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Research paper

N-Trimethyl chitosan chloride as absorption enhancer in oral peptide drug delivery. Development and characterization of minitablet and granule formulations

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Abstract

In this study, minitablet and granule formulations were developed as solid oral dosage forms for the delivery of peptide drugs with the absorption enhancer *N*-trimethyl chitosan chloride (TMC). Minitablets were deemed suitable as a dosage form due to their ability, as components of multiple unit dosage forms (MUDFs), to disperse from each other, before disintegration, effectively increasing the area in which the polymer can assert its absorption-enhancing effect. The polymer should be released from the dosage forms prior to the release of the peptide, which was, together with achieving maximum release of both ingredients, the main focus of this study. Desmopressin (1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (DDAVP) was used as model peptide drug. The optimized minitablet formulation consisted of two types of granules, namely DDAVP and TMC granules. DDAVP granules, containing tetraglycerol pentastearate (TGPS), were specifically aimed at delaying the release of the peptide from the dosage form. Burst release of TMC was attempted with TMC granules. Both these granule types were included in the granule formulation. Release profiles for both the optimized minitablet formulation as well as the granule formulation showed that the release of DDAVP was effectively delayed from the formulation compared to the formulation where no attempt at delaying the release was made. In comparison, more TMC was released, and at a faster rate, from the granule formulation than the optimized minitablet formulations. Both the optimized minitablet formulation and the granule formulation show suitable release profiles for the delivery of peptide drugs with TMC as absorption enhancer in solid oral dosage forms.

Keywords: *N*-Trimethyl chitosan chloride; Minitablet; Granule; Mucoadhesive; Peptide; Multiple unit dosage form; Dissolution profile

1. Introduction

One of the critical issues when designing an effective delivery system for drugs with poor permeability is to ensure predictable and reproducible absorption without wasting up to 99% of the drug. Normally poor bioavailability of peptides and proteins from oral and non-oral mucosal routes is a result of the interplay of poor permeability characteristics, instability towards proteolytic enzymes, cell metabolism and non-enzymatic clearance mechanisms such as the first-pass effect and excretion in the bile [1]. The poor or highly variable absorption of the therapeutic agent may limit the development of a non-parenteral dosage form. If the limited absorption of a compound is due to its inability to cross biological membranes, rather than any problems with instability or pre-absorptive metabolism, the co-administration of a safe absorption-enhancing agent offers a potential means for overcoming this barrier [2]. For most therapeutic agents, administration via a non-parenteral route is the preferred choice, with the oral route as the main preference [3].

In recent years chitosan ((1 → 4)-2-amino-2-deoxy-β-D-glucan) has attracted much attention as a potential absorption enhancer across mucosal epithelia, especially for peptide drugs [4]. Chitosan is regarded as a biocompatible, biodegradable, natural origin polymer and is widely used in the food industry [5–7]. Chitosan is known to improve peptide transport across the epithelial barrier,

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however, this polymer is only soluble in an acidic environment. *N*-Trimethyl chitosan chloride (TMC), a derivative of chitosan, is soluble in the entire pH range and has proven to be a potent absorption enhancer of peptide drugs by opening the tight junctions between epithelial cells, thereby facilitating the paracellular transport of hydrophilic compounds [4,8]. TMC with a high degree of quaternization (60%) proved to be a potent absorption enhancer for the paracellular transport of hydrophilic marker molecules and peptide drugs in vitro in Caco-2 cell monolayers, as well as in vivo after intestinal administration both in rats and pigs [9–11]. Furthermore, to study the possible membrane damaging effect of the polymer, Caco-2 cell monolayers were stained with fluorescent probes after treatment with TMC polymers with different degrees of substitution, and no substantial cell membrane damage could be detected [12].

Although TMC proved to be a potent and safe absorption enhancer of peptide drugs both in vitro and in vivo, until now it has always been administered as a solution. The impracticality of administering a solution as well as the fact that most peptides are unstable in the presence of water has led to the need for a solid oral dosage form.

