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Novel peroral dosage forms with protease inhibitory activities. II. Design of fast dissolving poly(acrylate) and controlled drug-releasing capsule formulations with trypsin inhibiting properties

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Abstract

The purpose of this study was to develop a dosage form for peroral peptide drug delivery which is able to increase the stability of the model substrate *N*-α-benzoyl-L-arginine ethyl ester (BAEE) against degradation by trypsin. Different capsule formulations, containing carbomer (C934P) and its neutralized freeze-dried modification (FNaC934P), were investigated in a specially designed dissolution test apparatus. The capsules were placed in a dissolution medium with 10 IU trypsin/ml. Carbomer was found to be more efficient in inhibiting trypsin activity than FNaC934P. The recovery of the substrate BAEE was highly dependent on both the swelling velocity of the polymers and the pre-incubation time of trypsin with the poly(acrylates) in the incubation medium. Pre-incubation for at least 20 min in carbomer or FNaC934P dispersions was required to achieve sufficient trypsin inhibition. From all the formulations investigated, a two-phase capsule preparation consisting of a rapid swelling FNaC934P part as the first phase and microparticles of polyglycerol esters of fatty acids containing carbomer particles and the peptide model drug BAEE as the second phase, had the most profound effect on trypsin activity inhibition.

Keywords: Poly(acrylic acid) derivatives; Carbopol® 934P; Freeze-dried sodium Carbopol® 934P; Polyglycerol ester of fatty acid (PGEF); Trypsin inhibition; Peroral solid dosage form; Peptide drug delivery

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1. Introduction

In the last decade, many attempts in peroral peptide drug delivery have been made both to inactivate the luminal enzymes and to overcome the metabolic barriers located in the brush border linings limiting their systemic absorption (Lee et al., 1991). The colon, showing less polypeptide degradation, has also been under investigation, in spite of its poor epithelial permeability (Touitou, 1992; Rubinstein et al., 1996) and highly variable absorption (Kompella and Lee, 1992). Another approach is to promote peptide absorption already in the small intestine which has a higher epithelial permeability, but also shows high luminal enzyme activity. Possibilities to overcome the metabolic barriers are the modification of the peptide structure (Hashizume et al., 1992), coadministration of protease inhibitors (Zhou, 1994), and using special formulations. Many formulation approaches for peptide delivery have been described, such as water-in-oil microemulsion (Drewe et al., 1992; Constantinides et al., 1994), nanoparticles (Michel et al., 1991), liposomes (Fukunaga et al., 1991) or dosage forms for colon targeting (Saffran et al., 1986). They are designed not only to protect the drug from contact with the luminal proteases, but also to release the drugs in areas which are favourable to their absorption.

Mucoadhesive drug delivery (Longer et al., 1985; Lehr et al., 1990; Leung et al., 1991) is one of the formulation approaches to enhance the peptide drug absorption by localizing the dosage form at the site of optimal absorption. Lehr et al. (1992) described that the weakly crosslinked poly(acrylic acid) derivative polycarbophil is able to enhance the absorption of the vasopressin derivative DGAVP from the small intestine. Lundin and Vilhardt (1986) found that another vasopressin analogue (DDAVP) was absorbed in the duodenum and the ileo-caecal junction, but not in the colon even though the small intestinal enzyme activity was high compared to that in the colon. Inhibition of mucolysis in the pig colon (Hutton et al., 1990) and inhibition of pepsin activity from the pig stomach by carbomer have been found (Foster et al., 1994). In addition, Lueßen et al. (1995) showed that polycarbophil or carbomer had a strong inhibitory effect on the hydrolytic activity of trypsin, dependent on the incubation time of trypsin with the poly(acrylates) (Lueßen et al., 1994). Lueßen et al. (1996) also reported that these poly(acrylates) in a homogeneous dispersion inhibited α-chymotrypsin, carboxypeptidase A and cytosolic leucine aminopeptidase as well, because of the high binding affinity of the poly(acrylates) to both Ca^{2+} or Zn^{2+} ions. These bivalent cations are important for the thermodynamic stability of the enzymes, or are essential co-factors. However, enzyme deactivation by these poly(acrylates) is a time-dependent process and homogeneous gel formation of the poly(acrylates) has to take place first to activate the poly(acrylates). Hence, a simple

Table 1
Formulations used in trypsin inhibition experiments and recovery of BAEE in the medium containing trypsin (10 IU/ml; 40 ml; 37°C).

