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Improving the release characteristics of water-soluble drugs from hydrophilic sustained release matrices by in situ gas generation

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Summary

Potassium chloride release from a number of compressed hydrophilic polymer tablets is investigated with a view to designing a simple zero-order release system. The approach used is based on incorporation of low levels of effervescent mixtures within the table matrix. Supporting work on related polymeric systems is also discussed.

Introduction

Compressed hydrophilic polymer matrices are still widely used as a cheap sustained release dosage form. They are readily manufactured and make use of technology that even the most modest pharmaceutical development laboratory has ready access to. Unfortunately, however, these sustained release dosage forms are among the most difficult to model and none can be relied on to produce true time-independent release. Despite these difficulties a number of groups have attempted to improve and better understand these sustained release hydrophilic polymer matrices. Notable examples are Lapidus and Lordi (1966, 1968), Peppas et al. (1980), Korsmeyer et al. (1983) and Bamba et al. (1979). Much of these developments of course rely on earlier work of Higuchi (1961), Higuchi (1962), Schwartz et al. (1968) and Desai et al. (1966a) on release of drugs from other types of matrices. Such successful attempts at applying diffusion theory (Barrer, 1941; Jost, 1952; Crank, 1975) have made the design of sustained release systems much more rational.

In this report the compressed hydrophilic polymer matrix system is further investigated with a view to exploring whether the kinetics of release could be modified to produce time-independent release of a water-soluble drug without a significant increase in the complexity of the processing required during subsequent manufacture. Salomon et al. (1979) have previously described the use of laminated tablets to produce time-independent release from hydrophilic polymer matrices. The current approach attempts to exploit the chance observation (Korsmeyer et al., 1983) that entrapped air led to zero-order release of potassium chloride from compressed hydroxypropyl methylcellulose matrices.

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Materials and Methods

Metolose S.M-100 was used as the hydrophilic polymer and was supplied by Shin-Etsu Chemical Co., Japan. Metolose S.M-100 has both methoxy (27.5–31.5% $-OCH_3$) and hydroxypropoxy groups ($-OC_3H_6OH$) although the percentage of the hydroxypropoxy groups is not defined (Shin-Etsu Product booklet).

Polyvinyl pyrrolidone of molecular weight about 700,000 was purchased from BDH Chemicals, U.K., as were high-density polyethylene and potassium chloride. Citric acid was supplied by Fisons Scientific Apparatus, U.K. Sodium bicarbonate B.P. was obtained from MaCarthys, U.K.

The release of potassium chloride was monitored either by using a standard dissolution (whole surface) set-up or by release from a single surface using the system reported by Salomon et al. (1979).

Single surface release

The tablet was mounted onto the perspex holder as described by Salomon et al. (1979) except that one face of the matrix was set flush with one face of the holder.

Exposure of the second surface to the dissolution medium was prevented by a rubber closure. To maintain good mixing in the receiver a magnetic stirrer was used at a speed of 100 rpm. All the experiments were run at 37°C.

Preparation of matrices

All the materials used in the formulations were dried at 50°C to constant weight in an oven, and were then sieved through 90 μm and 45 μm test sieves (Endecotts, U.K.). Only the 45–90 μm fraction of the powders was used for making up the matrices. Sieved material was stored in a desiccator when not in use.

The powder mixes used in the formulations were prepared in glass containers with a whirlimixer (Fisons Scientific Apparatus, U.K.). Preweighed 500 mg quantities of the powder mixes containing 250 mg potassium chloride each were compressed with a hydraulic press (Specac, U.K.) fitted with a 13-mm punch and die set and a vacuum pump (Crompton Parkinson, U.K.). The matrices were compressed at the required pressure, with air evacuation, for 10 min. Tablets were subjected to release studies immediately after preparation.