In order to optimally make use of the absorption-enhancing properties of TMC in solid dosage forms, the polymer should be able to dissolve rapidly and then be allowed to spread over a wide area across the epithelium in the small intestine. The opening of tight junction is a time-dependent process [4] and it is therefore necessary that most of the TMC should be released from the dosage form prior to the release of the peptide drug. Furthermore, the site at which the peptide is released should coincide with the site where the TMC is opening the paracellular pathway in order for the maximum amount of peptide to be transported via the paracellular route. Multiple-unit dosage-forms (MUDFs) have been used in the past to control the release of drugs. Although the behaviour of the MUDFs are controversial, these dosage forms show more reproducible release, less absorption variability and a lower risk of dose dumping [13], and mainly consist of minitablets, pellets, granules or particles which are enclosed in a gelatin capsule [14]. Minitablets are tablets with a diameter equal to or smaller than 2–3 mm and can be easily filled into capsules directly or after coating. Because of the manufacturing process, defined sizes and strengths can easily be produced, and the variability within a batch is small [13]. Minitablets, as with other MUDFs, have been shown to be more reliable in prolonging gastric residence time in contrast to single unit dosage forms (SUDFs) where an 'all or nothing' emptying process is generally obtained [15].

Desmopressin (1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (DDAVP)) was chosen as a model peptide for this study. DDAVP, which is currently on the market in a tablet formulation (Minirin), is indicated for the management of primary nocturnal enuresis in children. Although tablets are considered to be a discrete mode of administering DDAVP to these patients, the absolute bioavailability from this tablet formulation is only 0.1% [16], which clearly illustrates the necessity of incorporating an absorption enhancer in the formulation. In the present study, the rationale behind the delivery of TMC and DDAVP as minitablets and as a granule formulation will be described, resulting in the optimal formulations selected by suitable release profiles.

2. Materials and methods

2.1. Materials

Chitosan (Chitoclear, 97.6% deacetylated, viscosity 552 mPa s) was purchased from Primex Ingredients ASA (Avaldsnes, Norway). Avicel PH-101 was obtained from FMC Corporation (Philadelphia, PA, USA) and Ac-Di-Sol from FMC Biopolymer (Philadelphia, PA, USA). DDAVP was kindly donated by Ferring Pharmaceuticals (Malmö, Sweden). Tetraglycerol pentastearate (TGPS, HLB 2.6) was obtained from Sakamoto Yakuhin Kogyo Co. (Osaka, Japan) and used as polyglycerol esters of fatty acids (PGEFs). Size 1 gelatin capsules were obtained from Spruyt-Hillen (Vianen, The Netherlands) and disposable cuvettes from Sarstedt (Nürnberg, Germany). Cibacron brilliant red 3B-A was obtained from Aldrich Chemical Co. (Milwaukee, WI, USA). Pectin, from apple (USP), was purchased from Sigma (Steinheim, Germany) and Carbopol 934P was a gift from B.F. Goodrich (Cleveland, OH, USA). Mucus (partially purified porcine gastric mucin type III) was obtained from Sigma (Dorset, UK). All other chemicals were of analytical grade.

2.2. Synthesis of TMC

TMC was synthesized from chitosan (Chitoclear) in a two-step reaction according to the method of Sieval et al. [17]. ^{1}H-Nuclear magnetic resonance (NMR) was used to calculate the degree of substitution of the synthesized polymer [17]. The ^{1}H-NMR spectrum was recorded in D_2O with a Bruker 600 MHz spectrometer (Bruker-Biospin, Rheinstetten, Germany) at 80 °C. A TMC polymer with a degree of quaternization of 55% was obtained. In the following paragraphs, the polymer will be referred to as TMC. The absolute molecular weights of the free base polymer as well as the synthesized polymer were determined with a size exclusion chromatograph (SEC) connected to a multiple angle laser light scattering detector (MALLS) as previously described by Snyman et al. [18] and were found to be 260 400 g/mol and 241 400 g/mol, respectively. Both polymers were classified as having a high molecular weight compared to polymers with the same chemical structure used in previous studies. The aqueous solubility of the synthesized TMC was determined to be approximately 20 g/100 ml. However, it should be stated

that although the product is clear it is very viscous and can no longer be classified as a solution, but should rather be classified as a gel.

