Evaluation of ethylcellulose and its pseudolatex (Surelease) in preparation of matrix pellets of theophylline using extrusion-spheronization

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**ABSTRACT**

**Objective(s):** This study evaluates the effect of substitution of microcrystalline cellulose (MCC) with ethylcellulose (EC) on mechanical and release characteristics of theophylline pellets.

**Materials and Methods:** The effect of addition of EC was investigated on characteristics of pellets with varying drug content prepared by extrusion-spheronization. Also the effect of type of granulating liquid (water or Surelease) was investigated on characteristics of selected pellets. The pellets were characterized for particle size (sieve analysis), mechanical strength, morphology (microscopy), thermal (DSC) and dissolution behaviors.

**Results:** The extrudability of the wet mass was reduced upon inclusion of EC so that complete replacement of MCC was not possible. Increase in EC percentage led to lower production yield and formation of pellets with larger diameter and slightly rough surfaces. Inclusion of EC also affected the mechanical properties of pellets but had negligible effect on drug release profile. The surface of selected pellets became smoother and their mechanical properties improved. The rate of drug release decreased to some extent when Surelease was used.

**Conclusion:** Preparation of theophylline pellets with EC alone was not possible in process of extrusion-spheronization. Partial replacement of MCC with EC changed physico-mechanical properties of pellets but hardly affected drug release. Although the use of Surelease as granulating liquid slightly decreased the rate of drug release, desirable matrix pellets with sustained drug release could not be produced. Despite this outcome however, these pellets could benefit from reduced coating thickness for drug release control.

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**Introduction**

Pellets are spherical, free-flowing granules with a narrow size distribution which have numerous pharmaceutical applications. Extrusion-spheronization is a widely used multi-stage technique capable of producing spherical pellets with almost uniform sizes (1, 2). Up to now, the major excipient utilized in pellet production by the extrusion-spheronization technique, has been microcrystalline cellulose (3). Thus, the pellet matrix could not provide much control on drug release rate. Different researches revealed that a change in the pellet formulation as well as the production technique could lead to remarkable changes in shape, size, mechanical and release properties of drug (4-6) and consequently affect the pellet performances in processes such as coating and compression (7, 8).

The substitution of microcrystalline cellulose (MCC) with some hydrophilic gel forming polymers such as chitosan (9, 10), pectin (11, 12), alginate (13, 14), hydroxypropylmethylcellulose (15) and k-carrageenan (16) have been attempted in several studies. However most of these studies have been accompanied with little success in terms of control on drug release rate. The use of water insoluble polymers such as Eudragit RS and/or RL have also been noticed in structure of pellets (17, 19).

Ethylcellulose (EC) is a hydrophobic and water insoluble polymer with no taste, odor and color which has extensive applications in controlled release drug delivery systems (20, 23). It can be found in different forms such as powder in various viscosity grades as well as in form of aqueous dispersions (Surelease and Aquacoat). Surelease is known as a pseudolatex coating material which is plasticized aqueous dispersion of EC with 25% (w/w) solid content. Surelease E-7-19010 which was used in this study consists of EC, oleic acid and medium chain triglycerides as plasticizers, in ammonium hydroxide solution. Surelease has been utilized as film coating material (24) and also as a granulation liquid (25).
Application of EC as a coating material on pellets is a common practice to sustain the rate of drug release (24, 26). However, some attempts have been made to use EC as a rate controlling polymer in the structure of granules or pellets. The inclusion of EC in the formulation of granules was investigated and it was shown that metoprolol tartrate granules containing EC and hydroxypropylmethylcellulose required coating in order to extend drug release beyond 3 hr (27). The use of EC in the process of hot-melt extrusion has also been attempted to produce sustained release mini matrices of metoprolol tartrate (28).

