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Characterization and drug release from extended-release matrix pellets with montelukast sodium

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The undisputable benefits of pellets, associated with improved bioavailability, make them ideal for presenting in extended-release formulations. Unfortunately, despite the many advantages of wet extrusion and spheronization, extended release is difficult to be achieved, even with commonly used release modifying agents like cellulose derivates, polyethylene oxides, sodium alginate, etc. In order to sort out this problem, we included ethanol in the kneading liquid and investigated its influence on the properties of ethylcellulose (EC) pellets and the release behaviour of montelukast sodium. Differential scanning calorimetry of EC showed increase in heat capacity, associated with increased amount of ethanol, which proved that ethanol changes the thermo-mechanical properties of EC. Moreover, evaporation of ethanol during spheronization caused partial melting and dissolution of EC provoking agglomeration, rounding and smoothing, which reflected in the formation of a hydrophobic film around the particle. As a result, the increase in ethanol concentration in the kneading liquid led to obtaining pellets with narrower particle size distribution, higher dimensions, improved sphericity, flatter surface, longer mean dissolution time (MDT) and slower release of montelukast sodium.

Keywords: Matrix pellets; Wet extrusion and spheronization; Extended-release; Ethylcellulose

INTRODUCTION

Utilization of pellet systems is gaining much attention due to their potential advantages: increased bioavailability; reduced local stomach irritation; no risk of dose dumping; flexibility to mix pellets with different compositions or release patterns in order to achieve desired release rate, etc. Several technologies for preparation of pellets are available (spray-drying, extrusion/spheronization, solution/suspension layering, etc.), but wet extrusion/spheronization technique has the advantages of obtaining high-density matrix pellets with high drug loading capacity [1]. The desirable properties of the pellets include uniform spherical shape and size, good flow properties, high mechanical strength, low friability, low dust and smooth surface. Most workers usually report the size and size distributions produced as an indication of the quality of the product, because they have significant influence on the release kinetics, as well as for reproducible packing in hard gelatine capsules or sachets [1]. The shape is critical for a number of processing properties of beads, such as flowability, uniformity of coating, etc., and uniform regular spherical shape is highly desirable [2].

Microcrystalline cellulose (MCC) is the golden standard as a diluent for wet extrusion. However, sometimes it is not the first choice due to the lack of disintegration and the inability to extend the release [3]. Although a number of polymers such as hydroxypropylmethyl cellulose, polyethylene oxide (PEO), sodium alginate, and even ethylcellulose (EC) are successfully used to produce extended-release matrix tablets, their inclusion in matrix pellet formulations (prepared by wet extrusion/spheronization) does not result in significant delay in the release rate. The small diameter and the large free surface area of the pellets lead to rapid penetration of the solvent into the system and reduction of the drug diffusion pathway [4-7]. However, in the study of Hamelelniel *et al.* [8] a delay in the initial release of a drug was achieved from pellets with MCC and EC caused by changing pure water with 16% ethanol as a kneading liquid. EC swells and dissolves in ethanol, which leads to the formation of a hydrophobic film after evaporation of the solvent. This gives us the reason to investigate the influence of the kneading liquid on the properties of ethylcellulose matrix pellets with montelukast sodium, prepared by wet extrusion and spheronization.

Montelukast sodium was chosen as a model drug because it is an appropriate candidate for presenting in an extended-release formulation due to its intensive hepatic first pass metabolism and short biological half-life (2.5-5.5 hours) [9].

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Materials

The active pharmaceutical ingredient (API) Montelukast sodium was obtained from Inchem Laboratories (India). The excipients sodium alginate, general grade and Avicel PH 101 were obtained from Fisher Scientific (UK) and Evonik (Germany), respectively, and ethylcellulose N46 and PEO 6000000 - from Sigma-Aldrich (USA).

Methods

Differential scanning calorimetry (DSC) of ethylcellulose. For thermal characterization of ethylcellulose, as well as for studying the influence of the type of the solvent on its thermo-mechanical properties, a differential scanning calorimeter, Perkin-Elmer DSC 7, USA, was used. Five samples were prepared for this purpose, as follows: A. Pure substance EC; B. EC treated with water; C. EC treated with 40% ethanol; D. EC treated with 60% ethanol: E. EC treated with 95% ethanol. The experiment required measurement of the loss on drying at 105ºC of the pure substance EC N46, which served as a standard (sample A). The treatment of the other samples included spraying of 1.5 g of the corresponding liquid (water, 40%, 60% and 95% ethanol - w/w) onto 3 g of pure substance, manual mixing in glass vials with a steel spatula and subsequent drying to a loss on drying equivalent to that of the pure substance. The analysis was performed with heating/cooling run from 25 to 200ºC as follows [10]: 3-5 mg of test sample was placed in a sealed aluminum pan at a 5ºC/min heating/cooling rate with a 70 ml/min nitrogen flow rate.

