Pharmaceutical Sciences
December 2016, 22, 244-250
doi: 10.15171/PS.2016.38
http://journals.tbzmed.ac.ir/PHARM

Research Article

Engineering of Piroxicam Agglomerates by Additives Using Wet Agglomeration Technique

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Article Info

Article History:
Received: 8 June 2016
Accepted: 22 August 2016
ePublished: 30 December 2016

Keywords:
-Wet agglomeration
-Span 80
-Talc
-Binder liquid

ABSTRACT

Background: Wet agglomeration is a method wherein the crystals of dispersion are held together in aggregates by small amount of a liquid acting as an intercrystal binder. In present study, in order to study the possible modification of agglomerate structure, low concentrations of additives (0.1-1%) were added to binder liquid.
Methods: Piroxicam agglomerates were produced by wet agglomeration method by three solvent systems including a good solvent (dimethylformamide or acetone), antisolvent (water) and a binder liquid (ethylacetate or isopropylacetate). Span 80, talc, ethylcellulose and Eudragit RS in different concentrations were used as additives. The agglomerates were evaluated for production yield of agglomerates, size, friability and drug release properties.
Results: The results showed that formation of agglomerates was possible in presence of span and talc. However, no agglomerates could be obtained with polymers tested (ethylcellulose and Eudragit RS). Talc increased agglomerate size, whereas the obtained agglomerates were more susceptible to breakup. However, using span as opposed to talc resulted in agglomerates with higher strength but smaller particle size. The dissolution tests showed that both additives adversely affected the dissolution rate of piroxicam from the agglomerates.
Conclusion: Result of this study suggested that additives even in small amounts played a major role in agglomerate properties.

Introduction

One interesting crystallization technique in which synthesis, crystallization, separation and agglomeration can be achieved at once has been defined as wet agglomeration. In this method limited quantities of an agglomerating inducing liquid named binding liquid are used to get agglomerates of crystals. The binding liquid is immiscible with the crystallization system, but able to wet the crystals and gather them without any chemical effect.[1-6] The chance of agglomeration of crystals during crystallization process supplies a very simple and economical way to particulate design for engineering pharmaceuticals and chemicals and present many benefits for the following processing and handling of the particles. Indeed, this technique can promote the effectiveness of mixing, filling and tabletting procedures via producing agglomerates with improved physicomechanical properties like compressibility, packability and flowability.[7,8] This method is also reputed to increase dissolution rate of various drugs.[9,10] In spite of many advantages of this method, it is still not widely used in industry because the mechanisms of this technique have not been fully clarified. Some studies dealing with wet agglomeration were carried out to assess the effect of agglomeration variables such as stirring speed, temperature of operation,[11] amount of binder liquid and injection means,[12] the crystal size on the properties of the prepared agglomerates.[13] However, lack of complete understanding the effect of method variables on the agglomerates properties lead to difficulties in managing the procedure that let making of agglomerates with preferred properties. Many studies showed that the presence of low concentrations of an additive in the crystallization system can noticeably modify the crystal character.[14] In this study we focused on the influence of various additives on the wet agglomeration procedure. For this aim, four additives including span80, ethylcelloluse, eudragit RS and talc displaying a range of typical properties were added to binder liquid. Knowledge of the

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basic correlation between the additives used in binder liquid and changing the agglomerates properties will let conducting of agglomeration procedure in a controlled way to make agglomerates with preferred properties as well bring more insight into the mechanisms of wet agglomeration.

Materials and Methods

Piroxicam (Shasun Chemicals & Drugs, India), Eudragit RS100 (Rohm GmbH, Germany), ethylcelloluse (Sigma-Aldrich), talc (Shandong Yuwang Chemical, China), and span 80 and all solvents (Merck, Germany) were used.

