Drug Release From Hydrocolloid Embeddings with High or Low Susceptibility to Hydrodynamic Stress

Wolfram D. Lindner[1] and Bernhard C. Lippold[1,2]

Received February 10, 1995; accepted April 30, 1995

Purpose. The subject of the study was the influence of hydrodynamic stress on the drug release from direct compressed hydrocolloid embeddings. Additionally a correlation between the release kinetics and different polymer characterising parameters was attempted.
Methods. The drug release was fitted to an expanded Korsmeyer equation to describe the release kinetics. The influence of the stirring rate of the paddle in the USP paddle apparatus on the Mean Dissolution Time (MDT) was expressed as quotient of the MDT's at the stirring rate of 200 and 100 min^{-1}.
Results. If the drug release followed the square root of time kinetics, nearly no effect of the agitation speed on the release rate was observed. To achieve this diffusion controlled drug release the developing gel layer had to be hydrated very well and resistant against erosion (viscosity of at least 4000 mPa · s of the 2% polymer solution and a small expansion of the swelling gel especially at the beginning of the release). The erosion controlled zero order release was generally much affected by the hydrodynamic stress except for some hydrocolloids with incomplete swelling. Thus, it was possible to define a new release mechanism, the polymer particle erosion. The drug release was controlled by the attrition of partially swollen polymer particles and not by the polymer dissolution or drug diffusion.
Conclusions. Polymer particle erosion or diffusion control should be the release controlling mechanisms for negligible influence of hydrodynamic stress.

KEY WORDS: hydrocolloid embeddings; $\sqrt{t}$ kinetics; zero-order release; hydrodynamic stress; diffusion control; erosion control.

INTRODUCTION

One of the most important characteristics of soluble hydrocolloid embeddings used for dosage forms with modified drug release is the dependence of the release from hydrodynamic conditions. In general the influence of the stirring rate is negligible for releases according to the square root of time law (1–4). But if erosion prevails and the drug release changes to zero order kinetics, the rate of the drug release often increases dramatically by raising the stirring rate (1,2,5).

The mechanism of drug release from swellable and erodible hydrocolloid systems is complex and even in progress of understanding (2). After contact with aqueous fluids the hydrocolloid embeddings take up water and the initially glassy polymers undergo a relaxation process which is observed macroscopically as gelation and swelling (5). The tablet thickness increases as a viscous gel layer is formed, which gradually penetrates into the dry core. A soluble drug dissolves rapidly from the surface creating a burst effect. Soon after the outer gel layer becomes fully hydrated and begins to dissolve. As a result of these processes two fronts can be distinguished: the swelling front (glassy polymer/gel interface) and the eroding front (gel/dissolution medium interface). The rates of swelling, erosion and drug diffusion determine the mechanisms and the release kinetics. Two extreme cases with different controlling mechanisms may be distinguished: diffusion of the drug through the gel and erosion of the gel barrier (1,2).

If the erosion of the swollen gel is very slow, the drug is released from a swollen hydrocolloid matrix according to the classical Higuchi equation (6,7). Anomalous transport or zero order kinetics prevail if the difference between the penetration of the diffusion front and the erosion front is not too high. Two different phenomena are under discussion as the rate limiting step for constant drug release. Baveja (8), Ranga Rao (9) and Colombo et al. (10) explain as the rate determining step for the constant drug release the diffusion of the drug through a gel layer of constant thickness after "front synchronisation" of the advancing swelling and eroding fronts (diffusion layer model). According to Möckel (5,11) the zero order drug release may be a passive process as a consequence of polymer dissolution (polymer dissolution model).

The aim of this work is to examine the dependence of drug release on the hydrodynamic conditions by varying the stirring rate. Drug release profiles and parameters respectively are compared to properties of the hydrocolloids like viscosity and elasticity of the 2% solutions, cloud points, polymer content of swollen gels, gel strength, swelling velocities and expansion by swelling to explain the influence of the stirring rate. The effect of compression force during preparation of the embeddings, the particle size of the polymers, and the solubility of the drugs are also investigated to understand the different susceptibilities of the release profiles to hydrodynamic stress.