2.3. Determination of the intrinsic mucoadhesivity of TMC

The mucoadhesive properties of TMC used were determined with a tensile separation test according to the method of Snyman et al. [19]. Pectin, Carbopol 934P and a clean plate were used as reference standards. Briefly, films of TMC, Carbopol 934P and pectin were prepared on aluminium plates. After drying, the total weight of each film was 0.05 g. The prepared aluminium plates were suspended from a microbalance (Hugo Sachs Elektronik (Force Transducer F30 Type 372), Germany) and the plates were lowered until contact was achieved with a 30% (w/v) solution of mucus in distilled water at 25 °C. The downward pressure of the plate on the mucus was 2 g. The plate was left in this position for different intervals (ranging from 20 to 120 s) for complete hydration of the polymer to occur, after which it was once again lifted at a rate of 0.25 mm/s. The separation was registered by the software Chart for Windows v3.4 (Powerlab System, Oxfordshire, UK) and the maximum detachment force was noted. All experiments were performed in triplicate. To determine the intrinsic mucoadhesivity (IM) of the polymers the maximum detachment force was calculated at a time of 120 s. The IM was used to rank the polymers according to their mucoadhesive strength. Pectin was chosen as the 100% reference to which TMC and Carbopol 934P were compared. The baseline (clean plate reference standard) was subtracted from the IM value of each of the polymers and the percentage mucoadhesivity of the polymer to pectin was calculated.

2.4. Preparation of solid oral dosage forms

Table 1 summarizes all the formulations that are described in this section, indicating the different types of granules prepared as well as the ratios in which they were used. Avicel PH-101 was used as a filler/disintegrant and Ac-Di-Sol as a superdisintegrant. In all mixing procedures a specially designed miniature V-mixer was used, making it possible to mix the components for up to six minitablets, efficiently. TMC/DDAVP and TMC granules, both used to attempt immediate release of TMC, were prepared by wet granulation with ethanol and the granules were dried at ambient temperature. To prepare the DDAVP granules the specific amounts of DDAVP and TMC were mixed. TGPS, which was used to delay the release of DDAVP from these granules, was melted and the peptide and polymer mixture was dispersed in the melted TGPS. TMC was additionally included in these granules due to its mucoadhesive properties. These types of microparticulate mucoadhesive systems were previously described for Carbopol 934P by Akiyama et al. [20]. Due to attachment of the granules to the mucus in the gastrointestinal tract the residence time of the granules is further increased for DDAVP, which is then released at the site of absorption. The TGPS solidified within seconds after the heat was removed, resulting in a brittle mass, which was easily crushed with a mortar and pestle. The ratio of granules corresponding with each formulation was mixed with the specific amount of Ac-Di-Sol needed. A single-punch die with a diameter of 3 mm was used to manufacture the minitablets and the final mixtures to be compressed were individually weighed with an analytical balance. The relative amount of granules for the granule formulation was easily filled into gelatin capsules (size 1) for dissolution testing.

Table 1
Composition of minitablet and granule formulations

	Minitablets			Granules
	1	2	3	
TMC granules				
TMC	–	10	5	50
Avicel PH-101	–	10	5	32
Ac-Di-Sol	–	5	3	20
DDAVP granules				
TMC	–	5	2.5	20
DDAVP	–	0.1	0.05	0.5
TGPS	–	15	7.5	60
TMC/DDAVP granules				
TMC	10	–	–	–
Avicel PH-101	10	–	–	–
Ac-Di-Sol	5	–	–	–
DDAVP	0.1	–	–	–
Total amount of granules	25.1	45.1	23.05	182.5
Intergranular Ac-Di-Sol	5	5	5	7.5
Total weight per tablet/capsule	30.1	50.1	28.05	190

All weights are indicated in milligrams.

2.5. Dissolution and release studies

The aim of the dissolution studies was not only to study the release of DDAVP from the dosage form, but also the release of TMC. The dissolution assays were performed with a Sotax AT7 Smart dissolution apparatus (Sotax AG, Basel, Switzerland) with special minicells and minipaddles supplied by Sotax to fit the system. The total volume of each minicell was 200 ml. Although this is not a USP approved method, it is necessary to use these miniature cells and paddles due to the small amount of peptide present in each minitablet. The rotation speed of the paddles was 100 rpm and the dissolution medium was phosphate buffer solution (PBS) with a pH of 7.2 at 37 ± 0.5 °C. PBS was prepared according to the method of the USP XXIII. For each minitablet formulation, six replicates were tested, all from the same production batch. From each cell, 600 μl of

dissolution medium was withdrawn at predetermined intervals and replaced with the same amount of pre-warmed dissolution medium. The samples of three of the replicates were pipetted directly into disposable cuvettes and analysed for TMC content, as described in Section 2.7. The second set of replicates were analysed for DDAVP content, as described in Section 2.6.

