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Oral-based controlled release formulations using poly(acrylic acid) microgels

Marie Wahlgren[1], Karin Löwenstein Christensen[2], Erik Valentin Jørgensen[3], Anna Svensson[4] and Stefan Ulvenlund[5]

[1]Division of Food Technology, Department of Food Engineering, Lund University, Lund, Sweden, [2]Egalet a/s, Værløse, Denmark, [3]Nycomed, Roskilde, Denmark, [4]Department of Plastics Technology, Danish Technological Institute, Taastrup, Denmark and [5]Department of Product Development, Astrazeneca R&D Lund, Lund, Sweden

Abstract

Aim: To investigate the release of hydrophobic and hydrophilic substances from tablets containing Pemulen and Carbopol as excipients. *Method*: The dissolution patterns of a hydrophobic (diazepam) and a hydrophilic active substance (midodrine-HCl) from different tablet formulations containing a nonmodified polyacrylic microgel (Carbopol 981 F) or a hydrophobically modified polyacrylic microgel (Pemulen®) have been studied. Possible differences in dissolution in phosphate buffer (pH 6.8) and in 0.1 M HCl between tablets produced using wet granulation and direct compression were also investigated. *Results*: Tablets produced by wet granulation had a greater effect on the release of active substance from the tablets. No major differences were observed in the release patterns of the hydrophilic substance midodrine-HCl from wet granulated tablets based on Carbopol and Pemulen. However, the release pattern of the more hydrophobic drug substance, diazepam, differed considerably between the two polymers. Wet granulation gave reproducible release patterns. The release patterns from the polymers differed considerably at pH 6.8 but were similar at low pH. *Conclusions*: The release of the diazepam from the hydrophobic polymer Pemulen was very slow, and the release was close to zero order.

Key words: *Carbopol; controlled release tablets; cross-linked poly(acrylic acid) microgels; dissolution kinetics; Pemulen*

Introduction

Cross-linked poly(acrylic acid) microgels have been studied extensively for use in pharmaceutical formulations. The types of formulations include buccoadhesive tablets[1–9], in nasal applications both as spray[10–12] and as particles[12–14], in ocular delivery[15–17], and finally in suppositories[18]. Poly(acrylic acid) microgels have also been used in oral delivery in tablets[19] and microparticles[20] and as coating[21,22] for microspheres. However, hydrophobically modified cross-linked poly(acrylic acid) microgels have not been as thoroughly investigated for use in pharmaceutical formulations. To our knowledge, the only studies performed so far on tablet formulation are those by Aboofazeli and Mortazavi[23,24]. They concluded that Pemulen was not suitable as an excipient for the pharmacokinetic profile required. One reason for the lack of interest in these excipients in tablet formulations is that the commercially available polymers have not yet been approved for oral use. Most of the studies on Pemulen, the commercially available hydrophobically modified cross-linked poly(acrylic acid) gel, have been on its use for topical delivery[25,26]. However, these types of polymers have interesting properties for controlling release, especially that of active substances characterized by a high log *P* value, which could also be interesting for oral dosage.

From a drug formulation point of view, the bioadhesive properties of poly(acrylic acid) microgels could be very interesting, provided that the release of the active substance can be controlled[27]. Paulsson and Edsman

Address for correspondence: Marie Wahlgren, Division of Food Technology, Department of Food Engineering, Lund University, PO Box 124, SE-221 00 Lund, Sweden. Tel: +46 46-222 8306, Fax: +46 46-222 4622 E-mail: marie.wahlgren@food.lth.se

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have investigated methods of obtaining controlled release from polyacrylic gels, either by adding surfactants to the gel system[28–31] or by interaction between hydrophobic active substances and hydrophobically modified polyacrylic gels[31]. They found that the higher the log *P* value of a charged substance, the greater the probability of interaction with surfactants or polymer network[30]. In systems with surfactants, they found that the strongest effects on the release rate were seen for hydrophobically modified polymer gels in which the drug and the oppositely charged surfactant form vesicles, but that systems with micelles also gave slower release[30]. They also showed that a decrease in release could be obtained by using lipophilic substances without the addition of a surfactant, provided that a hydrophobically modified poly(acrylic acid) gel was used[31].