MATERIALS AND METHODS

Materials

The following materials were used: Proxyphylline, c_s in pH 4.4 buffer at 37°C (g/100 ml) 59 (11); diprophylline 17.68 (5); etophylline 8.14 (5); theophylline 1.12 (5) (Knoll, Ludwigshafen, Germany); theobromine 0.07 (12) (Caelo, Hilden, Germany); lactose (Meggle, Reitmehring, Germany); methylhydroxypropyl cellulose USP 2208, 2906, 2910 (MHPC) (Synthapharm, Mülheim-Ruhr, Germany, and Shin-Etsu Chemical, Jpn-Tokyo); hydroxypropyl cellulose (HPC) (Klucel GF and HF, Aqualon, Düsseldorf, Germany); methylhydroxyethyl cellulose (MHEC degree of substitution ≈1,5 and MHEC B degree of substitution ≈1,8) (Hoechst, Frankfurt, Germany); hydroxyethyl cellulose (HEC) (Hoechst, Frankfurt, Germany, and Union Carbide Chemicals GmbH, Düsseldorf, Germany); all cellulose ethers with different viscosities of the 2% solution (see Fig. 1); modified starch C*Top 12610, 12616 (Cerestar, Krefeld, Germany); polyvinyl alcohol (PVAI), 88% of hydrolysis of the corresponding polyvinyl acetate, 13 mPa · s of the 4% solution (Wacker Chemie, Burghausen, Germany).

[1] Department of Pharmaceutical Technology, Heinrich-Heine-Universität, D-40225 Düsseldorf, Germany.
[2] To whom correspondence should be addressed.

0724-8741/95/1100-1781$07.50/0

Methods

Preparation of the Embeddings. Biplane, cylindrical tablets were manufactured by the direct compression of materials with a particle size of 100–140 µm, applying a pressure of about $3.8 \cdot 10^2$ MPa in a hydraulic press (Perkin Elmer, Überlingen, Germany). The tablets (300 mg, radius 13 mm, thickness about 2 mm) were given into a tight-fitting die, leaving one side of the tablet uncovered, so that the release could occur from one tablet surface only (A = 1.3 cm^2), and the size of the releasing area remained constant throughout the experiment (5).

Release Kinetics. In general, the die was fixed with a holder (12) (releasing area towards bottom 8 cm beneath the water surface) in the beaker of the USP paddle apparatus for release experiments (every experiment 6 times). If not otherwise stated, formiate-buffer was used at 37°C, ionic strength 0.1. The tablets usually contained 5% of the drug and 95% polymer (sometimes mixtures of lactose and polymer or of two polymers). For better comparison the release profiles were plotted as percentage ($Q/Q_\infty \cdot 100$) vs. time. The released amounts of the drug Q were determined by UV spectrophotometry via a flow-through cell (Lambda 2 UV/VIS spectralphotometer, Perkin-Elmer, Überlingen, Germany).

Polymer Characterising Parameters. The *cloud point* was determined as the temperature which was needed to dehydrate the hydrocolloid completely in a 1% polymer solution, this meant that the clear solutions became turbid. The quotient of the heights before and after the swelling of hydrocolloid tablets placed in a vial (diameter 14 mm) was characterised by the *expansion factor.* The *swelling time* was the time interval the tablet needed to swell completely and translucently. It was examined by measurement of the light transmission with a photo diode in the case of HEC, but by visual inspection with all other polymers. The *consistency* of the gels was described by the penetration of a pin (penetrometer PNR 6, Sommer & Runge KG, D-Berlin). The *polymer content* of the gels was gravimetricaly determined; for further details see (12).

Characterisation of the Release Profile

To describe the release profile, the common exponential equation of Korsmeyer and Peppas (Eq. 1 (13,14))

$$\frac{Q}{Q_\infty} = k \cdot t^n \tag{1}$$

is extended with the constant b (Eq. 2). The exponent n is calculated from all the experimental data with $Q/Q_\infty < 0.8$:

$$\frac{Q}{Q_\infty} = k \cdot t^n + b \tag{2}$$

Q is the amount released at the time t, Q_∞ the overall released amount, k a release constant of the nth order, n a dimensionless number and b the y-axis intercept, characterising the burst effect.