To evaluate the release of TMC and DDAVP from the granule formulation, three replicates were tested. Two samples with a volume of 300 μl were withdrawn from each cell at predetermined time intervals. The samples were diluted to fall within the linear range of both assays, with one set analysed for TMC content and the other for DDAVP content.

2.6. HPLC analysis of DDAVP

DDAVP content in the samples were determined by high-performance liquid chromatography (HPLC) with a Spectra-Physics system consisting of a P200 gradient pump, AS 100 autosampler, ABI UV/Vis detector and datajet integrator (Darmstadt, Germany). 'Winner on Windows' (Thermo-Separation, Breda, the Netherlands) was used as software package to evaluate all measurements. The stationary phase was a Chromspher 5 C18 100 × 3-mm column (Chrompack, Middelburg, The Netherlands). Isocratic elution was performed with 0.067 M (pH 7) phosphate buffer containing 16.67% acetonitrile at a flow rate of 1 ml/min. The wavelength for UV detection was 220 nm and the injection volume was 100 μl. The retention time of DDAVP was 5.4 min.

2.7. TMC colorimetric assay

For TMC to be active as an absorption enhancer, the polymer should be in solution. Therefore, the amount of the polymer released from the dosage form should be determined parallel to the amount of peptide released. A colorimetric method for determining chitosan in an aqueous solution was described by Muzzarelli previously [21]. This method was used as the basis for the present TMC colorimetric assay. A solution of Cibacron brilliant red 3B-A was prepared in deionized water, at a concentration of 1.5 mg/ml. Aliquots (5 ml) of the stock solution were made up to 100 ml with 0.2 M PBS at a pH of 7.2. The final concentration of the dye solution was 75 μg/ml. To prepare the standard curve, a stock solution of TMC was prepared at a concentration of 400 μg/ml. Dilutions were made by pipetting different volumes of the stock solution directly into disposable cuvettes, after which the volume in each cuvette was filled to 600 μl with PBS at a pH of 7.2. Aliquots of the dye solution (2.4 ml) were added to each cuvette and the absorbance was recorded within 5 min, after adding the dye, at a wavelength of 572 nm with an Uvikon 923 Double Beam UV/Vis Spectrophotometer (Kontron Instruments, Beun DeRonde, Abcoude, The Netherlands). Background subtraction was performed at 700 nm. Samples, obtained from the dissolution studies, were analysed in a similar way. If the samples had a volume of only 300 μl, an additional 300 μl of PBS was added to the cuvettes prior to the addition of the dye.

3. Results and discussion

3.1. Mucoadhesive properties

It is known that with an increase in the degree of quaternization of TMC the mucoadhesive properties of the polymer decreases [19]. Fig. 1 depicts the IM of TMC and Carbopol 934P as a percentage relative to pectin. Pectin exhibits relatively poor mucoadhesive properties, but the advantage is that small deviations from the accepted values (obtained with different set-ups) are obtained and it is therefore a suitable reference standard [19]. Carbopol 934P is a polymer that portrays excellent mucoadhesive properties [22]. Values for both Carbopol 934 P and pectin compared well with data presented in literature and were sufficient to calibrate the system [23,24]. A difference of 33% between the IM of TMC (165%) and Carbopol 934 P (198%) was calculated. Considering the high degree of quaternization (55%) of the polymer, the IM of TMC compares well to the IM determined for Carbopol 934P, which as previously mentioned portrays excellent mucoadhesive properties.

3.2. Solid dosage forms: preparation and in vitro release studies

TMC is a sticky white powder, and initial experiments (not shown) revealed that TMC is very easily directly compressed into tablets. However, if these tablets are dispersed in an aqueous solution, they only swell at the outer surface. No disintegration of the tablets is observed and there is no release of the polymer. Even with very high percentages of superdisintegrants (ca. 40%) it was not possible to disintegrate the tablets. This effect was very

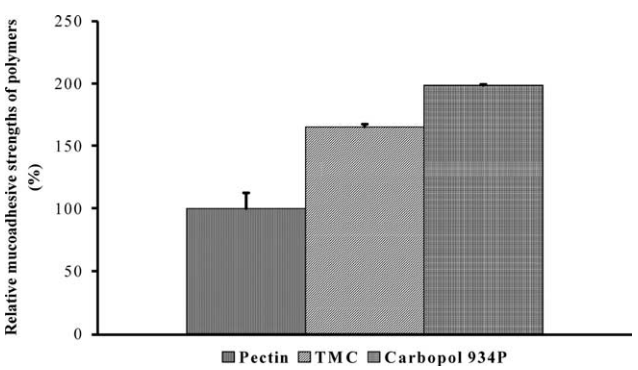

Fig. 1. Intrinsic mucoadhesivity of pectin, TMC and Carbopol 934P. Data are expressed as the mean ± SD of four experiments.

