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IN VITRO DRUG RELEASE STUDIES FROM A NOVEL LYOPHILISED NASAL DOSAGE FORM

Panna Thapa*, Howard N.E. Stevens, Alan J. Baillie

Department of Pharmaceutical Sciences, Strathclyde institute for Biomedical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow, G4 0NR, UK

* Present address: Department of Pharmacy, School of Science, Kathmandu University, Dhulikhel, Kavre, NEPAL

*Corresponding author: pannathapa@ku.edu.np

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ABSTRACT

In vitro release of nicotine hydrogen tartrate (NHT) into phosphate buffer saline (PBS), pH 7.4 at 37°C was studied in a diffusion cell, which, with a minimal dissolution volume on the donor side, was intended to mimic the low hydration environment of the nasal mucosa. Lyophilisates prepared from different concentrations (0.25, 0.5, 1, 2 & 3% w/w) of Methocel K4MP solution and K100LVP, K15MP, K100MP solutions (1 & 2%) containing NHT were placed on the diffusion cell membrane which was maintained just in contact with the constantly agitated liquid phase of the receptor compartment. Samples were withdrawn at regular time intervals from the receptor compartment, replaced by fresh medium and analysed spectrophotometrically at 260nm after appropriate dilution. As controls, nicotine release profiles from NHT powder & aqueous solution, Methocel K solutions, and simple powder blends of K4MP were also measured. The nicotine release was dependent on the concentration of Methocel K polymer, whether the donor side of the cell was presented with a solution or lyophilisate of NHT in polymer. Nicotine release decreased with increasing polymer concentration ($t_{50\%}$ = 25 min and 75 min for lyophilisate prepared from 1% and 3% w/w K4MP respectively). However at any polymer concentration, nicotine release was faster from solution than from lyophilisate. The difference in nicotine release between solution and lyophilisate became more prominent at higher polymer concentration. Interestingly, nicotine release was independent of Methocel K molecular weight. *In vitro* nicotine release took place by anomalous diffusion.

Keywords: *In vitro* drug release; lyophilisation; nasal drug delivery; hydroxypropyl methylcellulose (HPMC), nicotine.

INTRODUCTION

The nasal mucosa is readily accessible and nasal drug delivery is potentially a convenient route of drug administration. The effects produced by nasal administration may be local or systemic, and nasal delivery has received recent attention as a means of administration

of polypeptides or proteins which have poor oral bioavailability (Mitra and Harris, 1998). The nasal route has also been considered as an alternative to intravenous administration of drugs like diazepam (Bechgaard *et al.*, 1997). Generally, conventional nasal formulations take the form of liquid drops or sprays, both of which however are cleared rapidly from the nose and residence times in man of 12-15 minutes have been described (Anderson and Proctor, 1983) and there is general agreement that the delivery of topical nasal medication by sprays is suboptimal (Homer and Raine, 1998). Although the residence time of a liquid vehicle can be increased by increasing its viscosity (King, 1980), viscous solutions are difficult to administer as drops or sprays. Powder formulations have been shown to have longer nasal residence times (Nagai and Machida, 1990) than solutions, but precision of dosage is difficult to achieve.

The formulation strategy employed in this current study was to freeze dry a solution of a hydrophilic polymer converting it into a solid unit (Stevens *et al.*, 1998; Thapa, 2000) sufficiently robust to withstand handling (Thapa *et al.*, 1999a; Thapa *et al.*, 1999b; Thapa, 2000). In contact with a mucosal surface the lyophilisate absorbs water, hydrates and forms a viscous (bioadhesive gel) with anticipated prolonged retention properties (Thapa *et al.*, 1999b; Thapa *et al.*, 1999c; Thapa, 2000). We used hydroxypropyl methylcellulose (HPMC) which has been extensively used as hydrophilic polymer matrix for controlled release of both water soluble and water insoluble drugs. Drug release from such systems, involves the penetration of water causing polymer relaxation to a viscous rubbery region (gel layer). This gel controls drug release by viscous resistance to drug diffusion and/or matrix erosion. Classically, the diffusion of a water soluble drug through the gel layer can be shown to be linearly dependent on the square root of time (Korsmeyer *et al.*, 1983; Peppas, 1985; Shah *et al.*, 1993). To accommodate a dual release mechanism, i.e. drug diffusion through the gel and erosion of the gel layer, the Peppas transport equation

$$M_t/M_\infty = kt^n \qquad (1)$$

(where M_t/M_∞ is the fraction dissolved at time t, with k a constant and n the diffusional exponent) (Peppas, 1985) has been employed for the first 60% of release curve, regardless of dosage form shape to investigate the drug release kinetics (Skoug *et al.*, 1991; Chebli *et al.*, 1999; Eyjolfsson *et al.*, 1999).

We are developing a lyophilised HPMC insert as a means of achieving dosage precision and the retentive properties of hydrated HPMC gel in nasal drug delivery. This paper describes the *in vitro* release characteristics of nicotine hydrogen tartrate from lyophilisates prepared from different concentrations of Methocel K (K4MP, K15MP, K100MP and K100LVP) solutions.

MATERIALS AND METHODS

Nicotine (-) hydrogen tartrate (NHT) (lot 17H1206) and phosphate buffer saline (PBS), pH 7.4 were purchased from Sigma Chemical Company. D (-) mannitol (GPR),

potassium dihydrogen phosphate (HPLC grade) and potassium phosphate, dibasic trihydrate (HPLC grade) was purchased from BDH.