The exponent n gives information about the release mechanism, n = 0.5 characterises the square root of time kinetics, $0.5 < n < 1.0$ anomalous (non Fickian) transport and n = 1.0 zero order kinetics in case of the release from a slab (2). The drug diffusion and polymer erosion control the release process in equal parts if n = 0.66 (5,11). All determined n-values are related to a stirring speed of either 100 or 200 min^{-1}. The value $\bar{n}$ is the mean of the respective exponents. The intercept b is very important, because its disregard leads to a poorer correlation of the experimental data with the calculated curves. Also wrong n values, describing the release from 0% to 80% of Q_∞, are obtained without consideration of b (e.g. with a burst of 2,5% (MHEC 30000 B) n = 0,85 (without b) and n = 1,06 (with b)). The constant k is a measure of the release rate. Since k has the dimension $time^{-n}$, these release constants of different kinetics cannot be compared directly. To characterise the drug release rate, the mean dissolution time (MDT) is applied. MDT is the sum of different periods of time during which drug molecules or fractions of the dose stay in the polymer before release, divided by the total number of molecules or the total dose respectively. MDT is calculated according to Eq. 3 (15):

$$MDT = \sum_{i=1}^{n} \bar{t}_i \cdot Q_i/Q_\infty \tag{3}$$

in which Q_i is the fraction of dose released in time $\bar{t}_i = (t_i + t_{i-1})/2$, and Q_∞ is the overall released amount. The MDT is expressed in terms of MDT-80% because the release area cannot be held constant for Q_i greater than 80% of Q_∞. The influence of the hydrodynamic conditions is assessed by the MDT-80%-quotient ($MDT\text{-}80\%_{200}/MDT\text{-}80\%_{100}$) for the MDT-80% at the stirring rate 200 and 100 min^{-1}. Independence of the release rate from hydrodynamic stress is described by a MDT-80%-quotient of 1 (12).

RESULTS AND DISCUSSION

Release From Gel Matrices With Almost No Erosion

Drug release with an approximate square root of time dependence was achieved, if very well hydrated polymers like MHPC (USP 2208) or HPC HF were used. During the release experiments the tablets changed from opaque to translucent, beginning from the surface. At the end of the release process of hydrocolloid matrices with square root of time kinetics (exponent n near 0.5), most of the polymer matrix could still be seen. The 2% solution of these polymers showed a viscosity of at least 4000 mPa · s. Increasing the molecular weight of the polymers and thus the viscosity of the 2% solution of 4000, 15000 and 30000 mPa · s had nearly no effect on the release rate from MHPC matrices (Fig. 1). The reason for this is that the expansion factor during swelling increased with the higher viscosity grade of the polymers from 6 to 7.5 and thus the polymer content in the swollen gel layer decreased from 9.1 to 7.7% (12). The consistency of the swollen gel layers, examined with a penetrometer, were approximately equal (penetration of the pin 11–12 mm). This implies that the measurement of the penetration of the gel is a better way of characterising the suitability of a polymer to form resistant gel matrices than measurements of the viscosity and even the elasticity of the polymer (12). Hence the viscosity of the 2% solution and similarly the elasticity could