Application of EC in the process of extrusion spheronization was studied by number of researchers. Kojima and Nakagami prepared EC pellets which were cylindrical and needed further annealing process to achieve sustained release of drug (29). Properties of atenolol pellets containing mixtures of EC and MCC at 20% level of EC was studied and it was concluded that the shape of pellets and release of drug were influenced not only by the operational parameters, but also by the nature of the wetting liquid (30). Producing matrix pellets of ambroxol hydrochloride was reported by Chi et al using combination of waxy glyceryl behenate and EC (31). Mallipeddi et al reported that inclusion of coarse EC along with polyethylene oxide (PEO) into the pellet formulation did not provide much control on drug release rate and this was attributed to formation of pores in the structure of pellets upon dissolution of PEO (32). However their attempt to produce pellets without any PEO was unsuccessful. Mallipeddi et al also employed fine particle EC as the diluent in the production of pellets containing PEO and MCC through extrusion spheronization process in an attempt to improve smoothness of the pellet surface (33). The results indicated that neither fine particle EC nor changes in process variables could slow drug release to a profound extent and this was attributed to presence of PEO. However no attempts were made to manipulate drug release by changing the EC level in all of these studies.

In the most of studies outlined above the effect of combination of EC with other polymers has been evaluated on properties of pellets prepared by extrusion spheronization. The small number of studies concerning the effect of incorporation of EC and changes in its level on properties of pellets prepared by extrusion spheronization and some contraindicatory reports on the effect of inclusion of EC on drug release profile from matrix multiparticulate drug delivery systems indicate the importance of performing new investigation in this field.

This study was performed in order to evaluate the effect of substitution of MCC with varying amounts of EC on mechanical and release properties of theophylline matrix pellets prepared by extrusion spheronization process.

### Materials and Methods

#### Materials

Theophylline and microcrystalline cellulose (Avicel ®PH101) were provided by Darupakhsh (Tehran, Iran), ethylcellulose (ETHOCEL standard 7 premium) and Surelease (E-7-19010) were kindly donated by Colorcon (Dartford, England) and polyvinylpyrrolidone (PVP-K30) was supplied by Fluka (Buchs, Switzerland). All the materials were used as received.

#### Methods

**Preparation of pellets**

The components used for production of pellets and their percentage are listed in Table 1. The solid components of each formulation (total amount of 20 g) were mixed using a kitchen mixer for 10 min at 40 rpm. The required amount of granulation liquid was slowly added to the dry blend to make a wet mass with proper consistency. It should be noted that pellets with the least drug release rate (pellets with 30% drug loading and 43% EC) were granulated with either water or Surelease in order to study the effect of granulation liquid type on drug release and also to allow addition of more EC into the pellet structure. The wet mass was passed through a screw extruder (Khazar, Iran) with a 1.2 mm screen. The extrudates were processed in a spheronizer (Khazar, Iran) fitted with a cross-hatched plate rotated at 400 rpm for 2 min. The obtained pellets were dried at 40°C for 12 hr in a conventional oven.

**Sieve analysis and yield of pellets**

The pellets were sieved using nest of standard sieves 150, 180, 250, 425, 850, 1000 and 1180 µm shaken for 3 min on a sieve shaker (Retsch-Germany). The pellets retained on each sieve were weighed and the obtained data was used to calculate the geometric mean size and geometric standard deviation (σg). The size range of 850-1180 µm was considered appropriate and the weight of pellets in this range was reported as yield of pellets.

**Mechanical tests**

The crushing strength (the load needed to break the pellets) and elastic modulus of 20 pellets were determined using a Material Testing Machine.

### Table 1. The components and their percentage of materials used in different pellet formulations

| Formulation               | A    | B    | C    | D    | E    | F    | G    | H    |
|---------------------------|------|------|------|------|------|------|------|------|
| Theophylline (T)          | 10%  | 10%  | 20%  | 20%  | 30%  | 30%  | 30%  | 30%  |
| Avicel (A)                | 83%  | 30%  | 73%  | 20%  | 63%  | 30%  | 20%  | 20%  |
| Ethylcellulose (EC)       | -    | 53%  | -    | 53%  | -    | 33%  | 43%  | 43%  |
| Polyvinylpyrrolidone (PVP) | 7%   | 7%   | 7%   | 7%   | 7%   | 7%   | 7%   | 7%   |
| Distilled Water (mL)      | 23.2 | 17.8 | 21.0 | 14.5 | 17.3 | 16.0 | 14.5 | 17.3 |
| Surelease (mL) (S)        | -    | -    | -    | -    | -    | -    | -    | 24.2 |

