PREVENTION OF CRYSTAL GROWTH IN ACETAMINOPHEN SUSPENSIONS BY THE USE OF POLYVINYL PYRROLIDONE AND BOVINE SERUM ALBUMIN

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ABSTRACT

The ability of polyvinyl pyrrolidone (PVP) and bovine serum albumin (BSA) in inhibition of the crystal growth in suspensions containing Acetaminophen as a model drug was evaluated. For this purpose sedimentation volume, resuspendability, cake formation, particle size distribution, volume surface diameter (d_{vs}), and crystal growth after freeze-thaw cycling of the several suspensions were evaluated. ANOVA followed by Tukey test was used to determine significant differences ($P<0.05$). PVP in comparison with BSA showed a better crystal growth inhibition and at concentrations of 50-100 mg/100 ml inhibited crystal growth over 150 days. The combination of PVP and BSA showed an inhibition of acetaminophen crystal growth after 45 and 150 days respectively. The combination of PVP (50 mg/100 ml) and BSA (80 mg/100 ml) showed interesting results regarding sedimentation volume, resuspendability, prevention of cake formation, and crystal growth inhibition; and offer new perspectives in the preparation of suspensions.

Keywords: Acetaminophen suspension, Crystal growth inhibition, Polyvinyl Pyrrolidone, Bovine Serum Albumin,

INTRODUCTION

Oral suspensions are dosage forms that supply insoluble and often distasteful substances in a form that is pleasant to the taste (1). Also degradation of a drug in the presence of water may preclude its use as an aqueous solution and in this case it may be possible to synthesize an insoluble derivative of the drug and to formulate it as a suspension. In addition, some materials are required to be present in the gastrointestinal tract in a finely divided form and formulation of them as suspensions will provide the desired high surface area (2). Preparation of pharmaceutical suspensions is often associated with problems of physical stability (3). sedimentation, caking, and difficulty of dispersibility of sediment and crystal growth often occur (4,5). The resuspendability associated with flocculation-deflocculation behavior of drugs and the polymer-induced flocculation has been of great interest since most pharmaceutical suspensions contain hydrophilic polymers as suspending agents (6-8). Surfactants are generally added to dispersion media in order to maintain uniform dispersibility (9-11). Crystal growth in pharmaceutical suspensions may cause a drastic change in the particle size distribution that might affect physical stability and bioavailability of suspensions (12,13). It is well known that aggregation of particles, settling rate and density of sediment depends upon the choice of the excipients, their concentration, as well as concentration and particle size distribution of active ingredients (14). A number of additives such as surfactants (15,16,11), polyvinyl pyrrolidone (17,18), benzalkonium chloride (19), sucrose esters and low substituted n-octenyl succinate esters of waxy corn starch (7) have been proposed to prevent crystal growth. Bovine serum albumin (BSA), a peotein type polymer is also effective in crystal growth inhibition of some materials (18).

This study reports the use of polyvinyl pyrrolidone (PVP) and bovine serum albumin (BSA) as crystal growth inhibitors and advantages of these materials for their synergistic effects on inhibition of crystal growth of acetaminophen as a model drug.

MATERIALS AND METHODS

Materials

Acetaminophen with particle size of less than 125 µm was received from Zahravi Co. (Tabriz, Iran); Tween 80 (HLB 15), Methyl and Propyl

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Paraben, Glycerin, Propylene glycol, and Polyvinyl Pyrrolidone (PVP, MW = 25000 d), were purchased from Merck Co. (Germany). Bovine Serum Albumin (BSA) was received from Raritan Co. (New jersey, USA). Microcrystalline cellulose (Avicel RC-591) was purchased from Dow Chemical Co., USA.

Preparation of suspensions

Suspensions which were investigated in this study contained 3.2 %(w/v) of acetaminophen and 2.5% (w/v) Avicel as suspending agent. Methyl Paraben (0.18% w/v) and Propyl Paraben (0.02% w/v) were used as preservative agents. The tensioactive agent (Tween 80) was used at a concentration of 0.4% (w/v). Propylene glycol and glycerin were used as wetting agents, at the concentration of 5% (w/v). PVP and/or BSA were used at a concentration range between 10-100, and 50-100 mg per 100 ml of suspension, respectively (Table 1).