	A	B	C	C*	D	D*	E	F	G	H	I	J
TGPS	—	—	—	—	50	50	100	100	150	—	—	—
TGMS	—	—	—	—	50	50	100	100	150	—	—	—
Kollidon® CL	—	200	100	100	—	—	—	100	—	—	—	—
FNaC934P	100	—	100	100	100	100	—	100	100	—	100	—
C934P	—	—	—	—	—	—	100	100	100	—	—	100
BAEE	20	20	20	—	20	—	20	20	20	20	20	20
Total	120	220	220	200	220	200	320	520	520	20	120	120
AUC(0–180 min); % min	165	886	1374	—	1824	—	1715	5563	5725	1090	2413	13 960

Values in mg; TGPS, tetraglycerol pentastearate; TGMS, tetraglycerol monostearate; each formulation from A to G is placed in a capsule; H, BAEE in buffer solution shown as blank; I and J, 0.25% (w/v) FNaC934P and C934P dispersion, respectively.

dosage form is primarily not appropriate to exert a sufficient enzyme inhibitory effect and therefore suitable dosage forms fulfilling this demand and to release the peptide drug at the right time have to be designed.

In the previous study (Akiyama et al., 1996), we reported about a rapidly dispersing and drug-releasing capsule containing neutralized, freeze-dried carbomer. The purpose of the present study was to design a fast dissolving polymer and controlled drug-releasing capsule formulation containing the poly(acrylate) derivative and *N*-α-benzoyl-L-arginine ethylester (BAEE) as a model substrate for trypsin. Rapid disintegration, immediate formation of a gel and inhibition of trypsin activity of the capsules containing the poly(acrylic acid) derivatives were considered as important prerequisites of a suitable dosage form for peptide drug delivery.

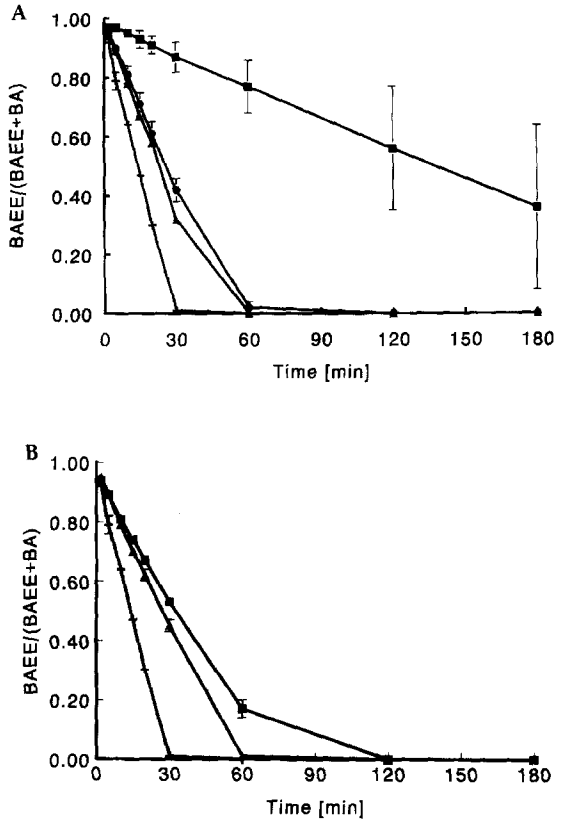

Fig. 1. Effect of various concentrations of C934P (A) and FNaC934P (B) on trypsin activity; pre-incubation time, 2 min. (A) C934P: (+) 0% (blank), (▲) 0.05%, (●) 0.10%, (■) 0.25%. (B) FNaC934P: (+) 0% (blank), (▲) 0.15%, (■) 0.25%.

2. Experimental

2.1. Materials

Carbomer (Carbopol® 934P; C934P) was kindly supplied by BF Goodrich (Cleveland, OH). Freeze-dried sodium salt of Carbopol® 934P (FNaC934P) was prepared as described previously (Akiyama et al., 1996). Tetraglycerol pentastearate (TGPS) and tetraglycerol monostearate (TGMS) are poly(glycerol esters of fatty acids) (PGEFs) and supplied by Sakamoto Yakuhin Kogyo, Osaka, Japan. *N*-α-benzoyl-L-arginine ethylester (BAEE), *N*-α-benzoyl-L-arginine (BA), trypsin (EC 3.4.21.4; TPCK treated type XIII) and bovine serum albumin (BSA) were purchased from Sigma (St Louis, MO). Kollidon® CL was obtained from BASF AG (Ludwigshafen, Germany). All other chemicals were of reagent grade. The capsules used in this study were of size # 0 or # 1 and obtained from Spruyt-Hillen, Vianen, The Netherlands.