[10] - [11]
Table 2. Production yield, mean particle size, crushing strength and elastic modulus of pellets

| Formulation | Production yield (%) | Geometric mean size (µm) ± σy | Crushing strength (N ± SD) | Elastic modulus (MPa) ± SD |
|-------------|----------------------|-------------------------------|----------------------------|---------------------------|
| A           | 56.9                 | 557.2 ± 1.8                  | 25.3 ± 1.8                 | 407.4 ± 68.0              |
| B           | 42.9                 | 665.3 ± 1.8                  | 10.2 ± 1.3                 | 124.4 ± 21.8              |
| C           | 57.8                 | 587.5 ± 1.6                  | 23.0 ± 2.3                 | 364.2 ± 56.5              |
| D           | 55.6                 | 755.1 ± 1.8                  | 9.9 ± 0.9                  | 138.4 ± 18.2              |
| E           | 46.5                 | 476.4 ± 1.8                  | 17.5 ± 1.4                 | 454.0 ± 50.0              |
| F           | 47.1                 | 524.8 ± 1.8                  | 12.8 ± 1.3                 | 224.7 ± 36.8              |
| G           | 40.5                 | 566.2 ± 1.7                  | 11.2 ± 0.5                 | 184.5 ± 31.0              |
| H           | 70.5                 | 605.3 ± 1.6                  | 10.5 ± 0.7                 | 175.4 ± 19.3              |

Pellets with the size range of 850-1180 µm were used in this test in order to minimize the size dependent variations. The speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Force-displacement graphs were obtained by a computer system attached to the apparatus (QMAT, Hounsfield, UK). Thereafter, the average hardness and elastic modulus of pellets for each formulation together with its relevant standard deviations were computed. The elastic modulus was obtained from the slope of the linear portion of stress-strain graphs.

**Morphology studies of pellets**

The shape and surface of pellets were investigated by a stereomicroscope (Kyowa, Japan). Pellets were placed on a dark backgrounds and a light source was used to reduce the influence of shadow on the image.

**Differential scanning calorimetry (DSC)**

DSC analysis was performed on theophylline, EC, polyvinylpyrrolidone, Avicel and their physical mixtures as well as pellets of groups G and H (Table 1), using a differential scanning calorimeter (Mettler Toledo DSC 822e, Switzerland) and STARe software version 7.01 (Mettler Toledo, Switzerland). The instrument was calibrated with an indium standard. Samples (3-5 mg) were weighed and sealed into aluminum pans. The samples were cooled to 0 °C and DSC runs were conducted over a temperature range of 0-350 °C at a rate of 10 °C/min. All tests were run under a nitrogen atmosphere.

**Dissolution studies**

The dissolution tests were carried out on accurately weighed samples (n=6) containing 40 mg of theophylline in automated dissolution testing equipment (Pharma test, Germany). The test was performed using USP apparatus I, at 100 rpm, in medium of 1000 ml distilled water, at 37 °C. The samples were taken from the vessels by a peristaltic pump (Alitea, Sweden), and assayed at 271 nm by a multi-cell transport spectrophotometer (Shimadzu, Japan).

Comparison of dissolution profiles were performed by calculating the fit factors (difference factor (f1) and a similarity factor (f2)). Fit factors were adopted by FDA Center for Drug Evaluation and Research (CDER) as a criterion of similarity between two in vitro dissolution profiles. The difference factor (f1) indicates the percent of difference between two curves at each time interval and is a measure of the relative error between those curves. These parameters are calculated as follow:

\[
f_1 = \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i} \times 100 \tag{1}
\]

\[
f_2 = 50 \log \left[ \left( 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{-0.5} \right] \times 100 \tag{2}
\]

in which n stands for the time intervals and R and T are the released percent of drug in the reference sample and the test sample, respectively.

**Statistical analysis**

Data between groups were compared statistically by t-test for comparisons. Values of P<0.05 were considered statistically significant.

**Results**

Mean particle size, the yield of pellets, crushing strength and elastic modulus of pellets are tabulated in Table 2. Inclusion of EC led to formation of larger pellets and it was found that the mean particle size of pellets was dependent on the percentage of EC in the formulation. The yield of pellets was in the range of 40.5-70.5% and was influenced by EC percentage and type of granulation liquid. The results of Table 2 also indicated that crushing strength and elastic modulus decreased in pellets containing EC (P<0.001).

