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Original Article

Effect of Formulation Variables on Phenobarbital Release from HPMC Matrices

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Abstract

Controlled release swellable tablets of phenobarbital were prepared by a simple direct compression process using hydroxypropyl methylcellulose (HPMC) as the matrix former. The effects of the viscosity grades of HPMC and HPMC/lactose ratio and ethylcellulose (EC)/sodium carboxymethylcellulose (NaCMC) and their concentrations on the release behavior of phenobarbital from HPMC matrices were investigated. In order to determine the mode of release, the data were analyzed based on the equation $Q= K t^n$. Higher drug release rate was found for formulations with lower HPMC/lactose ratios and lower HPMC viscosity grades. The viscosity of HPMC polymer has a large influence on the erosion rate of matrix tablet. Use of low viscosity grade of HPMC polymer is desired for drugs that are poorly water soluble such as phenobarbital since the erosion rate of tablet matrix is the controlling factor for drug release. As the proportion of EC or NaCMC in admixture with HPMC increased, the release rates gradually increased. It is also observed that the amount of HPMC played a dominant role, affecting the drug release in binary mixtures. *In vitro* release studies demonstrated that use of an appropriate blend of HPMC and EC or NaCMC enables to better control of drug release profiles and approach to zero order kinetic.

Keywords: Controlled release; Hydroxypropyl methylcellulose; Phenobarbital.
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1. Introduction

A controlled-release system is regarded as desirable to produce minimal plasma fluctuation and to decrease adverse drug reaction incidences. The purpose of this study was to achieve controlled-release of phenobarbital by preparing swellable systems using hydroxypropyl methycellulose (HPMC) as matrix former. Swellable and erodible systems prepared by incorporating drugs in hydrophilic polymeric matrices have received considerable attention for sustained release formulations. Different types of hydrophilic

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polymers have been reported and used in these systems.

Among the hydrophilic polymers, HPMC is frequently used due to its non-toxic nature and ease of manufacturing.

Drug release mechanisms from swellable and erodible hydrophilic matrices have been described by several authors [1-3]. As a matrix exposed to aqueous liquid, the surface polymer hydrates to form a viscous gel layer. The gel layer forms a diffusional barrier that retards further water uptake and the release of the dissolved drug. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, whilst poorly water-soluble drugs are released predominantly by the erosion mechanism [4]. The contribution of each release mechanism to the overall drug release process is influenced both by drug solubility and also by the physical and mechanical properties of the gel barrier that forms around the tablet. Although outwardly simple, drug release from hydrophilic matrix system is a complex phenomenon resulting from the interplay of many different physicochemical processes. In particular, the formation and physical properties of the hydrated surface barrier are an important determinant of subsequent behavior and drug release performance.

Several factors, such as the polymer type and concentration, the drug particle size and the presence of additives and excipients in the final formulation can modify the drug release from the matrices [5-8]. The effect of polymeric excipients on drug release from matrices has been investigated by Dabbagh *et al*. [9] and Baveja *et al*. [10]. They used blends of HPMC and sodium carboxymethyl-cellulose (NaCMC) to achieve a zero-order release of propranolol hydrochloride [9, 10].

The objectives of the present study were to investigate the *in vitro* release characteristics of phenobarbital from various controlled release matrices: (a) to examine the effect of various viscosity grades of HPMC on the release profile of drug; (b) to study the effects of soluble filler (lactose) and binary polymer blends (ethyl cellulose (EC)- HPMC and NaCMC- HPMC) on the release behavior; (c) to utilize the drug release data to gain insight into the mechanism of drug release from the matrices studied.

2. Materials and methods

2.1. Materials

HPMC K100M, K15M, K4M, NaCMC, and ethyl cellulose (EC) were obtained from Colorcon, UK. Phenobarbital and lactose monohydrate were from Merck, Germany; and magnesium stearate was purchased from BDH Chemicals Ltd, Poole, Dorest, UK.

2.2. Tablet formulation and preparation

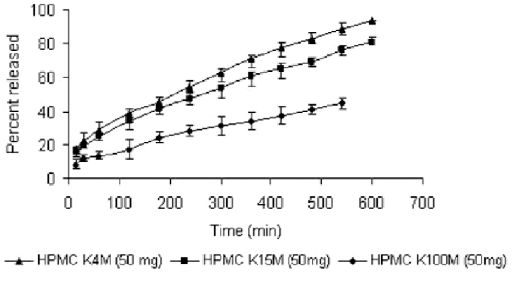

Figure 1. The release profile of phenobarbital from formulations with various HPMC viscosity grades.