2.2. Preparation of C934P and FNaC934P dispersion

C934P or FNaC934P in concentrations of 0.5% (w/v) was added to 0.05 M phosphate buffer (pH 6.8), and vigorously agitated with a magnetic stirrer overnight. After obtaining a homogeneous dispersion, the pH was adjusted to 6.8, and the 0.05 M phosphate buffer was added to obtain polymer concentrations of 0.05, 0.1, 0.15 and 0.25% (w/v), respectively.

2.3. Preparation of capsules

In general, all physical mixtures were made by thoroughly mixing the ingredients in a mortar with a pestle, whereas the microparticles were prepared as described previously (Akiyama et al., 1996). Formulations A, B, C and C* were pre-

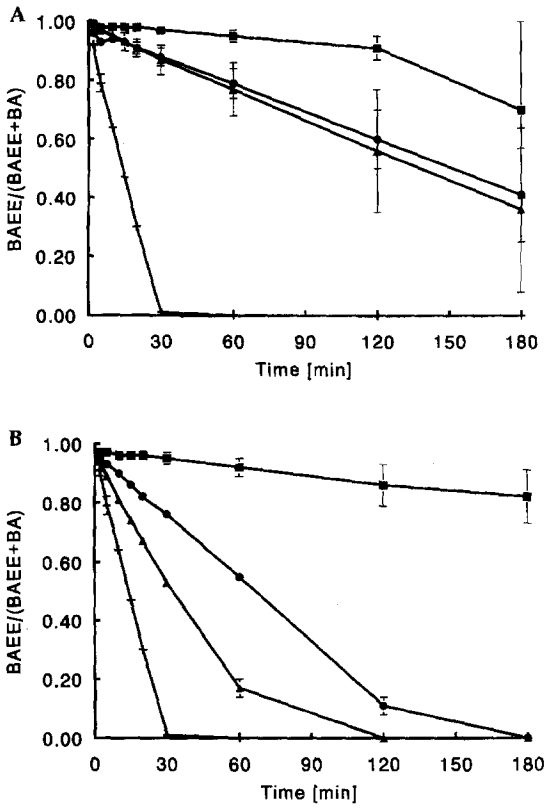

Fig. 2. Effect of pre-incubation time of trypsin with 0.25% C934P (A) and 0.25% FNaC934P (B) on the inhibition of trypsin activity. Incubation was performed in a medium of 0.05 M phosphate buffer (pH 6.8; 40 ml) containing trypsin (10 IU/ml); 37°C; 100 rev./min; mean ± S.D. (N = 3). Pre-incubation time: (+) 0 min (blank), (▲) 2 min, (●) 10 min, (■) 20 min.

pared by filling capsules with mixtures of the ingredients as shown in Table 1. Formulations D and D* were prepared as follows: TGPS and TGMS were melted at 85°C. BAEE and FNaC934P were dispersed in the melted PGEFs. The mixture was cooled and crushed. After sieving, particles of less than 200 μm were filled in a no. 1 transparent capsule. Formulation E was prepared as follows: BAEE and C934P were dispersed in melted TGPS and TGMS. The mixture was cooled and crushed. Particles of 200–500 μm in diameter, obtained by sieving, were placed in a no. 0 capsule (formulation E; the particles without a capsule are referred to as formulation E*). Formulation F was obtained by mixing formulation E* and Kollidon® CL/FNaC934P (1:1) mixture (i.e. C*) and filling the mixture in a no. 0 capsule. Formulation G was prepared by mixing formulation E* and PGEF microparticles containing FNaC934P (1:1), i.e. D* (< 200 μm), and placing the mixture in a no. 0 capsule. All formulations are listed in Table 1.

2.4. Measurement of trypsin activity and release of BAEE

2.4.1. Measurement of trypsin activity in dispersions of C934P or FNaC934P

An amount of 400 IU trypsin was added to 40 ml of a dispersion containing FNaC934P or C934P in different concentrations, i.e. 0, 0.05, 0.1, 0.15 and 0.25% (w/v), in the dissolution apparatus as described previously (Akiyama et al., 1996). To avoid aspecific binding of the enzyme, all parts of the dissolution equipment were pretreated with 0.1% (w/v) BSA. After pre-incubation for 2, 10 or 20 min, 0.5 ml of a BAEE stock solution (pH 6.8, 40 mg/ml) was added. Volumes of 50 μl were taken at predetermined time intervals, and diluted with 1 ml of a stop solution (phosphoric acid, pH 2.0). Intact BAEE and the formation of the metabolite BA were determined by gradient HPLC.