For the preparation of suspensions, the Avicel and Tween 80 were initially dispersed in water containing the preservative agents. In the next step, acetaminophen which was wetted by glycerin and propylene glycol, was added to the vehicle and dispersed with a double bladded mixer (Ika-werk, Germany) by stirring at 300 rpm for 20 minutes. Finally PVP and/or BSA were added to the mixture.

The suspensions were transferred to the stoppered 100ml graduate glass cylinders and stored at room temperature under static conditions.

Evaluation of suspensions

Sedimentation volume

The sedimentation volume (F factor) was measured in 100 ml graduated glass cylinders. Each suspension was shaken to ensure uniform dispersion prior to the sedimentation study. The sedimentation volume was recorded at 0, 45, and 150 days storage periods for three samples of each formulation. Sedimentation volume was expressed as the ratio between the height of the sediment at the specified time of evaluation and the height of the suspension at the time of 0.

Resuspendability

The resuspendability of suspensions was evaluated qualitatively. The test was performed by shaking the cylinder manually at 180° movement, after sedimentation was completed (for three samples). Based on the numbers of shaking required to convert the sediment to uniformly dispersed suspension, the formulations were evaluated. Cake formation was also evaluated qualitatively. In formulations which had resuspendability more than 10 times, the cake formation were considered as "+".

Particle size determination

The particle size of all formulations (three samples) was determined using light microscope (an Olympus BH-2 microscope, Japan) equipped with a camera. Two hudreds particles (in different fields) were observed per sample for their size distribution after vortexing the formulation for 1 min. The photograph was then taken from sample and Feret's diameter was measured. The size of 200 acetaminophen crystals were determined at 0, and after 45 and 150 days for three samples. Mean diameter of particles were calculated based on the volume-surface mean (d_{vs}) by the following equation:

$$d_{vs} = \Sigma nd^3 / \Sigma nd^2$$

in which "n" is the number of particles in certain range of particle size with mean of "d". This diameter is important pharmaceutically because it is inversely related to S_w, the specific surface (1).

Freeze-thaw cycling test

All formulations were frozen at -4°C and thawed at +20°C, for 6 times and the crystal growth was evaluated by direct microscopic observation using an Olympus BH-2 microscope (Japan) equipped with a camera.

Statistical analysis

ANOVA followed Tukey test was used to determine significant differences between groups and "$p<0.05$" was considered significant.

RESULTS

Sedimentation volume and resuspendability

Results of the measurement of sedimentation volume (F factor), resuspendability and cake formation at 45 and 150 days after formulation are summarized in table 2. These results show that sedimentation volume for those suspensions containing both PVP and BSA (MS10 & MS11); were greater than formulation of MS1, which had none of these additives. These observations were more significant after 150 days. In other formulations, PVP at concentration of 100 mg/100 ml (MS6) showed significant differences in sedimentation volume (F factor) in comparison with MS1.

Particle size distribution

In this study particle size data were built on the basis of numbers and are presented as a plot of

the cumulative percentage frequency oversize against mean diameter at various time intervals. Fig. 1 compares evolution of crystal size distribution of suspensions containing PVP (at a concentration range between 10-100 mg) in comparison with suspensions without PVP. Crystal size distribution in all suspensions containing PVP showed smaller evolution than formulation MS1. Fig 2 shows the crystal size distribution of acetaminophen suspensions prepared by increase in concentration of BSA. These results show that evolution of acetaminophen crystal size distribution didn't decrease by increase in the BSA concentration. Fig 3 compares the evolution of acetaminophen crystal size distribution in suspensions containing different amounts of both PVP and BSA. Results showed that these formulations, had the least evolution of crystal size distribution in comparison with other suspensions.