Preparation of matrix pellets with montelukast sodium via wet extrusion and spheronization

The extrusion was performed with a radial screw-feed extruder (4M8Trix, Procept, Belgium) equipped with a standard die having 1.2 mm diameter aperture and rollers rotating at 75 rpm. The extrudate fell directly into the spheronizer fitted with a cross-hatch friction plate, 13.5 cm in diameter where it was rounded off at 2100 rpm rotating speed for 10 min. The appropriate use and level of each excipient, as well as processing parameters were determined by conducting preliminary trials. Based on them for the present experiment MCC was used as diluent, EC as release modifying agent, Na-alginate as pore-forming agent and PEO as spheronization aid (Table 1).

Determination of pellet size and pellet size distribution

Pellet size and pellet size distribution were determined by performing a sieve test using a set of standard test sieves (0.5–2.5 cm with $2^{0,25}$ progression) and a sieve shaker (VEB MLW Labortechnik Ilmenau, Thvr 2, Germany) operated with 50 g pellet sample for 5 min at a frequency of 50 Hz and an amplitude of 1 mm.

Table 1. Composition of pellet formulations (weight/weight ratio).

Excipients	Formulation №			
	E1	E2	E3	E4
Montelukast sodium	0.5			
Avicel PH 101	4.15			
EC N46	4.15			
Sodium alginate	1			
PEO 600000	0.2			
Kneading liquid	water	30% ethanol (w/w)	40% ethanol (w/w)	50% ethanol (w/w)

The weight retained in each fraction was determined by an analytical balance (model AG204, Mettler-Toledo, Greifensee, Switzerland) and the percentage of each fraction was calculated. These results were used for building a cumulative particle size distribution curve and calculating the average pellet diameter ($d_{av.}$) and span value following equations 1 and 2, respectively:

$$d_{av.} = \frac{\sum \% \text{ pellet fraction retained x average sieve aperture (mm)}}{100}. \quad (1)$$

$$\text{span} = \frac{(\mathbf{d_{90}} - \mathbf{d_{10}})}{\mathbf{d_{50}}} \quad (2)$$

Determination of pellet shape

The shape of the model pellet compositions was characterized by the aspect ratio (AR), which represents the ratio of the maximum and minimum values of Feret diameter of each particle. It can be found in the range of 0-1, as higher value indicates that the shape of the pellets is more regular and spherical. The AR value was obtained by making a series of images for each sample with a digital camera (E61MID02 uEye UI-1545LE-C CMOS 1.3 MP) attached to a tripod and pointing to the surface of the particles, which were spread over a flat surface by spatula. Each image was processed with Image J software and measured in millimeters the maximum and minimum values of Feret diameter of 500 particles.

Determination of pellet morphology

Scanning electron microscope (Jeol JSM-5510, Japan) was used to observe the physical properties (shape and texture) and surface modification of the prepared pellets. Samples of pellets from each formulation were mounted on a disk using an adhesive. For better conductivity, the samples were

coated with gold using a Jeol JFC-1200 Fine coater and observed at an accelerating voltage of 25 kV.

In vitro release studies

Due to the pH-dependent solubility of montelukast sodium, as well as the inability to achieve sink conditions with commonly used buffers, a 0.5% aqueous solution of sodium lauryl sulfate was used as a medium for the *in vitro* dissolution study. Drug release from 208 mg bead sample with size fraction of 1.25–1.4 mm in 500 ml medium solution at 37◦C was studied using an Apparatus 2 – Paddle Apparatus USP 37 (RC-8D, KHP, Germany) with a 100 rpm stirring rate. Samples were collected at specified time intervals (15 min, 30 min, 1, 2 3, 4, 5, 6, 7, 8 h) and centrifuged at 150000 rpm for 3 min on a micro-centrifuge (D2012, Dragon Lab., China). The assay of API released at each time interval was measured spectrophotometrically at 285 nm (spectrophotometer RAYLEIGH UV-9200, China) and calculated based on a calibration curve equation. Dissolution tests were repeated six times for all formulations. The mean dissolution time (MDT) was used to characterize drug release and to compare the drug release profiles of the prepared formulations, because this parameter indicates the drug release retarding efficiency of polymers. It was calculated from the dissolution data using equation 3:

