Voyutskii[20] has examined the concept of autohesion in more detail. While he agrees with the concept stated by both Brown and Bradford, he postulates that the physical contact of two polymer particles and the presence of the solvent between them is not enough to account for the final strength of the particles which results upon drying[3]. He suggests that the diffusion of the polymer chain ends from one particle to another forming a strong interface with the surface tension and the capillary pressure of the liquid dispersion produce the driving force necessary for solid-solid diffusion to occur.

III. Methods to Study Autohesion

A variety of methods have been employed to attempt to study the degree of autohesion, both quantitatively and qualitatively. In general, there are two methods used to characterize the materials[26]. The first approach requires the simultaneous rupture of the entire bonded interfacial contact area. This is accomplished by utilizing a dynamometer such as the one developed by Voyutskii[27]. With this approach, it was found that the contact area at the interface must not be too large since the force required to separate the material will become excessive and the material may not break cleanly at the interface. If the break is not clean at the interface then a value for the shearing rate will be obtained rather than the desired tensile stress value which is a measure of the degree of autohesion.

The second method utilizes two strips of fabric on which a thin layer of polymer dispersion is applied. The two strips are doubled so as to bring the polymer layers in contact, and the force required to separate the polymer layers is measured. This force can be related to the theoretical work of autohesion[28,6] (Au).

$$Au = \frac{2LPg}{Lb} = \frac{2Pg}{b} \qquad \text{Equation 2}$$

where P is the mean force of separation, L and b are the length and width of the strip of polymer-polymer contact, and g is the acceleration due to gravity.

By utilizing one of the above quantitative approaches the degree of autohesion can be evaluated under varying conditions. A number of investigators have built instruments to measure the degree of autohesion. Among them are: an Autohesiometer by Voyutskii[29], a Tackmeter by Skewis[12], a modified Instron by Forbes[13], and Tel-Tak instrument by Beatty[16].

Another interesting approach used to measure the degree of autohesion was developed by Bueche and coworkers[30]. They utilized radiotracer techniques to study the degree of autohesion in poly(n-butyl acrylate) and plasticized polystyrene as a function of temperature. Bresler[31] also used tracer techniques to measure diffusion coefficients of tritium labeled polyisoprene. An excellent summary of these tracer experiments has been authored by Amerongen[32] and Voyutskii[33].

Skewis and coworkers[15] concluded that macroscopically, diffusion is a very slow process and is difficult to measure, but on a microscopic scale a considerable amount of intermingling of polymer chains across the polymer-polymer interface occurs within seconds after the polymer layers are brought into contact. This diffusion is so rapid that no differences in self-diffusion coefficients could be measured for several types of polymers of comparable molecular weight.

Qualitatively, microscopy studies have shown changes in the degree of autohesion with time and temperature for materials used in the latex[5,8,9,10,34,35] and rubber industries[36]. These studies indicate that the degree of autohesion increases with increasing time and temperature. These studies also support the fact that the degree of autohesion continues to increase even after the material has been dried.

IV. Parameters Affecting Autohesion

A. Polymer Properties

The autohesion of polymers with varying molecular weight has been studied[29] utilizing polyisobutylene with molecular weights of 20,000 to 200,000. Slurries were made with benzene and the polymer was applied to fabric strips. These strips of fabric were then doubled and subjected to the Voyutskii peeling test. The results indicate that the degree of autohesion decreases as the molecular weight increases. Further, the maximum value for the work of autohesion was found to increase with increase in molecular weight [29], although autohesion was found to occur faster for lower molecular weight polymers than higher molecular weight polymers.

In another study[29], the degree of autohesion of polyisobutylene of varying molecular weights was studied as a function of temperature. The activation energy was obtained by measuring the force of peeling using a dynamometer and applying equation 3:

$$P = P_0 e^{-E/RT} \qquad \text{Equation 3}$$

where P is the peeling strength of the bonded specimen, E is the activation energy of the process, R is the gas constant, T is the absolute temperature, and P_0 is a constant. Analysis of a plot of Ln P versus 1/T yielded an activation energy characteristic of the diffusion process. These results indicate that the activation energy is independent of the molecular weight of the polymer.