Table 1. Composition of formulations

[a]Formulation	PVP (mg/100 ml)	BSA (mg/100 ml)
MS1	-	-
MS2	10	-
MS3	30	-
MS4	50	-
MS5	60	-
MS6	100	-
MS7	-	50
MS8	-	100
MS9	50	50
MS10	50	80
MS11	100	50

[a] Acetaminophen (3.2% w/v), avicel (2.5% w/v), glycerin (5% w/v), propylene glycol (5% w/v) and Tween 80 (0.5% w/v) in preserved water.

Volume-surface diameters of acetaminophen particles in formulations at the time of zero, 45 and 150 days periods are presented in Table 3. These results show that the highest crystal growth was observed in MS1 (without PVP or BSA) and the lowest growth was observed in formulation of MS10 (containing 50 mg PVP and 80 mg BSA). Employing PVP at concentration more than 50 mg/100 ml inhibited crystal growth.

Figure 4 shows the microscopic photographs of particles in suspensions due to freeze- thaw cycling. These results show that crystal growth in suspension of MS1 was higher than other formulations. PVP had inhibitory effect on the crystal growth either by itself or in combination with BSA.

DISCUSSION

Redispersibility is one of the major considerations in the assessment of a suspension, and after formation should be easily dispersed by moderate shaking to yield a homogenous system. Measurement of the sedimentation volume and the ease of the redispersion form are two methods of the most common basic evaluative procedures (20). Table 2 shows the sedimentation volume (F), resuspendability (Res.) and cake formation in formulations containing PVP and/or BSA in different concentrations. Except formulation MS1 that contained no PVP or BSA ($p<0.001$), the sedimentation volume of other formulation did not change significantly from 45 to 150 days ($p>0.05$). There was not any increase in sedimentation volume in formulations MS2-MS6 (by increasing the amount of PVP) after 150 days ($p>0.05$). However when PVP concentration increased from 10 mg (MS2) to 100 mg (MS6), a significant increase in F factor was observed after 45 days ($p<0.001$). The effect of PVP on sedimentation volume in comparison with MS1 (without any PVP) was observed in formulation of MS6 containing 100 mg of PVP after 150 days ($p<0.01$). Other formulations with different concentrations of PVP didn't show any significant effect on F factor in comparison with MS1. Utilization of BSA alone didn't show any significant effect on sedimentation volume. Formulations MS10 and MS11 which contained both PVP and BSA, showed a significant increase in F factor after 150 days in comparison with MS1 ($p<0.001$). This effect for both MS10 and MS11 were the same ($p>0.05$). A comparison of MS7 with MS11 show that in the presence of PVP, differences between sedimentation volumes after 45 and 150 days were significant ($p<0.001$). These differences were not observed when MS7 and MS9 are compared. The comparison of MS4 with MS9 and MS10 (containing 50 mg PVP) showed that in the presence of BSA (80 mg), there was a significant difference in F factor after 150 days ($p<0.001$). Evaluation of sedimentation volumes in formulations MS6 and MS11 (containing 100 mg PVP) didn't show any significant difference. Total evaluation of these formulations showed that suspension MS10, containing PVP (50 mg) and BSA (80 mg) had greatest sedimentation

Table 2 Results of evaluation of sedimentation volume, resuspendability and cake formation

Formulation	[a] After 45 days (n=3)			After 150 days (n=3)		
	[b] F	[c] Res.(time)	Cake [d]	F	Res.(time)	Cake
MS1	0.930 ± 0.029	3.0 ± 1.7	-	0.770 ± 0.045	4.0 ± 2.9	-
MS2	0.840 ± 0.045	3.0 ± 0.0	-	0.800 ± 0.076	13.0 ± 4.5	+
MS3	0.880 ± 0.062	2.0 ± 1.7	-	0.820 ± 0.107	3.3 ± 2.6	-
MS4	0.920 ± 0.061	1.7 ± 1.9	-	0.833 ± 0.038	15.3 ± 2.6	+
MS5	0.936 ± 0.073	3.7 ± 1.9	-	0.793 ± 0.066	16.0 ± 4.5	+
MS6	0.996 ± 0.010	2.3 ± 1.0	-	0.900 ± 0.062	15.0 ± 4.5	+
MS7	0.830 ± 0.069	5.3 ± 2.6	-	0.806 ± 0.095	5.7 ± 2.6	-
MS8	0.853 ± 0.036	2.7 ± 1.0	-	0.830 ± 0.035	14.0 ± 1.7	+
MS9	0.920 ± 0.052	5.3 ± 2.6	-	0.873 ± 0.066	12.0 ± 4.5	+
MS10	1.000 ± 0.000	1.0 ± 0.0	-	0.990 ± 0.017	2.3 ± 2.9	-
MS11	1.000 ± 0.000	1.0 ± 0.0	-	0.980 ± 0.173	3.0 ± 1.7	-