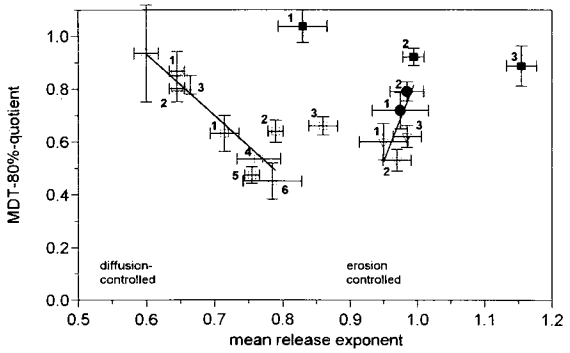

Fig. 1. MDT-80%-quotients of swollen hydrocolloid embeddings vs. the mean release exponent $\bar{n} = (\bar{n}_{100} + \bar{n}_{200})/2$; 5% proxyphylline (n = 5–6, mean ± SD). Translucent gels: △ HPC HF (1500–2500 mPa · s, 1% solution); ○ 1 MHPC 4000 (USP 2208), 2 MHPC 30000 (USP 2208), 3 MHPC 15000 (USP 2208); □ embeddings with anomal transport: 1 MHEC 1000 B, 2 MHPC 4000 (USP 2906), 3 MHPC 50 (USP 2910), 4 HPC GF (150–400 mPa · s), 5 PVAI (13 mPa · s, 4% solution), 6 MHPC 100 (USP 2208); ▽ 1 MHPC 3 (USP 2910); 2 MHPC 6 (USP 2910), 3 MHPC 15 (USP 2910); Transition: ● 1 MHEC 30000 B, 2 MHEC 4000; Opaque gels: ■ particle erosion model: 1 Stärke C*Top 12610, 2 Stärke C*Top 12616, 3 MHEC 10000 B, Left regline: r: 0,919; Right regline: r: 0,703.

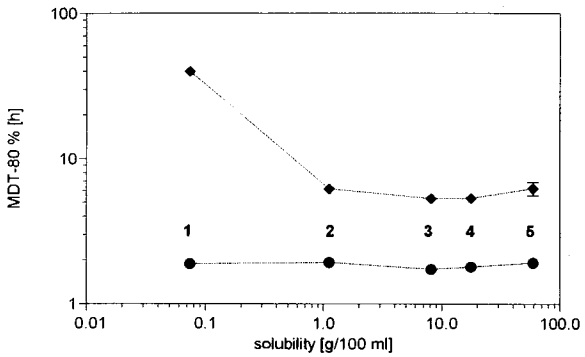

Fig. 2. MDT-80% vs. solubility of xanthine drugs, drug content of the embedding 5% (n = 5–6, mean ± SD). ♦ translucent swollen MHPC 4000 (USP 2208), ● turbid swollen MHEC 10000 B: 1 theobromine, 2 theophylline, 3 etophylline, 4 diprophylline, 5 proxyphylline.

only be coarse parameters of the polymer selection. Higher elasticity implied more resistant gel layers.

The MDT-80% quotients were greater than 0.8 (Fig. 1, upper left). Therefore the hydrodynamic stress was of little importance for the drug release as expected for matrices. A lower content of the gelling agent MHPC 4000 (USP 2208, 95 to 30%) lead to a faster drug release of the highly soluble proxyphylline (MDT = 16.5 to 6 h) with a better adjustment to $\sqrt{t}$-kinetics ($\bar{n}$ = 0.65 to 0.52). This exchange of polymer by lactose did not dehydrate the translucent swollen MHPC because of its high cloud point of 71°C and the influence of agitation speed further decreased with a smaller overall release time (MDT-80% quotient 0.87–0.94).

Variation of the compression force (3.8 to 9.4 · 10^2 MPa) and particle sizes of the polymer < 45 μm up to 140 μm had nearly no influence on the release profiles. Disintegration of the matrix occurred with coarser particles. Exchange of 200 ml water by a soja oil emulsion (Lipofundin S 10%, Braun Melsungen, Melsungen, Germany) to simulate dissolution in presence of food lengthened the MDT about 18% because of an adhesion of the oil drops to the releasing area (12). Drug release was independent of the drug solubility, if it was greater than 1 g/100 ml (theophylline, Fig. 2, upper curve). If sparing soluble drugs like theobromine were incorporated, the resulting change from solution to suspension matrix caused a higher MDT-80%.

Transition From Gel Matrices to Erosion Controlled Embeddings

If the gel layer, which had, for example, been formed by hydrocolloids like MHEC 1000 B or PVAI, was not resistant enough, erosion took a greater place in the drug release control. At the lower agitation speed of 100 min^{-1} the drug release was controlled in equal parts by drug diffusion and polymer erosion (n = 0.63 and 0.66), but at higher hydrodynamic stress it changed to anomalous transport with a greater part of erosion control (n = 0.80 and 0.85). The greater the increase of the release exponent n was, and this meaning more erosion, the higher was the influence of the stirring rate, in other words decreasing MDT-80%-quotients (Fig. 1, lower middle and Fig. 3 (r of the regline = 0,867)).