The purpose of this investigation was to evaluate the dissolution pattern of a hydrophobic and a hydrophilic drug substance from different tablet formulations containing a nonmodified polyacrylic microgel (Carbopol 981 F) or a hydrophobically modified polyacrylic microgel (Pemulen TR2). As it is known that the method of tablet production may influence the release profile and swelling of Carbopol-based tablets[32,33], possible differences in dissolution between tablets produced using wet granulation and direct compression of the active substances with the polymers were also investigated.

The substances used in this study, diazepam and midodrine-HCl, were chosen in order to investigate the effect of Carbopol and Pemulen as excipients on substances with different log *P* values. Diazepam is a benzodiazepine with central nervous system-depressant properties. It is used to relieve anxiety, muscle spasms and seizures, and to control agitation caused by alcohol withdrawal, and is sold under the brand name Valium[34]. Midodrine is a drug used to treat low blood pressure (hypotension). It acts by stimulating nerve endings in blood vessels, causing the blood vessels to constrict, causing the blood pressure to increase[34]. Figure 1 shows the structures of the two substances.

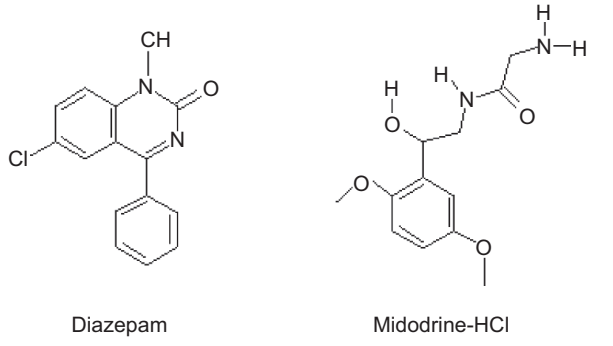

Figure 1. Chemical structure of the two active substances.

Table 1. Physical properties of the active substances studied.

	log P[a]	pK_a	M_W
Diazepam	2.988	3.4[b]	284.74 g/mol
Midodrine-HCl	1.215	7.8[c]	290.74 g/mol

[a]Calculated *X* log *P*[34]. [b]Kallinteri[35]. [c]RXlist [accessed July 15, 2005][36].

These substances were chosen as they have similar molecular weights, but differ in solubility and pK_a. Table 1 gives some physical properties of the two substances.

Thus, the purpose of this paper is to investigate the hypothesis that Carbopol and Pemulen can be used to produce controlled release tablets, that the choice of polymer will affect the release mechanism, and that the effect of choice of excipient is stronger on hydrophobic active substances than on hydrophilic ones. We also believe that the degree of swelling of the polymer will influence the release and thus release at low pH (nonswollen polymer) and at neutral pH is investigated. Furthermore, we aim to investigate whether the production method influences the release mechanism.

Materials and methods

Production of tablets

Tablets were produced using the active substances and excipients and the compositions listed in Table 2. Midodrine-HCl was obtained from Nycomed Austria GmbH (Linz, Austria) and diazepam from Fabrica Italiana Sintetic (Milano, Italy). The polymers used were Carbomer type A [Carbopol 981 F and Acrylates/C10-30 alkyl acrylate cross-polymer (Pemulen TR2)] from Lubrizol Advanced Materials, Inc. distributor Bionord Biokemi AB (Stenungsund, Sweden). Two different methods of production were used: wet granulation and direct compression.

Wet granulation

The dry excipient, lactose, polymer (Carbopol or Pemulen), and the active substance were dry mixed for 5 minutes in an intensive mixer prior to granulation. During wet granulation, ethanol (70%) was added via a pump at a rate of 9 g/min during mixing. The ethanol was added gradually at intervals of 1–3 minutes to visually evaluate the granulate quality, and 1–2 minute periods of mixing without the addition of ethanol. The total granulation time was about 15–20 minutes, of which 5–8 minutes were used for the addition of ethanol. The total amount of ethanol added is given in Table 2. The granulate was sieved through a 2.0 mm mesh sieve onto drying trays and then dried at 50°C for

Table 2. Compositions of the tablets studied.