Results and Discussion

Release of drug from a matrix consisting of drug uniformly dispersed in a matrix in which the drug has a finite solubility follows the now widely accepted equation derived by Higuchi (1961):

$$Q = \sqrt{D \cdot t(2A - C_s)C_s} \tag{1}$$

where Q is the amount of drug released per unit area after time t, D is the diffusion coefficient of the drug in the matrix, A is the concentration of drug present in the matrix at time 0 and at any time beyond the moving boundary and C_s is the solubility of the drug in the matrix. The assumptions made in the derivation of equation 1 are that: (i) the particles of drug are much finer than the thickness of the matrix; (ii) the initial concentration of drug is much above the drug solubility in the matrix; and (iii) the receiver acts as a perfect sink. To apply Eqn. (1) to systems in which the drug is dispersed in a matrix in which the drug is essentially insoluble as in the present study, Higuchi (1963) has suggested the modifications shown in Eqn. 2:

$$Q = \sqrt{\frac{D \cdot \epsilon}{\tau}(2A - \epsilon \cdot C_s)C_s \cdot t} \tag{2}$$

The C_s term is now the solubility of the drug in the permeating fluid and the diffusivity now refers to that of the drug in the permeating fluid. In such a system porosity (ϵ) needs to be taken into account as does tortuosity (τ) although some authors (Rowe et al., 1972) have suggested the use of an alternative model based on cylindrical capillaries representing pores formed between polymer particles and pores formed by dissolving drug. This model, proposed earlier by Michaels (1959), suggests that Eqn. 2 may indeed not be as discriminative as is often assumed. While adherence to Eqn. 2 and indeed to the model proposed by Michaels (1959) may be observed, they

are not as specific as is often assumed. A number of studies have attempted to rigorously test Eqn. 2 (Desai et al., 1965; Desai et al., 1966a, b and c) with some success. However, the difficulty in isolating any single factor means that none of the studies reported so far have comprehensively excluded other equations as being better alternatives. Indeed most of the rigorous work reported has been on hydrophobic polymers rather than on the hydrophilic alternatives.

Lapidus and Lordi (1966) in two elegant studies showed that the release of chlorpheniramine maleate from a hydrated methylcellulose matrix followed Eqn. 2 and demonstrated the importance of porosity and tortuosity although again, exact quantification of tortuosity and porosity and more importantly dissociation of the two parameters were non-ideal.

Despite the limitations discussed, it is clear that the rate of release of drugs from the matrices considered follows a square-root of time profile. This has been shown by numerous authors and is further illustrated by the data in Fig. 1 where the % drug released is plotted against square-root of time for a system consisting of potassium chloride compressed with HPMC. The range of linearity extends from about 15 to 95% of the amount of drug released.

Since a number of studies investigating the effect of compression rates on release rates on seemingly similar systems have yielded conflicting results, it was felt necessary to investigate this aspect for our system before the effect of other factors on the release rate can be considered. Our data (Fig. 1) show that compression pressure (148–443 $MN \cdot m^{-2}$) did not affect the release rate in accordance with data reported by Ford et al. (1985) who used pressures ranging from 93 to 1395 $MN \cdot m^{-2}$ for compressing promethazine hydrochloride/HPMC mixtures. Similar data have been reported by Salomon et al. (1979) working with potassium chloride/HPMC mixtures at pressures ranging from 57 to 283 $MN \cdot m^{-2}$. In a more recent study, however, Korsmeyer et al. (1983) reported that compression pressure on the same system at pressures ranging from 28 $MN \cdot m^{-2}$ to

