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Research Article

FABRICATION OF MATRIX HOLLOW FIBERS FOR CONTROLLED ZERO ORDER DRUG RELEASE

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ABSTRACT

Controlled release verapamail hydrochloride matrix hollow fibers constituting Gelucire (Polyglycolised glycerides) were developed in this study in an attempt to design a dosage form that manifests desirable release profile and thorough adherence to official monographs. Matrix hollow fiber formulations were prepared by combination of Gelucire and HPMC (hydroxypropylmethylcellulose) in varying proportion with fixed percentage of verapamail hydrochloride. Hollow fibers containing only Gelucire with the active ingredient demonstrated a rapid rate of drug release with an initial burst effect. Incorporation of HPMC in the matrix hollow fibers prolonged the release of drug with subsequent minimization of burst effect as confirmed by mean dissolution time release data. Among the batches containing HPMC, a direct relationship was obtained between release rate and the different grades of HPMC used. A suitable controlled release profile was obtained with the matrix hollow fibers containing 75% Gelucire and 20% HPMC. Another approach to increase the erosion rate of the gel core of the matrix-in-cylinder system was to replace part of the HPMC by MC as the MC polymers might affect the gel strength. This shows that it was possible to achieve complete drug release at a 1:5 HPMC/MC-ratio, according to zero-order kinetics (R^2 = 0.977±0.003).The formulation showed close resemblance to commercial products and compliance with USP specification. The results were explored and explained by the difference of dimensions of the hollow fibers.

Keywords: Verapamil hydrochloride, HPMC, Methyl cellulose.

INTRODUCTION

In the last several decades, many different types of controlled-release dosage forms have been Developed to improve clinical efficacy of drug and patient compliance (Merkus, 1986; Jantzen, 1996)[1].Controlled release formulations are usually intended to optimize a therapeutic regimen by providing slow and continuous drug delivery over the entire dosing interval in combination with reduced side effects, whilst also providing greater patient compliance and convenience (Chien, 1982)[2]. The classical way to design an oral sustained release dosage form is by coating tablets, pellets or capsules with insoluble, pH-independent polymers (reservoir type). However, coating is a time-consuming and expensive process with possible problems related to reproducibility of drug release and dose dumping. Another common sustained drug delivery system is the matrix type (where the drug is uniformly dissolved or dispersed throughout the rate controlling polymer) because of its effectiveness, low cost and ease of manufacturing (ChienV DS, 1982)[2]. Especially hydrophilic polymer-based (e.g. cellulose derivates) sustained release dosage forms are very popular. However, drug release from a hydrophilic matrix is generally characterised by a time-dependent profile. Initially, the drug present at the surface of the matrix is released

quickly; yielding a burst effect, then with time, as the diffusion path length increases the release rate is progressively reduced. A burst effect is often undesirable since it is unpredictable and may have negative therapeutic consequences such as toxicity due to drug concentrations increasing beyond the acceptable limit, especially on repeated administration. Moreover, any drug released during the burst stage may be metabolized and excreted without being effectively utilized, reducing the effective lifetime of the device and requiring more frequent dosing (Huang and Brazel, 2001)[3]. Over the years considerable efforts have been made in the development of new drug delivery concepts in order to achieve zero-order release, since constant rate delivery is the primary goal of sustained release systems, especially for drugs with a narrow therapeutic index. Many authors have described various approaches to limit the burst effect from matrix systems in order to obtain zero-order drug release. A number of variables able to affect the release pattern of polymeric matrix devices were evaluated: physico-chemical properties (solubility, viscosity) of the drug and polymers, drug/polymer weight ratio, administration form and manufacturing processes (Salomon et al., 1979; Alderman, 1984; Ford et al., 1987; Gander et al., 1987)[4, 5, 6, 7]. However, it appeared rather difficult to achieve a constant drug release rate by changing these variables. Scott and Hollenbeck (1991)[8] investigated the concept of non-uniform drug distribution; in which drug is more concentrated in the deeper layers of a matrix, in order to prevent the burst effect. They prepared non-eroding diffusional matrix pellets, containing a non-uniformly distributed drug, using a fluid bed suspension layering technique (Scott and Hollenbeck, 1991)[8]. These dosage forms exhibited an almost linear drug release profile with some discontinuities due to the fact that four discrete layers were used to approximate a continuous drug gradient in the matrix. Although this technique showed promise at preventing burst release, difficulties during manufacturing to achieve non-uniform drug loading made this concept impractical in most situations. When such a system is exposed to an aqueous medium it does not disintegrate, but immediately after hydration it develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the centre of the matrix system (Talukdar et al., 1996)[9].