From time of contact studies, it was found that the rate of the degree of autohesion increases with decrease in the molecular weight of the polymer. Since autohesion is probably caused by the diffusion of the polymer chains across the interface, it is postulated that the shorter polymers have more chain ends to diffuse than the larger ones. However, if given enough time the longer, higher molecular weight polymers may diffuse further across the interface and cause a greater degree of autohesion than the shorter polymers[29].

The effect of the shape of the polymer on self diffusion has been studied extensively[4,28]. According to the diffusion theory of autohesion, the bulkier the polymer the harder it is for the polymer material to diffuse and intermingle with other polymer strands. Therefore, high molecular weight polymers with a regular structure should autohere to a greater degree than polymers with irregular structures[4]. This effect was verified by Naunton[37]. Voyutskii and Shtarkh[4,29] explained that structural branching of polymers exhibit a lesser degree of autohesion due to steric factors. Their work was done on butadiene polymers with varying degrees of substitution (ie. carbonyls, esters, etc.).

The effect of adding varying amounts of acrylonitrile on the degree of autohesion of butadiene copolymers was studied by subjecting the samples to the Voyutskii peeling test[29]. It was found that the degree of autohesion decreased with increasing amounts of acrylonitrile. According to the diffusion theory of autohesion, the electrostatic interactions between the polar groups, such as the nitrile groups found in acrylnitrile, decreases the mobility of the polymer chains. This causes the activation energy for the autohesion process to increase and, thus, the rate of diffusion of the polymer chains to decrease. However, if polar solvents or plasticizers are added to the system the polar groups are shielded from each other allowing more movement of the polymer chains.

The effect of the degree of crystallinity on autohesion has been investigated by Voyutskii and coworkers[4,29]. While polyisobutylene and polyethylene have similar chemical structures, polyisobutylene is amorphous while polyethylene is crystalline at normal temperatures. The amorphous polyisobutylene was found to exhibit a high degree of autohesion, while the polyethylene was found not to autohere. It was postulated that the polymer chains of the crystalline material are locked into a rigid crystalline lattice and, thus, have little mobility compared to the polymer chains of amorphous materials. Indeed, upon heating the crystalline polyethylene above its glass transition temperature, the polyethylene became amorphous causing a decrease in the viscosity of the polymer; the polymer chains become more mobile and the degree of autohesion increased.

On the other hand, Belorossova, Farberov and Epstein[38] feel that crystallinity promotes autohesion by causing the ends of the polymer chain to interact simultaneously due to their ordered arrangement. This interaction firmly anchors the polymer molecules across the interface resulting in a strong stable link.

Further work by Epstein[39] suggests that crystalline polymers exhibit a greater degree of autohesion at lower temperatures; at elevated temperatures a sharp decrease in autohesion is observed due to the melting of the crystals[40]. Voyutskii severely questioned the validity of Epstein's interpretation of his experimental results as Epstein failed to consider factors influencing autohesion other than the degree of crystallinity.

The effect of viscosity on autohesion of high molecular weight polymers is very important. According to diffusion theory the lower the viscosity the more mobile the polymer chains become and the easier it is for self-diffusion to occur. However, experimentally it was found that at too low a viscosity, the polymer becomes too fluid and the adhered surfaces are readily separated. Therefore, an optimal viscosity is necessary in high molecular weight polymer systems for a high autohesive strength to exist[11]. Polymer viscosity is influenced by properties such as polymer size, degree of branching, flexibility , presence of polar groups, and in general, all other properties that affect Brownian motion[20].

Forbes and McLeod[13] attempted to study the relationship between viscosity and autohesion of high molecular weight polymers. They measured the degree of autohesion of several polymers as a function of viscosity. It was found that polymers exhibit non-newtonian viscosity as the relative degree of autohesion was found to decrease linearly with increase of the logarithm of the shear viscosity.

