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XEDS-mapping for explaining release patterns from single pellets

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Abstract

A common way to formulate controlled-release (CR) pharmaceuticals is to coat pellets of active substance with a polymer film, decrease the size of the pellets and distribute them as multiple-unit dosages in capsules. To increase the understanding of the release mechanism, the pellet shape and surface structure of pellets, before and after release in microtitre plates, have been studied by scanning electron microscope and X-ray energy-dispersive spectrometry. By performing these studies we associate release profiles during the first few hours to the microscopic structure. Pellets were divided into three classes (spherical pellets, dumbbell shaped pellets and twin-pellets) according to pellet form. Cases of burst release occurred for all three shape classes due to "open-window-defects" at the surface. Areas of thinner polymer film in the neck-region of dumbbell shaped pellets broaden the range of intermediate release rates for this pellet shape. The surface of twin pellets and dumbbell shaped pellets showed more defects, which increases the release rates in comparison to spherical pellets. All pellets with high release rates revealed ruptures in the polymer film, whereas only small cracks could be traced for pellets with slow release rates. The information gained is necessary for the development of future formulations and mathematical modelling of release patterns. The pharmaceutical used as model was remoxipride coated with a polymer film of ethyl cellulose and 10 wt.% triethyl citrate.

Keywords: Controlled release; Ethyl cellulose; Single pellet; SEM; XEDS; Pellet shape

1. Introduction

The purpose of this work is to describe how SEM, scanning electron microscope, in combination with XEDS, X-ray energy-dispersive spectrometry, can be used to shed light on release mechanisms as a part of developing new drug formulations or as a method to explain large unexpected variations in the release rate from single pellets.

The number of controlled release pharmaceuticals is increasing as they offer more convenience for the patients and lower risks for side effects. Usually, the release is controlled by coating a core containing active substance with a polymer film. When distributing such polymer coated pellets as multiple units the mass

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transfer area for release increases and the risk for dose dumping from defect pellets decreases (Aulton, 2002). This makes multiple unit dosage forms more reliable for a time controlled release than single unit dosage pharmaceuticals (Schultz and Kleinebudde, 1997).

The release behaviour of multiparticulates is determined by the individual pellets (Dappert and Thies, 1978; Jorgensen et al., 1997; Folestad et al., 2000; Sirotti et al., 2002). Since the individuals have different kinetics than the total population, single pellets have to be studied to understand the release mechanism (Dappert and Thies, 1978; Hoffmann et al., 1986a, 1986b). Results from single pellet experiments can then be used to simulate the release behaviour on dose level (Borgquist et al., 2002, in press). There is an active research in simulations of drug release from multiparticulates, since it is assumed that simulation can save time and money in the process of developing new pharmaceuticals, by quickly predicting release patterns through a wide parameter space (Sirotti et al., 2002). Simulations also give insight into which parameters that have the greatest influence on release pattern for active feedback into modifying processes (Borgquist et al., 2002). However, most simulations and mathematical descriptions of release are based on release experiments on a complete dose level (Ragnarsson et al., 1992; Zackrisson et al., 1995; Folestad et al., 2000; Sirotti et al., 2002; Lectome et al., 2003). This makes it difficult to correlate experiments to model simulations when sample variation is unknown on the single-pellet level (Folestad et al., 2000; Lectome et al., 2003), e.g. osmotic pressure effects and ruptures in the polymer coating (Lectome et al., 2003).

There are few previous publications describing single pellet release measurements, the first reported by Hoffmann et al. (1986a). Subsequently, Jorgensen et al. (1997) measured release from single pellets in specially designed vessels, and Schultz and Kleinebudde (1997) measured release from single pellets in flow-trough cells. Previous work has also been performed using the same apparatus for single-pellet release utilised in this work (Folestad et al., 2000; Borgquist et al., 2002). A common method to study the release from single particles have been by measuring conductivity or absorption spectrometry in small cells or wells (Hoffmann et al., 1986a, 1986b; Folestad et al., 2000). Among the parameters that have been shown to be important for determining the release are surface area, film thickness, diffusivity, coating porosity and pellet shape. The aim when producing pellets for multiple unit systems is to achieve spherical pellets, as this shape gives more free-flowing pellets during filling of capsules (Chopra et al., 2002b) and a more predictable release pattern. The filling of pellets into capsules is only possible when the aspect ratio of the pellets is below 1.2 (Podczeck et al., 1999). Thus, spherical pellets are often assumed when describing drug release from controlled release subunits (Ragnarsson et al., 1992; Sirotti et al., 2002) even though this may be far from the real picture.

Previous work on the influence of pellet shape on release behaviour, have been based on comparison of bulk release in USP-vessels. Lorck et al. (1997) assessed pellet morphology by dividing them into *rough* and *smooth* pellets, where spherical pellets were classified as smooth, and all other shapes were denoted as rough. They noticed that rough pellets had a higher release rate than smooth pellets after about 2 h of release (Lorck et al., 1997). Chopra et al. (2002a) intentionally processed batches differently to obtain shape variations, neglecting variations of shape within each batch. These investigations prove that there is a clear effect of the shape of the pellet but does not provide any detailed explanation why.