Batch	Active substance (g)	Polymer (g)	Lactose (g)	70% ethanol	Magnesium stearate (g)	Silica? (g)
(1) Carbopol with diazepam, direct compression	Diazepam 18.8	Carbopol 37.5	191.0	50 mL	1.75	2
(2) Carbopol with midodrine-HCl, direct compression	Midodrine HCl 37.5	Carbopol 37.5	172.2	50 mL	1.75	2
(3) Carbopol with diazepam, wet granulation	Diazepam 18.8	Carbopol 37.5	191.0	39 g	1.75	2
(4) Carbopol with midodrine-HCl, wet granulation	Midodrine-HCl 37.5	Carbopol 37.5	172.2	48.9 g	1.75	2
(5) Pemulen with diazepam, direct compression	Diazepam 18.8	Pemulen 37.5	191.0	50 mL	1.75	2
(6) Pemulen with midodrine-HCl, direct compression	Midodrine-HCl 37.5	Pemulen 37.5	172.2	50 mL	1.75	2
(7) Pemulen with diazepam, wet granulation	Diazepam 18.8	Pemulen 37.5	191.0	≈35	1.75	2
(8) Pemulen with Midodrine-HCl, wet granulation	Midodrine-HCl 37.5	Pemulen 37.5	172.2	37	1.75	2

2 hours. The dried granulate was sieved through a 1.2 mm mesh Erweka FSG sieve. The granulate was mixed with silica and polymer for 5 minutes in a cubic blender at a speed of 27 rpm. Magnesium stearate was sieved through a 0.3 mm mesh sieve and added to the granulate. The powders were then mixed for an additional 5 minutes.

Direct compression

Direct compression was employed to obtain a formulation in which the polymer powder and the active substance were dry mixed. Owing to problems of flowability of the powder, dry mixing of all the ingredients was not possible. Thus, the active substance was granulated together with lactose. Lactose and the active substance were dry mixed for 5 minutes in the intensive mixer. Ethanol (70%) was then added via a pump at a rate of 3 mL/min during mixing for ~15 minutes. The total amount of ethanol added is given in Table 2. The granulate was sieved through a 2.0 mm mesh sieve onto drying trays and was dried at 50°C for 2 hours. The dried granulate was sieved through a 2.4 mm mesh sieve. The granulate was then mixed with silica and the polymer (Pemulen or Carbopol) for 5 minutes in the cubic blender at a speed of 27 rpm. Magnesium stearate sieved through a 0.3 mm mesh sieve was added and mixing was continued for an additional 5 minutes.

Tabletting

Tablets were produced in a Diaf tablet machine using an 8 mm diameter round punch. Tablets were produced with a range of hardness. The tablet weight was around 200 mg. The average weight and crushing strengths were measured for 8–10 tablets. Tablets were produced at a variety of tablet hardness and the tablets studied concerning release profiles had a hardness of 4–9 kp.

Dissolution testing

Dissolution testing was performed using the Ph. Eur., USP-described dissolution apparatus 2 with a paddle speed of 50 rpm at a temperature of 37°C. The release and dissolution of diazepam and midodrine-HCl were continuously analyzed using UV spectroscopy at wavelengths of 283 and 290 nm, respectively. The tablets were tested in two media: 0.1 M HCl and 0.1 M phosphate buffer at pH 6.8. The dissolution volumes were 600 and 1000 mL for midodrine-HCl and diazepam tablets, respectively. The difference in dissolution volume and in content of active substance in the tablets is to ensure that the diazepam is investigated at sink conditions and to obtain high enough concentration of midodrine-HCl to use UV spectroscopy as the analytical method. The dissolution profiles presented are averages of three tablets per experiment, expressed as the percentage release of the nominal content.

Results

Tabletting

The two polymers behaved quite differently during tablet production, especially during wet granulation. Both produced rather sticky wet granulates. The Pemulen granulate was more sensitive to moisture and less ethanol was needed to form a granulate (see Table 2). It is important to add the granulation solution slowly and to allow time for mixing between additions of the solution to avoid snowballing.

Table 3. Physical properties of the tablets.

Batch	Average weight of tablet (mg)	Crushing strength (kp)
(1) Carbopol with diazepam, direct compression	214 ± 5	7.3 ± 1.6*
(2) Carbopol with midodrine-HCl, direct compression	202 ± 3	4.4 ± 1.2*
(3) Carbopol with diazepam, wet granulation	203 ± 2	8.5 ± 0.7
(4) Carbopol with midodrine-HCl, wet granulation	195 ± 3	7.2 ± 0.7
(5) Pemulen with diazepam, direct compression	207 ± 3	5.7 ± 2.3
(6) Pemulen with midodrine-HCl, direct compression	204 ± 4	4.6 ± 1.3*
(7) Pemulen with diazepam, wet granulation	200 ± 6	8.5 ± 1
(8) Pemulen with midodrine-HCl, wet granulation	196 ± 4	8.5 ± 0.4

Average of 8* or 10 measurements.