$$MDT = \frac{n*K'(-\frac{1}{n})}{n+1} \quad (3)$$

RESULTS AND DISCUSSION

Thermal characterization of ethylcellulose

Based on the obtained thermograms (Fig. 1), glass transition temperature (Tg) and heat capacity (delta Cp) were determined by the specific software of the apparatus. The results are presented in Table 2. Glass transition temperature (Tg) is one of the most important characteristics of polymers. This temperature is the temperature range in which the polymer passes from a solid, glass-like state to a soft rubbery state. Tg is characteristic of polymers that have an amorphous structure or have an amorphous region in their molecule (such as ethylcellulose).

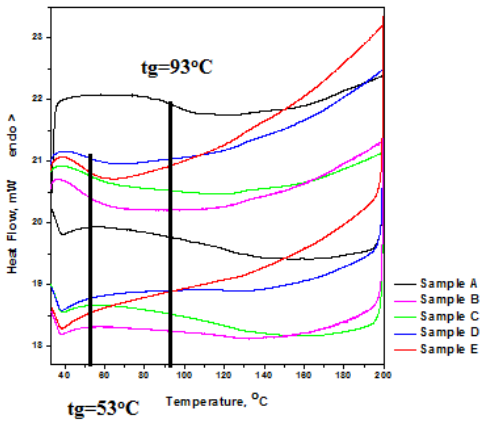

Fig. 1. DSC thermograms of ethylcellulose from samples A-E.

Tg can be lowered by substances called plasticizers, which improve the processability, flexibility and elasticity of the polymers [11]. In this line of thought, it is clear from Table 2 that the contact of ethylcellulose with water (whether pure water or water-ethanol mixtures) had a significant effect on Tg, expressed as a decrease in its value from 93 to 53°C (40°C difference), which confirmed literature data that water had a plasticizing effect on EC [12].

The heat capacity (delta Cp) is a measurable physical quantity equal to the ratio of the heat added to (or removed from) an object to the resulting temperature change or the energy required to raise the sample temperature by 1°C or 1K [11]. A change in the heat capacity means a change in the thermo-mechanical properties of EC. Regardless of the same Tg for samples B-E, a decrease in the water content, respectively an increase in the ethanol content induced an increase in the value of heat capacity: 0.45 J/g*°C - for the sample with pure water and 1.67 J/g*°C - for the sample with 95% ethanol. This gave us a reason to believe that ethanol changes the thermo-mechanical properties of EC, which could affect the release rate of API of systems in which ethanol was included in the kneading liquid.

Table 2. Values of Tg and delta Cp for samples A-E

Sample №	A	B	C	D	E
Composition	Pure EC	EC + water	EC + 40% ethanol	EC + 60% ethanol	EC + 95% ethanol
Tg (°C)	93	53			
delta Cp (J/g*°C)	0.67	0.45	0.78	1.36	1.67

Pellet size and pellet size distribution

The screening experiments indicated unimodal non-monodispersible particle size distribution (Fig. 2) with average pellet diameter varying between 1.029 and 1.901 mm (Table 3), indicating a profound influence of formulation variables. It was demonstrated that with the increase in ethanol concentration in the kneading liquid the average pellet diameter tended to increase significantly, whereas span value decreases. Moreover, except of formulation E1, all the other samples had d_{av} values higher than the extruder's die diameter. This was caused by the agglomeration occurring during spheronization - apart from breaking and smoothing, adhesion of finer to larger particles was observed. Due to the heat generated by the friction of the pellets, the ethanol started to evaporate, which led to the dissolution of EC from the bead surface of formulations E2-E4 and to a partial melting of the polymer, which could explain the occurring agglomeration of formulations E2-E4. Decreasing span value associated with increased amount of ethanol in a kneading liquid was a reflection of the homogeneity and narrower size distribution.