slightly decreased with the minitablets, although the effect was not significant. It should be stated at this point that due to the small size of the minitablets, this dosage form could not be tested in a disintegration apparatus as specified by one of the pharmacopoeias. Disintegration referred to by the authors was observed as the dissolution tests were performed. With wet granulation it was possible to manufacture granules, which were easily mixed with a superdisintegrant, resulting in an increase in the disintegration of the tablets. However, if the granules only consisted of TMC, minitablets did not disintegrate. Disintegration of minitablets was only possible if a filler/disintegrant was added in the same amount as TMC to the formulation, effectively 'diluting' the sticky properties of TMC. The TMC/DDAVP granules prepared in formulation 1 (Table 1) contained equal amounts of TMC and Avicel PH-101, the latter functioning effectively as a filler and disintegrant, as well as Ac-Di-Sol as a superdisintegrant. The prepared granules were additionally mixed with Ac-Di-Sol (extragranular) and compressed as minitablets. With this formulation, it was initially thought that the TMC might still delay the release of the peptide from the dosage form; however, this was not observed.

Fig. 2. depicts the release of both DDAVP and TMC from formulation 1. The maximum release of the polymer was obtained within 25 min (53%), in contrast to a total peptide release within 5 min. As previously mentioned, the absorption enhancer should be released from the dosage form prior to the release of peptide. Although DDAVP is a more stable peptide drug than some other peptides, enzymes in the small intestine rapidly degrade most peptides. Release of TMC prior to the release of DDAVP will allow the polymer to open the tight junctions between the epithelial cells for the maximum amount of DDAVP to be absorbed by the paracellular pathway before degradation.

Minitablet formulation 2 (Table 1) attempted to delay the release of peptide from the dosage form, but not the release of TMC. This formulation consisted of TMC granules, which were similar in design to the TMC/DDAVP granules of formulation 1, except for the absence of DDAVP from the granules. With these granules, rapid release as seen in the context of the properties of the polymer, could still be

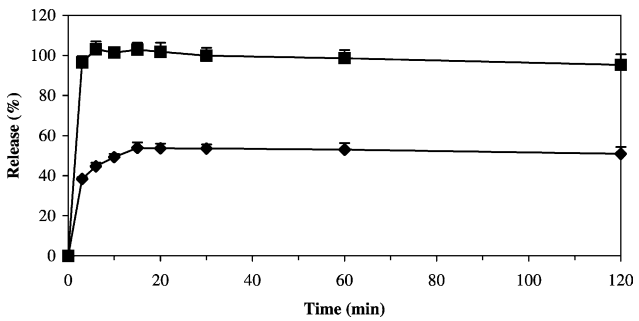

Fig. 2. Release of DDAVP and TMC from minitablet formulation 1. (■) DDAVP; (◆) TMC. Data are expressed as mean ± SD ($n = 3$).

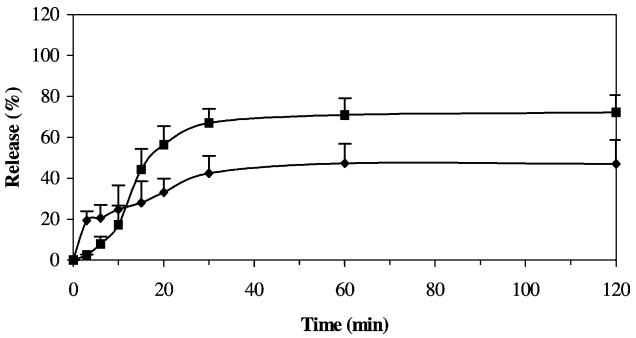

Fig. 3. Release of DDAVP and TMC from minitablet formulation 2. (■) DDAVP; (◆) TMC. Data are expressed as mean ± SD ($n = 3$).