Hydroxypropylmethylcelluloses (HPMC), Methocels K4MP (lot KC31012N11), K15MP (lot KE03012N12), K100MP (lot KC04012N11) and K100LVP (lot JL08012N21) were obtained as a gift from the Dow Chemical Company, Michigan, USA. The numbers that follow K identify the viscosity (mPa.s) of that product at 2% concentration in water at 20°C, 'M' represents 1000, 'P' represents premium Methocel products and 'LV' represents special low viscosity grade. The different type K Methocels differ in the degree of substitution of methoxyl and hydroxypropyl groups in the molecule (Dow Chemical Company, 1996).

Diffusion cell

The Plexiglass diffusion chamber consisting of donor and receiver compartments with sampling ports was fabricated to the design of Cornaz Gudet *et al.*, 1996. With a minimal dissolution volume, the donor side is intended to mimic the moist nasal mucosa. In effect the donor compartment contains air saturated with water. The receptor compartment contained constantly agitated PBS, pH 7.4 at 37°C. The test sample (lyophilisate, powder or solution) was placed on the filter paper membrane (595 S & S filter paper, 90 mm diameter; Schliecher & Schuell, Germany) between the donor and acceptor compartments was maintained just in contact with the receptor liquid phase (Thapa *et al.*, 1999a; Thapa *et al.*, 1999c; Thapa, 2000).

Preparation of nicotine hydrogen tartrate loaded Methocel K solutions

The different formulation solutions containing NHT, Methocel K and mannitol were prepared by dissolving NHT and mannitol in 1/3 of the required volume of distilled water and then sprinkling Methocel powder into this solution with constant agitation by either magnetic follower or high shear stirrer. Concentrated solutions of Methocel required high shear stirring to avoid lumping. When the Methocel particles were thoroughly wetted and evenly dispersed, the remaining volume of water was added to make 100 grams of solution and stirring continued until no lumps were seen. These solutions were then left standing at 4°C overnight to ensure complete hydration. The concentrations of Methocel K4MP solutions used were 0.25, 0.5, 1, 2, and 3% w/w. K15MP, K100MP and K100LVP were used at 1 and 2% w/w. In all cases the formulation solutions also contained 1% w/w mannitol.

The weight of NHT (molecular weight 462.4) used was calculated on the basis that the final lyophilisate (freeze dried plug) would contain 4 mg of nicotine base (molecular weight 162.2) per plug (2.85 mg of NHT is equivalent to 1 mg of nicotine base).

Preparation of lyophilisates

0.66 ml of solution, which gave 4 mg of nicotine base per plug, was filled into micro centrifuge polypropylene tubes (bullet shaped, internal diameter at tube mouth 6.0 mm, and 2.5 cm long). The filled tubes were flash frozen by dipping into liquid nitrogen. The

tubes were lyophilised for 24 hour on a laboratory freeze dryer (Modulyo, Edwards) at a condenser temperature of -55°C and 0.08 mbar chamber pressure. At the end of the process the chamber was vented with air. The length of lyophilised plug was 2.5 cm approximately.

Preparation of K4MP and NHT powder formulations

Three different batches of K4MP powder formulations (powder blends) were prepared in such a way that the per-unit-dose for the first batch contained the same quantity of K4MP, mannitol and NHT as lyophilisates prepared from 1% w/w K4MP solution. Similarly, the second and third batches contained the same quantity of K4MP, mannitol and NHT as lyophilisates prepared from 2 & 3% w/w K4MP solutions respectively. The required amount of K4MP, mannitol and NHT were accurately weighed (total weight of each batch = 10 g), hand shaken for few minutes then thoroughly mixed using Turbula W. A. B mixer (Basel, Switzerland).

For the *in vitro* release of nicotine from the powder blends, 25, 31.5 and 38 mg respectively of the first, second and third batches of powder blend were used. These weights contained 11.4 mg of NHT (equivalent to 4 mg of nicotine base) and were equivalent to the weight of lyophilisates prepared from 1, 2, and 3% K4MP solutions respectively.

Total content of nicotine in powder, lyophilisate, and formulation solution

To determine their nicotine content, individual plugs were dissolved in 100 ml, pH 7.4 PBS and analysed by UV spectrophotometry at 260 nm against a PBS blank. The nicotine content of formulation solutions and powder blends was similarly determined.

In vitro release of nicotine

The various formulations of NHT were placed on the membrane (pore diameter 12 μm) on the donor side of the diffusion cell at zero time. Samples of 0.5 ml were then withdrawn at regular time intervals from the acceptor compartment, replaced by fresh medium and after appropriate dilution to the assay concentration range, spectrophotometrically analysed at 260 nm for nicotine content.

The following formulations of NHT were studied for their ability to release nicotine; solutions of 0.25, 0.5, 1, 2 & 3% w/w K4MP containing 1% w/w mannitol, lyophilisates prepared from these various K4MP mannitol solutions, Lyophilisates prepared from 1 & 2% w/w solutions of different molecular weight grade K Methocels (K4MP, K15MP, K100MP, and K100LVP) each containing 1% w/w mannitol, Solutions of 2% w/w of K4MP, K15MP, K100MP containing 1% w/w mannitol powder mixes of NHT in K4MP and mannitol, NHT powder. Each formulation was examined at least in triplicate and the nicotine release curves are drawn through data points which are the mean of not less than 3 determinations.