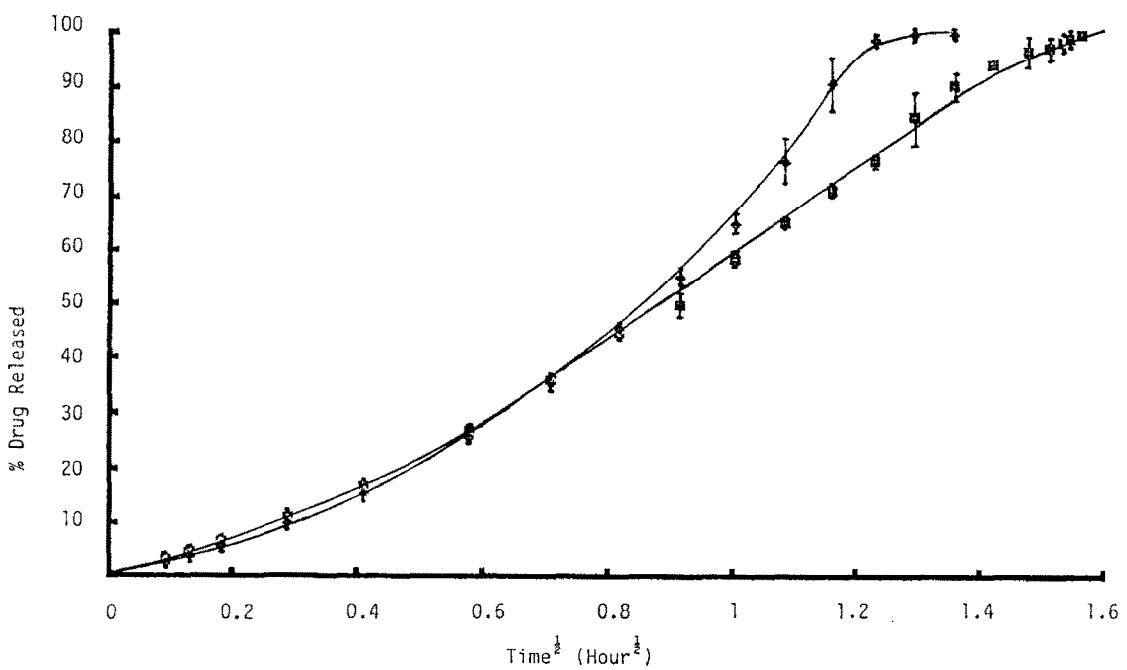

Fig. 1. Release profiles for potassium chloride/HPMC (■) and potassium chloride/PVP (◆) tablets with varying compression pressure (148–443 $MN \cdot m^{-2}$).

TABLE 1

Fitting of release data from Fig. 1 for the formulation containing potassium chloride/HPMC mixture, to a square root of time release behaviour

Compression pressure ($MN \cdot m^{-2}$)	r	Slope ($h^{-1/2}$)	Intercept	Time lag (h)	$t_{50\%}$ (h)
148	0.998	0.810	−0.210	0.067	0.767
296	0.995	0.770	−0.178	0.053	0.774
443	0.995	0.805	−0.192	0.057	0.738
Average		0.795 ± 0.022	−0.193 ± 0.016	0.059 ± 0.007	0.760 ± 0.019

The range of linearity was: 15–95% of amount of drug released. $t_{50\%}$ denotes the time when 50% of the amount of drug was released.

280 $MN \cdot m^{-2}$ showed some effect on the release rate. This effect was particularly marked during the first 4 h of release and could be ascribed to entrapped air (Korsmeyer et al., 1983). In our system involving evacuation of air during compression, this effect would of course not be observable and Table 1 lists the relevant data for release profiles.

Comparison of the data in Table 1 with those in Table 2 giving corresponding data with a system in which HPMC was replaced by polyvinylpyrrolidone (PVP) in the same weight ratio, shows that the potassium chloride was released more rapidly in the latter system. The range of linearity was also narrower, an observation which can be rationalised on the basis of PVP being more hydrophilic and hence zones of the matrix containing drug at the initial concentration A would disappear faster. Eqn. 1 would of course no longer hold beyond this point. Both HPMC and PVP could be used for the subsequent work and HPMC was chosen. Based on these results, work could then start on the design of a sustained released dosage form which is technically easy to manufacture and yet provides a better release profile than the standard square-root of time relationship. Better release profile is here defined as closer to zero-order release. As already indicated, Korsmeyer et al. (1983) observed that entrapped air seemed to improve the release profile of potassium chloride from hydrophilic polymeric matrices. In an attempt to capitalise on this, low levels (< 5% w/w) of gas-generating mixtures were added to the formulation. An equimolar sodium bicarbonate/citric acid mixture was an obvious choice. The low concentrations of effervescent mix used are an attempt not to disrupt the matrix during the release phase but despite this, erosion was observed during the course of the release.