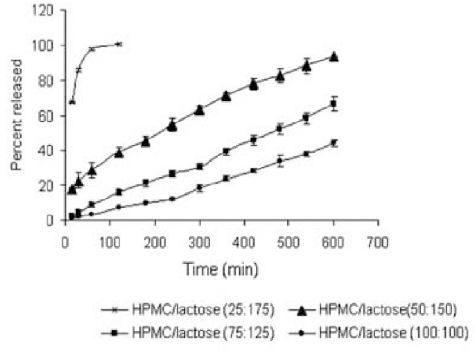

Figure 2. The effect of lactose on the release rate of phenobarbital from HPMC K4M matrices.

Compaction was accomplished by direct compression of blends containing 100 mg phenobarbital, 100 mg lactose, 100 mg polymer and 2% w/w magnesium stearate. The blends were made using a tumbler mixer and a mixing time of 10 min. By holding the tablet weight constant, the surface area and volume of the dry compacts were essentially fixed. Direct compression with a manual hydraulic press (Riken Seiki Co, Japan) at 100 kg/Cm^2 pressure was used to prepare tablets.

Tablets were prepared to quantify the following variables.

1) The effects of various viscosity grades of HPMC. Formulations with 50 mg HPMC and 150 mg lactose were used in all of the viscosity grades (K100M, K15M and K4M).

2) The effects of the HPMC/lactose weight ratio. In these experiments, K4M was used as the model polymer since its properties have been well documented [1, 3]. The HPMC/lactose weight ratios were used in the study included 100:100, 75:125, 50:150 and 25:175.

3) HPMC K4M- polymer blends. Tablets containing either EC: HPMC K4M or NaCMC: HPMC K4M were made containing 100 mg of polymer admixture at the ratios 1:0, 1:3, 1:1, 3:1.

2.3. Dissolution studies

Tablets of each formulation were subjected to dissolution testing using a USP paddle-typed dissolution apparatus, in 900 ml distilled water. The rate of stirring was 50 rpm. The amount of phenobarbital was 100 mg in all formulations. The dissolution medium temperature was maintained at 37±1 °C. At each sampling interval, 5 ml of the dissolution medium was withdrawn and an equal volume of fresh distilled water was replaced. Phenobarbital was determined at 240 nm using an ultraviolet spectrophotometer (Shimadzu 120A, Japan). Experiments were performed for three tablets in each formulation and mean values were obtained.

2.4. Analysis of dissolution data

Numerous mathematical models describing drug release formulation has been developed. But probably the most important aspect when developing new pharmaceutical products or evaluating drug release mechanism is suitable predictive ability and accuracy of model. In many cases, the use of simple empirical or semi-empirical models such as classical Higuchi equation and so called power law is fully sufficient [11].

Dissolution data (M_t/M_∞ <0.6) were analyzed using the equation proposed by Ritger and Peppas [12] to describe the mechanism of drug release from matrices.

$M_t/M_\infty = Kt^n$ Equation (1)

where M_t corresponds to the amount of drug

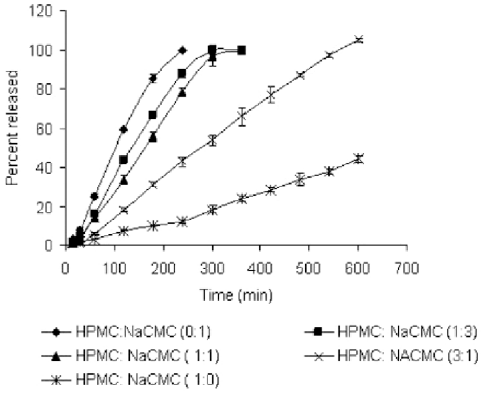

Figure 3. The release profile of phenobarbital from HPMC K4M- NaCMC matrices.

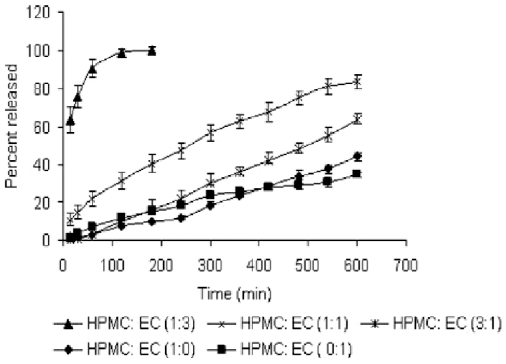

Figure 4. The release profile of phenobarbital from HPMC K4M- EC matrices.