Indications of how shape influences release behaviour can be approximately predicted at dose level, but, as the dose behaviour is governed by the behaviour of the single subunits, the exact cause for unintended variations in dose behaviour must be determined and used at the subunit level (Folestad et al., 2000). According to Donbrow et al. (1988) every possible release pattern can be designed by mixing single pellets with different release behaviours.

As the pharmaceutical coating methods are moving from organic solvent based methods to water based, there is an urgent call for methods that can explain causes for variations in release pattern. Compared to organic solvent-based coatings, aqueous coatings require higher expenditure for process optimization and process validation (Lorck et al., 1997; Larsen, 2004).

Hoffman noticed in 1986 localized internal dissolution of cores coated with ethyl cellulose providing evidence of release through pores in the film (Hoffmann et al., 1986b). By investigating Roxiam® CR with AFM, atomic force microscopy, during release, Ringqvist et al. (2003) noticed crystalline material on the surface of

the pellets that instantaneously dissolved. This proved the possibility that active substance embedded in the polymer film results in pores through which release of core material occurs. The drawback of AFM in comparison to electron microscopy is that it does not provide information on variation in chemical composition. The element distribution in the material can easily be detected by analyzing the X-rays that result from the interactions of the electrons with the substrate in a SEM-instrument (Lyman et al., 1990).

The use of scanning electron microscopy to study the morphology of controlled release pellets is already described in the literature (Schultz and Kleinebudde, 1997; Chopra et al., 2002b). The advantage in comparison with light microscopy is the better resolution that SEM microscopes offers. Previously, light microscopy have been used for investigation of pellet size, coating thickness (Gunder et al., 1995; Borgquist et al., 2002) and pellet surface structures (Gunder et al., 1995; Lorck et al., 1997), but light microscopy was found to be insufficient for the features of essence in this study. Until now, X-ray emission generated in the SEM has been neglected for the use of identification and localisation of the leaking active substance. The major prerequisite for this method is that the pharmaceutical has an element specific for the active substance and not the coating, something that is true for most cases. XEDS-analyses can be used to trace active substance on the surface or in cracks where active substance is exposed.

In this study the effect of pellet shape on release profile distributions for single pellets has been investigated for the multipellet pharmaceutical Roxiam® CR produced in pilot plant experiments on a large scale using a Wurster coater. The release profile distributions determined here have already successfully been used in a recent investigation to simulate release at dose level (Borgquist et al., 2004). The pellets in Roxiam® CR are coated with a film of ethyl cellulose. To confirm the formation of pores through the film during release, the pellets have been investigated by SEM and XEDS before release, and after 1 h release. The release profile distribution, obtained in the conventional way, showed that 1 h was sufficient to state the release behaviour of that individual pellet. The same individual pellet was then investigated by scanning electron microscopy and XEDS. This made it possible to correlate release behaviour with defects of the polymer film.

The variability shown and discussed in this study is most probably present also in production scale as the experimental material was produced in a fairly large pilot plant unit.

2. Materials and methods

2.1. Formulations

The pharmaceutical used as model in this work was Roxiam® CR obtained from an experimental work (Zackrisson et al., 1995) at AstraZeneca Tablet Production Sweden Södertälje. Mean pellet weight is about 1 mg and each pellet contains approximately 75% of the active substance, remoxipride (Fig. 1). After extrusion, spheronization, drying and sieving of the core substance, the pellets were coated with a polymer film. The polymer film, consisting of ethyl cellulose with 10 wt.% triethyl citrate, was applied in a fluidised bed, with a top spray at a temperature of 60 °C. Ethanol was used as the solvent (Zackrisson et al., 1995; Ringqvist et al., 2003; Borgquist et al., 2002, 2004).

2.2. Sampling for single-pellet release

Pellets to be used for release experiments were taken during an initial non-optimized scale-up study ranging from 60 to 125% of the nominal amount of film. In this study, release measurements were performed only on pellets coated with a polymer film corresponding to 70 mg polymer/g pellet equivalent to a film thickness of approximately 13 μm (Borgquist et al., 2004; Ringqvist et al., 2003). The analysis with XEDS-

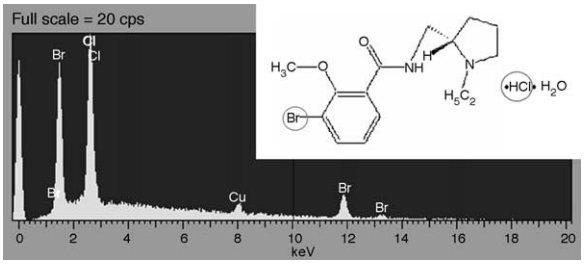

Fig. 1. XEDS-spectrum of the pure active substance remoxipride. It contains two elements, bromine and chlorine, that can be used for identification. The small copper peak originates from the support stub.

mapping on pellets that were not subjected to release experiments was extended to also include pellets with thinner polymer film (40 mg polymer/g pellet) for comparison of surface features.