obtained. Release profiles for both DDAVP and TMC from formulation 2 are depicted in Fig. 3. Within 5 min 20% of the TMC was released from the minitablets with a further release of an additional 27% at a decreased rate. The maximum release of TMC from this formulation was 47% within 60 min. To delay the release of DDAVP, a mixture of the peptide and TMC was dispersed in melted TGPS (HLB 2.6). At 15 min only 44% of the total amount of peptide was released from these minitablets (Fig. 3). Maximum release (72%) of DDAVP was obtained at 60 min. Although maximum release of both TMC and DDAVP were obtained at 60 min from minitablet formulation 2, the release rate of DDAVP was slower than the release rate of TMC and delay of the release of DDAVP was mostly achieved in the first 20 min. The initial rapid release of TMC was due to the fast disintegrating TMC granules and subsequent dissolution of TMC. Although the required release profiles were obtained, the minitablets increased considerably in weight (Table 1) and almost doubled in size due to the inclusion of TGPS.

With minitablet formulation 3 (Table 1) it was attempted to obtain similar release profiles as with formulation 2 and to decrease the size of the tablets in order to obtain minitablets with a height of no more than 3 mm. Minitablets from formulation 2 had a height of approximately 6 mm. From a practical point of view, minitablets with a height greater than 3 mm are difficult to fit into a gelatin capsule. The release profiles of minitablet formulation 3 for DDAVP and TMC are depicted in Fig. 4. In the first 5 min, 15% of

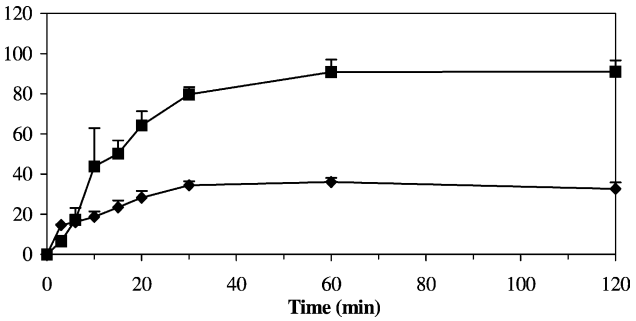

Fig. 4. Release of DDAVP and TMC from minitablet formulation 3. (■) DDAVP; (◆) TMC. Data are expressed as mean ± SD ($n = 3$).

the total amount of TMC was released from the dosage form with a further release at a decreased rate. Maximum release of the polymer (36%) was obtained within 60 min. In the first 15 min, 50% of the total DDAVP amount was released form the dosage form with a maximum release (91%) of DDAVP at 60 min. With formulation 2, suitable release profiles were obtained with a delayed release of DDAVP compared to the release of the polymer. A more suitable size (3×2.5 mm) for minitablets was obtained with formulation 3. If formulation 2 is compared to formulation 3 it is noticed that more DDAVP was released from formulation 3 than formulation 2. The opposite is true for TMC where more TMC was released from formulation 2 than formulation 3. The reason for the differences in release percentages might be due to the fact that all tablets were manufactured on small scale by hand. This might have resulted in more of the polymer or TMC adhering to the manufacturing surfaces.

It was thought that due to the nature of the polymer, tableting should have an effect on the release of both TMC and DDAVP. To study the influence of tableting on the release of TMC and the peptide from the dosage form, the release of DDAVP and TMC were measured from a granule formulation. Release profiles from this formulation are depicted in Fig. 5. In the first 5 min, no release was observed for DDAVP or TMC. This is due to the time it took for the gelatin capsule to dissolve. At 10 min 24% of the total amount of TMC was released and 17% of the total amount of DDAVP. The maximum amount (54%) of TMC was released at 60 min compared to the maximum amount (77%) of DDAVP, which was released at 30 min. From Fig. 5 it is evident that more TMC is able to dissolve from the granule formulation compared to minitablet formulations 2 and 3. The release rate of DDAVP from the granule formulation is approximately the same as it is for formulations 2 and 3. Before any TMC or DDAVP could be released from the minitablet formulations, the tablets had to disintegrate into the separate granules at least. The disintegration step is not included in the dissolution process of the granule formulation due to the formulation.