Crystallization system

Dimethylformamide and acetone were chosen as good solvents and piroxicam (0.5 g) was dissolved in 5 ml of each of these solvents. Then, the obtained solutions were added immediately into 95 ml of water placed in a cylindrical vessel (250 ml) equipped with three baffles under agitation (400rpm) using a propeller type stirrer. After 5 min agitation the solvent used as a binder liquid was introduced into the crystallization medium in a drop wise manner (during 5 min) and agitation continued for 10 min. Ethylacetate (EA) and isopropylacetate (IPA) were used as binder liquid for dimethylformamide and acetone, respectively. The agglomerates were separated from the solution through filtration under vacuum and then were placed in a thin layer in an oven at 60°C for 3 h. Experiments were also performed with four different additives added to binder liquid including Span 80, talc, ethylcellulose and Eudragit RS at various concentrations (0.1, 0.5 and 1% w/v) .

The agglomerates characterization

Determination of yield and drug content of agglomerates

All agglomerates were prepared in triplicate. Agglomerates dried at 60 °C for 3 h were then weighed and the yield of preparation of agglomerates was calculated using the formula:

$$Agglomeration\ yield\ (\%) = \frac{Total\ mass\ of\ obtained\ agglomerates}{Total\ mass\ of\ raw\ materials} \times 100 \qquad \text{Eq.(1)}$$

The drug content was determined by dispersing a specified weight from each system in dimethylformamide with the aid of magnetic stirring for 15 min. solution were filtered and absorbance of piroxicam was measured spectrophotometrically (UV-160A, Shimadzu, Japan) after doing the appropriate dilution. The results were the mean of three determinations.

The particle size

Pictures of at least 60 particles of the agglomerates were taken using a CCD camera (Canon digital, Japan) connected to a light microscope (Nikon Labophot, Tokyo, Japan) and subsequently analyzed by an Image analyzing software (scion image 4.0.3.2 Alpha). The average particle size of a single particle was defined as the average length of the distance measured at two degree intervals joining two outline points passing through the center of gravity of the particle.

Friability

Friability of agglomerates was performed by subjecting agglomerates to attrition for 1h. The friability of the agglomerates was determined by weighing 1 g (I_{wt}) of initial agglomerates (250–1000µm) in a 100 ml container and then rotating at a speed of 145 rpm. At present time intervals, the weight retained on a 250µm sieve (F_{wt}) was determined after vibrating for 5 min at an amplitude of 2 mm. The friability was calculated:

as $((I_{wt}-F_{wt})/I_{wt})\times 100$ Eq.(2)

The measurements were made in triplicate.

In Vitro Drug Release Study

The level of drug release from agglomerates having diameters of between 500 and 700 µm was measured by the paddle method at 100 rpm in simulated gastric pH (pH =1.2). Equal 10 mg of agglomerates was dispersed in 900 ml dissolution medium. Perfect sink conditions prevailed during the drug release studies. Five ml sample was withdrawn and the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. Samples passed through a 5 µm membrane filter (Millipore), and analyzed spectrophotometrically employing a UV detector (UV-160A, Shimadzu, Japan) at 333 nm to determine the concentration of drug. All experiments were conducted in triplicate.

Statistical evaluation of data

Quantitative data were reported as the mean and standard deviation of at least three determinations. Statistical analysis was performed using the analysis of variance (ANOVA). Comparison between the two means was determined using the Tukey's test with statistical significance evaluated at $P < 0.05$.

Results and Discussion

Mechanism of agglomeration

The agglomeration of crystals in suspension comprises a ''wetting'' step followed by a fast-growth step. In the wetting step, crystals get in touch with binding liquid droplets, which results in the generation of agglomerate nuclei acting as precursor sites.[15]

In fact, binder liquid droplets wet the connected crystals and the agglomeration of crystals initiated immediately after the addition of the binding

liquid. The wetted crystals interrupt the binder liquid/crystallization system interfaces, move progressively towards the center of the droplet. Binder liquid dissolves partially the entrapped crystals and forms the binder liquid solution layer on the surface of these crystals.[16] Before saturation of the crystallization system with the binder liquid, the binder liquid diffuses into the crystallization system. This diffusion process causes a decrease in crystal solubility in the binder liquid, lead to the recrystallization (reprecipitation) of the dissolved crystals and a solid bridge creation between the primary crystals by fusion.[17] When the wetting step ended, and all crystals are took out of crystallization system, the fast-growth step begins consisting of the enlargement and compaction period by means of collision and coalescence of the agglomerates.[18] Compaction could be happened as a consequence of forces introduced by impacts between dispersed nuclei.[15,19] For enlargement to happen, compaction must progress to the point where the fraction of binder liquid saturation of the nuclei to be sufficient to permit the nuclei to stick and coalesce. In fact, the agglomerates densify corresponding to their enlargement by coalescence. It is obvious that coalescence terminates when the agglomerates develop into too dense to be arranged during the impact.