For each microtitre plate, the amount of pellets needed was weighed in, in a similar manner as for dose release experiments, to minimize sampling bias. The fact that the single pellet release data from this work was successfully used in a modelling work comparing single pellet release with release on dose level (Borgquist et al., 2004), supports the assumption that the sampling was representative.

2.3. Structural studies with SEM and XEDS

The SEM used was a JEOL JSM840A, working at 20 kV accelerating voltage. The microscope uses a W filament, and is equipped with an Oxford Instrument three-window XEDS detector mounted at a high-angle position. The active substance, remoxipride hydrochloride monohydrate (Fig. 1), contains two elements, bromine and chlorine, which are not present in any excipients used. Thus, it is possible to use XEDS for analysis and mapping. Pure active substance as well as pellets was attached to copper stubs using carbon tabs (Agar Scientific), and the surface was coated under vacuum (10^{-2} mbar) with a thin carbon film (approximately 15 nm) using double carbon thread at a working distance of 35 mm in a CED030 instrument (BALZERS, Liechtenstein). Spectra were normally recorded with 100 s live time at 3×10^{-9} A beam current, using the Be-window. Elemental maps with 256×200 pixel resolution were accumulated over at least 30 frames to ensure good statistics. Elemental maps of the bremsstrahlung background (proportional to the average Z^2), using the same number of channels as the peak windows were recorded simultaneously with the element maps in order to monitor any artefacts due to geometry or changes in density.

2.4. Release from single pellets

Single pellets were weighed with a modified Mettler Toledo AX26. The scale gives a standard deviation of 0.5% for pellets of this size. Single pellets were released in microtitre plates (Nunc, Denmark) (Folestad et al., 2000). Release media was 300 μl MilliQ-water thermostated to a preset temperature at 37 °C. The amount of active substance released was measured over time (every 10 min for 18 h) by absorption at 305 nm, with an absorbance microplate reader (SPEKTRAmax® 250 UV–vis-spectrometer, Molecular Devices, UK) on a stirring table for continuous agitation. Calibration was performed with solutions of remoxipride Chemical Reference Standard. In each microtitre plate one row was filled with reference solution and second row with Milli-Q water. The stirring speed was varied between 100 and 150 rpm, but was found not to have any appreciable effect on the release profiles.

The release was studied during the first 18 h (400 pellets) in the pellet shape influence investigation. To determine the correlation of film defects and release profile, the release time was shortened, to 1 h (160 pellets, absorbance measurements every 5 min), to have as intact pellets as possible for the subsequent analysis by SEM and XEDS. Release was stopped by soaking up the release media and letting the pellets air dry.

2.5. Optical imaging

Pellets were divided into three classes according to pellet form, using visual inspection of each single pellet ($n = 400$) from at least three angles in an optical stereomicroscope (Leica). Pellet form A consists of single, spherical pellets, pellet form B is characterized by a neck region (dumbbell shaped), and pellet form C consists of twin pellets (Fig. 2). For each pellet, the release profile, determined as weight active substance released per weight of pellet as a function of time, was fitted to a mathematical model, as described by Borgquist et al. (2004), to be plotted in a diagram for the respective pellet form.

3. Results and discussion

3.1. Categorisation of pellet form

Typical pellets from the three form classes (A–C) can be seen in Fig. 2. These pellets have been released in indicator solution during approximately 2 h, which is the cause of dark spots on the surface where release occurred. Macro photographs were used as a coarse guide for which part of the pellet surface that were of interest for further analysis by SEM. Results from the XEDS analysis indicate that the use of indicator solution was