The matrix-in-cylinder system under evaluation consists of a drug-containing matrix surrounded by a hollow insoluble cylinder in order to obtain slow and constant drug release. This chapter gives an overview of other pharmaceutical dosage forms using the principle of hollow cylinders as a method to control drug release. Only a limited number of studies appeared in literature exploring the use of hollow cylinders (also called 'hollow fibers') as delivery systems for pharmaceuticals. Some publications can be found reporting on the use of hollow fibers as oral controlled drug delivery system, as drug delivery platform to the periodontal pockets and as implant for sub dermal drug release. However, hollow fibers are interesting drug delivery devices since drug release can be controlled through their open ends as well as through the membrane sheet, and hollow fibers offer great flexibility in design since they can be manufactured by simple production methods.

METHODS

Hot-melt extrusion of hollow ethyl cellulose cylinders

Prior to hot-melt extrusion of the hollow pipes, ethyl cellulose was mixed with a plasticizer in a planetary mixer. Extrusion was performed using a MP 19 TC 25 laboratory scale co-rotating twin screw extruder of APV Baker. The machine was equipped with a screw profile with two mixing sections, an annular die with metal insert for the production of the pipes and a twin screw powder feeder. During the formulation study of the ethyl cellulose pipes the following extrusion conditions - based on preliminary research work - were used: a screw speed of 5 rpm, a powder feed rate of 0.14 kg/h and a temperature profile of 125-125-115-105-80°C from the powder feeder towards the die. The extrudates were inspected on their ability to form a solid but flexible structure which can be cut into smaller segments without splintering.

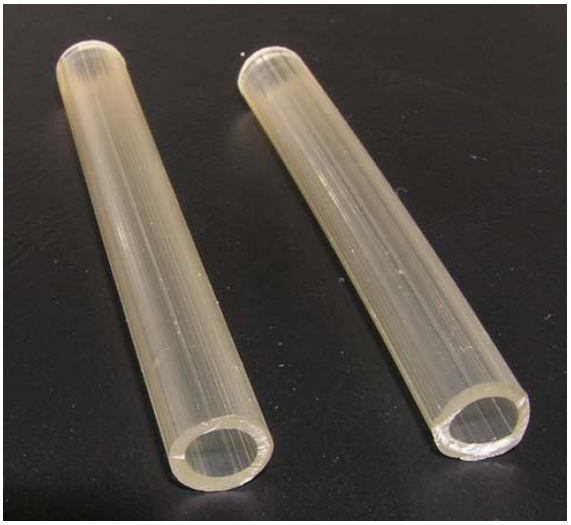

Fig. 1: Hot-melt extruded ethyl cellulose cylinders (containing 20 % dibutyl sebacate as a plasticizer)

PRODUCTION OF MATRIX-IN-CYLINDERS WITH A HPMC–GELUCIRE 44/14 CORE

The matrix-in-cylinder systems with a HPMC-Gelucire 44/14 core were manufactured as follows: after heating Gelucire 44/14 to 65°C, the molten material was admixed with the drug and HPMC and homogenised. An amount of this mixture was manually spouted into the hollow pipes using a syringe. After cooling, excess material was cut off.

PRODUCTION OF HPMC–GELUCIRE 44/14 EXTRUDATES

The HPMC-Gelucire-drug matrices without ethyl cellulose pipe were produced by means of extrusion using a MP 19 TC 25 laboratory scale co-rotating twin screw extruder of APV Baker. The machine was equipped with a screw profile with two mixing sections, a 5 mm-cylindrical die and a twin screw powder feeder. The following extrusion conditions were used: a screw speed of 25 rpm, a powder feed rate of 0.8 kg/h (verapamil hydrochloride and HPMC), a (molten) Gelucire addition rate of 1.6 kg/h (with a peristaltic pump) and a barrel temperature of 28°C.