Table 1. The kinetic of release of phenobarbital from various grades and concentration of HPMC (Equation 1).

	K100M /lactose (50/150)	K15M/lactose (50:150)	K4M/lactose (50:150)	K4M/lactose (100:100)	K4M/lactose (75:125)	K4M/lactose (25:175)
f 0.25h	9	16	18	2	3	68
f 3h	24	42	46	10	20	100
f10h	45	81	94	44	67	-
k	0.921	1.52	0.28	0.019	0.104	-
n	0.6	0.6	0.9	1.2	1	-
r	0.992	0.998	0.992	0.995	0.997	-

f: fraction of drug released in time 't'; r: correlation coefficient; n: the release exponent; K: the release rate constant.

released in time t, M_∞ is the total amount of drug that must be released at infinite time, K is a constant and n is a characteristic exponent (n acquires values between 0.43 and 1 depending on matrix geometry and release mechanism in cases of coupling diffusion and polymer relaxation phenomena or anomalous transport) [13].

3. Results and discussion

For the controlled-release device under investigation, the release should follow three steps. First step is the penetration of the dissolution medium in the tablet matrix (hydration). Second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet, to the surrounding dissolution medium. The co-existence of the other components in addition to HPMC should affect all the aforementioned steps or processes. Particularly, they may affect initially the liquid uptake and, therefore, the hydration rate, the swelling of the cellulosic component and the dissolution of the active ingredient as well. Also, they may reduce the relief of stress developed in the hydrated tablet matrix due to swelling and, therefore, promote the occurrence of erosion. Finally, they may affect the transport of the dissolved drug through the matrix pores, through the developed cellulosic gel or directly from drug surface of the eroded matrix to the surrounding liquid [14].

Release mechanism can be elucidated indirectly on basis of exponent 'n', in Equation (1). Correlation coefficient closer to 1 means better fitting.

The influence of HPMC viscosity grade on phenobarbital release is shown in Figure 1. A constant HPMC/lactose weight ratio of 50:150 was used while the viscosity grade of HPMC was varied. The fastest drug release rate was observed for the K4M formulation. The K15M formulation exhibited greater drug release rate than the K100M formulation. As observed in the results, the instantaneous drug release rate decreased with time for the viscosity grade series, which is reflected in the curvature of the percent of drug release profiles.

The 'n' value for both HPMC K100M and K15M is 0.6 which indicate that release is closer to Fickian diffusion than to erosion, for these systems, probably because dissolution of drug particles precedes matrix swelling and erosion. Thus, the dissolved drug is transferred by diffusion through the water pores to the surface of the tablet and surrounding liquid. After the matrix swelling, release proceeds by diffusion through the gel barrier formed by the cellulosic polymer.

Figure 2 shows the effect of HPMC/lactose ratio on phenobarbital release. The release rate increases as the mass fraction of lactose increases replacing HPMC (value of K in Table 1).

Given the complexity of these swellable matrix systems factors such as, differences in water penetration rate, water absorption capacity and swelling, polymer erosion and attrition which result from changes in the polymer content may contribute to this effect [3, 15].

Table 2. The kinetic of release of phenobarbital from polymer blend matrices (Equation 1).

	K4M/NaCMC (0:1)	K4M/NaCMC (1:3)	K4M/NaCMC (1:1)	K4M/NaCMC (3:1)	K4M/EC (0:1)	K4M/EC (1:3)	K4M/EC (1:1)	K4M/EC (3:1)
f 0.25h	3	0.98	1.3	0.27	2	63	11	0.11
f 3h	85	67	56	31	15	100	40	16
f10h	100	100	100(360')	100	35	-	83	63
k	0.546	0.415	0.334	0.214	1.031	-	0.156	0.079
n	1	1	1	1	0.56	-	1	1
r	0.997	0.993	0.997	0.993	0.996	-	0.992	0.999

f: fraction of drug released in time 't'; r: correlation coefficient; n: the release exponent; K: the release rate constant.

In the presence of lactose, as anticipated, water diffusion into the matrix is enhanced and drug is diffused out of the matrix more rapidly. Diffusion of drug out of matrix also is enhanced by decreasing the tortuosity of the diffusion path [16]. It is also apparent that by decreasing the polymer content, release tends to accelerate which may be explained by reduction in polymer concentration, and consequently more rapid disentanglement of polymer chains, which results in weakening of gel and complete dissolution of the system [17-20].

These results are consistent with previous reports [21, 22] and demonstrate that change in the HPMC/lactose ratio can be used to produce a wide range of drug release rates.