2.4.2. Dissolution test of BAEE combined with trypsin activity measurements

Following pre-incubation of trypsin for 2 min, different capsule formulations containing BAEE were added to the dissolution media. Thereafter, samples of 50 μl were withdrawn at predetermined time intervals and immediately centrifuged (800 × g; 15 min) after mixing with 1 ml stop solution. Further experimental procedures were as described in Section 2.4.1.

3. Results and discussion

3.1. Inhibition of trypsin activity by dispersions of C934P and FNaC934P

Fig. 1A,B shows the inhibition of trypsin activity by C934P and FNaC934P dispersions in vari-

Table 2
Degradation rate constants (K_d) of FNaC934P and C934P dispersion in a medium (pH 6.8; 0.05 M phosphate buffer; 40 ml) containing trypsin (10 IU/ml); mean ± S.D. (N = 3)

Concentration (%)	FNaC934P			C934P		
	Pre-incubation time (min)			Pre-incubation time (min)		
	2	10	20	2	10	20
Blank (0)	2.90			2.90		
0.05	—	—	—	1.94	1.58	1.35
0.10	—	—	—	1.94	1.49	1.07
0.15	1.63	1.04	0.81	—	—	—
0.25	1.46	0.68	0.09	0.29	0.18	0.06
C* (0.25)	—	—	1.23	—	—	—
D* (0.25)	—	—	1.43	—	—	—

Values expressed as × 10^{-3} M/h; —, not determined; BAEE, 1.46 mM; trypsin, 1.47 μM.

ous concentrations at pH 6.8. When BAEE was added after 2 min pre-incubation of trypsin in the C934P and FNaC934P preparations, it was found that the higher the polymer concentration, the stronger the inhibition of trypsin activity. Both polymers were able to reduce the activity of the enzyme. In comparison to FNaC934P, the non-neutralized C934P displayed a stronger inhibition. At a concentration of 0.25% (w/v) C934P, more than 40% of the substrate remained intact after 3 h.

Fig. 2A,B shows the effect of various pre-incubation time periods (2, 10 and 20 min, respectively) of trypsin in the polymer dispersions before starting the degradation experiment by adding the substrate BAEE to the incubation medium. The recovery of BAEE increased with increasing pre-incubation times of trypsin. The inhibition of trypsin was more effective in the C934P than in the FNaC934P preparations. While a pre-incubation time of 2 min in the case of C934P already strongly reduced trypsin activity, a pre-incubation time of 20 min for FNaC934P was required to allow nearly complete inhibition of BAEE degradation. These results suggest that if FNaC934P is used as the quick gel-forming polymer, there is a need to design a dosage form which provides a pre-incubation of about 20 min before the peptide drug is released, whereas with C934P, similar inhibition effects are already obtained after incubation times of 10 min.

The decrease in [BAEE/(BAEE + BA)] per hour was defined as degradation rate constant, K_d, whose values are summarized for C934P and FNaC934P in Table 2. The intrinsic elimination rate constant is determined in a 'blank' formulation without any polymer, as shown for formulation H in Table 1.

The weaker inhibitory effect of FNaC934P compared to C934P may be explained by two major reasons. Firstly, this might be due to the difference in carboxylic acid content per weight unit of polymer, since FNaC934P additionally contains sodium ions from the neutralization with NaOH. The second and probably more important reason is that Na^+-ions are also bound to the carboxylate groups, and because of competition they reduce the affinity of the polymer towards bivalent cations such as Ca^{2+}. Additionally, the difference in trypsin inhibitory activity might also be influenced by the difference in the gel structure between C934P and FNaC934P dispersions, which is expressed in different rheological properties of the two polymer systems. The viscosity values of 0.25% (w/v) dispersions of C934P and FNaC934P at pH 6.8 and 25°C are 2.52 and 4.44 cp, respectively.