IN VITRO EVALUATION

DISSOLUTION TESTING

The drug release from the matrix-in-cylinder was evaluated by in vitro dissolution testing. All dissolution tests were performed in threefold in a VK 7000 dissolution bath with a VK 8010 auto sampler. The system operated at 37±0.5°C and 100 rpm using the paddle method (USP 27). De mineralised water was used as a dissolution medium. Sink conditions were maintained. Samples were taken at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. The drug concentration in the samples was measured at 278 nm with a Perkin Elmer Lambda UV-Vis double beam spectrophotometer.

***IN VITRO* EVALUATION OF GELUCIRE-HPMC MATRIX CORE**

A dissolution medium (6.8 phosphate buffer) with an ionic strength of 0.14 was used. These dissolution conditions were used to provide physiologically relevant conditions (Abrahamsson et al., 1998)[10]. Sink conditions were maintained. Samples were taken at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. The drug concentration in the samples was measured at 278 nm (for verapamil hydrochloride) with a Perkin Elmer Lambda 12 UV-Vis double beam spectrophotometer.

Erosion experiments

Erosion of the matrices was evaluated under the conditions of the dissolution tests described above (n = 3). Each device having an initial mass X was removed from the dissolution medium at preselected time intervals and after removing excess water dried at 80°C to a constant weight (= mass Y). Matrix erosion at each time point was calculated as: [(X-HP)-(Y-HP)] x 100 / (X-HP) with HP being the weight of the hollow pipe. In order to assess the weight loss from the ethyl cellulose pipes, due to plasticizer leaching out into the dissolution medium, an erosion test with empty ethyl cellulose pipes was performed (n = 3). At each time point, the weight loss of the hollow pipes was less than 1.35 %.

FORMULATION TABLE

Table 1: Formulation of matrix-in-cylinders with a HPMC–Gelucire 44/14 core

INGREDIENTS	VH1	VH2	VH3	VH4	VH5
VERAPAMIL HCL	5%	5%	5%	5%	5%
METHYL CELLULOSE A4M	30%	-	-	-	-
HPMC F4M	-	30%	-	-	-
HPMC E4M	-	-	30%	-	-
HPMC K4M	-	-		30%	-
GELUCIRE 44/14	65%	65%	65%	65%	95%

Table 2: Formulation of HPMC–Gelucire 44/14 extrudate

INGREDIENTS	VH6	VH7	VH8	VH9	VH10	VH11
VERAPAMIL HCL	5%	5%	5%	5%	5%	5%
HPMC K100	30%	-	-	20%	-	-
HPMC K4M	-	30%	-	-	20%	-
HPMC K100M	-	-	30%	-	-	20%
GELUCIRE 44/14	65%	65%	65%	75%	75%	75%

Table 3: Formulation of matrix-in-cylinders with a HPMC–Gelucire 44/14 core in combination of methyl cellulose

INGREDIENTS	VHM1	VHM2	VHM3	VHM4
VERAPAMIL HCL	5%	5%	5%	5%
HPMC K4M: METHYL CELLULOSE A4M (30%)	1:5	1:2	1:1	2:1
GELUCIRE 44/14	65%	65%	65%	65%

Table 4: Formulation of matrix-in-cylinders with a HPMC–Gelucire 44/14 core with altering of dimensions of hallow pipes

INGREDIENTS	VP1	VP2	VP3	VP4	VP5	VP6	VP7	VP8	VP9
VERAPAMIL HCL	5%	5%	5%	5%	5%	5%	5%	5%	5%
HPMC K100	30%	30%	30%	30%	30%	30%	30%	30%	30%
GELUCIRE 44/14	65%	65%	65%	65%	65%	65%	65%	65%	65%
DIAMETERE	2 mm	2 mm	2 mm	4 mm	4 mm	4 mm	6 mm	6 mm	6 mm
LENGTH	10 mm	12 mm	15 mm	10 mm	12 mm	15 mm	10 mm	12 mm	15 mm