[a] Evaluations were performed for three samples of each formulation; [b] F factor (mean ± S.D.); the ratio between the height of sediment at time of evaluation and the height of the suspension at time zero; [c] Res. (resuspendability, mean ± S.D.); the number of times of shaking under 180° for homogeniziatior of the suspensions, [d] Cake: cake formation

Table 3. Volume-surface diameter (d_{vs}) of acetaminophen particles in suspensions at time zero, 45 and 150 days at room temperature without shaking;

Formulation	d_{vs} μm (mean ± S.D)		
	Day zero	Day 45	Day 150
MS 1	100.9 ± 2.2	161.9 ± 2.8	188.1 ± 7.6
MS 2	98.7 ± 2.9	153.1 ± 3.1	176.2 ± 5.0
MS 3	99.3 ± 1.2	150.1 ± 2.4	174.1 ± 6.6
MS 4	102.3 ± 3.1	145.0 ± 2.2	169.7 ± 3.6
MS 5	101.1 ± 2.8	140.8 ± 3.8	163.7 ± 4.1
MS 6	98.2 ± 1.6	134.1 ± 2.8	151.2 ± 2.6
MS 7	101.2 ± 3.1	158.2 ± 6.7	183.2 ± 7.9
MS 8	101.7 ± 2.8	153.9 ± 2.8	181.7 ± 5.4
MS 9	99.9 ± 3.3	156.3 ± 4.2	132.9 ± 2.8
MS 10	102.7 ± 2.9	125.9 ± 3.1	143.1 ± 3.1
MS 11	101.4 ± 3.1	128.1 ± 3.5	146.2 ± 4.1

volume in comparison with MS1 (q=11.365 and $p<0.001$). Adsorption of PVP to acetaminophen particles can increase controlled flocculation. The mechanism of flocculation is based on bridging and involves interaction of polymer molecules which are adsorbed on different particles of acetaminophen. PVP at certain concentration can form half coverage of particles for controlled flocculation (18). In this investigation PVP at concentration more than 60 mg/100 ml showed this effect, but the mechanism of BSA effect, in the presence of PVP, is not known. Since dilute suspensions tend to settle, resuspendability is an important quality of the formulation. Table 2 shows redispersibility and cake formation of investigated suspensions. In all suspensions, no cake formation was observed after 45 days; but after 150 days period, caking were observed in some formulations. In formulations which contained PVP (MS2-MS6), with exception of MS3 (which contained 30 mg PVP), other suspensions showed cake formation. Resuspendability in this formulation was less than others ($p<0.001$). Utilizing BSA showed that in concentration of 50 mg, there was no cake formation after 150 days. This phenomenon were observed for MS9 but the

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best situation were observed in suspensions MS10 and MS11. Evaluation of resuspendability showed that formulations MS10 and MS11 had the least resuspendability (q = 13.023 and 12.276 respectively). No significant difference of resuspendability was observed between MS11, MS10, MS7 and MS3. In addition, combination of PVP and BSA showed suitable effect on redispersibility.