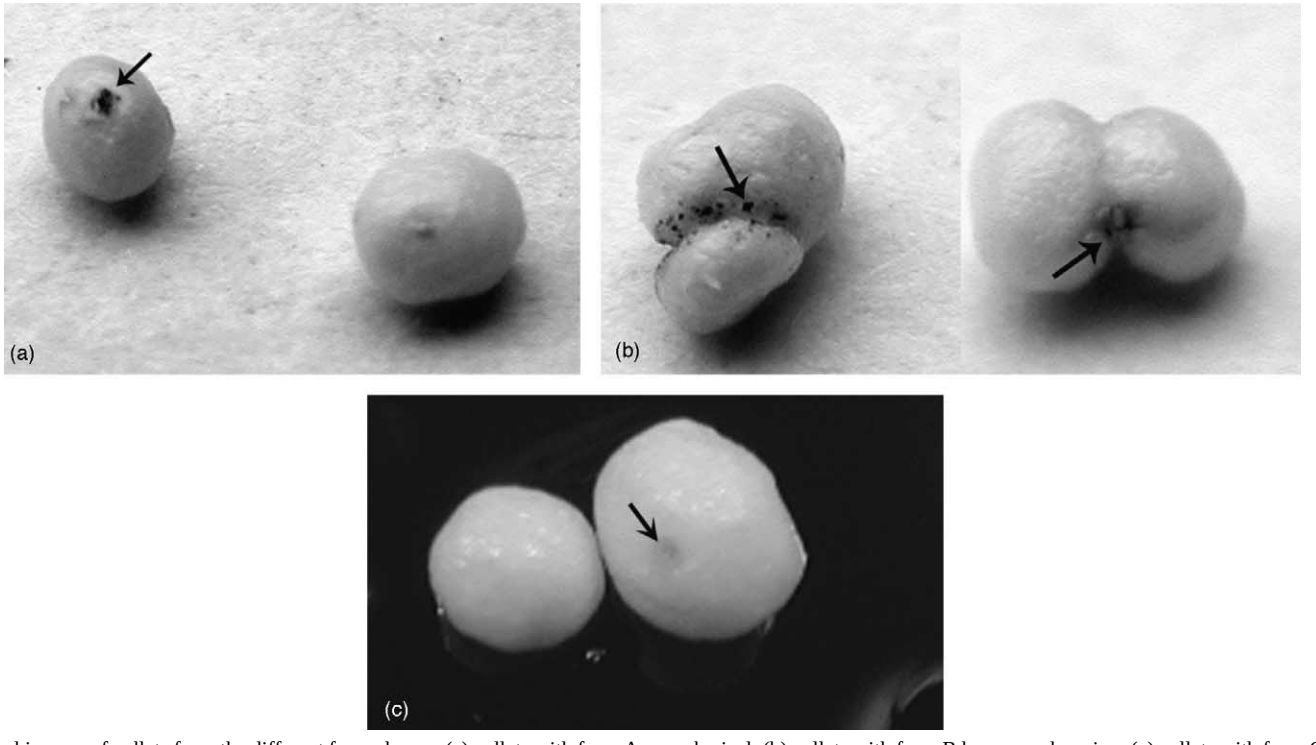

Fig. 2. Optical images of pellets from the different form classes: (a) pellets with form A are spherical; (b) pellets with form B have a neck region; (c) pellets with form C are twins. These pellets have been released in an indicator solution for approximately 2 h, and areas where release occurs can easily be traced (indicated by arrows).

not necessary to trace released active substance and the indicator solution and macro photographs were not further used. Efforts were made on adopting different computer algorithms for the categorisation of pellets into form classes from digital microscope images, exploiting parameters as e.g. convexity and roundness. However, the loss of the third dimension in the 2D projections provided a too high level of erroneous classifications and uncertainties, and this approach was discarded in favour of visual categorisation. The total pellet population consists of about 40% each of pellet form A and pellet form B and 20% of pellet form C (based on 400 investigated pellets).

3.1.1. Spherical pellets

The release profiles for pellets with form A fall into two categories, as shown in Fig. 3. In most cases the release rate is slow and the polymer films of these spherical pellets are homogenous, with small cracks, as shown by analysis with SEM. The other release category constitutes about 10% of the pellets with form A, and presents a fast release. Fig. 4 shows examples of pellets from this category. On the surface of these fast releasing pellets "open-windows" consisting of areas not covered by polymer film, can be revealed by XEDS-mapping. These holes are probably created when a twin-pellet (form C) is separated into two halves, as described later on.

3.1.2. Dumbbell shaped pellets

In Fig. 5, the release profiles for pellets of form B is shown. These release profiles falls into the same two categories as the release profiles for pellets of form A, but with a higher frequency in the intermediate region. Areas of thinner polymer film in the neck-region (Fig. 6a), due to unfavourable pellet forms during polymer coating, can be attributed to this release behaviour. By studying pellets coated with only 40 mg polymer/g pellet it was confirmed that the polymer film is thinner in the neck-region (Fig. 6b). Active substance was visible through holes at the neck of these pellets. This defect, where the film is thinner, broadens the range of intermediate release rates of form B in comparison with pellets of form A (Fig. 7).

3.1.3. Twin pellets

Pellets with form C were difficult to prepare for the SEM analysis as they frequently separate into two parts. It is possible that strain during manufacturing and during the release studies also cause rupture of the film on sides where the twins are attached to each other. The rupture occurs in several different ways and leaves re-