Release Going With Erosion

If translucent, very well hydrated MHPC matrices with a viscosity of a 2% solution <50 mPa · s (MHPC with a viscosity of the 2% solution of 3, 6 and 15 mPa · s, USP 2910) were used, drug release was linear at 100 min^{-1} (n = 0.92–0.97), MHPC 50 showed already a drug release with anomal transport. The MDT-80% decreased with an increasing stirring rate (fig. 4). The MDT-80%-quotient of about 0.6 for all examined matrices underlined the great effect of hydrodynamic stress (Fig. 1, lower right side). The maximum of polymer dissolution was not reached even at an agitation speed of 200 min^{-1}. This should also be impossible in vivo, because a stirring rate of 50–100 min^{-1} corresponds with the hydrodynamic stress in vivo.

In the case of highly soluble drugs like proxyphylline with a release exponent of approximately 1.0 (MHPC 6, Ta-

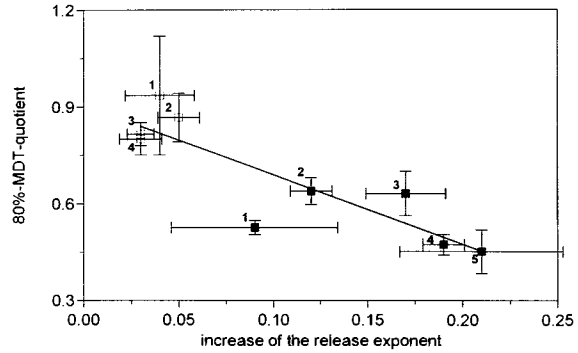

Fig. 3. MDT-80%-quotients of swollen translucent hydrocolloid embeddings vs. increase of the release exponent by raising agitation speed from 100 to 200 min^{-1}; 5% proxyphylline (n = 5–6, mean ± SD). □ 1 HPC HF, 2 MHPC 4000 (USP 2208), 3 MHPC 15000 (USP 2208), 4 MHPC 30000 (USP 2208); ■ embeddings with anomal transport: 1 HPC GF, 2 MHPC 4000 (USP 2906), 3 MHEC 1000 B, 4 PVAI, 5 MHPC 100 (USP 2208).

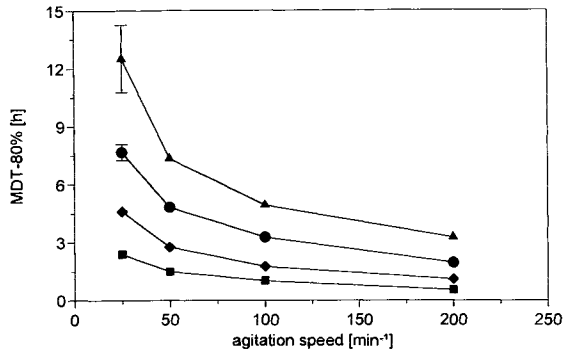

Fig. 4. MDT-80%-quotients of swollen translucent MHPC (USP 2910) embeddings vs. stirring rate; 5% proxyphylline (n = 5–6, mean ± SD). ■ MHPC 3, ◆ MHPC 6, ● MHPC 15, ▲ MHPC 50.

ble I) the diffusion layer model with the front synchronisation seemed to be acceptable. The thickness of the layer which the drug molecules had to penetrate could be calculated by Fick's law, for constant release through that gel layer, knowing the release rate, the releasing area, the concentration gradient and the diffusion coefficient. The upper limit for the diffusion coefficient is given by the value of $3.5 \cdot 10^{-6}$ cm$^2 \cdot$ s^{-1} for proxyphylline in the gel. It is calculated from experimental data of embeddings with MHPC (USP 2208) >4000 mPa · s according to the Higuchi equation. The lower limit is 10^{-6} cm$^2 \cdot$ s^{-1} for MHPC 6 (USP 2910) in water (estimated from diffusion coefficients of other macromolecules) (12). The calculated thickness between 490 and 140 μm at a release rate of about 21%/h (data from 30–80% drug release, MHPC 6 embedding) seemed to be realistic.