Crystal growth in pharmaceutical suspensions may cause problems in the stability and bioavailability of suspensions. Several authors described influence of PVP and other additives on crystal growth inhibition. Crystal growth can be minimized by utilizing the open network aggregate (floccule) suspension type, since particles can not sediment to a close proximity because of the rigidity of the aggregate. PVP can provide this network and inhibits the crystal growth (17, 18, 15, 7). The rate of crystal growth depends to a variety of parameters such as the solubility of the drug (i.e. the saturation concentration), temperature, the degree of supersaturation, and the temperature difference on storage and the frequency of temperature cycling. Any mechanical stress such as stirring must also be considered. Significant influences on both dissolution and crystalization are exhibited by PVP K 30 and PVP K 60 (18). Fig. 1 compares particle size distribution of formulations containing different amounts of PVP in comparison with MS1 which had no PVP and BSA. PVP in concentration between 50-100 mg inhibited crystal growth in suspensions under study. Based on results that are shown in table 3, an increase in the concentration of PVP had a significant effect on volume-surface diameter. In the presence of PVP at concentrations above 50 mg, a decrease in the crystal growth was observed after 45 days in comparison with MS1 ($p<0.01$ for MS4 and $p<0.001$ for MS5 and MS6). After 150 days, this decrease was observed for suspensions containing PVP in concentration above 30 mg ($p<0.05$ for MS3 and $p<0.001$ for MS4, MS5 and MS6). There were no differences between MS 5 and MS 6 ($p>0.05$) by increase in concentration of PVP from 60 mg to 100 mg after 150 days period; but differences were observed for MS4 and MS6 after 150 days ($p<0.001$). While in another investigation, it has been shown that PVP in concentration in excess of one percent inhibited crystal growth rate in sulfathiazole suspension (17), in this study crystal growth inhibitory effect of PVP was observed in lower concentration. Difference between suspending agents and presence of tween 80 in all of investigated suspensions may explain this phenomenon. It has been shown that PVP alone hardly absorbs on some suspended particles, and adsorption of PVP can be enhanced by coadsorption of surfactants (like sodium dodecyl sulfate) on dispersed particles. This effect has been observed in stabilization of alumina suspension (20).

Fig. 2 compares the evolution of particle size distribution in formulations containing BSA in concentration of 50 and 100mg respectively. These amounts of BSA didn't show any inhibitiory effect on crystal growth in comparison with suspensions without PVP or BSA (MS1) after 45 and 150 days ($p>0.05$).

Fig. 3 compares evolution of acetaminophen particle size distribution in suspensions containing both PVP and BSA. In all investigated formulations (MS9, MS10 and MS11), an inhibition on crystal growth was observed after 45 and 150 days ($p<0.001$). There was no significant in inhibitory effect on crystal growth of these formulations ($p>0.05$). It seems that BSA can inhibit crystal growth by interaction with drugs in aqueous solution and affects supersaturation degree (18). Comparing d_{vs} of suspension of MS7 with those of MS9 and MS10 (which contained 50 mg PVP) showed that there was no difference in crystal growth of formulations MS7 and MS9; but the difference between MS7 and MS10 was significant ($p<0.001$). On the other hand, an increase in concentration of BSA from 50 to 80 mg led to this difference, which shows the inhibitory effect of BSA on acetaminophen crystal growth in combination with PVP. Specific and strong interactions between functional groups of the drug and polymer are obviously a necessary, but not a sufficient, prerequisite to inhibit crystalization from supersaturated solutions of the drug suspensions. The second essential property of a protective substance seems to be formation of a polymer adsorbate on the surface of the drug crystals. It may be assumed that the structure of PVP and BSA adsorbates which are formed on acetaminophen in water as a good solvent are responsible for the crystallization-inhibition effect. The polymer is hydrated to a great extent in the adsorbate and attached to the crystal surface by some segments, which are called trains, and as a result water molecule remains in permanent contact with the crystal surface. By raising temperature, the dissolution