Microscopic examination of pellets showed that inclusion of EC affected the surface characteristics of the pellets and resulted in formation of pellets with rougher surface. The surface characteristics of the pellets with 30% drug are shown in Figure 1 as an
Preparation of ethylcellulose matrix pellet

Iran J Basic Med Sci, Vol. 20, No. 1, Jan 2017

Figure 1. Images of pellets; A) group E, B) group G, and C) group H

Figure 2. Thermograms of A) theophylline, EC, Avicel, PVP, B) physical mixture of theophylline with EC, Avicel or PVP and C) Groups G and H pellet formulation example (formulations of E, G and H). As it can be seen substitution of Avicel with EC resulted in formation of pellets with rougher surfaces. Whilst the use of Surelease, as the granulation liquid, led to production of pellets with smoother surface.

DSC thermograms of different samples are shown in Figure 2. A sharp endothermic peak was observed for the theophylline at 273 °C. This endothermic peak was also observed in thermograms correspondent to the physical mixture of theophylline and EC, PVP or Avicel, whilst a broad endothermic peak was observed in thermograms of formulations G and H, at this region.

Dissolution profiles of various formulations are shown in Figure 3. Comparison of the results presented in Figure 3 shows that in Avicel based pellets increase in drug content to 30% did not affect drug release profile. Inclusion of EC in pellet structure at 10 or 20% drug content hardly affected drug release profile. However in the pellets with 30% drug content some changes in drug release profile could be observed after substituting of Avicel with EC especially at higher percentage of EC. Furthermore, in pellets with 30% drug content changing the type of granulation liquid also affected the dissolution profile of the drug. As illustrated in Figure 3, employing Surelease as granulation liquid provides more control over drug release rate.

The images of the pellets after dissolution test for group E, G and H formulations are shown in Figure 4. As it can be seen most of the pellets in group E and G were disintegrated during dissolution test whilst group H pellets (those granulated with Surelease) remained nearly intact.
Discussion

The Avicel content of pellets was substituted with EC in order to provide some control on drug release rate from pellets prepared by extrusion spheronomization. Attempts to fully replace Avicel with EC were unsuccessful. It was observed that partial substitution of Avicel with EC in pellet formulation, made the process of extrusion and spheronomization more difficult so that it was not possible to increase the EC percent to more than 43 or 53% in pellets containing 30 or 10% drug content. In addition inclusion of EC resulted in formation of more cohesive extrudates with less brittle properties. Overall inclusion of EC and increase in its amount resulted in incomplete discharge of wet mass from the extruder chamber. These results could be due to decrease in volume fraction of Avicel with increase in EC content. In fact, Avicel with water uptake capability and water holding capacity as well as its plastic behavior in wet state, plays a crucial role in stages of extrusion and spheronomization (3). Based on our previous study on ethylcellulose matrices (34) Surelease was used as granulating liquid for selected pellets to investigate its effect on pellet properties and also to allow more addition of EC in pellet structure.

Employing Surelease as granulating liquid in pellets with 30% drug content facilitated the discharge of the wet mass from the extruder and improved its extrudability. This might be due to the presence of different components (plasticizer and lubricant) in Surelease formulation which could have a prominent role in the formation of wet mass with more plasticity, deformability and lubricity. The results depicted in Table 1 indicate that the required volume of granulating liquid decreased with increase in drug content in pellets (groups A, C and E). This could be due to the substitution of some part of Avicel by the drug. It is noteworthy to mention that Avicel is capable of absorbing a large volume of water. Thus, the lower the level of Avicel, the smaller is the volume of absorbed water in the formulation. In addition, the relative solubility of the theophylline in water is another effective factor in decreasing the water consumption in formulations with larger portions of drug. It has been reported that the level of water for preparation of proper wet mass was dependent on the characteristics of the formulation components (35). It has also been shown that if the components of the pellet formulation are soluble in granulating liquid, there is a need for smaller volume of the granulation liquid in order to produce a desired wet mass (14, 35, 36).

In pellet formulations containing EC (groups B, D, F and G), the required volume of water for preparation of wet mass decreased with an increase in the amount of EC. This was due to the less water absorption capability of the EC compared to Avicel. In pellets, in which the distilled water was used as the granulation liquid, the volume of granulation liquid was much less than the group which Surelease was used for the granulation. This seems to be due to presence of diverse components in the Surelease formulation that occupied a part of volume of the consumed granulation liquid.