RESULTS AND DISCUSSION

Gelucire base containing low concentrations of PEG esters, thus having a low HLB. Furthermore, its melting point (50°C) is higher than that of Gelucire 44/14, which could also slow down drug release. Matrix-in-cylinders containing Gelucire 44/14 – Gelucire 50/13 mixtures exhibited (near) zero-order kinetics (R^2 varied between 0.971 and 0.991), however it was difficult to tailor drug release to a once-a-day formulation as drug release was very sensitive to the Gelucire ratio.

As slower erosion rates were observed when higher verapamil concentrations were incorporated in the Gelucire 44/14 core, it was decided to increase the solids fraction of the core by incorporating an inert powder into the core to improve the sustained release characteristics of the system

From these experiments it could be concluded that a matrix-in-cylinder system with a Gelucire® 44/14 core showed sustained zero-order release properties at high drug loading (60 % verapamil hydrochloride). Decreasing the drug load resulted in an acceleration of drug release. Neither the incorporation of the more hydrophobic Gelucire 50/13 nor the incorporation of inert fillers into the Gelucire 44/14 core were able to provide a sustained and constant drug release from the matrix-in-cylinder system.

The previous experiments have shown that a matrix-in-cylinder system, containing Gelucire 44/14 as core material, resulted in a sustained drug release profile at high drug loading only. In order to sustain drug release from a Gelucire 44/14 core loaded with a low amount of drug (5 % vearapamil hydrochloride), classical fillers of different water-solubility were incorporated in the Gelucire base. However, these mixtures were not able to meet the zero order sustained release criterion. Therefore, it was chosen to mix Gelucire 44/14 with hydroxypropyl methylcellulose (HPMC), because the gel forming capacities of HMPC could be advantageous to the sustained release properties of the dosage form. HPMC polymers swell upon contact with water or physiological fluids, forming a barrier to drug release.

The combination of Gelucire and HPMC is quite unique. Only one report, describing the combination of a gel forming polymer and polyglycolised glycerides, was found in literature (Barthelemy and Benameur, 2001)[11]. This formulation, a Self Micro Emulsifying Drug Delivery System for sustained drug release, consisted of an active pharmaceutical ingredient, a lipophilic phase (such as Gelucire), a glyceride-based surfactant, a co-surfactant and a gel forming polymer (such as HPMC) and is capable of forming, in contact with physiological fluids, a gelled polymer matrix releasing the microemulsified active agent in a continuous and sustained manner (Barthelemy and Benameur, 2001)[11].

This describes the development of a matrix-in-cylinder system containing a HPMC-Gelucire 44/14 core for zero-order, sustained drug delivery. Different strategies to tailor the drug release rate were evaluated.

The drug release from the HPMC-Gelucire cores was very slow and proceeded according to zero-order kinetics (R^2 = 0.986±0.003, 0.990±0.011, 0.991±0.008 and 0.994±0.002 for Methocel® A4M, E4M, F4M and K4M, respectively). At constant viscosity grade, no differences were observed between the drug release rates of the different HPMC grades (Methocel E, F and K). However, the methylcellulose (MC) type matrices (Methocel A) exhibited a much faster drug release profile. To find an explanation for this difference in drug release rate, the matrix erosion profiles were examined. In general, drug release rates increased with increased matrix

erosion rates. This indicated that the swelling kinetics of the matrix, which controls the matrix dissolution, is an important determinant for drug release (Sung et al., 1996)[12]. Comparison of the drug release and the erosion profiles of the MC matrices indicated that the drug release matched the erosion profile (Figure 2). Microscopic examination revealed that the MC-Gelucire cores, surrounded by an ethylcellulose pipe, were unable to form a gel upon exposure to an aqueous medium, resulting in quick erosion of this matrix (Figure 2). On the contrary, the HPMC-Gelucire matrices formed a gel plug, which was much more resistant to erosion, releasing the drug slowly (Figure 2). Figure 2 indicated that drug delivery from the HPMC-type matrices was initially erosion-controlled, switching after about 8 hours to a release mechanism by means of a combination of erosion and diffusion. A possible explanation for this shift in the release mechanism is the low hydrodynamics inside the hollow pipe: the gelled polymer matrix near the open ends of the system eroded due to the strong agitation of the dissolution medium, however as the erosion front moved inwards during the initial hours of dissolution testing the stagnant dissolution medium in the pipe eroded the matrix more slowly, yielding a combined erosion-diffusion drug release mechanism (Figure 2).