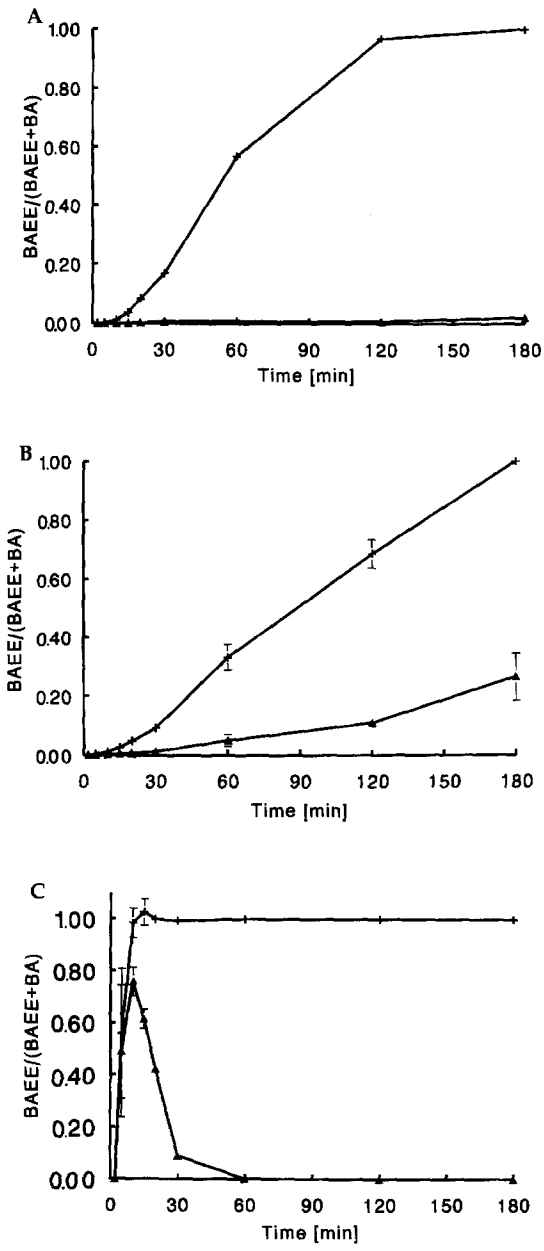

Fig. 3. Dissolution of BAEE and total (BAEE + BA) from capsules in a medium of 0.05 M phosphate buffer (pH 6.8; 40 ml) with trypsin (10 IU/ml); 37°C; 100 rev./min; pre-incubation time, 2 min; mean ± S.D. (N = 3). (A) Capsules containing FNaC934P (formulation A): (+) total BAEE + BA, (▲) BAEE. (B) Capsules containing PGEF-C934P-BAEE microparticles (formulation E): (+) total BAEE + BA, (▲) BAEE. (C) Capsules containing Kollidon® CL (formulation B): (+) total BAEE + BA, (▲) BAEE.

3.2. Release profiles of BAEE and inhibition of trypsin activity by capsules containing C934P and FNaC934P

Considering its quick swelling properties, FNaC934P is a good candidate to be used as an ingredient to prepare immediate gel-forming dosage forms. The release profiles of BAEE and the inhibitory effect on trypsin activity of the capsule formulations containing Kollidon® CL, C934P (dispersed in PGEF) and FNaC934P were evaluated. C934P was dispersed in PGEF according to Akiyama et al. (1995), because of its poor swelling properties. Kollidon® CL, which has already been proven to accelerate the quick gel-forming process of different carbomer formulations, was studied to evaluate the survival of BAEE in a burst-release capsule formulation. The compositions of all formulations used are depicted in Table 1. Fig. 3A–C shows the release profiles of the sum of the molar percentage of BAEE and BA ($BAEE_{total}$) and the molar percentage of the substrate (BAEE) from the capsule formulations A (FNaC934P), E (C934P) and B (Kollidon® CL), respectively. Formulation A, consisting of a powder mixture of FNaC934P and BAEE, displayed slow disintegration. A time period of 120 min was required for more than 90% BAEE completely released (Fig. 3A). The recovery of the substrate was very poor.

Formulation E, containing C934P dispersed in PGEF, released $BAEE_{total}$ very slowly (Fig. 3B), probably due to the slower gel-forming properties of C934P and thus delayed disintegration of the capsule. Because inhibition of trypsin is dependent on the poly(acrylate) concentration, quick swelling of the polymer is an essential prerequisite for a high BAEE recovery. Formulation B, containing only Kollidon® CL and BAEE, showed a quick release of the substrate (90% within the first 15 min; Fig. 3C). After 10 min, a concentration of about 80% intact BAEE could be detected in the incubation medium. Because Kollidon® CL is not able to inhibit trypsin activity, the released substrate was completely degraded already after 30–60 min.

