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The Influence of Fillers on Theophylline Release from Clay Matrices

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Abstract The objectives of this study were to investigate the suitability of magnesium aluminium silicate (MAS) (Veegum®) to control drug release of a model drug, theophylline, from tablet matrices. To this end, the performance of three commonly used fillers namely: lactose, microcrystalline cellulose (Avicel PH102; MCC), and pre-gelatinized starch, Starch 1500 PGS), were evaluated against Veegum®. The physico-mechanical properties of the tablet matrices were studied along with dissolution studies to determine the effect of single or binary mixtures of the excipients on the drug release pattern. A DSC hydration methodology was also employed to characterize the states of water present in the tablet matrices and to determine any impact on drug release. Formulations containing MAS alone produced compacts with the lowest hardness (4.5 kp) whereas formulations containing MCC alone produced the hardest tablets (17.2 kp). Dissolution studies suggested that matrices containing MAS alone released the theophylline quickest as compared to lactose, MCC or PGS. It was difficult to establish a trend of the bound and free water states in the tablet matrices; however the formulation containing only MAS had the highest bound water at 29 %. The results therefore show that theophylline does not interact with MAS. As such the dominant factor in controlling drug release using MAS requires interaction or intercalation with a cationic drug. In the absence of this however, other excipients can play a role in controlling drug release.

Keywords: *Veegum, clay matrices, DSC hydration, magnesium aluminium silicate, fillers*

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1. Introduction

Polymers such as hydroxypropyl methylcellulose (HPMC) have been extensively used to sustain, modify and extend drug release in formulations [1-8]. With the aim of obtaining zero-order release kinetics and further modification of drug release, several mixtures of polymers have also been exploited [9,10,11,12]. Clays are used in pharmaceutical products as stabilising agents as well as suspending agents in topical preparations. Their large specific surface area, good adsorption, ion exchange properties and the ability to form drug-clay interactions makes clay an attractive option for drug release modulation [13]. Magnesium aluminium silicate (MAS) (Veegum®) is a mixture of montmorillonites (MMT) and saponites, which are natural clays. These clays have a layered structure where each layer is made from tetrahedral arranged silica atoms fused into an edge shared octahedral plane of either aluminium or magnesium hydroxide [14,15].

These clay systems have been used in combination with sodium alginate (SA) to assess and characterise their potential as a film former [16]; and in combination with gelatin to generate nanocomposites as a result of the interaction between their functional groups [17]. In a previous study, the use of MMT as a sustained release carrier for ibuprofen was assessed and it was observed that release of ibuprofen from the ibuprofen/MMT composites was steady and pH dependent [18]. Another study investigated the use of propranolol-MAS intercalated complexes as drug reservoirs in HPMC tablets [19]. They observed that the complex tablets prepared with propranolol-MAS complexes were harder than tablets made with just propranolol or a physical mixture. In addition, drug release from the complex tablets followed zero-order release kinetic, while drug release from the other tablets was by anomalous transport. This led to the conclusion that propranolol-MAS complexes can be used as drug reservoirs in modified release tablets. One of the objectives of this study is to incorporate theophylline into clay matrices and evaluate the effect of fillers such as MCC (Avicel PH102), lactose monohydrate and starch 1500 on its release from these matrices.

Water in hydrogel systems can exist in three structurally distinct forms, each possessing different physical properties [20]. Type I (freezing or free, bulk-like water) melts at the melting point of pure water (0 °C). Type II (freezing or bound water) can interact weakly with macromolecules and displays a lower melting point than pure water (< 0 °C). Type III (bound water) interacts strongly with hydrophilic and ionic groups of the polymer and shows non-freezing behaviour. During the initial stages of dissolution, water penetrates into the matrix and usually acts as non-freezing (bound) water [21].