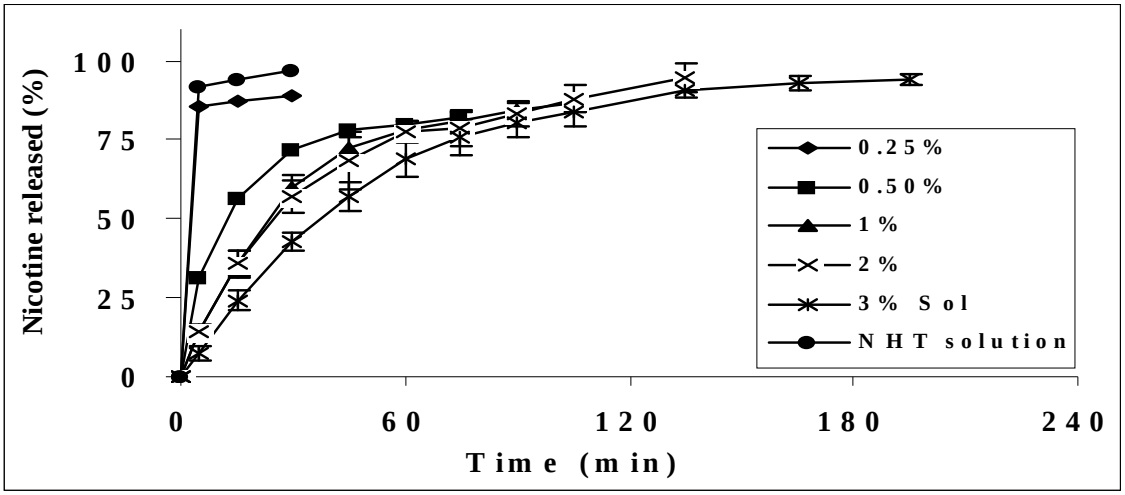
Scanning electron microscopy (SEM)

The morphological features of lyophilised plugs of K4MP and powder mixes containing NHT were examined by SEM. A lyophilised plug was stuck onto the aluminum stub with carbon tape, and coated with gold using a Polaron E5000 sputter coating apparatus. In the case of powder blends, they were thinly spread over the aluminum stub and stuck in position with carbon tape. Coated samples were scanned by using a JOEL JSM840A Scanning Electron Microscope at 10-15 kV under varying magnifications.

RESULTS AND DISCUSSION

Nicotine release from K4MP solutions and lyophilisates

The *in vitro* nicotine release profile from Methocel K4MP solutions and lyophilisates prepared from them are shown in Figs. 1 & 2 respectively. Nicotine release whether from solution or lyophilisate decreased with increasing polymer concentration however nicotine release was always faster from solution than from the corresponding lyophilisate. The times required to release 50% ($t_{50\%}$) of the nicotine content of a 3% w/w K4MP



solution and of a lyophilisate prepared from this solution were 45 and 75 minutes respectively.

Fig. 1 Release (%) profile of nicotine into pH 7.4 PBS at 37°C from different indicated concentrations of K4MP solution. A solution of nicotine hydrogen tartrate (NHT solution) with the same nicotine content (6.06 mg/ ml) as the K4MP solutions was used as a control. Each point is the mean ±s.d.of 4 experiments.

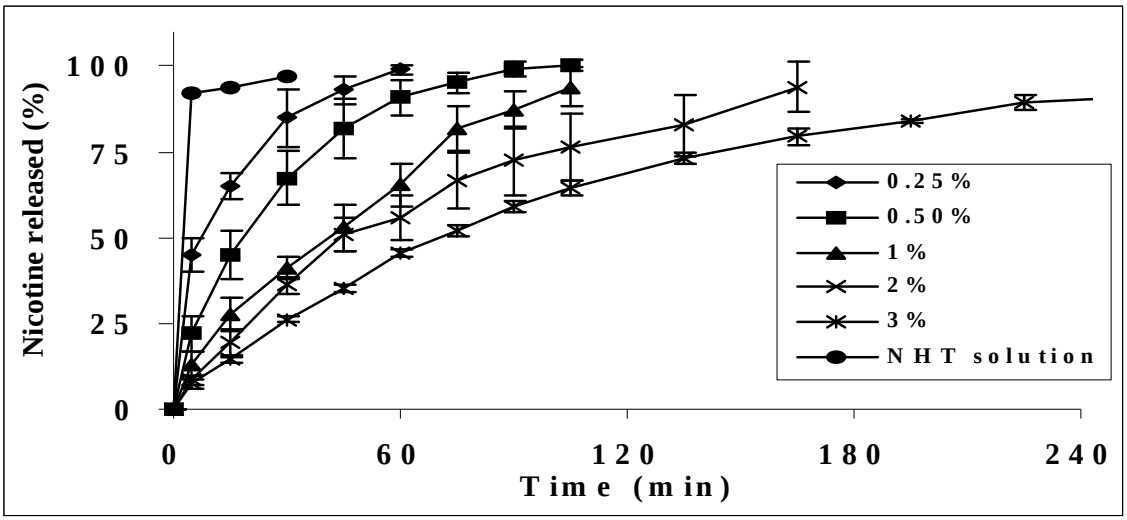


Fig. 2 Release (%) profile of nicotine into pH 7.4 PBS at 37°C from lyophilisates prepared from different indicated concentrations of K4MP solution. A solution of nicotine hydrogen tartrate (NHT solution) with the same nicotine content (6.06 mg/ ml) as the K4MP lyophilisates was used as a control. Each point is mean ±s.d.of 4 experiments.

The observed variability in the nicotine release data decreased as the polymer concentration was increased. Some of this variability could be attributed to the experimental factors which became less critical at higher polymer concentrations when more structured systems (gels) were formed. However the role of gel erosion in the release process may also have contributed to the variability at low gel strengths.

The diffusional exponent (n) values were determined by plotting log % nicotine released against logt (log form of Peppas transport equation) and are compiled in Table 1. These mean diffusional exponent values increased as the polymer concentration increased in the formulation (Table 1). In other words, the nicotine release profile had a tendency of showing time independent release at higher polymer concentration which is evident from increased values of n. However, for zero order or time independent release the diffusional exponent values must be one i.e. n=1. It can be seen that the values of the mean diffusional exponent (values between 0.5 and 0.89) indicate that in this system, NHT release was best described by an anomalous diffusion mechanism and was at least in part dependent on erosion or dissolution of the polymer gel. Similar results were described by Eyjolfsson (1999) for the release of an insoluble drug from tablets prepared from different ratios of Methocels K4MP and K100LV and by Skoug et al (1993) for the release of alprazolam from sustained release HPMC tablets.