Since AUC is a good index of recovery of intact BAEE, AUC values of the different capsule for-

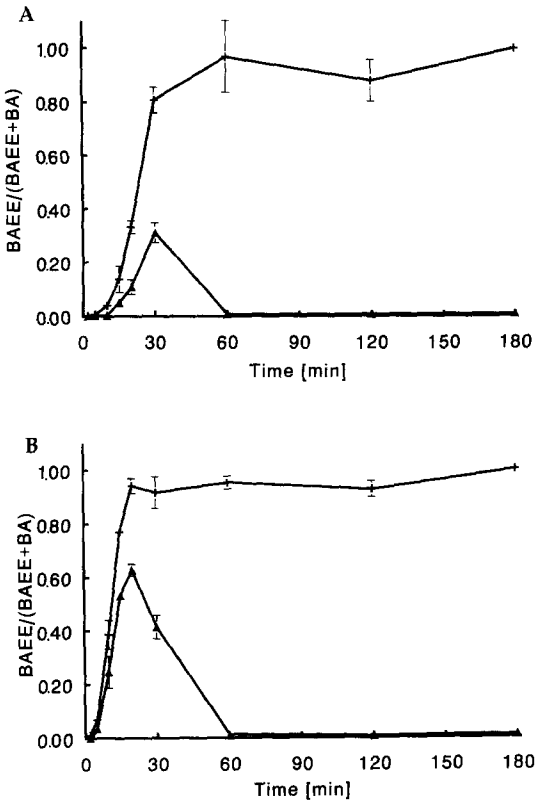

Fig. 4. Dissolution of BAEE and total (BAEE + BA) from capsules in a medium of 0.05 M phosphate buffer (pH 6.8; 40 ml) with trypsin (10 IU/ml); 37°C; 100 rev./min; pre-incubation time, 2 min; mean ± S.D. (N = 3). (A) Capsules containing FNaC934P/Kollidon® CL mixtures (formulation C): (+) total BAEE + BA, (▲) BAEE. (B) Capsules containing PGEF microparticles with FNaC934P (formulation D): (+) total BAEE + BA, (▲) BAEE.

mulations were calculated from 0 to 180 min, and presented in Table 1. Based on these values, it is apparent that the FNaC934P containing formulation D increased the recovery of BAEE compared to the Kollidon® CL-containing capsule formulation B.

Subsequently, the recovery of BAEE, numerically evaluated from the AUC values of the different formulations, was investigated from the quick drug-releasing capsule formulations C and D, whose release characteristics have been described previously (Akiyama et al., 1996). Both formulations are based on FNaC934P as a trypsin inhibitory excipient, whereby gel-forming was accelerated either by mixing FNaC934P with Kollidon® CL (formulation C) or by incorporating FNaC934P in PGEF (formulation D). The addition of Kollidon® CL to the FNaC934P powder led to 90% release of the substrate between 30 and 60 min, resulting in an increased recovery of intact BAEE (Fig. 4A). Much higher recovery of BAEE was achieved from the capsule formulation D, which released more than 90% of BAEE within 20 min (Fig. 4B). Differences in recovery from formulations A, C and D might be explained by differences in the swelling velocity of the poly(acrylate). In a one-phase system, as studied here, it is very possible that the release of the substrate is related to the dispersion time of the polymer in the aqueous dissolution medium. The elimination of BAEE from the formulations C and D was still rapid enough to be completely hydrolysed within the first 60 min. However, the AUC of PGEF microparticles consisting of FNaC934P (formulation D; 1824 %min) was lower than that of the 0.25% FNaC934P dispersion (2413 %min), whereas the AUC values of the PGEF microparticles (formulations F and G) were higher than for the other solid formulations. Nevertheless, even when a BAEE solution was added to the FNaC934P dispersions containing trypsin, most of the BAEE was degraded within 60 min. These results unequivocally indicate that the swelling of the poly(acrylate) should be completed before the substrate is released into the dissolution medium.

3.3. Effect of rapid gel-forming formulations with delayed BAEE burst-release formulations on inhibition of trypsin activity

It has been reported that deprivation of Ca^{2+}-ions out of the trypsin structure results in a loss of thermodynamic stability of the enzyme, leading to irreversible denaturation such as autodegradation (Delaage and Lazdunski, 1967; Gabel and Kasche, 1973; Bartunik et al., 1989). Lueßen et al. (1995) found that the strong Ca^{2+}-binding affinity of the poly(acrylic acid) derivatives polycarbophil and carbomer have a profound inhibitory effect on trypsin activity. They also observed that abolishment of the inhibitory effect of poly(acrylates) was dependent on the time