Subsequently, the water content of the matrix increases and freezable water is detected at levels that are related to drug release. Transport of solutes occurs mainly through the free water with a minimum being transferred through bound water. It was also claimed that bound water did not participate to any significant effect in the hydration process for hydrophilic polymeric gelatin gels and that the hydrolysis/water uptake rate depended mainly on the amount of free water present in the system [22]. Therefore, knowing the dynamics and state of water molecules in hydrogels enables a better understanding of the swelling process of hydrophilic matrices and the release of drugs from such systems [23]. As such, another objective of this study was to investigate the state of water in the clay matrices to determine if it relates to drug release.

2. Materials and Methods

2.1. Materials

Veegum F® EP (MAS) (R. T. Vanderbilt), Theophylline (TCI chemicals), MCC (Avicel PH102; FMC Biopolymer), lactose monohydrate (D.M.V Fonterra Excipients), PGS (Colorcon) and HPMC Methocel™ K4M (Colorcon) were used in the tablet formulations (Table 1). 66.67 mg and 3.33 mg of HPMC and magnesium stearate respectively were included in each formulation. HPMC was used at a low concentration so the effects of the various fillers were not masked.

2.2. Tableting

Tablets, with quantities of excipients as per Table 1, were prepared. All the ingredients, except magnesium stearate, were blended in a tumble mixer (Turbular T2C, Switzerland) for 8 minutes. The magnesium stearate was added to these mixtures and the samples were blended for a further 2 minutes. The tablets were compressed using a single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 2500 psi (9.87 kN).

Tablet hardness in kp thickness and diameter in mm were measured using the PharmaTest mechanical strength tester. The average values of three formulations were calculated as well as the standard deviation.

Table 1. Model clay matrices formulation

Formulation	Drug (mg)	Veegum (mg)	Lactose (mg)	MCC (mg)	Starch 1500 (mg)
B1	100	163.3	-	-	-
B2	100	-	163.3	-	-
B3	100	-	-	163.3	-
B4	100	-	-	-	163.3
B5	100	81.65	81.65	-	-
B6	100	81.65	-	81.65	-
B7	100	81.65	-	-	81.65
B8	100	41.6	121.7	-	-
B9	100	41.6		121.7	-
B10	100	41.6			121.7

Note: Each formulation contained 66.67 mg and 3.33 mg of HPMC and magnesium stearate respectively

2.3. Dissolution Studies

In-vitro dissolution was obtained in a USP II (paddle) method (PharmaTest) to characterise the release of theopylline from the matrix tablets. Sinkers were used in order to prevent the tablet from floating. The amount of drug in each tablet used was equivalent to 100 mg of drug. The studies were performed at 100 rpm rotation speed in a 900 ml vessel of release medium (deionised water) at a temperature of 37 ± 0.5 °C. Theophylline release was analysed by UV at a wavelength of 271 nm. These experiments were carried out in triplicate.

2.4. Dissolution Parameters

The mean dissolution time (MDT) is the mean time for the drug to dissolve under *in-vitro* dissolution conditions. MDT is a model-independent method and is suitable for dosage forms having different mechanisms of drug release. This parameter helps to characterize the drug release profile and enables comparison of drug release rates from the various formulations [24,25] and is calculated using Equation 1.

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (1)$$

where j = sample number; tj = midpoint of the jth time period (easily calculated with ((t + t-1)/2) and ΔM_j = additional amount of drug dissolved between tj and $t\text{-}1$.

The mean dissolution rate (MDR) can be calculated according to Equation 2.

$$MDR = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n} \quad (2)$$

where n = number of dissolution sample times; Δt = time at the midpoint between t and $t\text{-}1$ (easily calculated with [t + (t-1)/2].

The area under the dissolution curve up to the time, t, expressed as the percentage of the area of the rectangle is known as the dissolution efficiency (DE) of a pharmaceutical dosage form [26]. This is mathematically depicted as Equation 3.

$$DE = \frac{\int_0^T Y \times dt}{Y_{100} \times T} \times 100\% \quad (3)$$

where, y = the percentage of drug dissolved at time t.