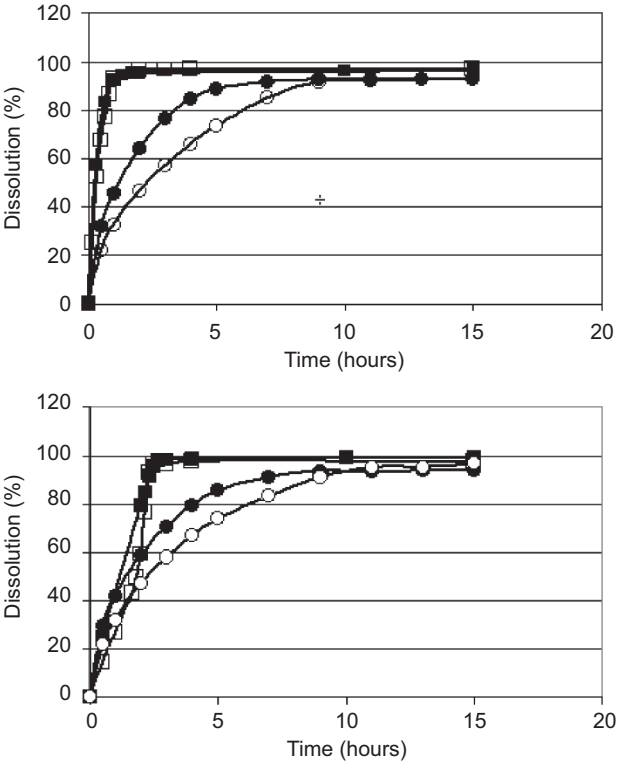

Figure 2. Dissolution profile (mean of three dissolution tests) of midodrine-HCl in Pemulen tablets (upper panel), in Carbopol tablets (lower panel), in 0.1 M HCl (filled symbols), and in 0.1 M phosphate buffer (pH 6.8; open symbols). Tablets were made by direct compression (squares) and by wet granulation (circles).

The aim was to produce the tablets either through direct compression or through wet granulation. However, due to problems of flowability of the powder, dry mixing of all the ingredients was not possible. Thus, the active substance was granulated together with lactose prior to mixing with the polymers.

The weight variation and the hardness of the tablets used in this study are presented in Table 3. As can be seen it was difficult to obtain direct compressed tablets with high hardness. Attempts were made to increase the crushing strength but these where not successful.

Dissolution

The dissolution profiles for tablets containing the hydrophilic active substance, midodrine-HCl, and diazepam are shown in Figures 2 and 3, respectively.

Effects of production method

The method of tablet production affected the release pattern. In all cases except for Carbopol tablets containing diazepam the release from direct compressed tablets was faster than from wet granulated tablets. Complete release was obtained after 1–2 hours for direct compressed midodrine-HCl tablets, while complete release was not obtained for the wet granulated tablets even after 7 hours. In the case of diazepam tablets, the release profile was normally faster for direct compressed tablets than for wet granulated ones. However, the release was slower than for midodrine-HCl tablets (in general between 2 and 5 hours). Furthermore, the release profile for the direct compressed diazepam tablets at pH 6.8 showed a large variation between the tablets tested, and, for the Pemulen tablets, it was not meaningful to present a mean dissolution curve. The wet granulated tablets had a better quality and all formulations gave reproducible release curves.

It can thus be concluded that the choice of production method considerably affects the release profile of these tablets and that wet granulation gave the longest extended release periods and better reproducibility.

Effects of release media

In the case of midodrine-HCl, only the wet granulated tablets showed any difference in release profile, between the two release media used. It showed a slightly slower release at pH 6.8 than at the lower pH of the 0.1 M HCl solution.

For diazepam tablets the release media were seen to affect the release from both direct compressed and wet granulated tablets. The release was always faster at low pH (0.1 M HCl solution). The release at pH 6.8 from both direct compressed and wet granulated Carbopol tablets showed a lag phase, which was not observed in the 0.1 M HCl solution.