B. Processing Factors

There are many processing factors that can affect the degree of autohesion. Since autohesion is a diffusional process, the processing factors that affect diffusion will affect the degree of autohesion[40].

The fact that the degree of autohesion increases with increased contact time between the two layers of polymer was first discussed by Priklonskaya[22] in his study which utilized rubber stock. Margolina[4] also studied the effect of contact time on the degree of autohesion of polyisobutylene and found that his results agreed with those of Priklonskaya. The experimental techniques used by Priklonskaya and Margolina were questioned and their results were only regarded as preliminary. However, the work of Voyutskii confirmed their findings with experiments which evaluated various molecular weight polyisobutylene materials[19,29] using a dynamometer. More recently Skewis studied styrene-butadiene and attained trends similar to those observed by Voyutskii on a Tackmeter[12].

All investigators have found that the degree of autohesion increases with an increase in contact time. It was observed that the degree of autohesion initially increased rapidly and then slowed as a maximum value was approached. This time dependent relationship indicates that diffusion is the basis for autohesion.

Forbes and McLeod[13] studied the contact time required to reach maximal strength at the polymer interface during the autohesion process. Their results demonstrated that some polymer systems require up to 17 hours of contact time to reach maximal strength.

Voyutskii also found a dependence on the degree of autohesion of polyisobutylene with contact pressure[6,19,29].

According to theory, pressure does not affect the extent of diffusion. However, it was found that a certain amount of pressure is required to attain maximal surface-to-surface contact of the material. Under increased pressure, surface irregularities of the particles either plastically or elastically deform and more surface-to-surface contact is achieved. The pressure at which the surface-to-surface contact is maximized corresponds to the maximum degree of autohesion[19]. Voyutskii determined that the critical pressure for polyisobutylene is 40 g/cm^2.

Voyutskii and Zamazii evaluated the temperature dependence on autohesion of polyisobutylene by using a laboratory dynamometer to measure the force of peeling[6]. It was found that the degree of autohesion increases exponentially with temperature. They attributed the rise in the degree of autohesion to faster diffusion of the polyisobutylene across the interface due to the increase in thermal motion of the macromolecules. However, this behavior was only observed at moderate temperatures. At higher temperatures the polymer may reach a state of viscous flow where complete coalescence of the polymer interface occurs very rapidly. At these higher temperatures oxidative degradation of many polymer systems can occur and affect the degree of autohesion[19,29].

The effect of milling on autohesion of high molecular weight polymers has been evaluted using polyisobutylene[6]. In this work, two portions of the polymer were milled using a roller mill for 15 minutes and 45 minutes, respectively. The samples were dissolved in benzene and the viscosity of the mixtures obtained. The material was coated onto fabric and the Voyutskii peeling test performed. The results indicate an increase in the degree of autohesion with increase of milling time. It was postulated that the increased milling time causes a decrease in the polymer particle size and decrease in the molecular weight of the polymer. This results in a decreased solution viscosity which allows the polymer to diffuse more readily. As particle size is reduced, more polymer chain ends are available for increased autohesion to occur[19]. This increase in the degree of autohesion will occur with decrease in particle size until the molecular length reaches a critical value. Below this critical length the degree of autohesion will begin to decrease.

The addition of plasticizers to high molecular weight polymers decreases the viscosity of the polymers. This causes an increase in the mobility of the polymer chain ends and increases the degree of interdiffusion across the polymer interface. Further, the plasticizer may shield the intermolecular forces between functional groups on the polymers causing the polymer to be even more fluid. While the plasticizer causes the diffusion of the polymer to increase, the plasticizer's ability to act as a intermolecular lubricant can cause the strength of autohesion to decrease. This was supported by the results of strength studies performed on polyisobutylene with various amounts of dibutylphthalate added as a plasticizer[19].