Agglomeration possibility with additive

With the purpose of modify efficiency of binder liquid, additives were selected in accordance with different strategies. It was noticeable that the experiments were done such a way that the agglomeration of crystals was possible without any additive. Firstly, binder liquid soluble additives able to increase viscosity of binder liquid were selected: Ethylcelloluse (EC) and Eudragit RS. The second approach was intended to make various interfacial tensions between binder liquid and dispersing system. Span 80 was selected for this purpose. Finally, the third type of additive was talc. This additive has hydrophobic nature and non binder liquid soluble. The results indicate that the procedure is possible with span and talc, whereas the EC and Eudragit RS obstructed the agglomeration. In late cases, a pasty mix was obtained which adheres to the wall of the container. The non possibility of agglomeration of crystal in presence of EC and Eudragit RS can be explained as follows, in term of second step of agglomeration process. As mentioned before, compaction of agglomerate nuclei is a decisive process. Indeed, the agglomerates to form suitably the nucleis must be sufficiently compacted and possess more than a minimum strength, in order to endure the impact forces imposed during the agglomeration procedure. From the viewpoint of mechanisms, some similarity can be between wet agglomeration and wet granulation method since the nucleation and enlargement of nucleis, also be present in wet granulation.[20] In wet granulation, which is more widely used in industry, it has been demonstrated that the compaction of nuclei possibly mainly hindered by viscous forces, when the viscosity of the binder liquid is high.[21-23] In present work, no creation of agglomerates by using EC or Eudragit RS perhaps also related to this fact. The compaction of nuclei of agglomerates is retarded due to high viscosity of binder liquid by using the polymers such that the nuclei cannot adequately account for energy dissipation by internal deformation and therefore, breakage happens and a paste is obtained. Indeed, in this discussion the theory is made that it is the impact strength of the nuclei which is the main factor which determines whether or not agglomerates form.

Table 1. Production yield, mean particle size and drug content of agglomerates.

Samples	Production yield (%) ±SD	d_{ln}±σ (µm)	Drug content (%w/w) ±SD
EA	76.9±6.4	1300± 181	99.8±0.2
EA(Talc 0.1%)	71.3±1.8	1324± 168	99.5±0.2
EA(Talc 0.5%)	72.3±3.5	1364± 238	97.8±0.3
EA(Talc 1%)	73.0±5.6	1395± 258	94.5±0.5
EA(span 0.1%)	57.0±4.6	1280± 280	98.2±0.2
EA(span 0.5%)	62.7±3.5	1253± 172	96.4±0.3
EA(span 1%)	68.3±5.8	1160±145	91.9±0.5
IPA	76.3±5.5	710±180	99.88±0.2
IPA(Talc0.1%)	74.7±3.1	718±228	99.2±0.3
IPA(Talc0.5%)	72.7±4.1	754±227	97.1±0.3
IPA(Talc 1%)	71.3±8.5	758±189	94.3±0.2
IPA(span0.1%)	58.0±5.0	697±275	98.6±0.2
IPA(span0.5%)	58.7±3.1	692±158	96.5±0.5
IPA(span 1%)	57.7±4.0	630±205	92.0±0.5

Determination of yield and drug content of agglomerates

The amount of drug in the agglomerates for the formulations is reported in Table 1.