The conception of drug release as a consequence of the polymer dissolution, the so-called polymer dissolution model (5), could be established for sparely soluble drugs (theobromine). The release rate was lower than for proxyphylline, however the particle size of the active agent had no effect on the release velocity (Table I). On the other hand the release exponent n increased with the particle size. Undissolved drug reached the dissolution medium, where it dissolved relatively fast. With elapsing time the fraction of not yet dissolved drug and thus the exponent increased. If the dissolution of the drug in the medium was not the controlling factor, the MDT-80% was approximately unchanged (Table I).

For hydrocolloids like MHEC 10000 B or the starchs which did not form a regular gel layer, the new particle erosion model for zero order kinetics had to be introduced. The very low consistency of the swollen "pseudo gel" (penetration of the pin >32 mm) was typical for these substances. The erosion front consisted of not completely swollen polymer particles. These were worn off at the same time as the swelling front moved into the matrix. The outer region was turbid but not translucent. The release was controlled by swelling, because the erosion front and the swelling front were practically identical. The solubility properties of the drug determined if it was released dissolved (proxyphylline) or undissolved (theobromine), parallel to the polymer particle erosion. The release exponents scattered between 0.83 and 1.16 because of the differences in the surface changes by particle erosion (Fig. 1, upper right corner).

If the swelling rate was sufficiently low and the expansion factor of the gel was not too high, the overall release time was about 4 hours (MHEC 10000 B: factor of expansion <9) with a negligible effect of the stirring rate (Fig. 1 and 5).

Table I. Influence of Nature and Particle Size of the Drug on the MDT-80% Values and Release Exponents n of Hydrocolloid Embeddings, Drug Content 5% (n = 5–6, mean ± SD)

Drug	Particle size [μm]	Stirring speed [min^{-1}]	MDT-80% [h]	Release-exponent n
		MHPC 6 (USP 2910)		
Proxyphylline	100–140	100	1.76 ± 0.09	0.97 ± 0.03
Theobromine			1.95 ± 0.09	1.15 ± 0.05
Theobromine	45–100	100	1.92 ± 0.13	1.22 ± 0.09
Theobromine	25–45	100	1.95 ± 0.09	1.10 ± 0.04
Proxyphylline	<25	100	1.67 ± 0.06	0.96 ± 0.01
Theobromine			1.88 ± 0.12	1.07 ± 0.11
Proxyphylline	100–140	200	1.10 ± 0.03	1.00 ± 0.03
Theobromine			1.13 ± 0.06	1.20 ± 0.09
Proxyphylline	<25	200	1.05 ± 0.04	1.02 ± 0.01
Theobromine			1.12 ± 0.02	1.11 ± 0.05
		MHPC 50 (USP 2910)		
Theobromine	100–140	200	3.66 ± 0.20	1.12 ± 0.05
Theobromine	<25		3.62 ± 0.18	1.03 ± 0.03
		MHEC 10000 B		
Proxyphylline	100–140	100	1.92 ± 0.06	1.18 ± 0.04
Theobromine			1.88 ± 0.06	1.34 ± 0.05

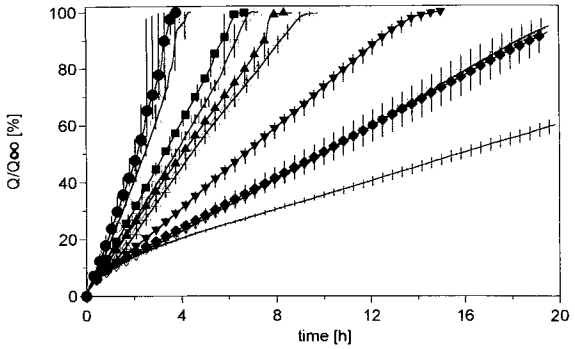

Fig. 5. Release curves of different MHEC/MHPC hydrocolloid embeddings; 5% proxyphylline (n = 5–6, mean ± SD) stirring speed: 100 min^{-1} empty symbols, 200 min^{-1} filled symbols.