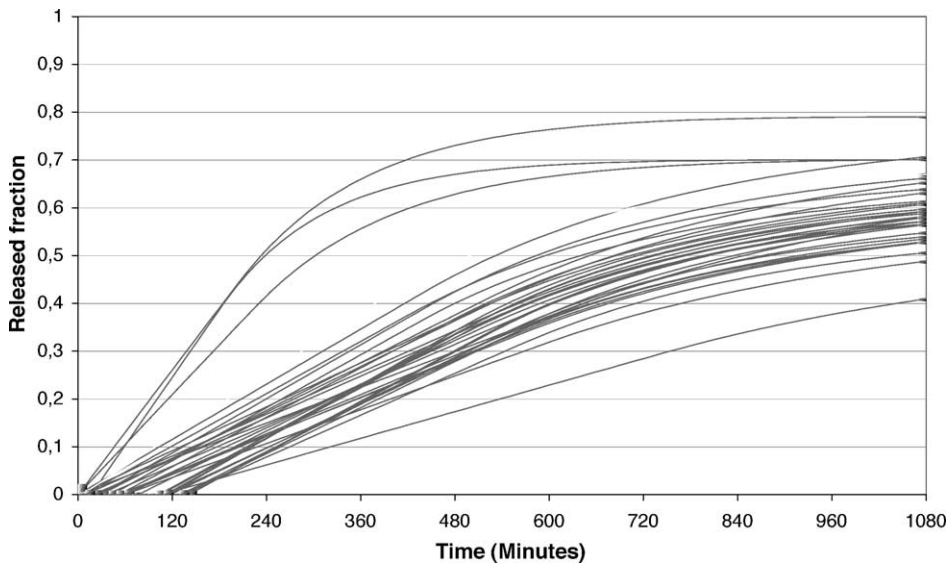

Fig. 3. Released amount plotted against time for pellets with form A. The release profiles fall into two categories.

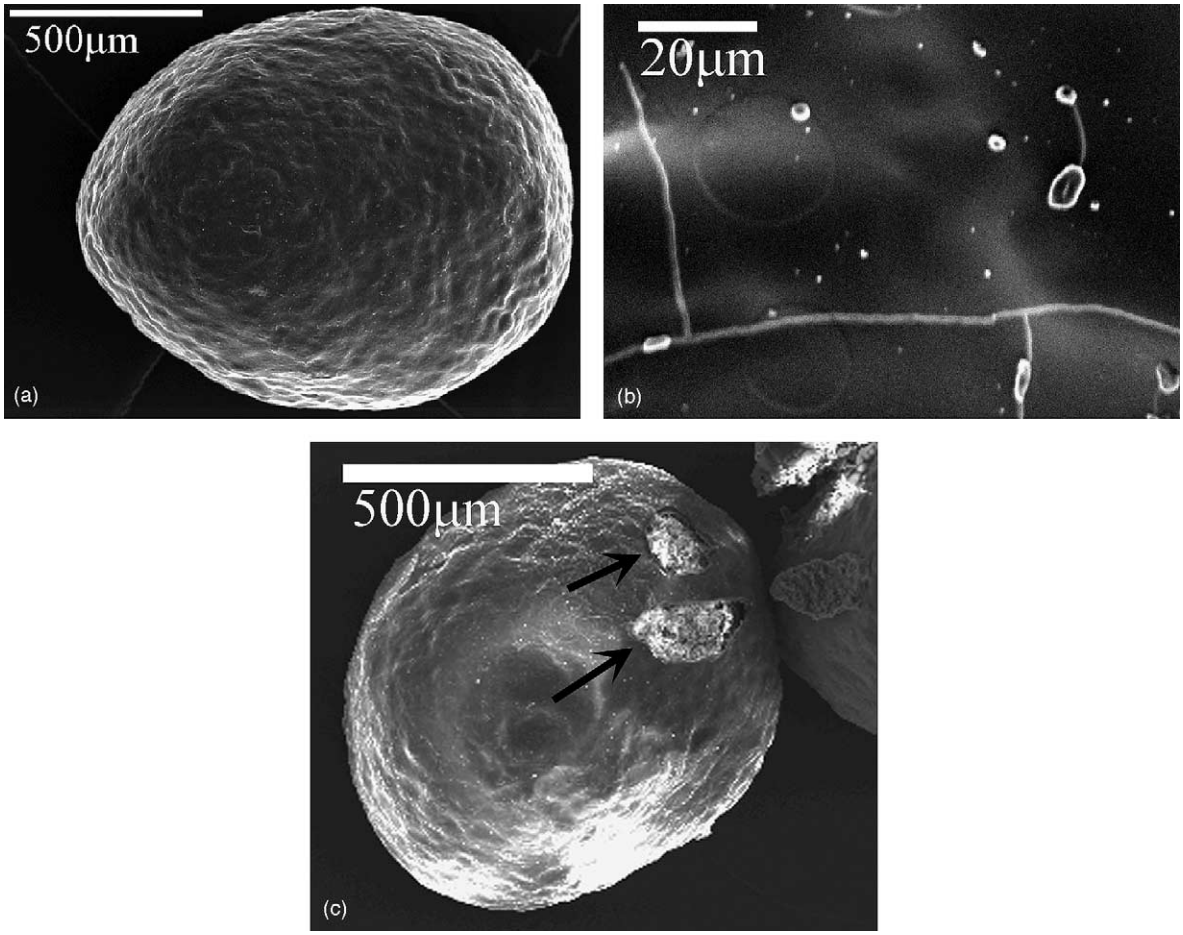

Fig. 4. SEM micrographs of pellets with form A: (a) the slow releasing pellets are spherical and the polymer film looks homogenous, apparently without cracks; (b) at higher magnification, however, small cracks in the polymer film can be observed. The disc structures in the image are dried coating droplets. (c) On the surface of the fast releasing pellets areas are revealed which are not covered by polymer film (indicated by the arrow).