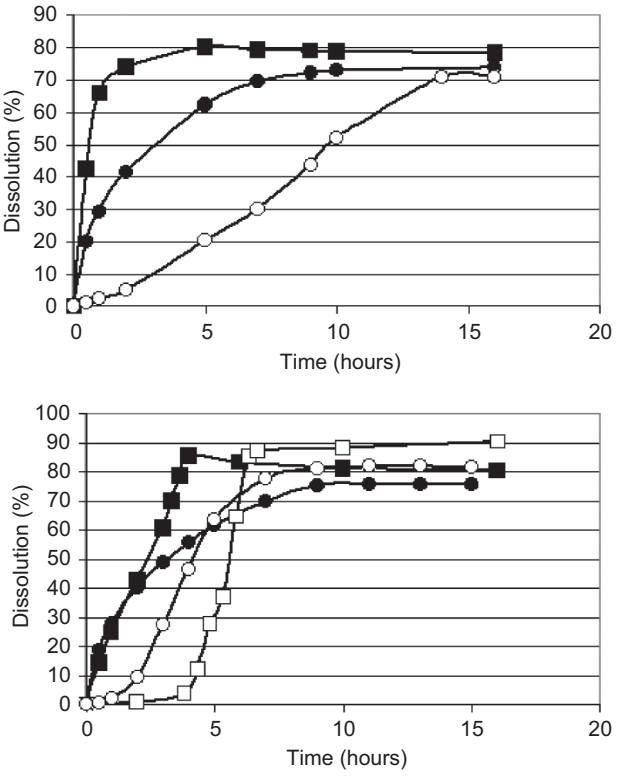

Figure 3. Dissolution profile (mean of three dissolution tests) of diazepam in Pemulen tablets (upper panel), in Carbopol tablets (lower panel), in 0.1 M HCl (filled symbols), and 0.1 M phosphate buffer (pH 6.8; open symbols). Tablets were made by direct compression (squares) and by wet granulation (circles).

Effects of excipients

As can be seen in Figure 2, there are very small differences between the release profiles for tablets based on Pemulen or Carbopol when the tablets contain midodrine-HCl. The largest difference between the polymers is seen between the direct compressed tablets, where the active substance was released slightly faster from the Pemulen tablets. In difference to this, the choice of polymer strongly affects the release of diazepam as can be seen in Figure 3. The release is considerably slower from Pemulen tablets, especially at pH 6.8. Furthermore, tablets that contained Pemulen, as an excipient, did not show any lag phase as was seen in the case of Carbopol tablets. It can thus be concluded that the choice of polymer mainly affects the release from diazepam tablets but not to any larger extent the one for midodrine-HCl tablets.

Discussion

Effect of tablet production method

It is not surprising that wet granulation gave better production conditions than direct compression as neither of polymers used were developed for direct compression. We have deliberately chosen the Carbopol polymer based on that it should have a viscosity that is in the vicinity of the one for the Pemulen and not for its tabletting properties[37]. It can of course not be fully excluded that the production problems that gave less hard tablets in the case of direct compression might to some extent affect the release. However, Genc et al.[32] have shown that at least for Carbopol 384 the hardness of the tablets has little influence on the dissolution. The purpose of the study was not to optimize tablet formulation from a production point of view and no further attempts were made to improve the tablets. However, we have still tried to work with wet granulated tablets that are in the same hardness range.

It is obvious that the production method strongly affects release profile of the tablet. This is also in line with what has been previously observed by Genc et al.[32] who observed much faster release from tablets produced by direct compression than with wet granulated ones. It is likely that the release from direct compressed tablets is less dependent on interactions between the active substance and the polymer and reflects the difference in physical properties of the tablets and the active substance. Thus, in the case of direct compressed tablets, the release is more dominated by disintegration of the tablets and dissolution of the active substance than by the swelling of the polymer matrix. This is further substantiated by the fact that no difference was observed in the release profiles for direct compressed tablets of midodrine-HCl between the two dissolution solutions employed. The difference seen for diazepam is probably related to the fact that at lower pH diazepam becomes charged, thus increasing its solubility[35].

Effect of excipients on midodrine-HCl tablets

Although it was expected that the hydrophilic substance midodrine-HCl would have little interaction with the Pemulen matrix, it is still surprising that the release profile is so similar for the two polymers. The results are also somewhat in contradiction to a previous investigation of lithium carbonate release from matrix-type tablets containing Carbopols, Pemulen, and Eudragits. These tablets, which contained a mixture of Pemulen and Carbopol, showed a considerable decrease in release rate compared to tablets containing only Carbopol[23,24]. The tablet mixtures in this latter study was, however, more complex than our tablets. Furthermore, the results from the wet granulated tablets are in line with the observed log *P* dependence of diffusion coefficients in Carbopol and hydrophobic Carbopol gels seen by Paulsson[29]. They saw no difference in diffusion in hydrophilic and hydrophobic Carbopol polymer gels for charged hydrophilic substances. Although our work as Aboofazeli concerns tablets and not gels as

