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Use of mathematical approximations in the elucidation of drug release mechanisms from a high viscosity grade sodium carboxymethylcellulose matrix

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Abstract

The mechanisms of sustained drug release from a high viscosity grade sodium carboxymethylcellulose (Nacmc) matrix were investigated using the concept of medium diffusion and erosion rate studies and some mathematical approximations. Theophylline, a drug with poor aqueous solubility and which is amenable to sustained release formulation was used as the test drug.
Result obtained indicated that the development of an optimum sustained release formulation with Nacmc could be achieved on the basis of the release mechanisms of the drug under consideration (especially drugs that are released in the intestine), based on the square root and first order release kinetics.

Keywords: Medium diffusion, erosion rate studies, theophyline, dissolution profile.

Introduction

Sodium carboxymethylcellulose (Naemc), a cellulose ether has recently been evaluated as potential hydrophilic matrix for sustained release formulations of chlorphenitamine maleate (1, 2) and theophylline (3). Reviews on the use of cellulose ethers in sustained release (SR) dosage forms been published (4-7). Sodium carboxymethylcellulose, like other cellulose ethers is classified as swelling polymer and is expected to produce swelling controlled release systems. In swelling controlled matrix system release of incorporated drug is controlled by (a) rate of medium diffusion into the matrix, which is normally followed by a relaxation process involving gelation or swelling) and (b) the rate of erosion of the matrix. These two processes take place simultaenously giving rise to a swelling front and eroding font. The distance between this two fronts is the diffusion layer thickness which depends on the relative rates at which the swelling and eroding fronts move in relation to each other (8)
Some mathematical models have developed to describe drug release from polymer matrics. Some of these mathematical approximations have been applied to elucidze mechanism of drug release from hydroxypropylmethylcellulose (HPMC), (9-11), Eudragits methylcellulose and carbopols (8,12). Mathematical modellings of these release kinetics of sustained release formulations reduce excessive number of experiments since they can be used (a) to predict solute release rates from and solate diffusion behaviors through polymers and (b) to elucidate physical mechanisms of solute transport by simply comparing the release of data to mechanical models (8). In the present study, medium diffusion, erosion rate studies and some mathematical approximations were employed in the simulated intestinal fluid. Theophyline was chosen as a drug test because it possesses most of the qualities suitable for sustained release formulation.

Experimental

Materials

The following materials were used: Sodium carboxymethylcellulose, high viscosity grade (Aqualon, USA), theophyline hydrate (Merck, Germany), lactose, (May and Baker UK) Ditab® (Stuffer, USA), Sodium hydroxide, sodium hydrogen, orthophosphate, dipotassium hydrogen phosphate (Sigma USA) searic acide (Baker USA)

Methods: Preparation of Nacmc-Lactose Compacts

A mixture of Nacmc and Lactose (2:1) was directly compressed in an F-3 Manesty single punch tabletting machine (Manesty, UK) fitted with 9.5mm punches. Compacts of mean weight 280= 2mg were produced at compression load of 470kg. These were stored in a well closed specimen bottle prior to medium and erosion rate studies.

Medium Diffusion and Erosion Rate Studies

Medium Diffusion and Erosion Rate Studies of the Nacmc-Lactose mixture compacts were studied using method of Tahara et al (11) with minor modifications. Compacts were individually placed in a plastic dishes of known weight and dimensions. The dishes were placed in 500ml capacity rectangular container. The container contained 200ml simulated intestinal fluid was chosen based on results of preliminary studies of the compacts in the two media. Precipitation of Namc occurs at low acidic pH (13). The dishes were removed at 1hr intervals, drained of adhering fluids, weighed and the Wet-Weight of each compacts was calculated. The contents of each dish was dried to constant weight at 60°C in a hot air oven and the weight of each compact was calculated. The present medium diffusion (Q_w) was calculated from the mean of triplicate determinations using equation 1:

$$Q_w = \frac{W_w - W_d}{W_w} \times 100 \qquad \text{----- 1}$$

The present erosions (Ep) was calculated from Equation 2,

$$E_p = \frac{W_i - W_d}{W_i} \times 100 \qquad \text{----- 2}$$

Where W_i is the initial weight of the compact before immersion into the medium

Preparation of Nacmc Matrix Tablets

Theophyline tablets were fornulated with drug to polymer ratio 5:3. Enough quantity of Ditab® was added as a direct compression filler binder. The mixture was lubricated with 1% w/w stearic acid previously screened through a 0.200mm stainless steel sieve prior to compression. Tablets of weights 330+5 mg were produced as stated below two hundred and fifty tablets was produced. The mean hardness of ten tablets chosen at random was 6.5+0.15kgf and their friability was <0.5%

Drug Release Testing

The in vitro release profile of theophylline was assessed in SIF using an Erweka dissolution apparatus (DT-D model, Erweka, Germany) fitted with a paddle that operated at 50+1.1rpm. The volume of the dissolution medium was 900ml. Samples were withdrawn at predetermined time intervals and analysed at 271 mm using spectronic 1201, Milion Roy, Germany).

Results and Discussions

The wet-weight of compacts prepared with Nacmc-lactose increased rapidly within the first one hour reaching up 80% within this period. There was continuous but gradual increase in the wet-weight of the compacts within the remaining seven hours (Fig. 1). This leds to profound swelling of the compacts. There was relatively low erosion of the compacts with Ep values with range of 31 to 36% and this occurred on the surface of the compacts on visual examination. When the values of Q_w were plotted according to the Higuchi's diffussion model (Eq. 3) a linear regression line was obtained, (Fig. 2) indicating the presence of diffusion mechanism (14).

$$Q_w - K_i t^{1/2} \quad \text{----------3}$$

(k_i - rate constant for the diffusion of medium into the interspace of the matrix). When the cube root of the dry weight was plotted as a function of immersion time according to the well known equation:

$$\{W_d/W_i\}^{1/2} = 1 - k_2 t \quad \text{----------4}$$

(k_2 - erosion rate constant), linear regression line was not obtained indicating that the rinsing out of the soluble lactose from the compacts was not consistent with the Hixson Crowell cube root kinetics (8). When the generated data from the dissolution profile study of theophyline was fitted into equation 3, two regression lines was obtained, the second occurring afater 80% drug release (fig. 2). This behaviour was attributed to possible changes that took place towards the end of this dissolution process a behaviour which has been reported previously (8,15). The data when fitted into Equation 4, did not obey the Hixson-Crowel cube root kinetics.

When the release data of theophyline fitted into the first order release kinetics, a single linear regression line was obtained (fig.3) with a regression equation of :

$$Y = 2.0 - 0.20x, r - 0.9048, \ldots\ldots\ldots 5$$

The results of these mathematical modellings indicate that release of theophyline from the high viscosity grade Nacmc in SIF involved the Higuchi's diffusion and first order release kinetics to great extents. These results suggested that it is possible to derive equations that express that the rate of fluid diffusion into and the release of drugs from high viscosity grade Nacmc matrix was based on Higuchi's diffusion and first order release kinetics.

The release profile of theophyline from the matrix tablets followed a sustained

release pattern (Fig. 1) and it followed the same pattern as the medium diffusion plot shown in the same figure. There was a steady rate of theophyline release throughout the release period studied. This indicates that a clinical formulation of theophyline with this polymer is most likely to result to a constant blood level of the drug in the body, and this is a crucial requirement of a sustained release formulation (16). The result of the present study also validates the use of medium diffusion and erosion rates studies in the elucidation of drug release mechanisms from swelling and erosion hydrophilic matrix systems.