2.5. DSC Hydration

Mini tablets of target weight of 25 mg were produced for all formulations. The mini tablets were produced using the single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 2500 psi (9.87 kN).

The mini tablets were hydrated using a previously reported method [27,28]. In brief, the mini tablets were hydrated using 25 mg purified water in the standard aluminium pans and then sealed with a lid. The pans were initially cooled down from room/ambient temperature (20 °C) to -30 °C at 55 °C/min so that any unbound water (free water) would freeze. The temperature was kept at -30 °C to allow for equilibration and then the samples were

heated from -30 °C to 50 °C at 10 °C/min under nitrogen. The amount of free and bound water in the tablets was determined using the endotherm scanning of the melted free water. A reference standard for determining amount of bound water in the theophylline mini tablets using distilled water was prepared using 25 mg purified water in standard aluminium pans sealed with a lid processed similarly to the hydrated tablets.

3. Results and Discussion

3.1. Effect of fillers on the physico-mechanical properties of the tablets

Table 2 shows the average thickness, diameter and hardness of the various formulations of theophylline. All formulations had relatively similar thickness (4.05 - 4.50 mm) and diameters (10.04 - 10.13 mm). However, the hardness test results were varied. Formulations containing MCC produced the tablet with the highest strength (B3, B6 and B9). As MCC is used as an excipient in the formulation of direct compressed tablets to harden tablets, this was to be expected. The results suggest that increasing the quantity or concentration of MCC produces harder tablets. PGS is a combination of maize starch and free amylose. It is used as a flow-aid, disintegrant, lubricant and binder in the formulation of tablets in direct compression and wet granulation [29]. Formulations containing PGS produced the tablets with the lowest mechanical strength (B4, B7 and B10). What was interesting to note was that the formulations containing MAS alone produced the weakest tablets. It was observed that MAS reduced the strength of the tablets prepared with Avicel.

Table 2. Physico-mechanical properties of the tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kp)	Bound water (%)
B1	4.05±0.006	10.25±0.02	4.5±0.2	29.4±4.24
B2	4.38±0.029	10.08±0.02	11.03±0.5	23.4±2.3
B3	4.35±0.021	10.04±0.06	17.17±0.12	19.0±0.35
B4	4.50±0.078	10.08±0.025	6.17±0.68	21.7±1.29
B5	4.20±0.021	10.14±0.025	6.03±0.31	24.6±1.68
B6	4.21±0.03	10.11±0.021	9.83±0.51	21.1±1.39
B7	4.29±0.072	10.13±0.017	5.63±0.23	22.2±1.77
B8	4.29±0.023	10.09±0.015	9.07±0.98	24.2±0.51
B9	4.25±0.021	10.10±0.025	14.4±1.00	20.7±0.06
B10	4.43±0.012	10.08±0.012	8.00±0.36	22.5±0.35