The amount of additive was taken as the difference between weight of agglomerates and the determined content of drug. The incorporation of the additives in the agglomerates increased accordingly as the additive amount in the binder liquid increased. For instance, span inclusion increased approximately from 2% to 8% as its percent in the binder liquid increased from 0.1% to 1% (w/v). Span as a soluble additive in binder liquid was included to the lower degree in comparison to talc ($p<0.05$). Lower incorporation of span as a surfactant may be attributed to loss of

this additive due to its cumulating in interface of binder liquid and crystallization medium.

Table 1shows the results of determining agglomerates yield. The results show that talc did not significantly influence the production yield of the agglomerates ($p > 0.05$). However, inclusion of surfactant into binder liquid resulted in lower yields of agglomerates ($p<0.05$), although the obtained agglomerates were stronger. This result may be related to effect of surfactants on drug solubility. Partial solvate of the crystals due to increasing solubility of drug by span leads to decreasing crystal content and consequently yield of the agglomerates.

The particle size

Table 1 indicates that smaller agglomerates formed by adding surfactant to binder liquid. The surfactant concentration would possibly affect on the final particle size of the agglomerates by changing the initial droplet size of the binder liquid. Decreasing the interfacial tension between the binder liquid and crystallization medium with the rising of surfactant concentration may led to the creation of smaller agglomerate nuclei and subsequently smaller final agglomerates. The reverse results were obtained for talc. By increasing talc concentration in binder liquid, particle size of the agglomerates enlarged.

It is supposable that entrapment of the fine insoluble talc particles through drug crystals resulted in decreasing the capillary space between the drug crystals. Smaller the capillary diameter, based on Poiseuille's law[24] resulted in increasing capillary pressure, driving force to liquid flow through capillary. It is obvious that a higher capillary pressure will result in acceleration of binder liquid flow to the surface of nuclei and increasing the chance of coalescence and subsequently the growth. Larger agglomerates formed with the incorporation of talc may also be the result of an increase in interfacial tension between binder liquid and medium in presence of hydrophobic talc, which consequently increases initial binder droplet size and accordingly final agglomerates size, as explained above.

Friability

Agglomerate strength is the most important feature in any size enlargement method. It has been shown that two factors play important role in the compressive strength of the agglomerates: loading the crystals compactly in the agglomerates and creation of solid bridges between the primary crystals.[12]

Results showed (Figure 1) that adding surfactant to the binder liquid made a significant difference in the friability of the prepared agglomerates ($P< 0.05$) in the manner that by increasing in the concentration of this additive in binder liquid the agglomerates were able to resist the shear rate more strongly. Physically powerful structure of these agglomerates may be related to positive effect of surfactant on the wetting step of agglomeration procedure. As explained before, in the first stage of the agglomeration, wetting stage, the binder liquid must wet the crystals. It is assumable that this stage to be accelerated by using wetting agents, i.e., surfactants. Once the binder liquid enters the suspension of crystals, a layer of crystals covers each droplet of the binder liquid. This coat hinders the immediate wetting of other crystals. The adhered crystals interrupt the interfaces between the binder liquid and crystallization system, move progressively towards the core of the droplet and gradually release surface for other crystals.[25] It is assumable that a surfactant by lowering the binder liquid / crystallization medium interface can increase speed the diffusion of crystals through the interfacial tension between the binder liquid and the crystallization medium and consequently leads to more intense packing of the crystals within the nuclei. It is clear that gathering the primary crystals more tightly in agglomerates leads to higher mechanical contribution and thus higher compressive strength of the agglomerates.

On the other hand, lower interfacial tension between the binder liquid and the crystallization medium results in smaller dispersion of binder liquid droplets. Finer binder liquid droplets present a higher potential for wetting of crystals and formation of denser nuclei, as a result of higher surface area existing for the wetting. Wet agglomeration of toner in order to deinking of toner-printed paper has demonstrated similar results. In this study, it has been shown that added surfactant in binder liquid and the wetting behavior of the binder liquid has an important role in compressive strength of the agglomerates. Formation of stronger agglomerates in presence of surfactant may also be attributed to probable consequence of surfactant on generation of solid bridges during agglomeration process. Considering the formation mechanism of crystalline bridges, as mentioned previously, it is assumable that by increasing solubility of drug in the binder liquid in presence of surfactant, recrystallization process of the crystals was accelerated which in turn led to creation of more crystalline bridges and accordingly formation of stronger agglomerates.