There are many that factors govern the release of drugs from swelling and erosion controlled matrix systems. These include: molecular size, water solubility of the drug and the amount of drug loaded in the matrix (8). When a swelling and eroding polymer (e.g. Nacmc) is employed as a hydrophilic matrix in a sustained tablets followed by erosion of the matrix tablets. Release of a soluble drug from the matrix involves the sequential process of diffusion of medium into the matrix, hydration and swelling of the matrix, dissolution of drug in the matrix and then leaching of the solubilized drug through the interstitial channels. The process can be described by Equation 6:

$$Q_d - S_q \frac{(DV_i(2A - V_iC_st)^{1/2}}{\gamma} = K_3t^{1/2} \quad \text{----------6}$$

(Q_d is the amount of drug released after t, D - diffusion coefficient of the drug in the diffusing medium γ = tortuosity factor of the capillary system in the matrix C_s - solubility of the drug in the diffusing medium, A - the amount of drug loaded in the matric, V_i - porosity of the matrix, S_q - total surface area, K_3 - fitting constant). In this system, (swelling and erosion controlled matrix system), drug release is thought to occur faster than erosion in situation where the drug is highly soluble in the diffusing medium. In the case, $V_i\ C_s \geq A$ and the drug release can be expressed by Equation 7:

$$\frac{S_qA(Dt)^{1/2}}{\gamma} \quad \text{.....7}$$

In this situation, all of the drug in the tablet would dissolve quickly into the infiltrating medium, followed by diffusion from the matrix system, and the release of drug from the system would depend on D(8). On the other hand when the amount of drug loaded in a tablet is high and/or the solubility in the dissolution medium is reasonable, drug release from the matrix tablet can be described by Equation 6. In this situation, V_iC_s will be slightly less than A and the percentage of drug released (Q_d/A) at time t can be expressed as:

$$Q_d/A = \frac{Sq(DV_iCt)^{1/2}}{\gamma_A} \quad \text{.....8}$$

Here the drug release is affected by Cs, A and D. The drug release profile in this situation is determined by the profiles of medium diffusion into the matrix tablet. The release profile of theophyline (Fig. 1) was considered to conform to the conditions in Equation 8.

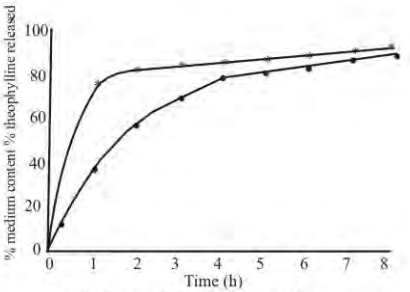

Fig. 1: Medium diffusion profile of Nacm-lactose compact and release profile of Theophylline in SIF medium diffusion profile (x) release profile of theophylline (o)

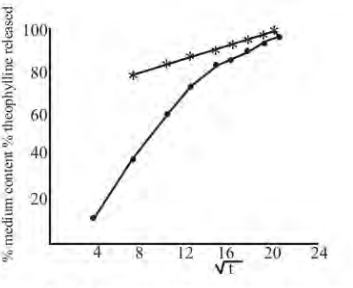

Fig. 2: Higuchi's diffusion plot for medium diffusion into Nacmc-Lactose

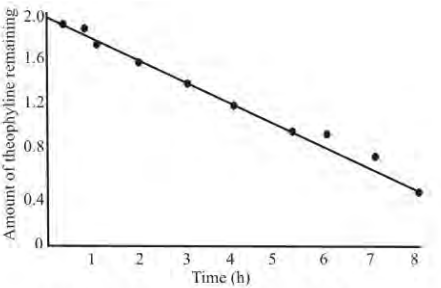

Fig. 3: First Order release kinetics of theophylline from Nacmc matrix

There are other methods for the determination of medium diffusion into tablet matrices and the erosion of a tablet matrix (9, 10, 17, 18). The present method offers the advantage of allowing a direct comparison of the ratio of medium to matrix and the percentage of tablet erosion as a function of time with drug release profiles under various conditions (8, 11)

Conclusion

The results of the present study show that release of a drug with reasonable solubility in SIF will depend on the drugs solubility, the amount of drug loaded and diffusion coefficient of the drug. There is the indication that apart from the diffusion mechanism after erosion of the tablet, the rate of drug dissolution from the released particles occurred as a first order release function. The development of an optimum sustained release formulations with Nacmc could therefore be achieved on the basis of the release mechanisms of the drug under consideration (for drugs that are released in the lower region of the intestine), based on the square root and first order release kinetics.

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