Table 1: Compilation of mean (n=4) intercept (log k) (log % nicotine released) and diffusional exponent (n) (slope) values, upto 60% release, from K4MP solutions and lyophilisates prepared from these solutions as determined using equation (1) (log % released vs. logt). For 0.25% K4MP, data shown was for upto 85% release.

	Type of Dosage Forms					
	Solution			Lyophilisate		
[K4MP][a] (%w/w)	Intercept (log k) ±s.d.	Slope (diffusional exponent (n) ±s.d)	r^2 ±s.d.	Intercept (log k) ±s.d.	Slope (diffusional exponent (n) ±s.d)	r^2 ± s.d.
0.25	1.9178±0.301	0.0189	1	1.40±0.096	0.365±0.070	1
0.5	1.1185±0.176	0.5387	1	0.888±0.144	0.641±0.067	0999±0.001
1	0.586±0.115	0.811±0.084	0.992±0.005	0.606±0.115	0.682±0.102	0.985±0.024
2	0.625±0.063	0.772±0.074	0.995±0.006	0.453±0.055	0.773±0.051	0.995±0.003
3	0.308±0.124	0.895±0.060	0.994±0.003	0.318±0.118	0.744±0.065	0.995±0.004

[a] All formulations contained 1% w/w mannitol.

The effect of K4MP concentration (solution or lyophilisate) on the intercept of the log % released vs. logt plots is shown in Fig. 3. The best exponential fit to the data points showed remarkably good agreement between the exponent of x for solution $y = 0.7249x^{-0.6584}$ (r^2=0.916) and lyophilisate $y = 0.6207x^{-0.5695}$ (r^2=0.992). This can be interpreted as meaning that the dependence of release mechanism on viscosity was the same for K4MP solutions and lyophilisates.

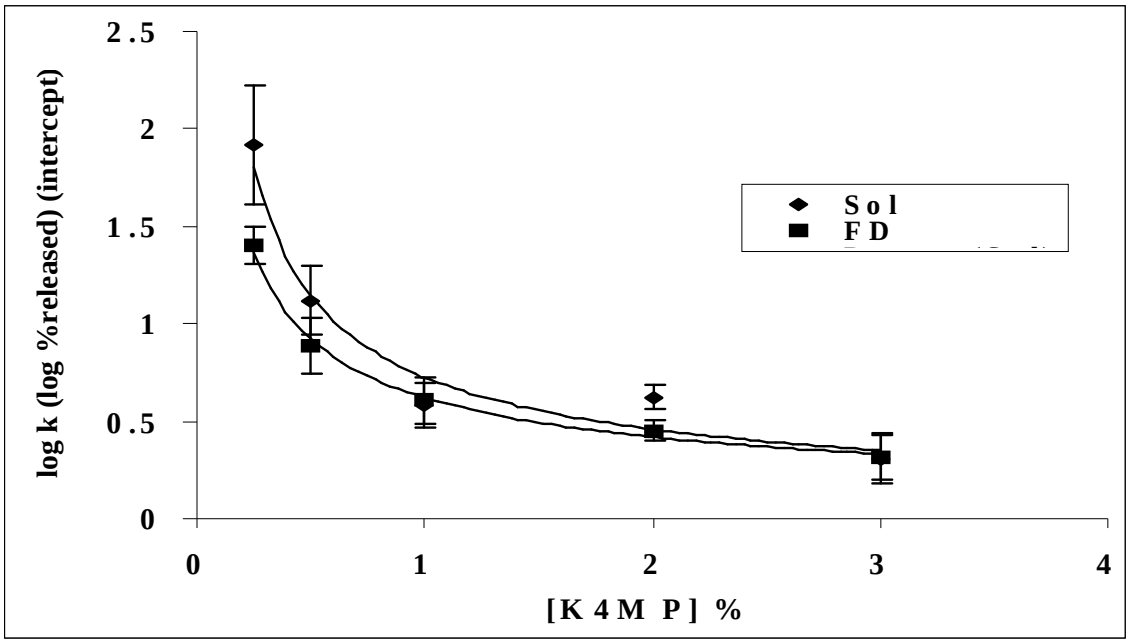


Fig. 3 The effect of K4MP concentration (%) either in the form of solution (Sol) or a lyophilisate (FD) on the mean intercept (n=4) ±s.d. of the log % released vs. logt plots data from Figs. 1 and 2 respectively. The best power fit to the data points gave y = 0.7249x-0.6584 (r2=0.916) for solution and y = 0.6207x–0.5695 (r2=0.992) for lyophilisates.

The observed difference in NHT release between a K4MP solution (Fig. 1) and its corresponding lyophilisate (Fig. 2) can be explained on the basis of the outcome of the hydration of the freeze dried plug in the diffusion cell. Under the experimental conditions, hydration of the lyophilisate was very rapid (instantaneous) and the formation of a penetration front (Skoug *et al.*, 1993) which could influence subsequent nicotine release can be discounted. The open, porous structure of a typical K4MP lyophilisate (Fig. 8) would explain the rapid hydration of the plugs observed during the experiments but importantly the concentration of K4MP solution formed on hydration of a lyophilisate was greater than the concentration of the solution from which it was dried. In effect, the result of hydrating a freeze dried K4MP plug (e.g. prepared from a 3% K4MP solution) in the diffusion cell yielded a K4MP solution with a concentration >3% from which nicotine release was slower than from a 3% solution. Lyophilisation allowed rapid hydration and the formation of a very concentrated K4MP solution, containing the NHT that slowed nicotine release. Moreover the hydrated lyophilisates were bioadhesive (Thapa, 2000).