Some low molecular weight materials called pseudoplasticizers, do not increase the diffusion of the polymer chains. Instead, they tend to accumulate in the microcavities found between the polymer molecules and physically block the polymer chains from diffusing into the cavities. Therefore, the diffusion of the polymer chains decreased causing the capacity for self-adhesion to be reduced[19].

The effect on the degree of autohesion upon the addition of a solvent to a high molecular weight polymer system is very similar to the effect observed upon the addition of a plasticizer. In both cases the diffusion of the polymer chains are enhanced. However, unlike the plasticizer, the solvent can be readily evaporated which causes the viscosity of the polymer to increase. This causes a decrease in the mobility of the polymer chains which become "locked" within the microcavities into which they diffuse. Further, if the surface tension of the solvent is sufficiently high the increase in capillary pressure while the solvent is evaporating, may cause the microcavities between the polymer particles to collapse trapping any polymer chains which may have diffused into them[5,35]. This capillary pressure effect can be described via the equation of Laplace[2,5,7,25,35]:

$$P = \frac{2\gamma}{r} \qquad \text{Equation 4}$$

where P is the capillary pressure built up by the solvent between particles (cf. Figure 2) as a result of evaporation of the solvent, γ is the surface tension of the solvent and r is the radius of the polymer particles.

Other materials called fillers are often added to high molecular weight polymers. If these fillers do not behave as plasticizers or solvents then they probably reduce the ability of the polymer chains to form surface-to-surface contact with other polymer chains by physically blocking access to the microcavities. This causes a decrease in the degree of autohesion. However, if the filler is also a high molecular weight polymer, the filler polymer chains may diffuse across the interface and cause polymer-filler-polymer interactions that would give additional strength at the interface. This process is known as adhesion. If the filler interacts chemically with the polymer then several possible effects may occur[6,19]. For example, the polymer chain length may be increased or decreased and the degree of autohesion may change drastically.

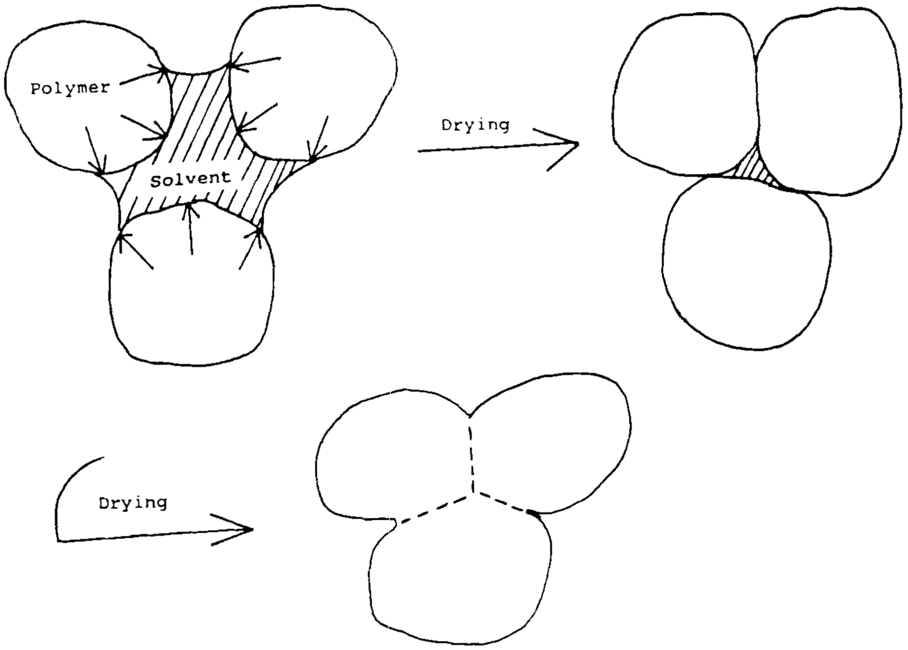

FIGURE 2
Collapse of microcavities between polymer particles due to capillary pressure caused by evaporation of solvent.