The data in Table 2 revealed that the mean particle size was desirable in all formulations. It was also demonstrated that replacing Avicel by EC led to production of larger pellets. These findings might be due to the more cohesive and less brittle properties of the wet mass containing EC as observed by the formation of more continuous and longer extrudates compared to Avicel based extrudates. Moreover, it was shown that in pellets with 30% drug, the use of Surelease as granulating liquid led to production of larger pellets. As a matter of fact, cohesive characteristics of Surelease improved binding of particles and as a consequence led to production of pellets with larger diameters. Previous studies also showed that granulation liquid alteration could affect the mean particle size of pellets (37, 38). According to Table 2, in pellets containing only Avicel, a difference was observed in crushing strength of pellets with different amounts of drug in pellet formulation (P<0.001). Increase in drug fraction decreased the pellet hardness. These observations could be justified through the level of Avicel in the pellets structure. In formulations with smaller amount of drug, the Avicel fraction becomes prominent in the pellet formulation, and due to adhesive properties of Avicel, the produced matrix is stronger and denser. These results are in agreement with the results already published for pellets made of Avicel and different amounts of ibuprofen (19). A comparison between pellets...
containing EC and those containing only Avicel, with the same amount of drug indicated a noticeable difference in crushing strength of pellets. The results showed that with increase in the EC fraction, the pellet crushing strength was reduced (P<0.001). Abbaspour et al have also reported similar results regarding the addition of Eudragit RS or RL on the mechanical properties of pellets containing ibuprofen and Avicel (19).

The elastic modulus results as shown in Table 2 were dependent on EC fraction in the formulation. The elastic modulus is a parameter which indicates the pellet resistance against the deformation and expresses the plastic properties of the pellets. This property is specifically important when compressing the pellets to make tablets. Increasing the EC fraction in the pellet formulation, effectively decreased the elastic modulus (P<0.001). These results could be mainly due to the plastic properties of EC (39). Utilizing the distilled water or Surelease as the granulating liquid did not make any remarkable difference in the elastic moduli of the pellets. Similar findings were reported by Afrasiabi Garekani et al who investigated the effect of Surelease as granulating liquid in preparation of sustained release granules of EC and theophylline (34).

The surface characteristics of the pellets, is a parameter that can influence the release characteristics of drug (24, 40). It was observed that pellets containing drug and Avicel had a smooth surface and almost a spherical shape (Figure 1a). Increase in drug fraction did not affect the pellet appearance (data not shown). On the other hand, some discontinuity was observed on the surfaces of pellets containing EC. The unevenness was more for pellets with higher EC fraction (Figure 1b). This could be due to decrease in fraction of Avicel in these pellets which is known as pelletization aid. Using Surelease as granulation liquid resulted in production of more spherical pellets with smoother surfaces (Figure 1c). This phenomenon could be attributed to the presence of plasticizer and other components in the Surelease formulation, which provide some plasticity for the wet mass and compensates the lack of enough level of Avicel in the formulation. In a similar research, it was shown that changing the type of granulation liquid improved the pellets appearance for alginate or chitosan based pellets and more spherical pellets were manufactured (13, 14, 41).

Figure 2 depicts the thermograms of different samples along with their physical combinations and two pellet formulations of G and H. Theophylline shows a sharp peak at 273°C. This is an endothermic peak related to the melting point of theophylline. In thermogram of EC a broad exothermic peak observed at around 200°C which was attributed to oxidative degradation of the polymer (42). The endothermic peak in PVP thermogram was probably due to evaporation of the absorbed moisture by PVP. It was noted that in DSC curve of physical mixtures of theophylline and EC, theophylline and PVP or theophylline and Avicel, the melting peak of theophylline has appeared at the same position. These results indicated that there was no interaction between the drug and EC, Avicel or PVP in their physical mixtures. An endothermic peak was observed at around 270°C in thermograms of pellets in groups G and H which was related to the melting of theophylline. The presence of this peak confirmed the existence of theophylline in the pellet formulation and also verified the lack of interaction between the drug and other components. Moreover, the smaller melting peak of theophylline along with its broadening could be attributed to the lower degree of crystallinity of the drug in pellets. This was probably due to the formation of some type of solid dispersion system in presence of PVP during the extrusion spheronization process.