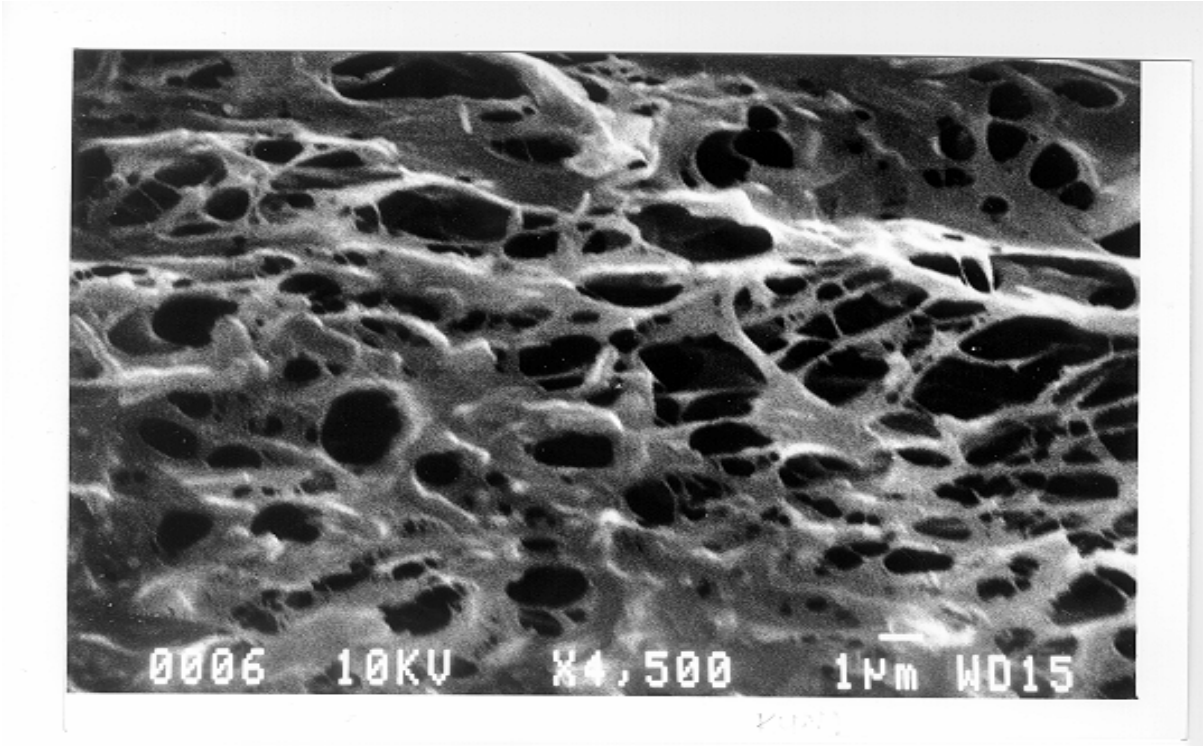


Fig. 8 SEM picture of a lyophilisate prepared from 2% K4MP solution containing NHT.

Nicotine release from different viscosity grade (molecular weight) Methocel solutions and lyophilisates

Release profiles of nicotine from different viscosity grade (molecular weight) Methocels, K4MP, K15MP, K100MP and K100LVP (solutions and lyophilisates prepared from them) are shown in Figs. 4 and 5. As is evident from the plots, nicotine release were not different among the Methocels K of different molecular weights irrespective of the type of formulation i.e. solution or lyophilisate. However for any particular Methocel, release was faster from solution than from lyophilisate (Fig. 6). The $t_{50\%}$ was 30 minutes from Methocel solution and 45-75 minutes from lyophilisates. As described above for K4MP, nicotine release was decreased with increased polymer concentration, a trend observed with Methocels K15MP, K100LVP, K4MP.

The plots of intercept (logk) determined as described in the previous section versus Methocel numbers for solutions (2%) and lyophilisate prepared from these solutions of different molecular weight Methocel K is shown in Fig. 6. It can be seen that a trend to slower release was observed between K4MP and K15MP (Fig. 6), although there was no significant difference in nicotine release between K15MP and K100MP. This result is supported by those of a previous study (Sung *et al.*, 1996) of HPMC matrix tablets using adinazolam mesylate as a model drug which suggested that drug release rate was fastest for a low viscosity grade (K100LV) formulation and that a K4M formulation exhibited a faster drug release rate than either K15M or K100M formulations. Here, K15M and K100M formulations had identical drug release profiles which suggested the existence of a 'limiting HPMC viscosity', around 15000 cps, for the systems studied at which drug

release rate no longer decreased with viscosity. In other words, nicotine release decreased with increasing Methocel molecular weight for various low molecular weight HPMC and became independent of molecular weight for high molecular weight HPMC. In this present study, a 'limiting viscosity' effect on release rate was also observed at high K4MP concentration (Fig.3).

Similarly, in another study of HPMC matrix tablets using promethazine hydrochloride (Ford *et al.*, 1985a); propanolol hydrochloride and aminophylline (Ford *et al.*, 1985b); propanolol hydrochloride and tetracycline hydrochloride (Mitchell *et al.*, 1993b); buflomedil pyridoxalphosphate (Bettini *et al.*, 1994); isoniazid, anhydrous caffeine, theophylline, salicylic acid and indomethacin (Kureshi *et al.*, 1996); it was found that in spite of a large difference in release rates among low viscosity grade HPMC, little difference was observed among higher molecular weight matrices. It may be argued that release rate is independent of molecular weight at least for a homologous series of polymers, which chemically have the same monomeric repeating units (building blocks). The influence of type of the substitution on the performance of methyl cellulose and HPMC in gels and matrices have been studied using propanolol as a model drug (Mitchell *et al.*, 1993a). This study suggested that propanolol dissolution rates varied according to the drug/cellulose ether ratio within the matrix but the performance differences of the three grades of HPMC (K4M, E4M, F4M) could not be distinguished.