When the data were plotted according to zero order, the formulations showed a high linearity with regression coefficient values (r2) between 0.9748 – 0.9895. It showed that the drug release follows zero order[13]. This is explained by Higuchi's equation. When the data were plotted according to Higuchi's equations, the regression co-efficient values (r2) were between 0.9630 – 0.9879. By using Korsmeyer-Peppas model, the mechanism of drug release was determined. If n = < 0.45, it is Fickian diffusion and if n= 0.45 – 0.89, it is non- Fickian diffusion transport[12]. The results of all the formulations showed that the n values are between 0.6739 – 0.6901. It proved that all formulations followed non-Fickian transport mechanism[13] both diffusion and erosion[14].

Table 5: In-Vitro Drug Release Profile of Matrix-in-Cylinders With a HPMC–Gelucire 44/14 core

S.NO	TIME	VH1	VH2	VH3	VH4	VH5
1	0	0	0	0	0	0
2	0.5	10	8	9	5	45
3	1	18	12	14	10	68
4	2	35	28	20	13	83
5	4	58	32	24	16	97
6	6	70	35	27	22	-
7	8	83	40	30	27	-
8	12	98	45	35	31	-
9	16	-	48	37	36	-
10	20	-	52	42	40	-
11	24	-	58	45	42	-

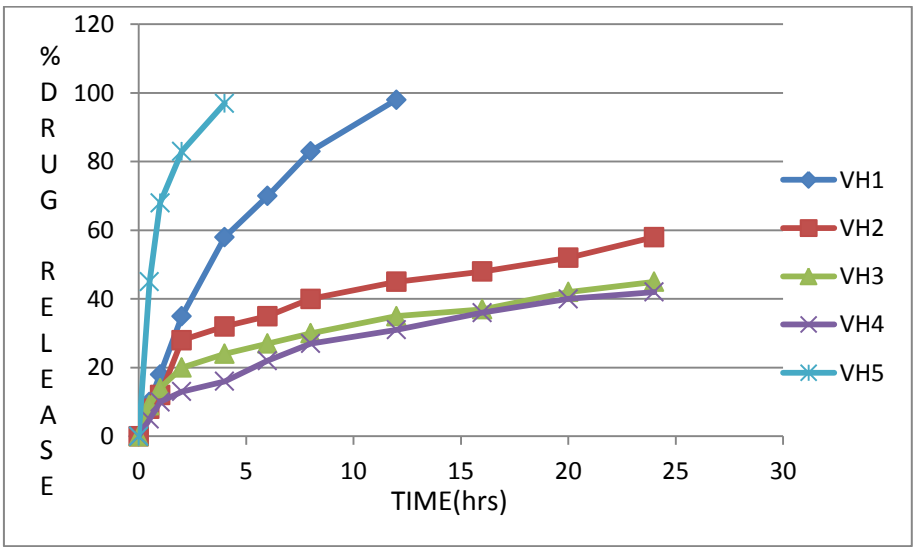

Fig. 2: In-Vitro Drug Release Evaluation of Matrix -In-Cylinders with a HPMC–Gelucire 44/14 Core

Table 6: In-Vitro Drug Release Profile of HPMC–Gelucire 44/14 Extrudates

S.NO	TIME	VH6	VH7	VH8	VH9	VH10	VH11
1	0	0	0	0	0	0	0
2	0.5	10	8	5	10	8	10
3	1	15	11	8	19	12	18
4	2	20	13	10	38	18	20
5	4	26	17	14	50	24	25
6	6	29	20	17	65	36	28
7	8	32	24	20	72	45	35
8	12	35	28	23	90	58	39
9	16	39	30	25	98	62	48
10	20	46	33	28	-	66	56
11	24	50	35	30	-	70	60