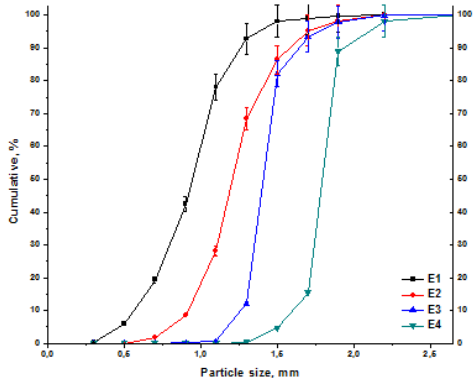

Fig. 2. Cumulative particle size distribution of formulations E1-E4; mean±SD; n=3.

Pellet shape

The bead shape was evaluated based on the aspect ratio. An aspect ratio of 1.0 indicates a perfect shape. However, an aspect ratio ≥ 0.8 has been considered good for pharmaceutical pellets. This specification was not achieved only for formulation E1 (AR=0.647) because of the swelling of the hydrophilic polymers sodium alginate and PEO, causing the formation of a tacky wet mass with extremely high plasticity resulting in the formation of an extrudate, which broke unevenly and resisted rounding up completely in the spheronizer. Formulations E2-E3 possessed high value of AR (above 0.8), which meant that they had the desired nearly spherical shape, demonstrating the success of spheronization under these conditions. The improved sphericity associated with increased amount of ethanol in the kneading liquid was caused by the partial melting and dissolution of EC under the influence of evaporating ethanol, which led to self-layering and rounding.

Table 3. Parameters of pellet formulations E1-E4

Formulation №	d_{av}., mm	Span	Aspect ratio	MDT, h
E1	1.029	0.69	0.647	0.04231
E2	1.327	0.49	0.881	0.20830
E3	1.529	0.18	0.889	2.36971
E4	1.901	0.13	0.920	4.39490

Pellet Morphology

The shape and surface characteristics of the prepared pellet formulations E1-E2 at 40× and 250× magnifications are illustrated in Fig. 3. As it was mentioned before, the final beads of formulation E1 showed heterogeneity in shape – only some of them possessed the desired spherical form. The texture of the pellets of formulation E1 at higher magnification (250×) showed that the surface of the beads was rough, porous and marked with irregularities for both spherical and dumb-bell shape pellets. SEM observations of formulations E2-E4 estimated that pellets were spherical in shape. A smoothing on the surface of pellets was observed with the increase in ethanol concentration. This was due to the fact that some of EC was partially dissolved in ethanol forming film pieces [8].

Drug release studies and analysis of release data

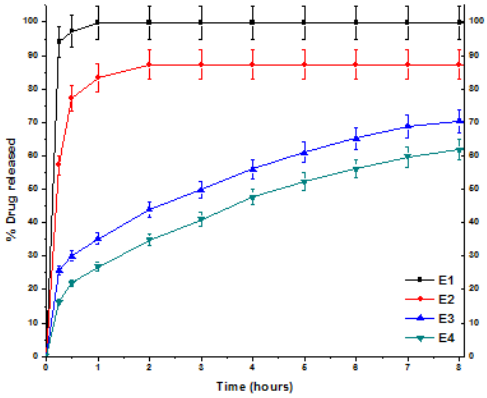

Fig. 4. *In vitro* release profiles of pellet formulations E1-E4; mean±SD; n=6.

Fig. 4 and Table 3 show the results from the release studies of the obtained formulations. The increased amount of ethanol in the kneading liquid

significantly delayed the release rate and increased MDT of API. As a result an immediate release product was obtained from formulations E1 and E2, whereas formulations E3 and E4 demonstrate extended release of montelukast sodium. The presence of both sodium alginate and PEO, as hydrophilic water-soluble polymers, resulted in the formation of pores on the pellets surface [6,7].