gions where the active substance is exposed. The two parts may separate according to Fig. 4c, resulting in two pellets of form A, where one part, from which the film was ripped off, shows a fast release and the other part a slow release. Alternatively, if the rupture arises early during spray coating, regions covered with a thinner inhomogeneous film will be created. This can be another explanation of the fast release profiles that occur for a portion of the pellet form A. The separation process may also produce cracks in both parts resulting in a high release rate from both of them. In addition, the parts may stay attached to each other and behave as two single pellets with a low specific surface area and slow release. The release mechanisms for pellets of form C are therefore not as easily described.

The diagram in Fig. 7 indicates that a slow release from both parts of a twin pellet is a rare outcome and that the polymer films of pellets with form C or B contain more defects, which increases release rates in comparison to pellets of form A.

3.2. Short-time release experiments coupled to XEDS analysis

In attempts to confirm the link between the open-window defect, as well as defects of the film in the

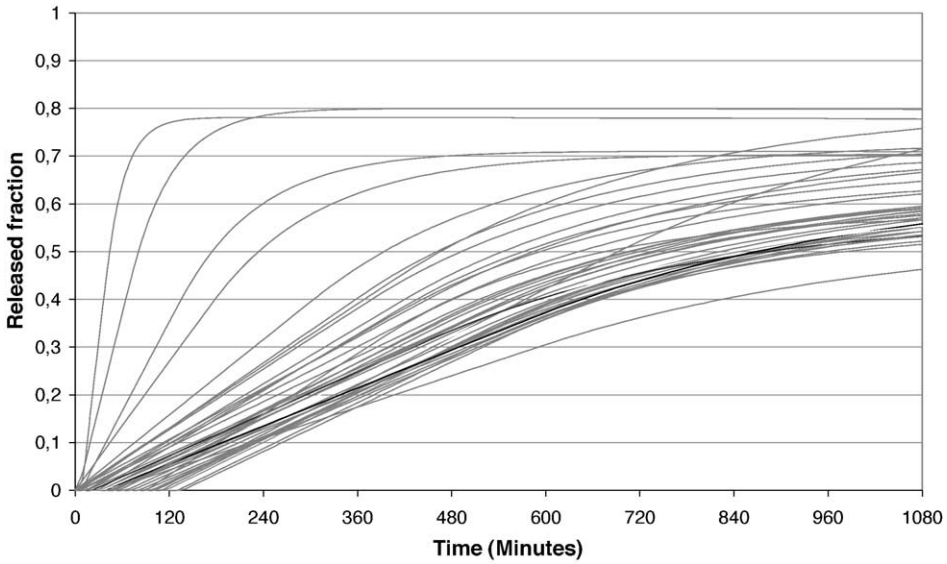

Fig. 5. Released amount plotted against time for pellets with form B. The release profiles fall into the same two release categories as pellets with form A, but also with a higher frequency in the intermediate region.

neck region, with high release rates, pellets were released in water during a shorter time. From the release profile distributions achieved from the 18 h release-experiment it was stated that 1 h of release was satisfactory to determine the release profile for the individual pellets. After 1 h of release the individual pellets were prepared for SEM analysis. By this procedure the release profile during the first hour could be directly connected to pellet form and surface structure and XEDS-mapping could be used to trace ruptures or cracks where active substances were exposed.

The active substance, remoxipride, has a characteristic XED-spectrum due to the presence of bromine and chlorine, as shown in Fig. 1. The small copper-peak in the spectrum is due to the supporting copper stub. In