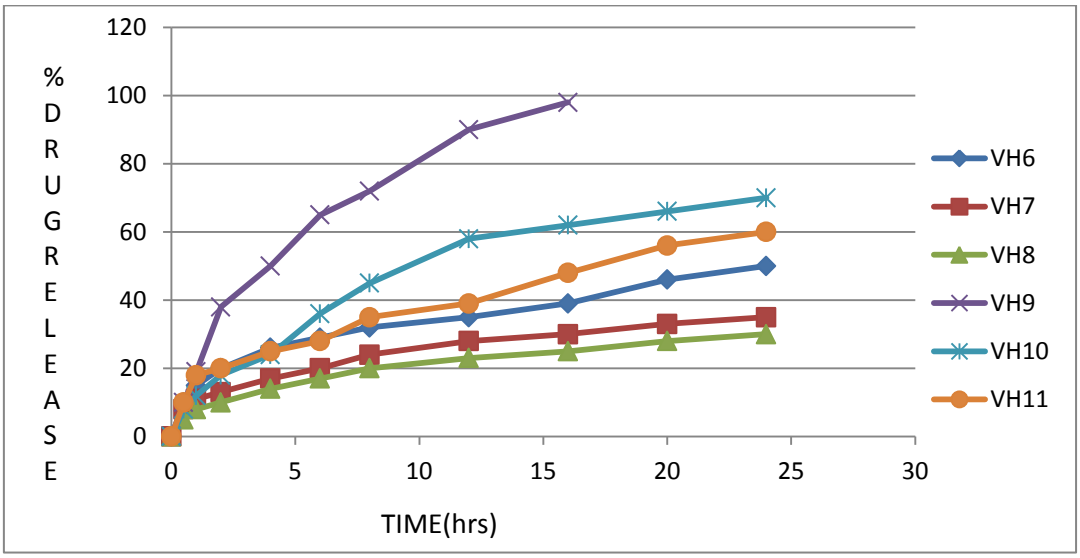

Fig. 3: In-Vitro Drug Release Evaluation of HPMC–Gelucire 44/14 Extrudates

Table 7: In-Vitro Drug Release Profile of Matrix-In-Cylinders with A HPMC–Gelucire 44/14 Core In Combination of Methyl Cellulose

S.NO	TIME	VHM1	VHM2	VHM3	VHM4
1	0	0	0	0	0
2	0.5	12	6	5	3
3	1	24	12	10	6
4	2	35	24	15	8
5	4	42	28	22	10
6	6	51	32	25	14
7	8	65	36	28	18
8	12	70	39	30	20
9	16	76	42	34	24
10	20	80	47	38	27
11	24	85	50	40	30