A plausible explanation for the nicotine release data is that although various HPMC solutions and HPMC gels formed after hydration of various lyophilisates have different macro-viscosities, they might have the same micro-viscosity as far as nicotine is concerned. Nicotine, as the diffusing species, has a much smaller molecular weight than the Methocels and could be seen as percolating through the non-viscous environment of the solution in the void spaces between the polymer chains. In other words, the effects of the polymer molecules on the macroscopic flow properties of the system (i.e. on macroscopic movement, evaluated as viscosity) do not necessarily correlate with effects on diffusion (i.e. movement at the microscopic scale). This has led some workers to suggest that micro-viscosity (i.e. a measure of viscosity at the microscopic scale) should be used instead of macro-viscosity as a predictor of drug diffusion rate in systems such as hydrophilic cellulosic and non-cellulosic polymers (Al-Khamis *et al.*, 1986; Smidt *et al.*, 1991). However, the power relationship observed between macro- and micro-viscosity suggested that the former may be of some value for the prediction of diffusion rates (Alvarez-Lorenzo *et al.*, 1999).

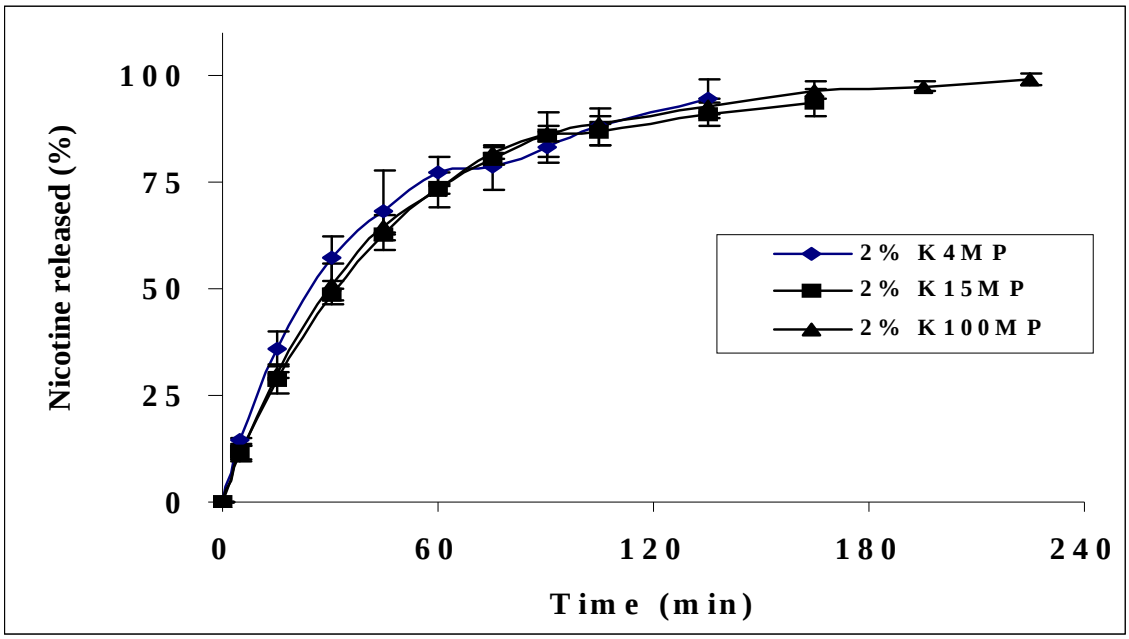


Fig. 4 Release (%) profile of nicotine into PBS, pH 7.4 at 37^0C from 2% w/w solutions of different molecular weight Methocels; K4MP, K15MP, K100MP. Each curve is mean±s.d. of 3 experiments.

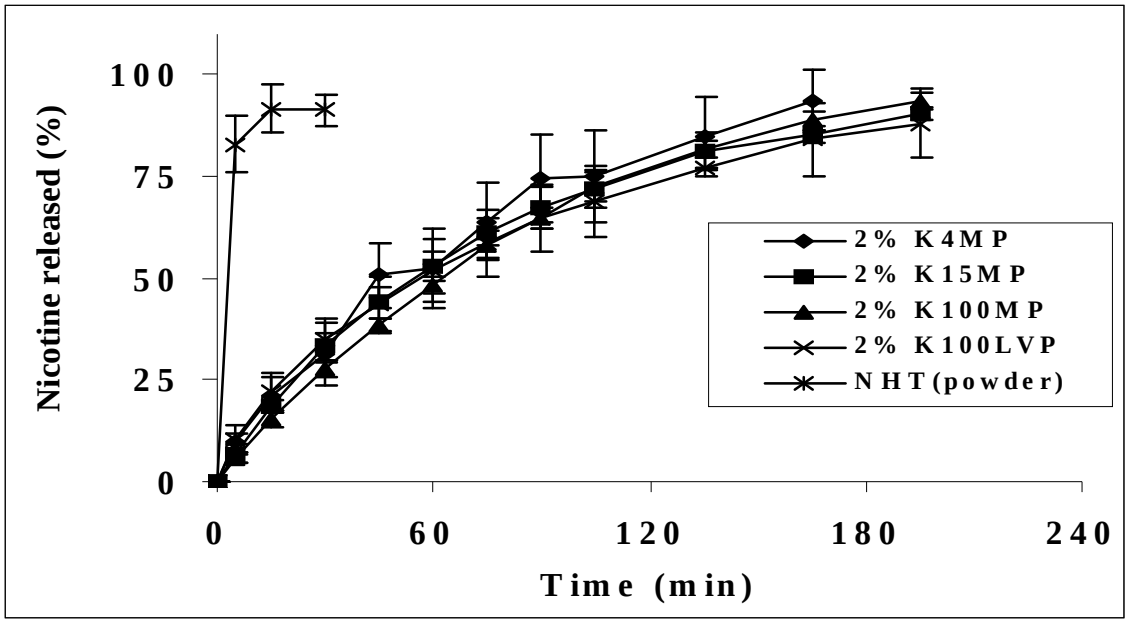


Fig. 5 Release (%) profile of nicotine into PBS, pH 7.4 at 37^0C from lyophilisates prepared from 2% w/w solutions of different molecular weight Methocel K solutions. Each curve is mean±s.d. of 3 experiments.

