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Research Article

DESIGN AND DEVELOPMENT OF MATRIX SYSTEMS USING HOLLOW FIBERS AS CARRIER

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ABSTRACT

Development of controlled delivery systems with less or no toxicity is the main objective of researchers in medicine, pharmaceutical scientists, medicinal chemists and other health related disciplines. Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods. Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form and ease of scale-up and process validation. The objective of this work was to develop a partially 'coated' matrix in order to obtain zero-order sustained drug release by means of a simple and flexible manufacturing method. The matrix-in-cylinder system, consisting of a drug-containing HPMC-Gelucire 44/14 matrix inserted in an ethyl cellulose pipe, showed to be a flexible tool to obtain linear, sustained drug release. the concept of a HPMC-Gelucire 44/14 core surrounded by an ethyl cellulose pipe seemed very promising to formulate a matrix system with zero-order release kinetics. However, drug release was too slow as in most cases less than 50 % of the drug was released within 24 hours. Whereas formulation FH10 shows the promising results which shows 70% of drug release from the matrix systems.

INTRODUCTION

Sustained 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)[1]. 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)[1]. 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)[2]. 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)[3, 4, 5, 6]. However, it appeared rather difficult to achieve a constant drug release rate by changing these variables. Scott and Hollenbeck (1991)[7] 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)[7]. 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.

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)[8]. 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.

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 Extrudates

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%

RESULTS AND DISCUSSION

IN VITRO EVALUATION

This experiment 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 % verapamail 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)[9]. 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)[9].

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.

Table 3: 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	-

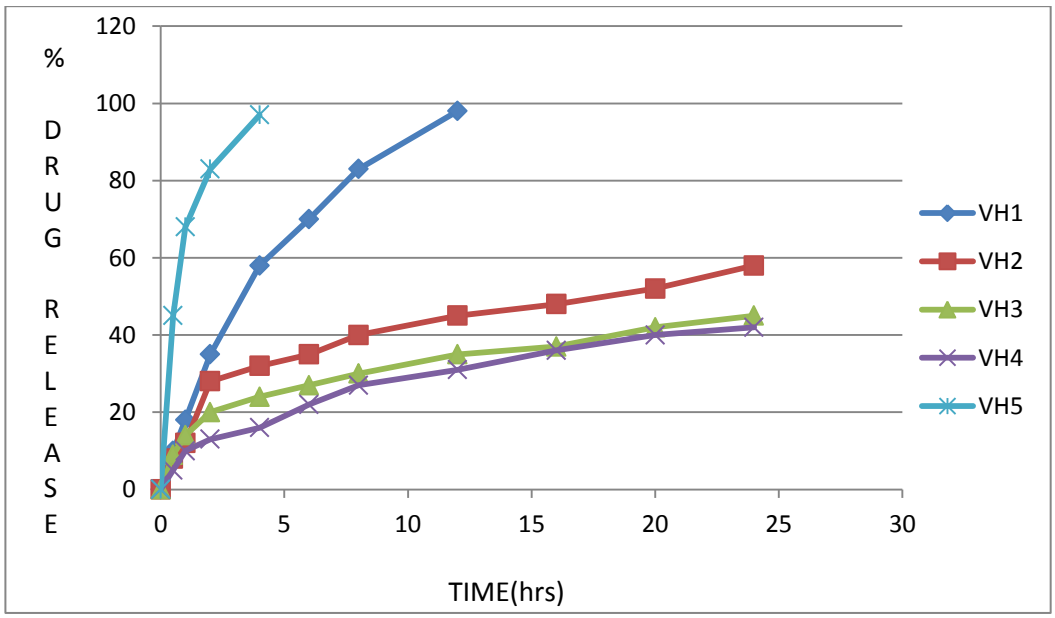

Fig. 2: In-Vitro Drug Release Evaluation of Matrix-in-Cylinders with a HPMC–GELUCIRE 44/14 core

Table 4: 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

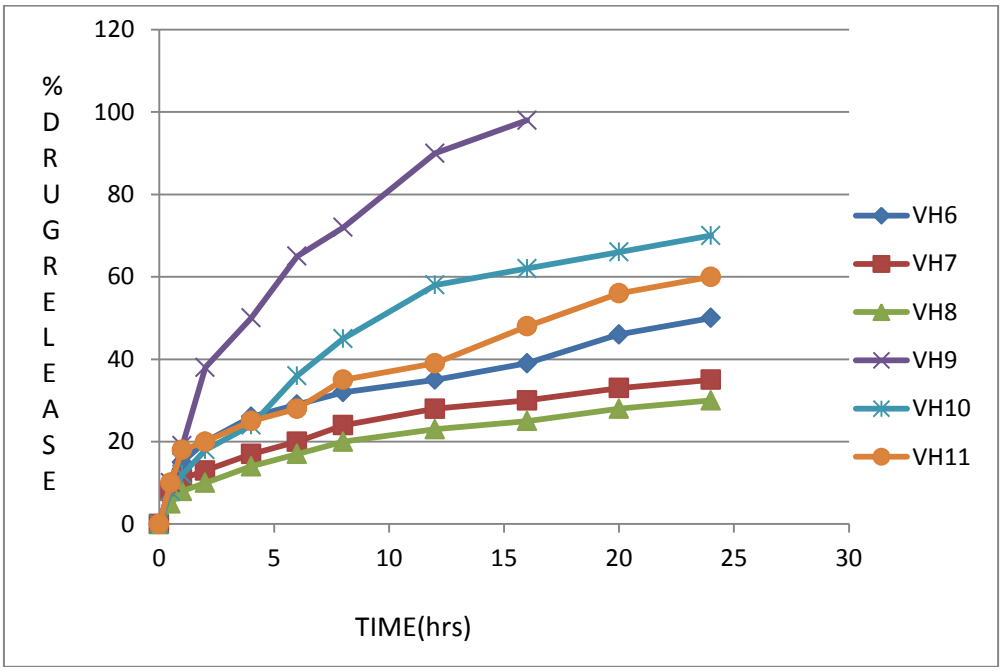

Fig. 3: IN-VITRO DRUG RELEASE EVALUATION OF HPMC–GELUCIRE 44/14 EXTRUDATES

Drug release from the matrix depended on the viscosity of HPMC: a matrix-incylinder containing 30 % HPMC K100 (the lowest evaluated viscosity grade) showed the quickest release profile (60 % drug released within 24 h) as this polymer had the highest susceptibility to erosion. Examination of the erosion profile of the matrix-in-cylinder containing 30 % HPMC K100 indicated that drug release proceeded by means of erosion. Similar drug release and erosion profiles were observed when incorporating high viscosity HPMC grades (the K4M and K100M formulations releasing 40 % of the drug over 24 h). The lack of difference in the drug release profiles for the K4M and K100M formulations suggested the existence of a 'limiting HPMC viscosity', i.e. for the system studied, the drug release rate did not decrease when the viscosity grade was increased above 4000 mPa. A 'limiting HPMC viscosity' was already described by Gao et al. (1996)[10] and Sung et al. (1996)[11] for HPMC-based tablets and was attributed to a similar drug diffusivity resulting from an identical gel layer thickness above the limiting viscosity grade.

The release rate kinetic data for all formulations is shown in Table 4. 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[12]. 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[12] both diffusion and erosion[13].

CONCLUSION

Based on these results the concept of a HPMC-Gelucire core surrounded by an ethyl cellulose pipe seemed very promising to formulate a matrix system with zero-order release kinetics. However, drug release was too slow as in most cases less than 50 % of the drug was released within 24 hours. Whereas formulation FH10 shows the promising results which shows 70% of drug release from the matrix systems.

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