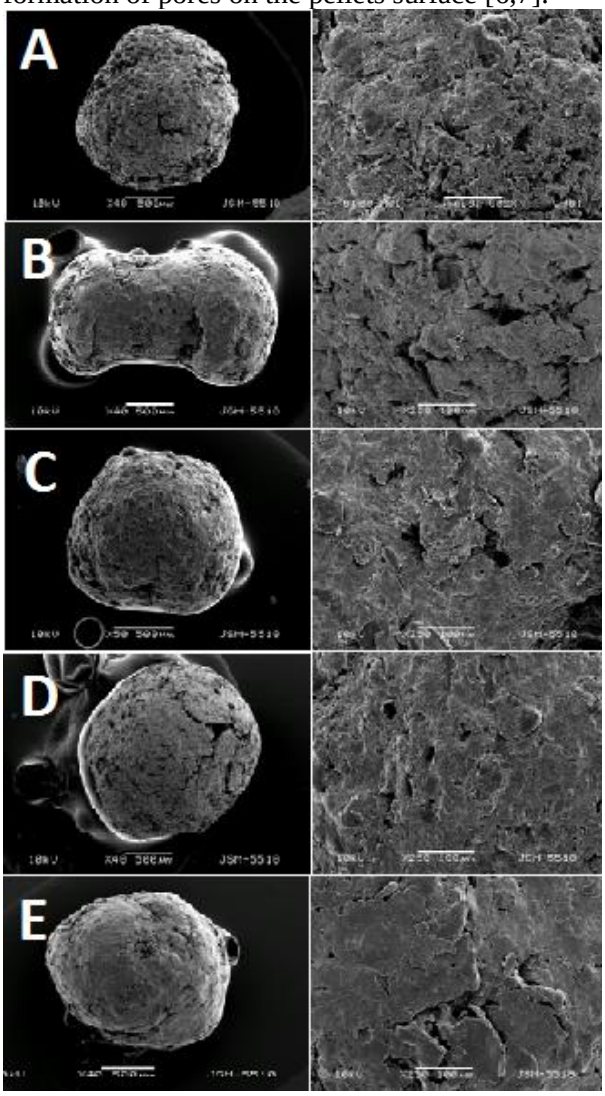

Fig. 3. SEM micrographs of pellets at magnifications 40× (right) and 250× (left): A. Formulation E1 – spherical pellet; B. Formulation E1 – dumb-bell shape pellet; C. Formulation E2; D. Formulation E3; E. Formulation E4.

The increase in ethanol concentration in the kneading liquid increased the amount of dissolved EC which led to obtaining of a thicker hydrophobic EC film, to increased MDT value and to a slower release rate of montelukast sodium [8].

CONCLUSION

The results from our studies demonstrated that the choice of a kneading liquid had a decisive impact on the size and size distribution, shape, surface morphology, as well as on the release behavior of the obtained pellets. Except for formulation E1, all the other batches (E2-E4) in the study were highly spherical and exhibited an extended release rate of montelukast sodium, which suggested that the composition and process conditions were optimal. Evaporation of ethanol during spheronization induced a change of thermo-mechanical properties of EC causing its partial melting and dissolution. These led to agglomeration, rounding and smoothing and reflected in the formation of a very strong hydrophobic film around the particles during the drying period. Due to this an increase in the ethanol concentration resulted in obtaining pellets with narrower particle size distribution, higher dimensions, better sphericity and MDT and slower release rate of montelukast sodium.

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ОХАРАКТЕРИЗИРАНЕ И ЛЕКАРСТВЕНО ОСВОБОЖДАВАНЕ ОТ МАТРИЧНИ ПЕЛЕТИ С УДЪЛЖЕНО ОСВОБОЖДАВАНЕ НА МОНТЕЛУКАСТ НАТРИЙ

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(Резюме)

Безспорните ползи от пелетите, свързани с подобрена бионаличност, ги правят идеални за изготвяне на лекарствени форми с удължено освобождаване. За съжаление, независимо от многото предимства на влажната екструзия и сферонизация, трудно се постига удължено освобождаване, дори с обикновено използваните агенти за модифициране на освобождаването, като целулозни деривати, полиетилен оксид, натриев алгинат и др. За решаване на този проблем ние включихме етанол в свързващата течност и изследвахме влиянието му върху свойствата на етилцелулозни пелети и освобождаването на монтелукаст натрий. Чрез диференциална сканираща калориметрия на етилцелулозата (ЕС) е установено повишаване на топлинния капацитет, свързано с увеличаването на количеството на етанол. Това показва, че етанолът променя термомеханичните свойства на ЕС. Освен това, изпаряването на етанол по време на сферонизацията предизвиква частично стапяне и разтваряне на ЕС, водещи до агломерация, закръгляне и заглаждане и образуване на хидрофобен филм около частиците. В резултат на повишаването на концентрацията на етанол в свързващата течност се получават по-големи частици с по-тясно разпределение по размери, подобрена сферичност, по-продължително средно време за разтваряне и по-бавно освобождаване на монтелукаст натрий.