3.2. MAS effect on theophylline release

Figure 1, Figure 2, and Figure 3 show the influence of MAS on theophylline release from the tablets. Figure 1 shows a comparison of 49 % MAS with formulations that had no MAS but 49 % lactose, 49 % MCC and 49 % PGS respectively. The tablet with the lowest hardness was formulation B1 which contained only 49 % MAS and this could be the reason why the DE of this formulation was high at 81.75 %. As such, when the tablet was immersed into the dissolution fluid, the water ingress weakened the already weak bonds causing the tablet to disintegrate and release the drug quickly; formulation B1 matrices released 100 % of the theophylline after 270 min. B2, B3 and B4 however were a lot more controlled and released 100 % drug release was observed after about 540 min. Theophylline is not ionised and there was no evidence of complex formation to retard the rate of drug release. Formulation B4, containing 49 % PGS, had a slow dissolution profile. In an attempt to increase the dissolution of a poorly soluble drug- ibuprofen using starch or sodium starch glycolate, Nokhodchi *et al*. [30] found higher concentrations of starch or sodium starch glycolate to have a detrimental effect on ibuprofen dissolution. They deduced that the presence of such high concentrations of starch around ibuprofen particles generates a very viscous solution around ibuprofen particles leading to slow penetration of dissolution media into the tablet hence poor dissolution. This may have been a contributory factor to the release pattern of B4 which also had the lowest DE value of 65.41 % (Table 3). According to the DE values, drug release was in the order B1 > B2 > B3 > B4 (Table 3). The formulations B5, B6 and B7 contain 24.5 % MAS so in a one-to-one ratio with lactose, MCC or PGS respectively. Drug release patterns from these formulations were very similar to that shown in Figure 2, however, there were small increases in DE, showing that the drug release was slightly faster in this media. DE values for these formulations were lower (67.80 -70.86) as compared to B1 containing MAS alone (81.75) indicating the beneficial effects of the fillers added to the clay matrix. Figure 3 shows a comparison of B1 to B8, B9 and B10. The amount of MAS has been reduced to 12.5 %. The DE values again follow the order B1 > B8 > B9 > B10 (Table 3). The results suggest formulation B10 to have the slowest drug release of all the formulations tested indicating a possible synergistic effect between PGS and MAS at that concentration.

Table 3. Dissolution parameters of clay tablet matrices

Formulation	DE_{720MIN} (%)	MDT (min)	MDR ($\%min^{-1/2}$)
B1	81.75	35.43	0.25
B2	70.74	30.63	0.21
B3	68.92	34.09	0.21
B4	65.41	30.53	0.19
B5	70.86	33.90	0.22
B6	72.21	31.73	0.21
B7	67.80	30.16	0.19
B8	75.95	31.37	0.23
B9	70.69	32.12	0.20
B10	64.80	28.06	0.18