Figs. 2 and 3 show that zero-order release could in fact be produced with the system proposed for much of the release profile. For clarity the extent of variability in the individual release profiles are only illustrated for the matrix containing 1% w/w

TABLE 2

Fitting of release data from Fig. 1 for the formulation containing potassium chloride/PVP mixture, to a square-root of time release behaviour

Compression pressure ($MN \cdot m^{-2}$)	r	Slope ($h^{-1/2}$)	Intercept	Time lag (h)	$t_{50\%}$ (h)
148	0.993	0.851	−0.221	0.067	0.717
296	0.996	0.952	−0.320	0.113	0.741
443	0.993	0.884	−0.232	0.069	0.686
Average		0.896 ± 0.052	−0.258 ± 0.054	0.083 ± 0.026	0.715 ± 0.028

The range of linearity was: 15–80% of amount of drug released. $t_{50\%}$ denotes the time when 50% of the amount of drug was released.

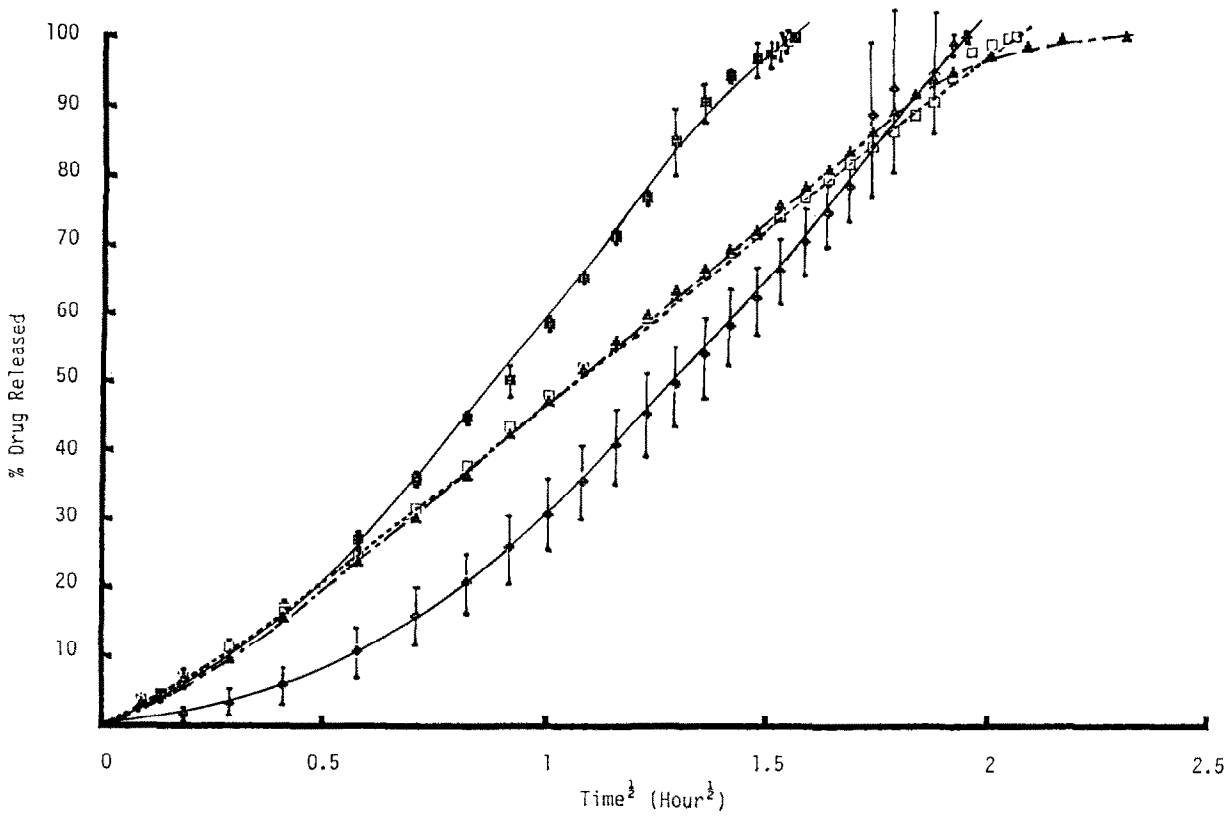

Fig. 2. Release profiles for potassium chloride/HMPC tablets in the absence (■) and in the presence of 1% w/w (◆), 2% w/w (□) and 5% w/w (▲) of sodium bicarbonate–citric acid mixture.

sodium bicarbonate/citric acid and the control system. It is worth noting that persistence of the zero-order release was highly dependent on the content of the effervescent mix. Levels higher than 1% w/w led to matrices behaving in the traditional manner (Figs. 2 and 3) with $t^{1/2}$ dependence.