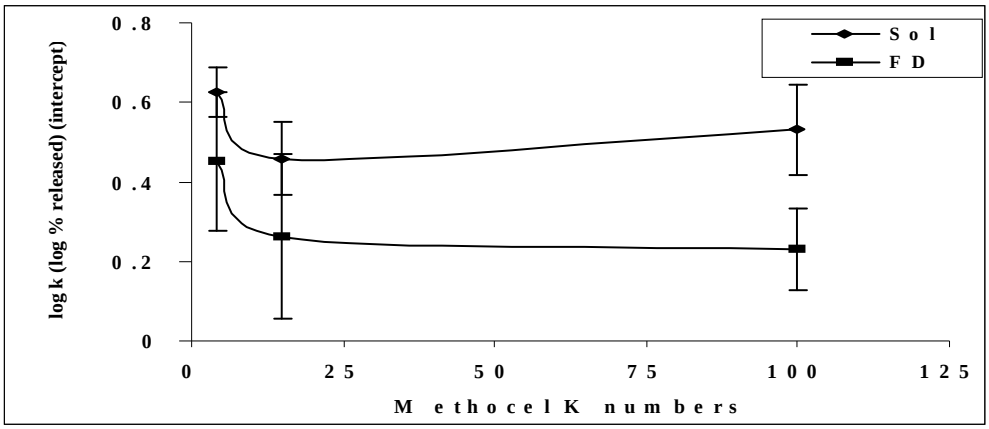


Fig. 6 The effect of Methocel K numbers (molecular weight) on the mean intercept (logk, log % nicotine released) from solutions (Sol) and lyophilisates (FD) prepared from these solutions.

Nicotine release from powder blends

The release profiles of nicotine from the powder blends are shown in Fig. 7. Nicotine release from the blends did not change with polymer content ($t_{50\%}$ < 15 minutes for K4MP 26-52% w/w) although release rates were lower than from NHT powder, $t_{50\%}$ = 3 minutes. In the powder blends, crystalline NHT was present as part of a simple powder mix which lacked the porous but homogeneous structure of the lyophilisate (Fig.8) and it is apparent that NHT could dissolve rapidly and largely independently of the hydration of the K4MP particles. There is thus an explanation for the similar and relatively rapid, nicotine release rates from powder blends of different K4MP content.

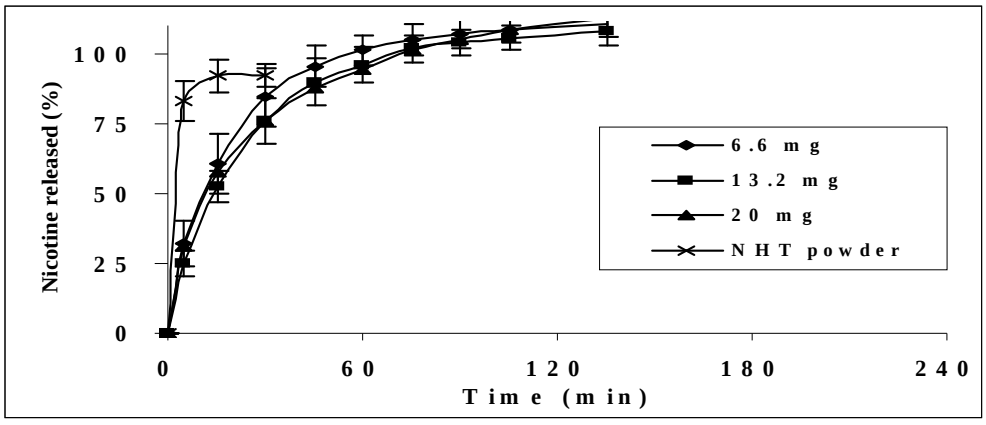


Fig. 7 Release (%) profile of nicotine from K4MP powder blends, each containing 4 mg nicotine base (as hydrogen tartrate). The amount of K4MP in the powder mixes indicated, 6.6, 13.2, & 20 mg, is the same as in lyophilisates prepared from 1, 2 & 3% K4MP solutions respectively. 11.4 mg nicotine hydrogen tartrate (NHT powder) equivalent to 4 mg nicotine base, was used as a control. Each data point is mean ±s.d.of three experiments.

CONCLUSIONS

In summary, the lyophilised plug offers a novel means of drug presentation to (nasal) mucosa and has the several advantages that the mechanical properties of the plug and its performance on hydration, adhesivity and drug release can be manipulated over a significant range. The mechanism of drug release from these plugs appears to be similar to the release characteristics described for the various solid dosage forms incorporating HPMC matrices. It would appear that the predictable *in vitro* release behaviour could be used to design drug specific release profiles.