Voyutskii and Zamazii[19] studied the effect on the strength of autohesion as a function of the thickness of the polymer layers applied to the fabric. On applying the peeling test with polyisobutylene, they found that as the amount of polymer per unit area increased, the resistance to separation initially increased then leveled to a constant value. These results indicate that after a certain thickness of applied polymer, the degree of autohesion does not increase further.

For polymer systems that exhibit poor autohesion, materials known as tackifiers have been incorporated to assist in bringing the polymer molecules together by forming a polymer-tackifier-polymer adhesive interaction. The effect on the degree of autohesion of high molecular weight synthetic rubbers by the addition of tackifiers has been studied by researchers in Russia[41] and Germany[42]. The results of these studies indicate that the addition of tackifiers increases the degree of autohesion. Belcrossova, Farberov, and Epstein[43] hypothesized that tackifiers adhere to the polymer via intermolecular interactions which bring the polymer chain ends into closer proximity thus allowing the autohesion process to occur.

V. Pharmaceutical Applications

Since the vast majority of polymers utilized in pharmaceutical formulations are similar in size and structure to those used in the latex paint and rubber industries, autohesion may also contribute significantly to the physical properties of solid dosage forms which contain these polymers. Therefore, formulators of these solid dosage forms should have an understanding of the properties of polymers and the processing variables which may affect the degree of autohesion and, thus, the physical characteristics of the dosage form.

An understanding of the factors that affect the degree of autohesion, in both the wet and dry states, may assist the formulator in designing drug delivery systems with desired strengths and release profiles. Some of the pharmaceutical processing factors that could affect the degree of autohesion in the wet state are:

1. The processing equipment which could affect the degree and intensity of mixing of wet granulations (i.e. planetary mixer, high shear mixer, extrusion, marumerization, wet milling, etc.).
2. The properties of the granulating solvent (i.e. surface tension, viscosity, vapor pressure, plasticizing ability, etc.)
3. The choice of polymer (i.e. a polymer with the proper characteristics such as, particle size, degree of polymerization, polarity, degree of crystallization, etc.).
4. The method, temperature, and rate of drying granulations and coated dosage forms (i.e. oven drying vs. fluid bed drying, inlet drying temperature in coating pan, etc.).
5. The addition of plasticizers, binders and/or fillers to the solid dosage forms and/or coating formulations.

Some of the pharmaceutical processing factors that could affect the degree of autohesion in the dry state are:

1. The duration, intensity, and method of dry milling which can alter the length of the polymeric chains. This can affect the degree of autohesion by either

altering the degree of crystallinity[44,45] and/or the degree of polymerization, thus, changing the number of polymer chain ends available for diffusion.

2. The contact or dwell time and/or the speed utilized to compact the dosage form[46,47].
3. The amount of pressure applied during the manufacture of tablets.
4. The incorporation of lubricants or other excipients to the final blend of the formulation.
5. The time and storage conditions of the final dosage form.

The strengths of solid pharmaceutical dosage forms are a concern to all formulators. A major goal in dosage form development is to optimize the strength of the dosage form so that it remains intact throughout the manufacturing and shipping processes without impeding drug release. The theory of autohesion may explain how dosage forms containing high molecular weight polymers attain their strength. With knowledge of the factors that affect the autohesion process the formulator may have the ability to control them and design the delivery system in a more rational and efficient fashion.

Earlier work has shown that the strength of pellets is dependent on the properties of the granulating solvent

[48]. Further, it has been shown that the manufacturing process also will affect the strength of the final dosage form [49]. Presently, we are working with wet granulations of high molecular weight polymeric excipients and the initial results suggest that the autohesion mechanism applies to the systems we have studied. Clearly, based on the literature from the latex paint and rubber industries, and on the results of these initial series of experiments, the autohesion mechanism must be considered when dealing with pharmaceutical formulations containing high molecular weight polymeric excipients.

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