Table 3 shows the good zero-order plot seen with the system containing 1% w/w sodium bicarbonate/citric acid while Table 4 gives the regression parameters obtained by square-root of time plots of data generated using the control and test systems containing 2 and 5% of the effervescent additive. Also given are the time taken for 50% drug release in hours ($t_{50\%}$).

The successful attempt at producing a zero-order release system based on gas generation in the matrix leads to the question of how this is achieved from a mechanistic point of view. Korsmeyer et al. (1983) suggest that air acts as a transport barrier. In an attempt to simulate the postulated barrier function of air, a hydrophobic excipient, high-density polyethylene, was added to the hydrophilic polymer (HPMC) and the drug, potassium chloride and the mixture, was com-

TABLE 3

Fitting of release data from Fig. 3 for the formulation containing 1% w/w of the sodium bicarbonate–citric acid mixture, to a time release behaviour

r	Slope (mg/h)	Intercept (mg)	Time lag (h)	$t_{50\%}$ (h)
0.999	70.138	5.34	−0.076	1.727

The range of linearity was: 0–80% of amount of drug released.

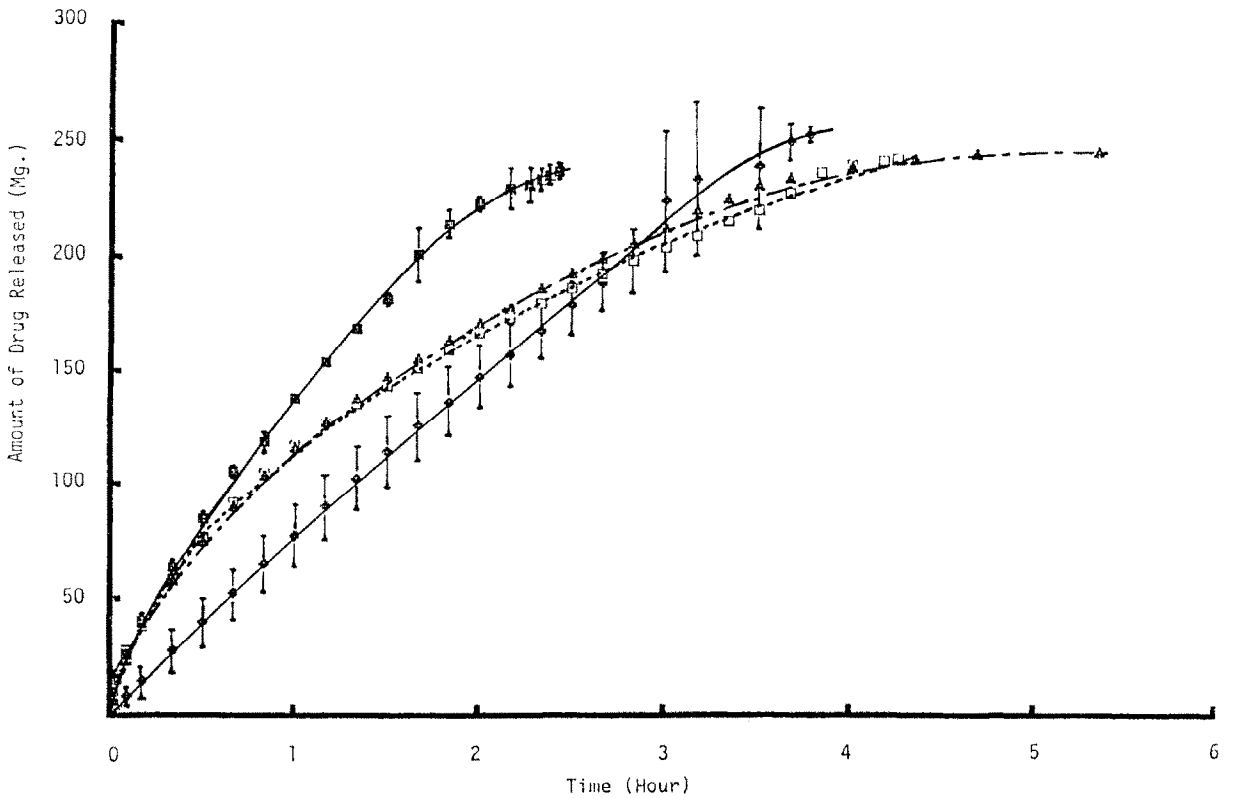

Fig. 3. Release profiles for potassium chloride/HPMC tablets in the absence (■) and in the presence of 1% w/w (◆), 2% w/w (□) and 5% w/w (▲) of sodium bicarbonate–citric acid mixture.

TABLE 4

Fitting of release data from Fig. 2 for the formulations containing 2% and 5% w/w of the sodium bicarbonate-citric acid mixture, to a square-root of time release behaviour

% w/w of the mixture *	r	Slope ($h^{-1/2}$)	Intercept	Time lag (h)	$t_{50\%}$ (h)
0	0.995	0.770	−0.178	0.053	0.774
2	0.999	0.514	−0.041	0.006	1.107
5	0.999	0.542	−0.071	0.018	1.111

The ranges of linearity for the above formulations were:
15–95% of amount of drug released, in absence of the Mixture *
10–85% of amount of drug released, in the presence of 2% w/w of the Mixture *
10–90% of amount of drug released, in the presence of 5% w/w of the Mixture *.

$t_{50\%}$ denotes the time when 50% of the amount of drug was released.
* Mixture denotes the sodium bicarbonate–citric acid mixture.

pressed as before. The polyethylene replaced part of the HPMC but the drug to total excipient ratio was maintained at 0.5. It is seen from Figs. 4 and 5 that although the addition of polyethylene decreased the release rate consistent with a barrier function to free diffusion of potassium chloride, there was no change in the release profile from the square-root of time dependence to one of zero-order. Fig. 6A and B are photographs of the matrices before and after complete exhaustion of potassium chloride thus demonstrating the absence of erosion. A static decrease in effective porosity due to entrapped air would not appear to explain the observed behaviour of the aerated zero-order system. The dynamics of air generation and release in the present system and air release in the Korsmeyer et al. (1983) system would appear to account for the observed effects. Non-linearity