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REFERENCES

1. Al-Khamis, K.I., Davis, S.S., Hadgraft, J., 1986. Microviscosity and drug release from topical gel formulations. Pharm. Res., 3, 214-217.
2. Alvarez-Lorenzo, C., Gomez-Amoza, J.L., Martinez-Pacheco, R., Souto, C., 1999. Microviscosity of hydroxypropylcellulose gels as a basis for prediction of drug diffusion rates. Int'l J. Pharm., 180, 91-103.
3. Anderson, I. and Proctor, D. F., 1983. Measurement of nasal mucocilliary clearance. Eur. J. Respir. Dis., 64, 37-40.
4. Bechgaard, E., Gizurarson, S., Hjortkjjaar, R. K., 1997. Pharmacokinetic and pharmacodynamic response after intranasal administration of diazepam to rabbits. J. Pharm. Pharmacol., 49, 747-750.
5. Bettini, R., Colombo, P., Massimo, G., Catellani, P.L., Vitali, T., 1994. Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. Eur. J. Pharm. Sc., 2, 213-219.
6. Chebli, C., Moussa, I., Buczkowski, S., Cartilier, L., 1999. Substituted amylose as a matrix for sustained drug release. Pharm. Res., 16, 1436-1440.

7. Cornaz Gudet, A.L., DeAscentis, A., Colombo, P., Buri, P., 1996. In vitro characteristics of nicotine microspheres for transnasal delivery. Int. J. Pharm., 129, 175-183.

8. Eyjolfsson, R., 1999. Hydroxypropyl methylcellulose mixtures: Effects and kinetics of release of an insoluble drug. Drug. Dev. Ind. Pharm., 25, 667-669.

9. Ford, J.F., Rubinstein, M.H., Hogan, J.E., 1985a. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methylcellulose matrices. Int'l J. Pharm., 24, 327-338.

10. Ford, J.F., Rubinstein, M.H., Hogan, J.E., 1985b. Propanolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropyl methylcellulose. Int'l J. Pharm., 24, 339-350.

11. Homer, J.J. and Raine, C.H., 1998. An endoscopic photographic comparison of nasal drug delivery by aqueous spray. Cli. Otolaryngol., 23, 560-563.

12. King, M., 1980. Relationship between mucus viscoelasticity and ciliary transport in guaran gel /frog palate system. Biorheology, 17, 249-254.

13. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., . Peppas, N.A., 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm., 15, 25-35.

14. Kurahashi, H., Kami, H., Sunada, H., 1996. Influence of physicochemical properties on drug release rate from hydroxypropyl methylcellulose matrix tablets. Chem. Pharm. Bull., 44, 829-832.

15. Mitchell, K., Ford, J.L., Armstrong, D.J., Elliot, P.N.C., Hogan, J.E., Rostron, C., 1993a. The influence of substitution type on the performance of methylcellulose

and hydroxypropylmethylcellulose in gels and matrix tablets. Int'l J. Pharm., 100, 143-154.

16. Mitchell, K., Ford, J.L., Armstrong, D.J., Elliot, P.N.C., Rostron, C., Hogan, J.E., 1993b. The influence of concentration on the release of drugs from gels and matrices containing methocel. Int'l J. Pharm., 100, 155-163.

17. Mitra, A. K. and Harris, A. S., 1998. Preface. Adv. Drug. Del. Rev., 29,1.

18. Nagai, T. and . Machida, Y., 1990. Bioadhesive dosage forms for nasal administration. In: Lenaerts, V. and Gurny, R. (eds.), Bioadhesive Drug Delivery Systems, CRC Press: Boca Raton, Florida, pp. 169-178.

19. Peppas, N.A., 1985. Analysis of fickian and non-fickian drug release from polymers. Pharm. Acta. Helv., 60, 110-111.

20 Shah, N., Zhang, G., Apelian, V., Zeng, F., Infeld, M.H., Malick, A.W., 1993. Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: Effects of polymer concentration. Pharm. Res., 10, 1693-1695.

21. Skoug, J. W., Borin, M. T., Fleishaker, J. C., Cooper, A. M., 1991. In vitro and in vivo evaluation of whole and half tablets of sustained release adinazolam mesylate. Pharm. Res., 8, 1482-1488.

22. Skoug, J. W., Mikelsons, M.V., Vigneron, C.N., Stemm, N.L., 1993. Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. J. Control. Release, 27, 227-245.

23. Smidt, J.H., Offringa, J.C.A., Crommelin, D.J.A., 1991. Dissolution kinetics of theophylline in aqueous polymer solutions. Int'l. J. Pharm., 77, 255-257.

24. Stevens, H.N.E., Baillie, A. J., Thapa, P., 1998. Freeze drying technology. British patent application number 9827292.5, Strathclyde University, Glasgow, Scotland, U.K.

25. Sung, K.C., Nixon, P.R., Skoung, J.W., Ju, T.R., Topp, E.M., Patel, M.V., 1996. Effect of formulation variables on drug drug and polymer release from HPMC-based matrix tablets. Int'l. J. Pharm., 142, 53-60.

26. Thapa, P., 2000. Studies of a lyophilised nasal delivery system. Ph.D. Thesis, Strathclyde University, Glasgow, United Kingdom.

27. Thapa, P., Stevens, H.N.E., Baillie, A.J., 1999a. Lyophilized dosage form for the nasal delivery of drugs. Proceed. 26th Int'l. Symp. Control. Rel. Bioact. Mater., 26, 331-332.

28. Thapa, P., Stevens, H.N.E., Baillie, A.J., 1999b. Characterisation of a lyophilised nasal dosage form: physicomechanical properties. J. Pharm. Pharmacol., 51(supplement), 326.

29. Thapa, P., Stevens, H.N.E., Baillie, A.J., 1999c. Characterisation of a lyophilised nasal dosage form: in-vitro drug release. J. Pharm. Pharmacol. 51(supplement), 5.

30. The Dow Chemical Company, 1996. The technical handbook.