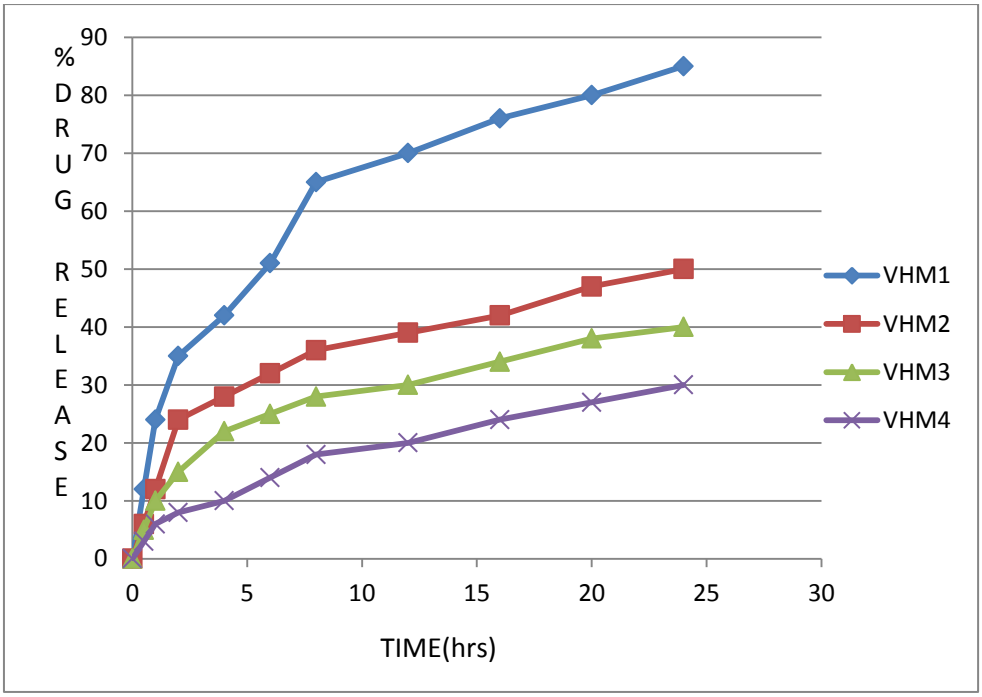

Fig. 4: In-Vitro Drug Release Evaluation of Matrix-In-Cylinders With A HPMC–Gelucire 44/14 Core In Combination of Methyl Cellulose

MODIFICATION OF DIMENSIONS

In order to determine the influence of the dimensions of the hollow pipe on drug release, matrix-in-cylinders with varying length (10, 12, 15 mm) and varying diameter (2, 4, 6 mm) were produced. Dissolutions tests were performed (Figure 5) and the influence of the length and the diameter of the matrix-in-cylinder on the AUC0-24h of the dissolution profiles was evaluated statistically (Table 8). A two-way ANOVA revealed no significant interaction ($p > 0.05$) between the length and the diameter. However, there was a significant main effect of the length of the matrix-in-cylinder ($p < 0.001$).

TABLE 8: IN-Vitro Drug Release Profile of Matrix-In-Cylinders with a HPMC–Gelucire 44/14 Core with Altering Of Dimensions Of Hollow Pipes

S.NO	TIME	VP1	VP2	VP3	VP4	VP5	VP6	VP7	VP8	VP9
1	0	0	0	0	0	0	0	0	0	0
2	0.5	10	8	4	10	8	5	6	4	4
3	1	22	16	8	28	12	9	12	8	9
4	2	34	24	12	41	18	14	28	11	12
5	4	42	36	18	52	26	19	45	22	16
6	6	58	42	22	67	34	24	63	32	19
7	8	65	51	26	73	41	27	71	39	24
8	12	75	56	30	79	47	30	80	44	27
9	16	80	60	34	85	54	36	87	47	32
10	20	92	65	46	91	59	41	92	53	37
11	24	98	70	50	96	65	45	97	60	40