The TMC release profiles of all formulations studied have similar characteristics. There is an initial burst release within 5 min and then a slow release of the polymer within the next

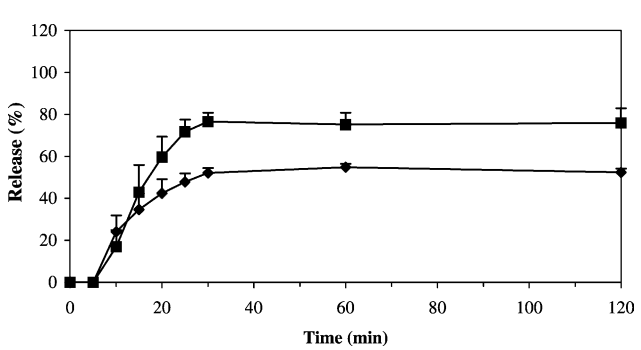

Fig. 5. Release of DDAVP and TMC from the granule formulation. (■) DDAVP; (◆) TMC. Data are expressed as mean ± SD ($n = 3$).

25 min. The TMC used in this study is a high molecular weight polymer and it is therefore not surprising that the dissolution rate is not very high if the fact that polymer was compacted during tableting was additionally taken into account. All the release profiles indicate that approximately 50% or less of the TMC is in solution. However, it is not excluded that non-released TMC in the granules still have positive charges exposed at the surface of the granules and still may be able to open the tight junctions. For the two minitablet formulations (formulations 2 and 3), attempting to delay the release of the peptide, less TMC dissolved than was observed for formulation 1. It should, however, be kept in mind that the percentage of release indicated is for the total dosage form, including the TMC present in the DDAVP granules. Any TMC released from the DDAVP granules will be able to open the tight junctions. However, it was noticed that these granules do not disintegrate and TMC release from these granules should therefore be minimal. This is in accordance with the results published by Akiyama et al. [20] where it was seen that the polymers hydrate and are clearly visible in their hydrated state as a gel on the surface of the prepared microspheres. As mentioned previously, the main reason for including TMC in the DDAVP granules was the polymer's mucoadhesive properties, which are described in Section 3.1. Following work previously published by Akiyama et al. [20] it is believed that TMC included in the DDAVP granules will localize the granules at the surface of the gastrointestinal tract. This will enable the granules to release DDAVP directly at the site where the TMC already acted as an absorption enhancer. Rapid absorption of DDAVP will result in less enzymatic degradation of DDAVP. Mucoadhesive polymers included in these previously described granules are known to swell at the surface of the granule and exert their mucoadhesive effect while the granules themselves do not disintegrate and therefore do not release the mucoadhesive polymers. The total release of the DDAVP was not, however, restricted but only delayed and can be explained in light of the extremely hydrophilic nature of the peptide as well as its much lower molecular weight compared to TMC.

Due to the larger surface area of a certain amount of minitablets compared to a normal tablet of the same weight, it is believed that the dissolution rate of TMC will be increased. The fact that the dosage form already consists of multiple-units might also increase the ability of the polymer to spread in the lumen of the gastrointestinal tract. As previously mentioned, because of their uniform size, smooth surface, low porosity and high attainable strength, minitablets should probably be coated more reproducibly than pellets or granules [14,25].

4. Conclusion

It was proven in recent years that TMC is a potent absorption enhancer for peptide drugs. TMC opens the tight

junctions between intestinal epithelial cells, to increase the paracellular transport of drugs. However, until now no solid oral dosage form has been developed to deliver TMC as an absorption enhancer.

In the present study, the development of minitablets as solid oral dosage forms for the delivery of TMC and DDAVP is described. Determination of the mucoadhesive properties of TMC showed that TMC has excellent mucoadhesive properties, which might be beneficial in peptide drug absorption. Suitable release profiles were obtained for DDAVP and TMC from minitablet formulations. In all formulations an initial burst release was obtained for TMC with a delayed release thereafter. The delayed release of TMC was attributed to the high molecular weight of the polymer, which influences its dissolution rate. The release of DDAVP was effectively delayed with the inclusion of TGPS in minitablet formulations 2 and 3, and TMC can thus be expected to unlock the paracellular route for transport before the release of DDAVP from the dosage forms. Both minitablet formulation 2 and 3 exhibited suitable release profiles for the delivery of TMC and DDAVP. However, due to the size of the minitablets of formulation 2 these minitablets cannot be filled into a gelatin capsule for administration and this formulation is therefore not considered to be suitable for in vivo evaluation. The granule formulation also exhibited suitable release profiles for the delivery of TMC as mucoadhesive absorption enhancer and DDAVP as model peptide. Future studies will include the in vivo evaluation of these formulations.

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