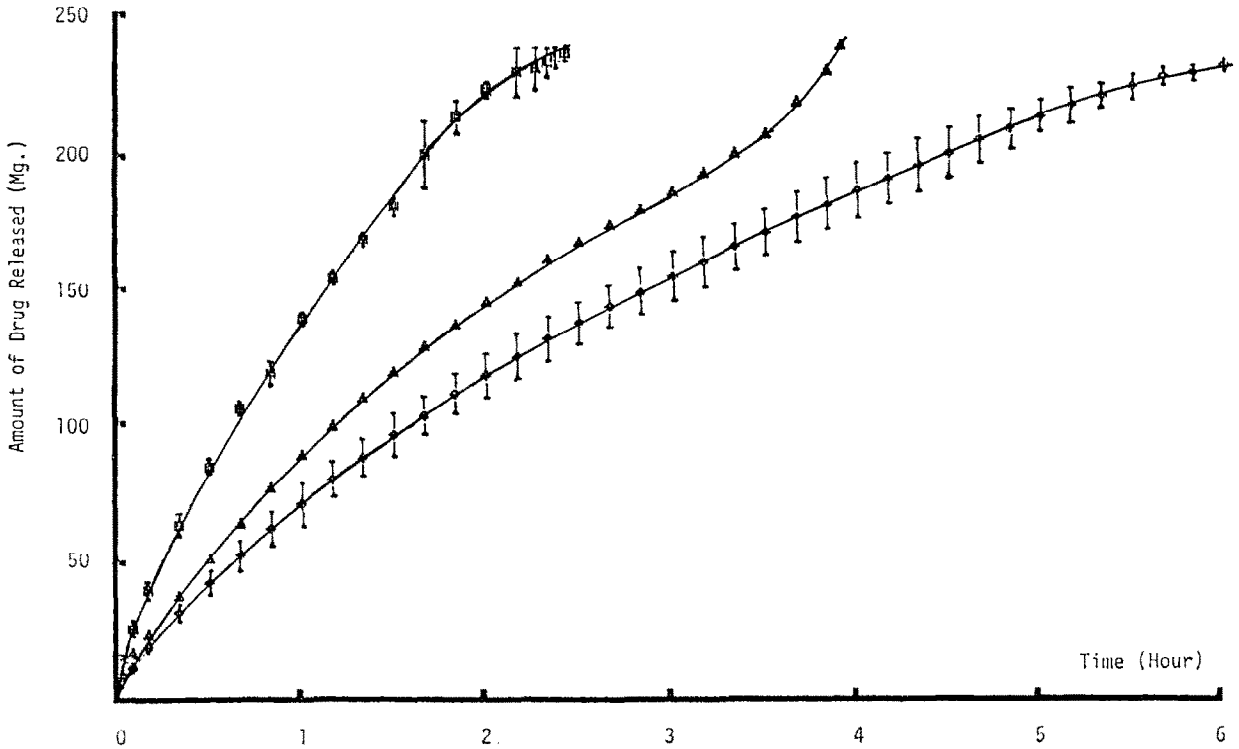

Fig. 4. Release profiles for potassium chloride/HMPC tables in the absence (■) and in the presence of 10% w/w (▲) and 20% w/w (◆) of polyethylene.