Paulsson the results indicates that in our case it is the diffusion through the gel that dominates the release pattern and not other effects such as erosion of the tablet matrix. The fact that there was absolutely no difference between the release profiles of the active substances from the wet granulation tablets based on Carbopol and Pemulen indicates that the two polymers swell to the same degree in wet granulated tablets, and that there is no interaction between the hydrophobic parts of the Pemulen polymer and midodrine-HCl. The first conclusion is drawn based on the observations made by Juang and Storey[33] that for Carbopol tablets the release rate seems to correlate directly to the swelling of the polymer gel.

Effect of excipients on diazepam tablets

Figure 3 shows the dissolution profiles for the tablets containing the lipophilic substance diazepam. As can be seen, 100% release is not reached for any of the tablets tested. We have not further investigated the reason behind this but we believe that this will not change any of the conclusions drawn on the behavior of Carbopol and Pemulen as excipients for controlled release tablets. If these tablets should be investigated for the use in clinical trials, stability testing is necessary to further understand the reason behind these losses.

The dissolution behavior of diazepam differs considerably from that of the hydrophilic substance, midodrine-HCl. The release is slower than for midodrine-HCl and for Carbopol tablets, the dissolution profile contains a lag phase at pH 6.8. Similar anomalous dissolution behavior of diazepam has been seen by others[38]. The formulation was in this case a solid dispersion of sugars and diazepam, and Drooge attributed the anomalous dissolution profiles to the formation of crystalline diazepam.

The effects seen is also most likely to be due to the hydrophobic nature of diazepam. This will affect factors such as wetting of the tablets and dissolution of the substance but also the interaction with the hydrophobically modified Pemulen polymer.

For the direct compressed tablets, it is likely that the most important factor affecting the release profile is the wetting of the tablets and the dissolution of diazepam. The dissolution rate will be affected if the diazepam is in amorphous or crystalline state as stated by van Drooge[38]. This would also be in line with the observation that there is no lag phase and no problems with reproducibility at the low pH where diazepam is charged and thus more soluble.

The lag phase seen in the release from the Carbopol tablets at pH 6.8 was not seen for Pemulen tablets produced by wet granulation. Slow release over 14 hours was observed from the wet granulated Pemulen tablets at pH 6.8. In contrast to the release at high pH, the release of diazepam from wet granulated tablets in 0.1 M HCl was not affected by the choice of polymer. The dissolution of the wet granulated tablets in 0.1 M HCl was complete within 9 hours, and the profiles were identical for Pemulen- and Carbopol-based tablets.

The results presented above indicate that there probably is a hydrophobic interaction between the C10–30 alkyl groups in the Pemulen polymer and the hydrophobic active substance diazepam. This interaction obviously leads to a slower release at pH 6.8. There are several evidences from other investigations that hydrophobically modified polyacrylic acids such as Pemulen in difference from nonmodified polymers interacts with hydrophobic and amphiphilic substances but not with charged hydrophilic substances[26,29,31]. The difference in dissolution profiles at the different pH studied could be attributed to the fact that at lower pH diazepam becomes charged, but also be influenced by that the polymers are likely to expand to a lower degree at this pH. The difference seen between midodrine-HCl and diazepam especially for the Pemulen tablets are well in line with the previous observations by Paulsson that release of substances with higher log P are more retarded by Pemulen gels than those with low log P[29,30]. However, to our knowledge this is the first time this has been shown to be valid for tablets and not only for pure gel formulations.

A simple model for the release profile

In order to further understand the release profiles from the wet granulated tablets, the release data were fitted to a simple two-component model of release based on the models suggested by Ritger and Peppas[39]:

$$\text{Release}\% = a\sqrt{t} + bt.$$

The first term in this model represents release through a water-swollen polymer (Fickian diffusion) and the second term represents zero-order release. When evaluating the parameters a and b, data in the lag phase and in the region of complete release were excluded. Furthermore, in performing the regression analyses, the restrain was that no negative solutions to the parameters of the equation were accepted. As can be seen from Table 4, this very simple model gave a very good fit to the data as the values of the regression coefficient (R) were very close to 1.