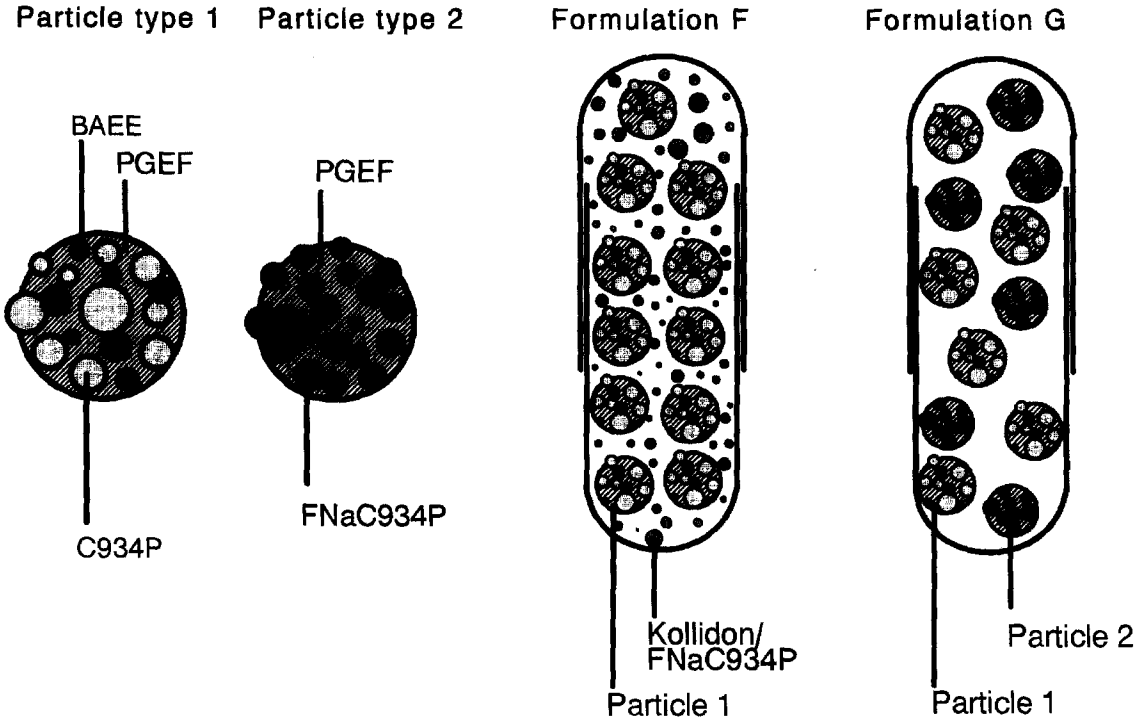

Fig. 5. A capsule filled with PGEF microparticles containing C934P and BAEE which are mixed with quick gel-forming FNaC934P in the form of either FNaC934P-containing microparticles (formulation F) or a mixture of Kollidon® CL and FNaC934 (formulation G).

point at which Ca^{2+} was added to the incubation medium. This phenomenon was explained by a time-dependent dissociation of Ca^{2+} from the trypsin structure, which is a prerequisite before it will be bound by the polymer. Therefore, it is suggested that a pre-incubation period of the poly(acrylic acid) derivatives with trypsin is necessary to improve the inhibitory effect. The substrate BAEE was rapidly released and eliminated within 60 min from the capsule containing PGEF microparticles with dispersed FNaC934P (formulation D), but the recovery of BAEE from this dosage form was not satisfactory. However, when BAEE was added to a dispersion of 0.25% FNaC934P at 20 min after pre-incubation of FNaC934P with trypsin, degradation of the substrate was very slow (K_d = 0.09). These results emphasize that, to achieve a strong inhibitory effect on trypsin activity, the design of capsules which immediately give a homogeneous dispersion of the poly(acrylate) and a delayed burst release of BAEE after a lag time of at least 20 min is necessary.

Before designing and preparing the final capsule formulation, the inhibitory effect of dispersions formed from Kollidon® CL/FNaC934P mixtures (formulation C*) or PGEF microparticles (formulation D*) was studied. When BAEE was added 20 min after to the medium containing 10 IU trypsin/ml dispersions of formulations C* or D*, the recovery of intact BAEE was increased as compared to formulations C and D. But even in the case of pre-incubation, most of the BAEE was eliminated within 60 min. The degradation rate constants (K_d) of BAEE in the formulations C* and D* after 20 min pre-incubation (1.28 or 1.43, respectively; Table 2) were only slightly lower than that with 0.25% (w/v) FNaC934P after 2 min pre-incubation (1.46). This implies that the rapid gel-forming formulation could not provide a satis-

factory inhibition of trypsin activities, even though the formulation contains a rapid gel-forming part which releases BAEE in a burst after a 20-min lag-time. This also indicates that gelation of FNaC934P was not sufficient and that a complete hydration could not be obtained within 20 min, when PGEF microparticles or Kollidon® CL mixtures with FNaC934P were added to incubation medium. However, a much longer lag-time may not be desirable, because it may result in drug-passing by the absorption site, considering the small intestinal transit time of the order of 3 h (Davis et al., 1986).