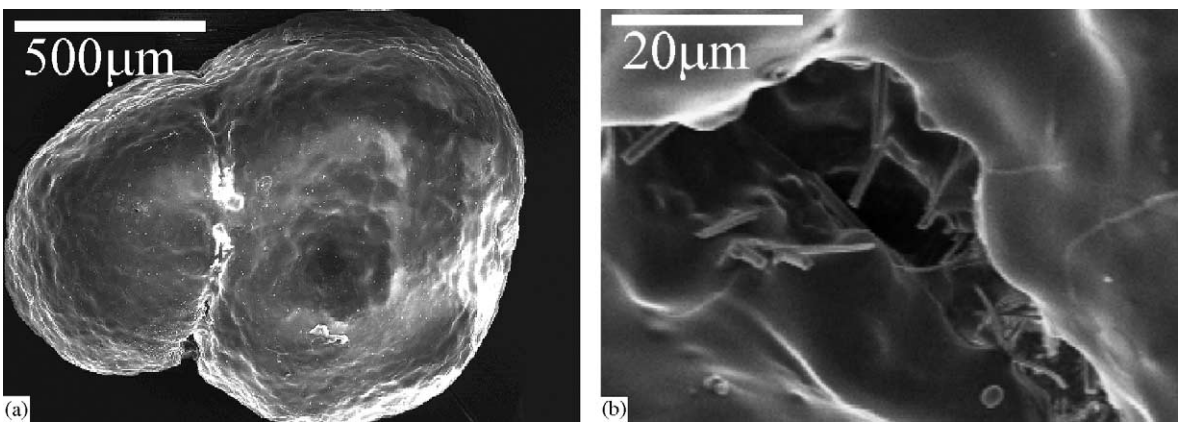

Fig. 6. SEM micrographs of pellets with form B: (a) in the neck-region areas with thinner polymer film can be found; (b) in the neck-region of a pellet with form B coated with 60% of the polymer film (40 mg polymer/g pellet), active substance can be seen through a hole. The active substance can be easily recognized by its needle shape and by using XEDS.

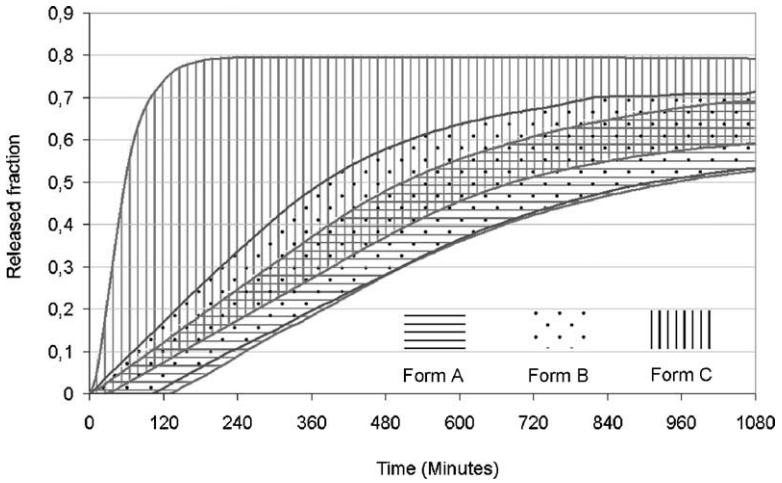

Fig. 7. Comparison of the interval of release profiles for 80% (limited by the 10th and the 90th percentile) of the pellets in each class shows that release from pellets with form C (vertical stripes, $n = 15$) is much faster and that the release rate interval for pellets with form B (dots, $n = 35$) is broader than the interval for pellets with form A (horizontal stripes, $n = 35$).

Fig. 8, the needle shaped structure of the pure, crystalline remoxipride particles can be seen.

The polymer coating (70 mg polymer/g pellet) appears to be thick enough to prevent any signal from the enclosed active substance. This can be seen in Fig. 9, where mapping of the X-ray signals corresponding to chlorine has been performed on a pellet with an intentional cut through the coating.

As expected, all pellets with high release rates revealed ruptures in the polymer film, whereas only small

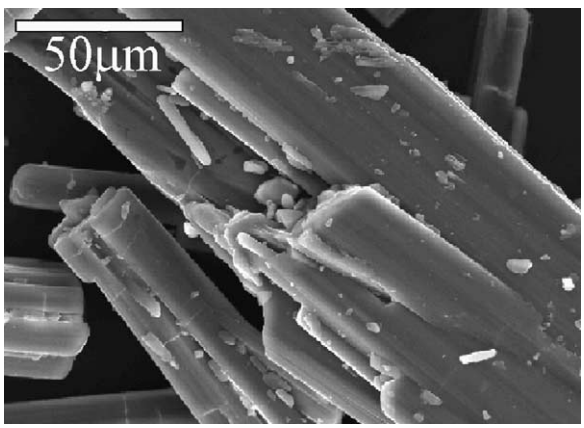

Fig. 8. SEM micrograph of crystals of pure active substance, remoxipride. The crystals are needle shaped, and with typical dimensions of 20 μm × 120 μm, though the size distribution is broad.

cracks could be traced on the surface of pellets with slow release rate. To confirm our statement that these small cracks are not present before release, unreleased pellets were also investigated. Small cracks could not be traced on these pellets. This also demonstrates that cracks are not a result of destructive interaction with the electron beam. To state that the cracks were not due to this interaction, artificial surface structures were provoked by contracting the beam to one small spot for a prolonged time. This gave rise to perforated structures, clearly distinguishable from the cracks.

Another potential source of artificial cracks could be the vacuum applied during carbon coating and SEM, the surface structure seen in this work was though compared with AFM-studies of the same kind of pellets (Ringqvist et al., 2003) in liquid cells and no difference was distinguishable. The time to acquire appropriate vacuum levels before carbon coating is an indicator of the water content in the sample. After air drying of the pellets, this time was short, and indicates a low level of unbound water in the samples. The shortening of the release time was also done to leave as much of the core substance as possible inside the pellets, to minimize artefacts due to the polymer film falling in.