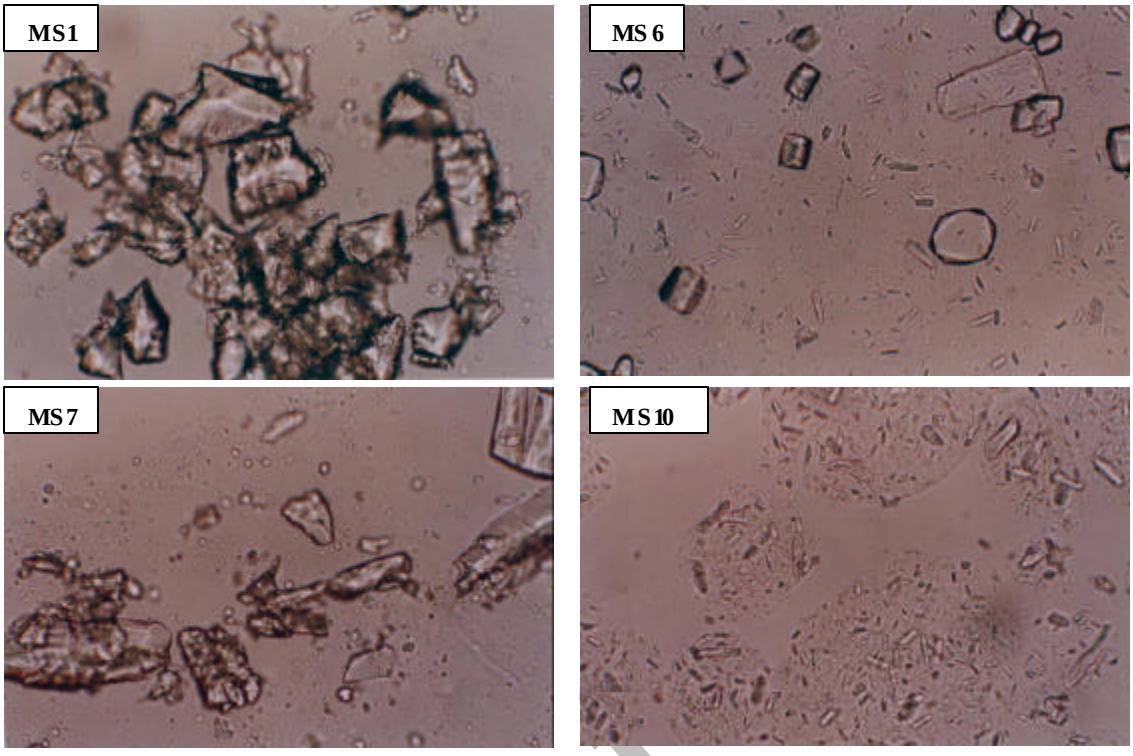

Figure 4. Acetaminophen particle size in some suspensions after freeze-thaw cycling procedure; MS 1: without PVP and BSA; MS 6: containing 100 mg of PVP; MS 7: containing 50 mg of BSA; MS 10: containing PVP (50 mg) and BSA (80 mg)

process can start immediately and the drug molecules resulting from dissolution of the crystal can diffuse through the adsorbate into the bulk liquid phase (18).

The freeze-thaw cycling technique is particularly applicable to stress suspensions for testing the stability. This treatment promotes particle growth and may be useful in prediction of the state of suspensions after long storage at room temperature. Thus it is of prime importance to be alert for changes in absolute particle size, particle size distribution, and crystal habit (21). A comparison of suspensions of MS11 and MS6, which had PVP in concentration of 100 mg showed no significant difference in crystal growth and d_{vs} after 45 and 150 days periods. These results were also observed by Freeze-thaw cycling tests (Fig. 4).

CONCLUSION

From the results of this investigation it may be concluded that BSA above a critical concentration in combination with PVP induces its inhibitory effect on crystal growth.