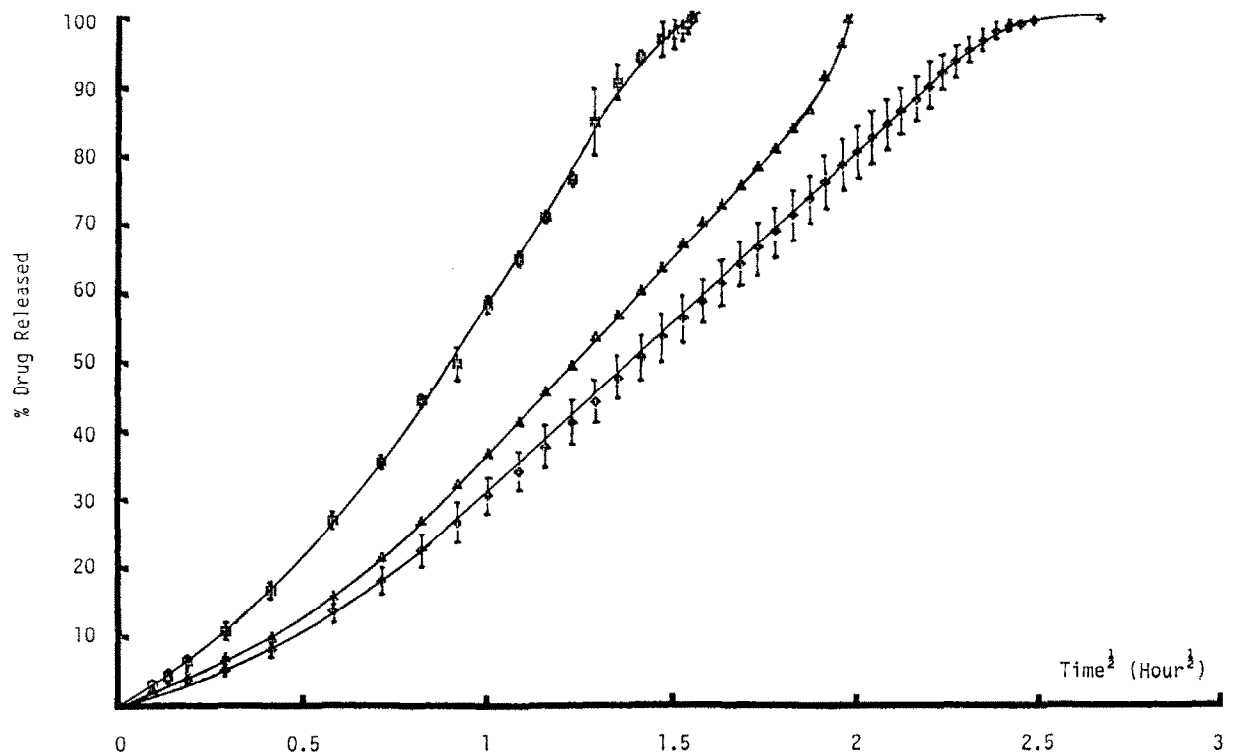

Fig. 5. Release profiles for potassium chloride/HPMC tablets in the absence (■) and in the presence of 10% w/w (▲) and 20% w/w (◆) of polyethylene.

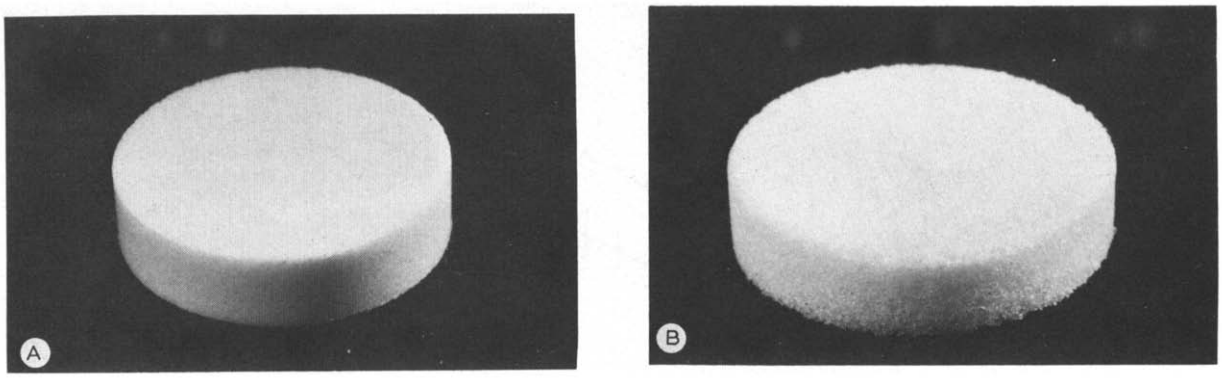

Fig. 6. Photographs of a potassium chloride/HPMC/polyethylene (50/30/20 % w/w) tablet. A: before. B: after complete release of the drug from a single surface release study. Magnification: (A) 7.8 ×; (B) 8 ×.

arises in the release profile obtained with the simple KCl/HPMC system as a result of an increase in effective diffusional path as drug diffuses out. To counteract this the entrapped or released air must exert an accelerating effect on the release rate. Observations suggest that constant erosion in the zero-order system is a possible explanation. In contradiction, however, overall release rate from the simple KCl/HPMC system is higher than the zero-order system which is of course characterised by a single rate constant for most of the release profile (Fig. 3). This is so despite observed erosion in the tablets containing effervescent components. Effective mathematical description of the system will have to await the results of further investigations to identify sensible simplifying assumptions.

Conclusion

The results presented in this study have confirmed those reported by Korsmeyer et al. (1983) indicating that air may cause deviations in the expected square-root of time profile for drug release for a hydrophilic matrix. A successful attempt was made to translate this observation into a zero-order drug release system which can easily be manufactured. This was achieved by incorporation of low levels of effervescent mixes. An air-induced increase in diffusional barrier can be accepted as a possible explanation for the observed change only for the initial slowing of the release. It does not adequately explain subsequent zero-order behaviour which requires a compensating effect for the increase in diffusional path as the extent of drug release increases. A possible explanation would be that constant dissolution takes place in contrast to the non-erodible systems free from the effervescent mix. However, overall release rate was paradoxically slower in the zero-order system than the square-root of time system. The work so far does not permit the desk-design of such a formulation and an empirical approach must still be used.

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