The interaction of water during release may cause cracks through two different mechanisms: introduction of water into the polymer film and diffusion of water into the pellet core (osmotic effect). Dasbach et al.

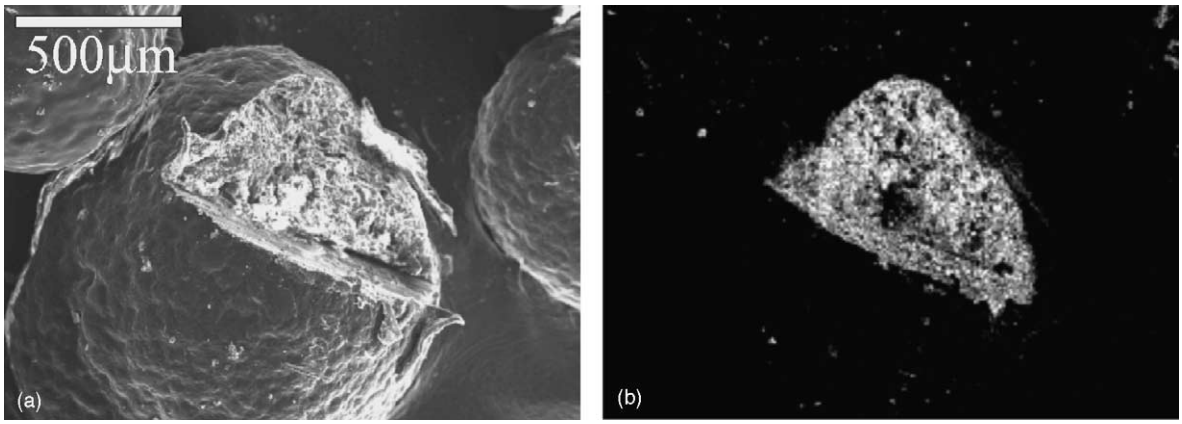

Fig. 9. (a) SEM micrograph of a pellet with an intentional cut through the coating and (b) mapping of X-ray signals from the same pellet corresponding to chlorine. The X-rays corresponding to chlorine is detected only from the open part of the pellet and from grains of active substance. This procedure was used to ensure that the polymer film was thick enough to prevent X-ray signals from enclosed material in the core.

(2003) noticed cracks in cast ethyl cellulose films after storage. The storing conditions introduced water into the films, and water acting as a poor solvent of the polymer caused crack formation. Ringqvist et al. (2003) noticed that the pellets swell slightly during the first part of the release. This swelling may be caused by diffusion of water into the pellet core. Using Raman spectroscopy they showed that active substance was embedded in the polymer film. When this water-soluble active substance is leached out, the polymer film may become semi-permeable and the active substance can be released by an osmotic pumping mechanism (Hjärtstam, 1998). The internal hydrostatic pressure then possibly influences the formation of cracks. If the coating layer is incomplete and contains some holes, an increased osmotic pressure will never occur. Neither will cracks appear, that are due to strain in the film after increased internal pressure (Schultz and Kleinebudde, 1997). Hence, osmotic pressure is a probable reason for crack appearance on the surface of the pellets investigated in this work, as no cracks are seen on the surface of pellets with holes.

The shape of the pellets within each form class showed a large variation, which prevented the use of a uniform geometric normalization factor. Therefore, the weight was used as the normalization factor for release instead of area. As the area-to-volume ratio decreases with increased volume, release normalized by weight should decrease as a function of weight, assuming constant density of all particles and constant coating thickness. This trend could not be detected, neither by plotting the normalized release rate for the remoxipride pellets against pellet weight, nor by using multiple regression analysis (not shown). The explanation may be either that the variations in shape are too large (Lorck et al., 1997) or that the pellet area for pellets formulated in this way does not have any intrinsic influence on the release rate. This is due to that release principally appears through cracks in specific regions. Hence, the area and film diffusivity in these regions should be the main rate determining factors and these factors are not correlated to the total area of the pellet.

4. Conclusions

The fact that release appears from film coated formulations, does not mean that the film is permeable. Release from tested pellets coated with polymer films of ethyl cellulose with 10 wt.% triethyl citrate has been proven to occur through cracks. These cracks may be due to swelling of the core due to e.g. hydrodynamic pressure (osmotic effects) and a too weak and brittle film. This cannot be revealed from release data for single pellets without investigating the pellet surface. As opposed to the commonly accepted method, using USP-vessels to investigate release, release in microtitre plates in combination with XEDS analysis may help in

understanding the release mechanism, and thus controlled release formulations may be improved. In this project, release profiles indicated that 10% of the pellets had defects in the film, resulting in immediate release and high release rates. Pellet form has great influence on where and when cracks occur, since pellet form influences the possibilities of getting a homogenous polymer film. This was verified by the structure studies with SEM and XEDS.

The information obtained from single-pellet release studies combined with SEM and XEDS studies gives an insight of new CR formulations, as well as indicating detrimental steps in the manufacturing procedure.

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