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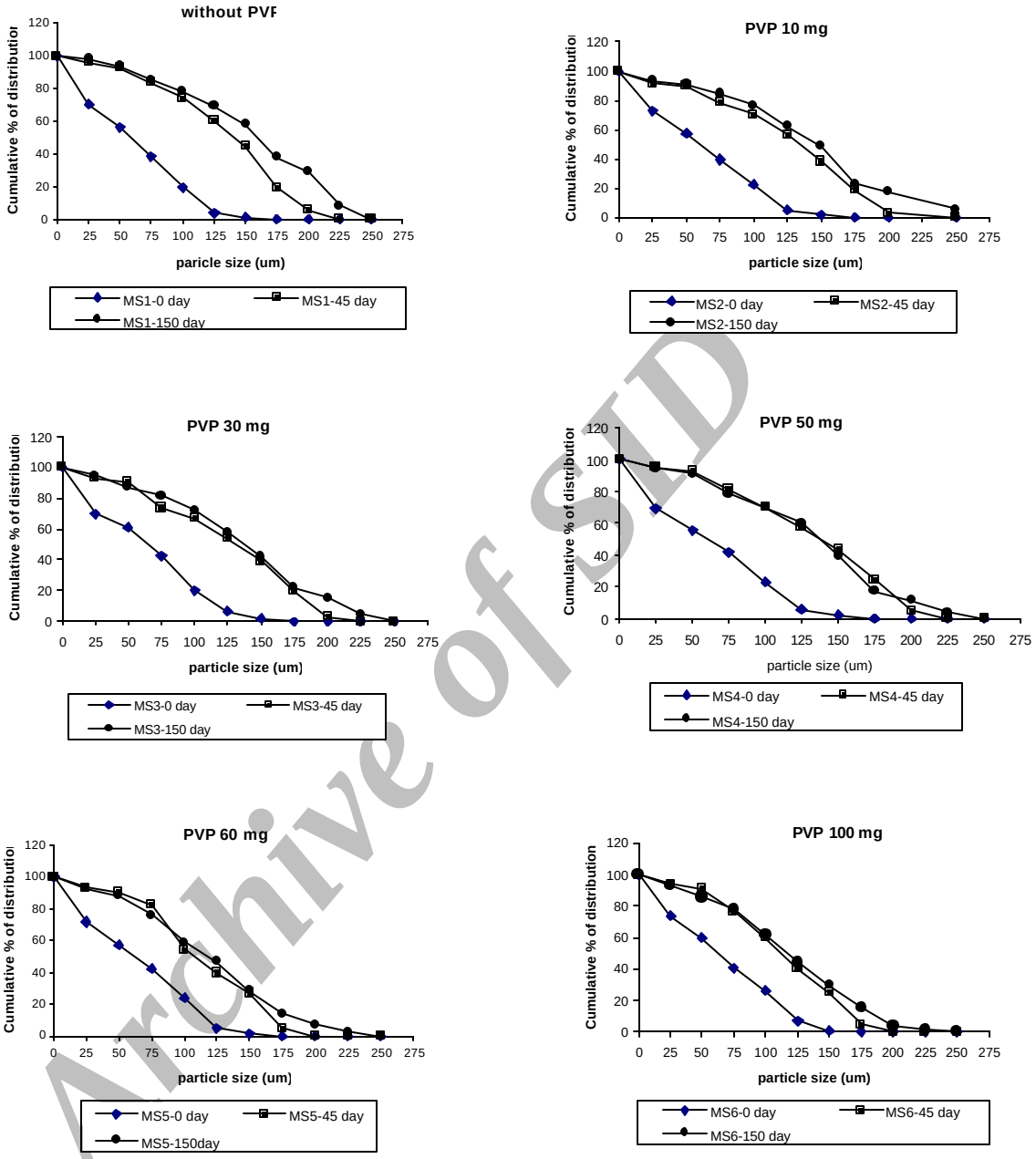

Figure 1. Evolution of Acetaminophen crystal size distribution in suspensions by the increase in concentration of PVP in comparison with suspensions without any PVP at the time of zero 45 and 150 days at room temperature without shaking;