The release profiles of different formulations are shown in Figure 3. As it can be seen in Avicel based pellets increase in drug content hardly affected drug release rate. It was expected that addition of EC into the pellet structure, due to its hydrophobic nature, led to decrease in rate of drug release. But, as shown in Figure 3a, for pellets containing 10% drug, substitution of Avicel with EC did not affect the release profile (t1=5.8, t2=56.8). Similar results were observed for pellets with 20% drug fraction (t1=5.9, t2=66.1). In pellets with 30% drug addition of EC up to 43% also did not affect the release profile (t1=10.2, t2=53.4). This almost negligible effect of EC on release profile of drug, despite its hydrophobic properties, might be explained by inability of EC powder to make strong matrices in pellet structure. As Table 2 shows, hardness of pellets containing EC is lower than pellets containing only Avicel. This issue allows the dissolution medium diffuse into the pellet structure more easily, and as a result, the drug release becomes faster despite of hydrophobic behavior of EC. Furthermore, large surface area of produced pellets prevents EC to have an effective role in decreasing the release profile of the drug. In a similar research conducted by Mallipeddi et al it was reported that addition of EC with different particle sizes into the pellet structure did not have a significant effect on the release profile of caffeine from pellets containing EC and PEO and both high surface area for drug release and water solubility of PEO were accounted for fast release of drug (32). In another study, Abbaspour, et al also reported that although addition of Eudragit RS PO and/or RL PO reduced the rate of ibuprofen release from pellets, but did not eliminate the need for coating (19).

The interesting point in release profiles of Figure 3 was that even though inclusion of EC did not affect the release profile of the drug, but by increase in drug fraction in the formulation the role of EC in the control of the release rate became more noticeable. Comparison of release profiles for pellets containing 30% drug produced by different granulating liquid
on extrusion/spheronization. A

spheronization. A

The use of Surelease as granulating liquid reduced the rate of drug release ($t_1$=24.5, $t_2$=38.8). The coating of the drug particles with Surelease during the pelletization could be one of probable reasons for slowing the release rate. Moreover, examining the images of pellets after dissolution (Figure 4) revealed that employing Surelease as the granulating liquid resulted in formation of pellets which were able to retain their structure after dissolution. This could also be another factor for having a lower release rate of drug from the pellets.

**Conclusion**

Results revealed that EC could not be used as a sole filler in production of theophylline matrix pellets by extrusion-spheronization and at least 20% level of Avicel was necessary in the formulation. Inclusion of EC changed the mechanical properties of pellet, however hardly affected drug release rate and therefore was unable to make sustained release matrix pellets. The use of Surelease as granulating decreased the release rate of the drug more efficiently but could not eliminate the need for coating the pellets; however, it could result in decrease in the thickness of the required coating.

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Figure 3c) showed that the type of the granulation liquid played a significant role on the release profile of the drug. This is in agreement with previous findings on the effect of Eudragit RS dispersion on drug release from pellets prepared by extrusion spheronization process (43). The results revealed that EC could not be used as a sole filler in production of theophylline matrix pellets by extrusion-spheronization and at least 20% level of Avicel was necessary in the formulation. Inclusion of EC changed the mechanical properties of pellet, however hardly affected drug release rate and therefore was unable to make sustained release matrix pellets. The use of Surelease as granulating liquid reduced the rate of drug release ($t_1$=24.5, $t_2$=38.8). The coating of the drug particles with Surelease during the pelletization could be one of probable reasons for slowing the release rate. Moreover, examining the images of pellets after dissolution (Figure 4) revealed that employing Surelease as the granulating liquid resulted in formation of pellets which were able to retain their structure after dissolution. This could also be another factor for having a lower release rate of drug from the pellets.

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**Conclusion**

Results revealed that EC could not be used as a sole filler in production of theophylline matrix pellets by extrusion-spheronization and at least 20% level of Avicel was necessary in the formulation. Inclusion of EC changed the mechanical properties of pellet, however hardly affected drug release rate and therefore was unable to make sustained release matrix pellets. The use of Surelease as granulating liquid reduced the rate of drug release ($t_1$=24.5, $t_2$=38.8). The coating of the drug particles with Surelease during the pelletization could be one of probable reasons for slowing the release rate. Moreover, examining the images of pellets after dissolution (Figure 4) revealed that employing Surelease as the granulating liquid resulted in formation of pellets which were able to retain their structure after dissolution. This could also be another factor for having a lower release rate of drug from the pellets.
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