Presence of talc imparted poor strength to agglomerates and obtained agglomerates showed higher friability ($p<0.05$) compared to agglomerates prepared without additive.

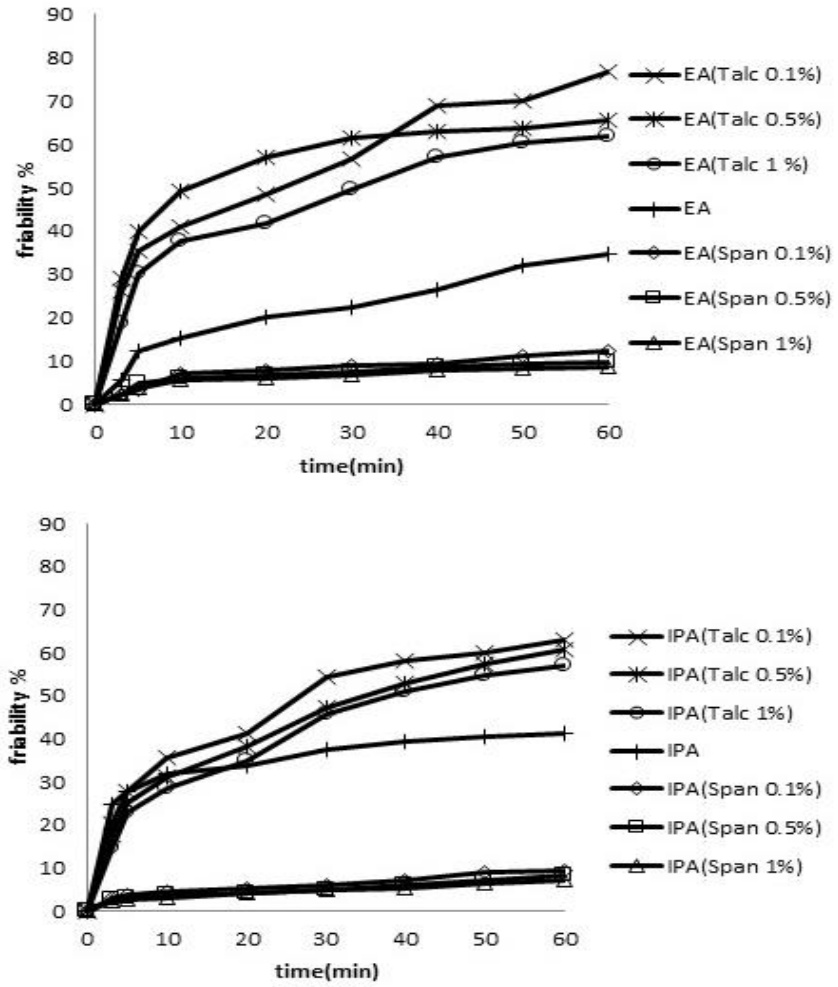

Figure 1. Friability of agglomerates prepared with EA and IPA.

This could be explained as a consequence of weak wetting process. It is supposable that talc due to hydrophobic nature causes higher interfacial tension between binder liquid and aqueous crystallization medium. As explained previously, higher the interfacial tension adversely influences the wetting step. Looser structure of these agglomerates is expectable from the hypothesis that agglomeration is mainly limited by the ability of the crystals to interrupt binder liquid droplets and suggesting again that the wetting behavior of the binder liquid had a major influence on agglomerate texture.