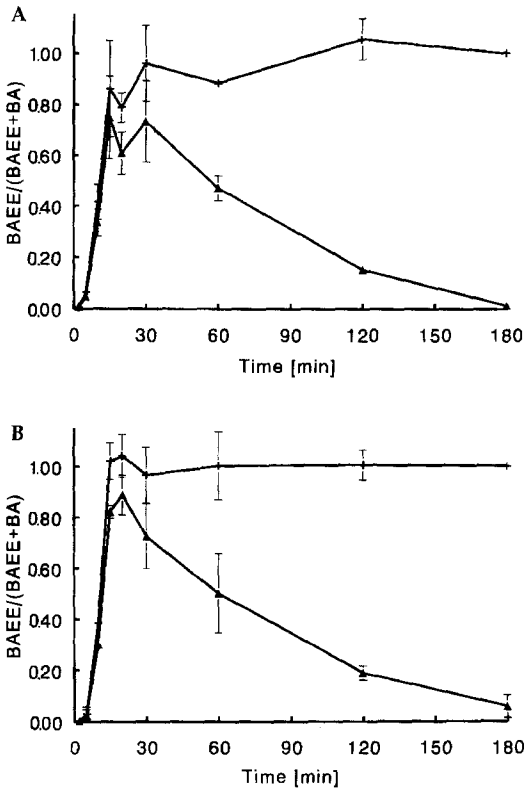

Fig. 6. Dissolution of BAEE and total (BAEE + BA) from capsules in a medium of 0.05 M phosphate buffer (pH 6.8; 40 ml) with trypsin (10 IU/ml); 37°C; 100 rev./min; pre-incubation time, 2 min; mean ± S.D. (N = 3). (A) Capsules containing PGEF-C934P-BAEE microparticles (formulation E) and FNaC934P/Kollidon® CL mixtures (formulation C*), designated as the novel formulation F: (+) total BAEE + BA, (▲) BAEE. (B) Capsules containing PGEF-C934P-BAEE microparticles (formulation E) and PGEF-FNaC934P microparticles (formulation D*), designated as the novel formulation G: (+) total BAEE + BA, (▲) BAEE.

3.4. Development of two phase capsule formulations

As a result of the studies described above, two capsule formulations consisting of two different phases were designed (Fig. 5). The first phase of these capsules consists of a rapid gel-forming part, based on the quick swelling properties of FNaC934P. One capsule was filled with the Kollidon® CL/FNaC934P mixture (formulation C*; Fig. 5A) and the other capsule with FNaC934P/PGEF microparticles (formulation D*; Fig. 5B). Formulation E, consisting of PGEF/C934P/BAEE microparticles as the drug carrying component, was used as the second phase in both capsule formulations. The aim for the use of this second phase was to integrate the more efficient enzyme inhibitory effect of carbomer with a slower release of the substrate into the formulation. The results of these two capsules on trypsin activity are presented in Fig. 6A and Fig. 6B. Both capsule formulations showed a 90% release of the substrate BAEE within the first 30 min. The more rapid release of BAEE from these capsules as compared to formulation E may be due to the embedding of the C934P microparticles into a quick disintegrating phase. The tendency of agglomeration of the C934P containing particles by swelling of the polymer is thereby reduced. The elimination of BAEE was relatively slow as compared to the FNaC934P formulations investigated. The pH values of the dissolution medium were continuously decreasing from 6.8 to 5.9 over 180 min, indicating that the swelling of C934P required more time than the release of BAEE. Approximately 20% of the substrate could still be detected after 120 min (Fig. 6A,B). The resulting $AUC_{0-180\ min}$ values for formulations F and G were 5563 and 5725 %min, respectively, and 3–4 times higher than those of the formulations containing FNaC934P without C934P (Table 1). These findings demonstrate that two-phase formulations consisting of the rapid gel-forming FNaC934P (first phase) as well as of the efficient enzyme inhibiting but more slowly swelling C934P

(second phase) can highly improve the recovery of the trypsin substrate BAEE.

4. Conclusions

From the results presented here, it may be concluded that delivery systems based on poly(acrylic acid) derivatives are able to increase the stability of peptide drugs against tryptic degradation. Capsule formulations, consisting of a two-phase composition with (1) a rapid gel-forming carbomer modification (FNaC934P) and (2) carbomer as a compound with highly trypsin inhibitory properties, have been shown to result in highly increased recoveries of the trypsin substrate BAEE. These capsules are expected to become an important tool to master the peroral delivery of peptide drugs in the near future.

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