Among these systems, the matrix tablets containing HPMC K4M:lactose (1:3) didn't maintain their integrity while swelling and almost 100% of drug released after 1 h. The 'n' value for HPMC K4M matrices are between 0.9 and 1.2. Taking in to account the high 'n' values (between 0.9 and 1.2), we can say that phenobarbital is released by anomalous diffusion, probably because of relatively quick matrix erosion [14].

Matrix erosion may result because the stress developed due to hydration and swelling of the cellulosic polymer cannot be compensated. Then depending on the mass fraction of polymer, the cellulosic polymer forms a more or less disrupted or continues and thick gel barrier and the release proceeds more or less by direct dissolution of the drug particles or by diffusion through the continuous gel barrier.

Figure 3 shows the release profile of phenobarbital from matrices containing HPMC, NaCMC and their combinations. According to Tables 1 and 2, the release percent of drug from matrices containing only 100 mg HPMC after 3 h is 10%, and it is 85% for matrices containing only 100 mg NaCMC. NaCMC matrices release the active component much more quickly than HPMC ones; in fact, from NaCMC systems, the total drug loaded is released in about 4 h with a mechanism mainly governed by polymer relaxation and erosion ('n' is 1). The high release rate is due to the high solubility of NaCMC. This polymer characteristic gives to the matrix a quick gel erosion rate and a high erosion degree of the overall system.

Figure 2 shows the effect of 100 mg HPMC K4M alone on the release pattern of drug. It is apparent that 100 mg HPMC K4M can sustain the drug release, but the pattern of release is not suitable. From this figure, it is obvious that the release of drug in early hours is very slow and after approximately 5 h the rate release appreciably increases. On the other hand, only 44% of drug released after 10 h. Therefore, this formulation cannot be practically useful. To correct the release pattern of drug from matrices, blend of HPMC and NaCMC were used as matrix former. The release fluctuation in these formulations decreased and the kinetic of drug release approached to zero order kinetic.

Phenobarbital release increased as the proportion of NaCMC increased in the HPMC- NaCMC blend. It is observed that the amount of HPMC played a dominant role, affecting the drug release in these mixtures (see K values in Table. 2).

Comparing the 'n' value (Table 2) for these formulations showed that the percentage of NaCMC had no significant effect on the release mechanism. Among these systems, the matrix tablets containing HPMC:NaCMC (3:1) had the desired rate and amount of release, namely 100 mg/10h as shown in Figure 3.

Figure 4 shows the release profile of phenobarbital from matrices containing HPMC, EC and their combinations. As the proportion of EC in the matrix increased, the release rate increased. The value of 'n' did not change when the matrices consisted of an admixture of the two polymers. This confirmed the report of Ford *et al*. [6] who investigated the effect of replacement of portion of HPMC within the matrices by diluents and found that it increased the release rates of promethazine hydrochloride, irrespective of whether the diluents were water solubility of the diluents. The exponent value from matrix tablets containing EC (0.56) indicates that the matrix exhibits mainly diffusional release mechanisms, whereas the exponent values from matrices containing various ratios of HPMCK4M: EC (1) indicates erosion mechanism. Visually, the matrices containing EC remained intact during the test whereas matrix tablets consisted of 1:3 HPMC:EC disintegrated slowly. In the later matrix a burst release was observed and more than 63% drug was released during the initial 15 min. of the dissolution test. This phenomenon could be due to the fact that when the proportion of EC in the matrix is high, the hydrophilic particles in the matrix were separated from each other and formation of a protective gel layer around the matrix did not occur. As the proportion of HPMC in the matrices increased, the matrix remaining at the end of dissolution became larger.

4. Conclusion

The release rate of phenobarbital from matrices containing HPMC can be modified using higher lactose/HPMC ratio and a lower viscosity grade of HPMC. In hydrophilic polymeric matrices, lactose should not be regarded as neutral or simple additive, as it is capable of altering the drug release rate and mechanism.

In the matrices containing HPMCK4M:NaCMC as the proportion of NaCMC increased the release rate gradually increased without altering the release mechanism. Similar behavior was seen for matrices containing HPMC:EC except when the ratio of HPMC:EC was (1:3), where the burst release of drug occurred.

Addition of an optimum concentration of EC/NaCMC to HPMC based formulations was found to provide the desired release with zero order kinetic.

Finally, a successful controlled-release swellable matrix tablet containing 100 mg phenobarbital was prepared by direct compression and with NaCMC/HPMC (1:3) matrix former. The drug was released from above mentioned matrix over the targeted period of 10 h with zero order mechanism.

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