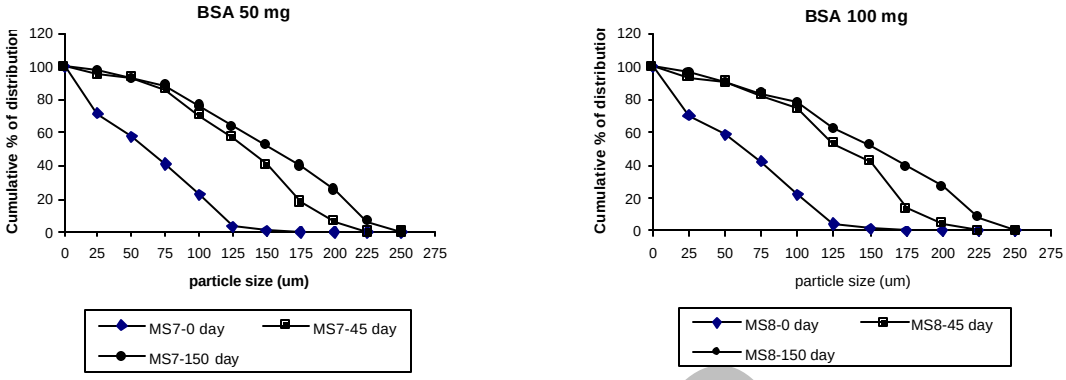

Figure 2. Evolution of Acetaminophen crystal size distribution in suspensions by increase in the amount of BSA at the times of zero, 45 and 150 days at room temperature, without shaking;

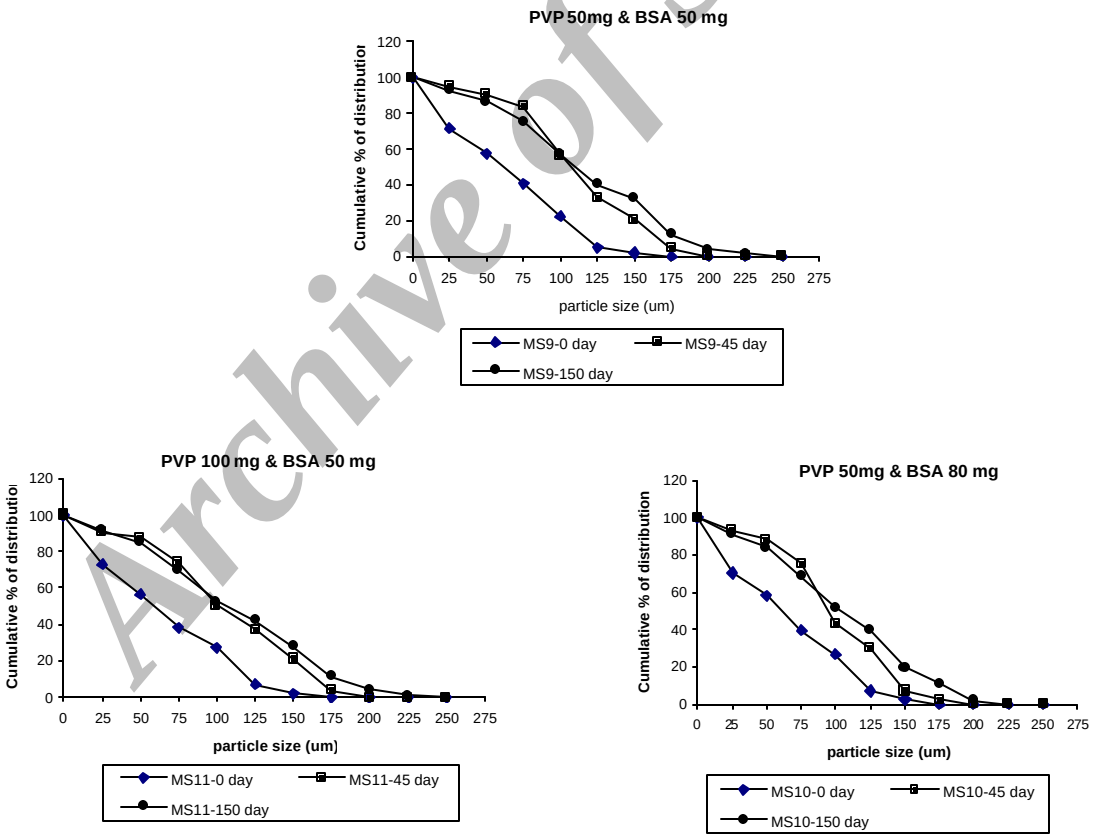

Figure 3. Evolution of Acetaminophen crystal size distribution in suspensions with different amounts of both PVP and BSA, at the times of zero, 45 and 150 days at room temperature without shaking;