In Vitro Drug Release

Figure 2 illustrates the release profile in terms of drug percentage. The dissolution tests were performed using the agglomerates in range of 500 to 700 µm. Piroxicam dissolution rate from control agglomerates appeared slow with less than 60% dissolving in 120 min. Poor solubility of piroxicam at acidic pH may be responsible of this slow dissolution rate. Piroxicam is a weak acid with pK_a 6.3 and so the amount of ionized drug is of the order of 2.5×10^{-6} at pH 1.2. The low ionization of drug at pH 1.2 may be responsible of the partial release of drug in this medium.[26] Considering porous structure of the agglomerates, it would be assumable that the agglomerates to have high surface area to contact with dissolution medium and, indeed, dissolution is supposed to occur from agglomerates surface in direct contact with the dissolution medium as well as from distribution through the water filled pores of the agglomerates. It is supposable that the release of drug from different formulations in SGF provides an idea about the effect of additives content on drug release from the agglomerates; the higher the additive content in agglomerates, the lower the drug release ($p<0.05$). In the case of talc, the retarded rate of water penetration in the presence of embedded hydrophobic talc might have contributed to drug release retardation.[27] However, when surfactant was added to binder liquid, the dissolution rate of drug from the agglomerates was lowest which may be due to positive effect of span on solidifying of agglomerates as discussed previously. It is expected that by higher densifying of agglomerates, penetration of SGF in the agglomerates would be lower and consequently dissolution rate decreased.

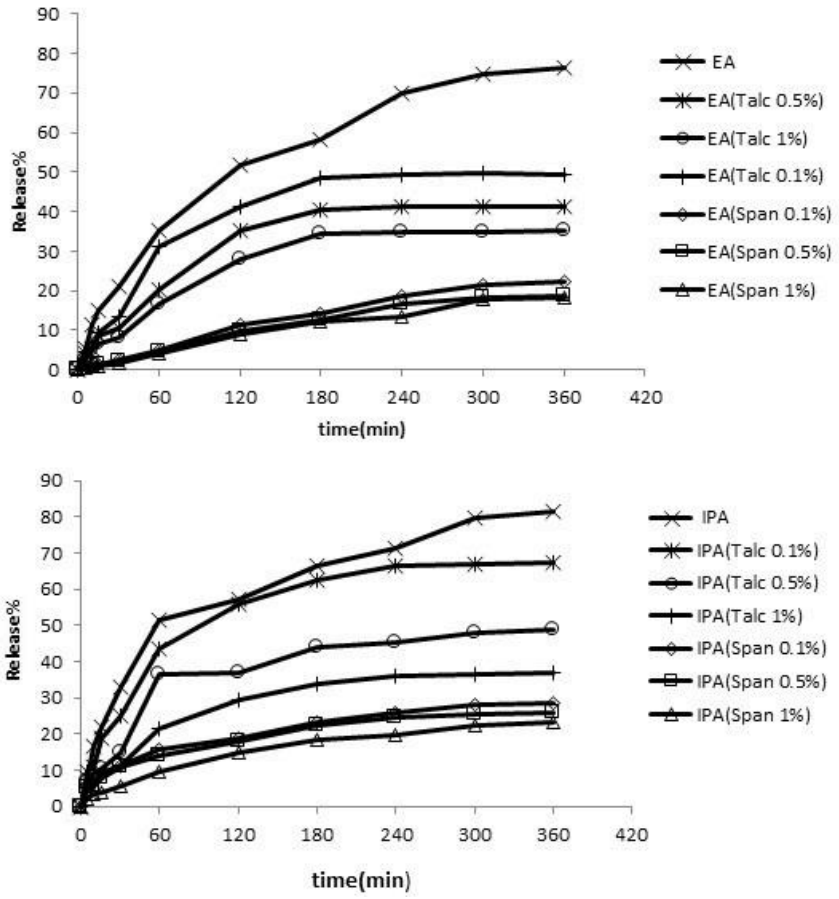

Figure 2. Release of piroxicam from agglomerates prepared with EA and IPA in pH=1.2.

Conclusions

In particular the aim of this work is to make relationship between properties of binder liquid induced by additives and obtained agglomerates. Additives in low concentrations could effectively modify the binder liquid ability to agglomerate the crystals by their potential to change the viscosity and /or the interfacial tension of binder liquid with crystallization medium. It is concludable that numerous liquids can be poor binding liquids when used alone, but they can be admirable binding liquids when an appropriate additive was used.

Acknowledgement

The financial support from the research council of Tabriz University of Medical Sciences is greatly acknowledged.

Conflict of interests

The author claims that there is no conflict of interest.

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