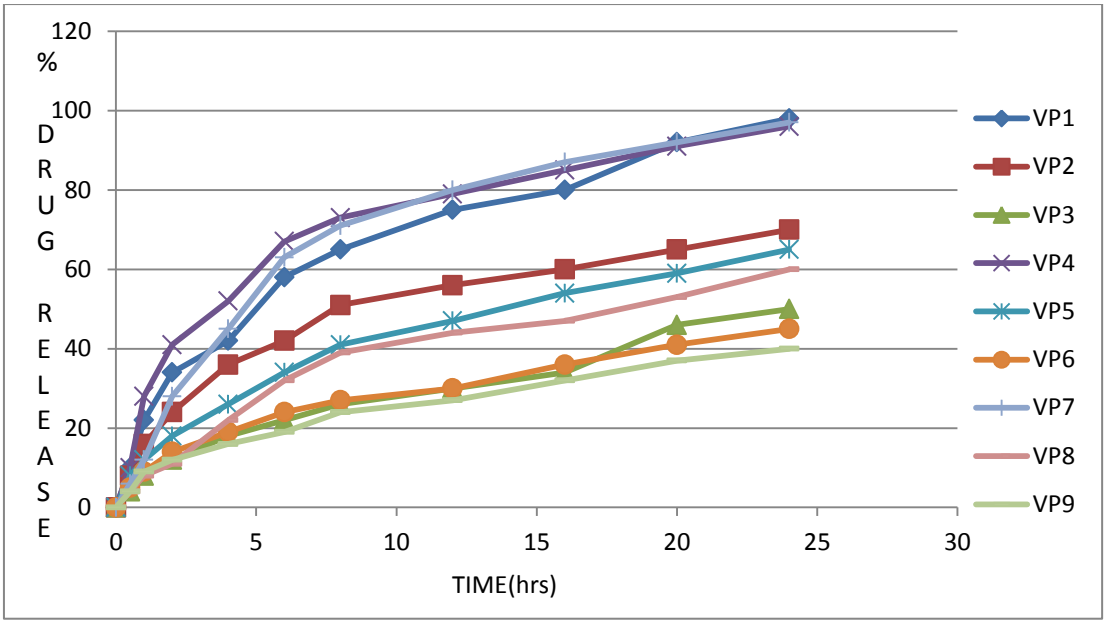

Fig. 5: In-Vitro Drug Release Evaluation of Matrix-In-Cylinders With A HPMC–Gelucire 44/14 Core with Altering of Dimensions of Hallow Pipes

CONCLUSION

It can be concluded that shortening the matrix-in-cylinder resulted in a quicker drug release. For example, short matrix-in-cylinders (l = 10 mm, d = 4 mm), containing 5 % verapamil hydrochloride, 30 % HPMC K100 and 65 % Gelucire 44/14, released 100 % of the drug over 24 h in a linear way (R^2 = 0.994±0.001), thus the formulation VP4 meeting the proposed zero-order sustained release criterion(figure:5).

REFERENCES

1. Merkus FWHM. In: Rate controlled drug administration and action (Struyker-Boundier,H. A.J Eds.) CRC Press, Boca Raton, FL. 1986;15-47.
2. Chien YW. Fundamentals of controlled-release of drug administration. In: Novel Drug Delivery System (Swarbrick, J., and ed.), Marcel Dekker, New York. 1982;465-574.
3. Huang X and Brazel CS. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J. Control. Release. 2001;73:121-136.
4. Salomon JL, Vaugnat P, Doelker E and Buri P. Importance de la technologie et de la formulation pour le méchanisme de libération du chlorure de potassium contenu dans des matrices hydrophiles. Pharm Acta Helv. 1979;3:86-89.
5. Alderman D. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Technol. 1984;5:1-9.
6. Ford JL, Rubenstein MH, McCaul F, Hogan JE and Edgar PJ. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Int J Pharm. 1987;40:223-234.
7. Gander B, Gurny R, Doelker Na and Peppas NA. Crosslinked poly (alkylene oxides) for the preparation of controlled-release micro matrices. J Control. Release. 1987;5:271-283.
8. Scott DC and Hollenbeck RG. Design and manufacture of zero-order sustained-release pellet dosage form through non-uniform drug distribution in a diffusional matrix. Pharm. Res. 1991;8: 156-161.
9. Talukder MM, Michoel A, Rombaut P and Kinget R. Comparative study on xanthan gum and hydroxypropylmethylcellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour. Int J Pharm. 1996;129:231-241.
10. Abrahamsson B, Alpsten M, Bake B, Larsson A and Sjögren J. In vitro and in vivo erosion of two different hydrophilic gel matrix tablets. Eur J Pharm Biopharm. 1998;46:69-75.
11. Barthelemy P and Benameur H. Composition with sustained release of active principle, capable of forming a

microemulsion. U.S. Patent 6 309 665 B2. 2001.
12. Sung KC, Nixon PR, Skoug JW, Ju TR, Gao P, Topp EM and Patel MV. Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. Int J Pharm. 1996;142:53-60.
13. Schwarz BJ, Simonelli AP and Higuchi WI. Drug release from wax matrix analysis of data of order of kinetic release and diffusion controlled model. J Pharm Sci. 1998;57:274-277.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanisms of solute release from porus hydrophilic polymers. Int J Pharm. 1983;15: 25-35.