	MHEC 10000 B	MHPC 4000 (USP 2208)
● ○	95%	0%
■ □	85%	10%
▲ △	75%	20%
▼ ▽	65%	30%
◆ ◇	55%	40%

Otherwise, in the case of a high expansion factor, which was realised in the first minutes (very high swelling velocity), the matrix disintegrated spontaneously or eroded drastically, influenced by the hydrodynamic stress. That explained why HEC polymers with expansion factors between 6.5 and 12.5 always disintegrated (12). It was possible to prolong the overall release time of MHEC 10000 B by mixing it with very well hydrating, high viscosity polymers like MHPC 4000 (USP 2208) in small amounts (≤20%). Higher amounts of MHPC implied anomalous transport with the described disadvantages (Fig. 5).

Compression force and particle size of the polymer (up to 400 μm) were negligible. Sparely soluble drugs lead to a higher exponent (Table I), because of the particular drug release. The MDT-80% were independent of the drug solubility (different xanthines) in contrast to the very well hydrated polymers like MHPC and the diffusion controlled drug release (Fig. 2). Addition of a soja emulsion reduced the matrix integrity and shortened the MDT-80% about 38% (12).

CONCLUSION

The hydrodynamic conditions had only little effect on the release rates, if the release kinetics showed a dependence on the square root of time in the case of very well hydrated, translucently swelling, high viscosity polymers (diffusion control) or otherwise constant rates in the case of turbid swelling embeddings (erosion control with polymer particle erosion). Zero order kinetics with very well hydrated, but low viscosity polymers should not be selected because of the great susceptibility to hydrodynamic stress. The same holds for anomalous transport.

ACKNOWLEDGMENTS

This research was supported by the minister of science and research of Nordrhein-Westfalen.

REFERENCES

1. H. Lapidus, N. G. Lordi. Drug release from compressed hydrophilic matrices. *J. Polym. Sci.* 57: 1292–1301 (1968)
2. W. D. Lindner, J. E. Möckel, B. C. Lippold. Controlled release of drugs from hydrocolloid embeddings. *Eur. J. Pharm. Biopharm.* in press
3. J. L. Ford, M. H. Rubinstein, J. E. Hogan. Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropyl-methylcellulose. *Int. J. Pharm.* 24:339–350 (1985)
4. L. S. C. Wan, P. W. S. Heng, L. F. Wong. Relationship between swelling and drug release in a hydrophilic matrix. *Drug Dev. Ind. Pharm.* 19:1201–1210 (1993)
5. J. E. Möckel, B. C. Lippold. Zero-order drug release from hydrocolloid matrices. *Pharm. Res.* 10:1066–1070 (1993)
6. T. Higuchi. Mechanism of sustained action medication. *J. Polym. Sci.* 52:1145–1149 (1963)
7. W. I. Higuchi. Analysis of data on the medicament release from ointments. *J. Pharm. Sci.* 51:802–804 (1962)
8. S. K. Baveja, K. V. Ranga Rao, D. Padmalatha. Zero-order release hydrophilic matric tablets of β-adrenergic blockers. *Int. J. Pharm.* 39:39–45 (1987)
9. K. V. Ranga Rao, D. Padmalatha. Swelling controlled-release systems recent developments and applications. *Int. J. Pharm.* 48:1–13 (1988)
10. P. Colombo, A. Gazzaniga, C. Caramella, U. Conte, A. La Manna. In vitro programmable zero-order release drug delivery system. *Acta Pharm. Technol.* 33:15–20 (1987)
11. J. E. Möckel. Mechanismus kontinuierlicher und gepulster Arzneistofffreisetzung aus Hydrokolloidmatrices *Ph.D. thesis,* Düsseldorf 1989
12. W. Lindner. Hydrodynamikunabhängigkeit der Arzneistofffreisetzung aus nichtionischen Hydrokolloideinbettungen insbesondere löslichen Celluloseethern. *Ph.D. thesis,* Düsseldorf 1994
13. R. W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N. A. Peppas. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 15:25–35 (1983)
14. N. A. Peppas. Analysis of fickian and non-fickian drug release from polymers. *Pharm. Acta Helv.* 60:110–11 (1985)
15. D. Voegele, D. Brockmeier, H. M. von Hattingberg, B. C. Lippold. Die mittlere Auflösezeit—ein Parameter zur Prüfung von Liberationsbedingungen auf Vergleichbarkeit. *Acta Pharm. Technol.* 29:167–174 (1983)