It is obvious that most of the tablet formulations follow release patterns that are indicative of Fickian diffusion through the swollen network of the polymers. In this case, the parameter a is dependent on the apparent diffusion constant in the polymer network, the geometry and surface area of the tablets, and the saturation

Table 4. Values of parameters obtained by fitting to the model: Release% = $a\sqrt{t} + bt$.

Formulation	a	b	R
Diazepam + Carbopol in HCl	3.5	3×10^{-14}	0.92
Diazepam + Pemulen in HCl	3.5	10^{-11}	0.99
Midodrine-HCl + Carbopol in HCl	5.25	8×10^{-13}	0.97
Midodrine-HCl + Pemulen in HCl	5.6	2×10^{-9}	0.99
Diazepam + Carbopol in PB	7×10^{-12}	0.18	0.92
Diazepam + Pemulen in PB	5×10^{-10}	0.079	0.98
Midodrine-HCl + Carbopol in PB	4.2	3×10^{-14}	0.99
Midodrine-HCl + Pemulen in PB	4.2	3×10^{-10}	1.00

HCl, dissolution medium HCl (pH 0.1); PB, dissolution medium phosphate buffer (pH 6.8); R, regression coefficient.

concentration of the drug. All these parameters may differ to some extent for tablets that swell during dissolution. It is thus remarkable that this parameter does not differ to any large extent between the tablets produced from the two polymers. As can be seen in Table 4, in the case of midodrine-HCl tablets, the parameter a is somewhat higher at low pH. The diffusion constant is not likely to be higher in the phosphate buffer (pH 6.8) than in 0.1 HCl, and the difference seen could be due to the influence of the swelling of polymer network on the geometry and area of the tablets, rather than diffusion.

For diazepam at pH 6.8, zero-order kinetics dominate completely over Fickian diffusion for tablets based on both polymers, although the release rate differed considerably between the tablets. It is not obvious why the kinetic profile of tablets containing the low-soluble substance differs regarding the type of release compared with the other cases. One possible reason could be that the release profile is dominated by the phase behavior of the active substance as discussed previously. The release could be affected by the phase behavior between the solid and solution of the low-soluble active substance as, for example, a local pH difference could lead to changes in solubility. Another important factor could be the possible interaction between diazepam and the polymer, leading to partitioning of the active substance between the bulk solution and the polymer. These complex phenomena could lead to apparent zero-order kinetics. Furthermore, the release could be dominated by erosion of the Carbopol tablets and not diffusion through the matrix. Investigations of direct compressed Carbopol tablets have shown that for a high-soluble substance (caffeine) Fickian diffusion dominated the release whereas for low-soluble substances (theophylline) erosion dominated the results[40]. This would be in line with our observations but would not be able to explain the large time difference in release between the two formulations and visual observations also indicates that at least for the Pemulen tablets erosion did not seem to dominate the initial release.

Conclusions

This investigation was conducted in order to investigate the following hypothesis:

- Carbopol and Pemulen can be used to produce controlled release tablets.
- The choice of polymer will affect the release mechanism.
- That the effect of choice of excipient is stronger on hydrophobic active substances than on hydrophilic ones.
- That the degree of swelling of the polymer will influence the release and thus release at low pH (nonswollen polymer) and at neutral pH should differ.
- That the production method influences the release mechanism.

The investigation showed that there are considerable differences in release profile between tablets produced via wet granulation and direct compression. The latter had a very fast release, but, provided wet granulation is used, the results indicate that both Carbopol and Pemulen can be used as excipients for controlled delivery. It also showed that for the hydrophobic active substance diazepam the choice of excipient strongly influence the release at pH values where the polymers have swelled. However, somewhat to our surprise there is no effect whatsoever by the choice of polymer on the release of the hydrophilic substance (midodrine-HCl). Although we had expected a less interaction between Pemulen and Midodrine than between Pemulen and Diazepam the fact that choice of polymer had no effect on the former was not an expected result. It does, however, show how important polymer–active substance interaction is for the controlled release from Pemulen polymers.

The results showed a difference in release rate dependent on the pH of the release media, but the difference was only substantial in the case of the Diazepam/Pemulen formulation.

The experiments reported above were performed mainly to investigate the possible interaction between drug substances and hydrophobically modified polyacrylic polymers. The aim was not to optimize the tablets in order to obtain specific release profiles. Thus, it is very promising that zero-order kinetics was observed at pH conditions close to that in intestinal fluids.

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