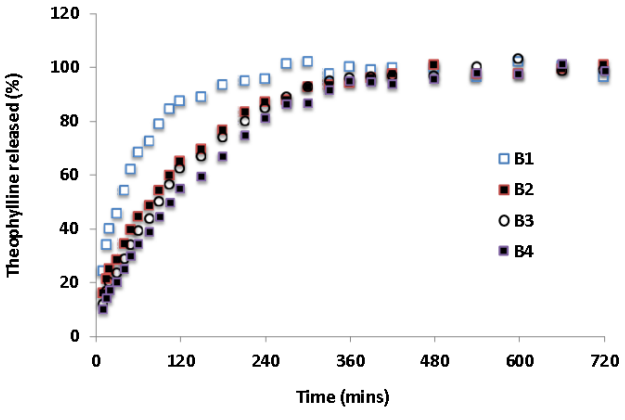

Figure 1. Effect of MAS concentration on theophylline release

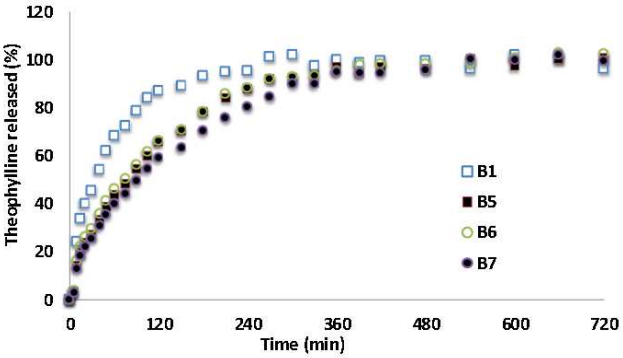

Figure 2. Effect of 24.5 % MAS concentration on theophylline release

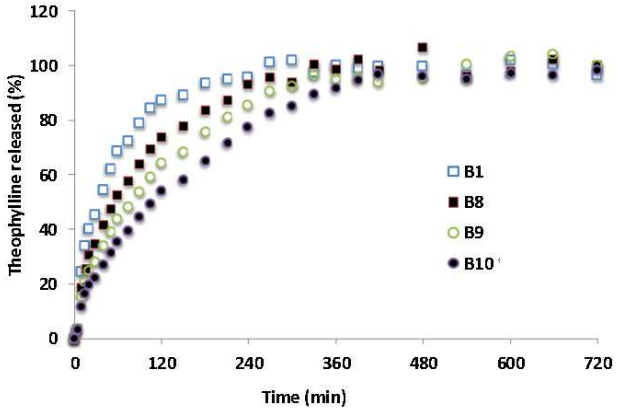

Figure 3. Effect of 12.5 % MAS concentration on theophylline release

3.3. Lactose effect on theophylline release

Figure 4 shows the influence of the inclusion of lactose on the release capacity of the MAS. B2, B5 and B8 contain 49 %, 24.5 % and 36.5 % lactose respectively. Lactose is used as an excipient in tablet formulations because it compresses well due to its elastic nature. Lactose is a disaccharide sugar and this could be the reason behind its increased DE as compared to the other fillers used although its DE values were all lower than that of B1 (Table 3). The addition of MAS to B5 and B8 resulted in an increase in the dissolution rate from 0.21 % min^{-1} to 0.22 % min^{-1} and 0.23 % min^{-1} respectively suggesting the inclusion of MAS could increase drug release from the compacts.

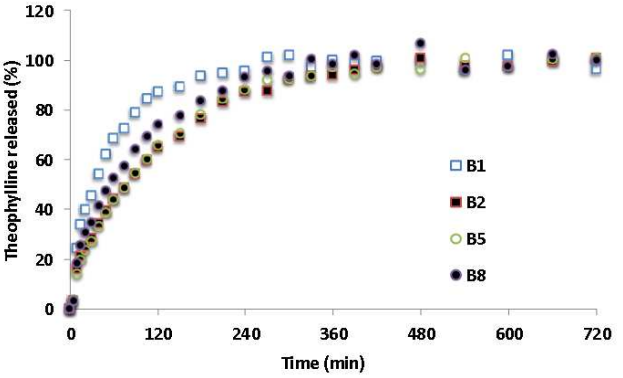

Figure 4. Effect of lactose concentration on theophylline release

3.4. MCC effect on theophylline release

Initially B3 released the drug slowly (Figure 5). However, as time progressed the tablets released more of the drug and this resulted in a DE value of 68.92 %. From the table of physico-mechanical properties of excipients, tablets containing MCC seemed to be the hardest (B3 > B9 > B6). This can also impact drug release, leading to a delay in the ingress of water into the tablet.

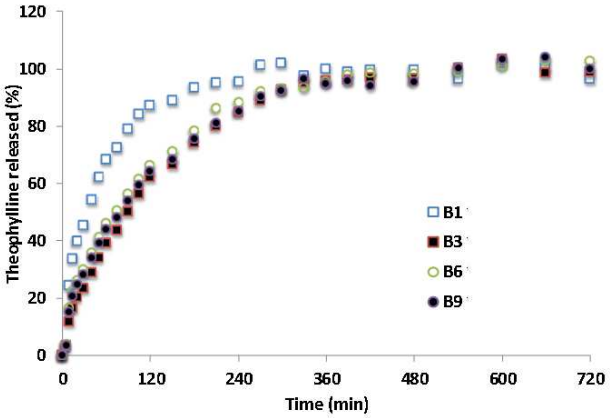

Figure 5. Effect of MCC concentration on theophylline release

3.5. PGS effect on the theophylline release

Figure 6 shows that an increase in the amount of PGS in formulations resulted in a general decrease in theophylline release. PGS is used as a disintegrant during the tablet manufacture process. When starch comes into contact with water it swells and causes bonds between particles in the tablet to weaken and then break up, leading to tablet disintegration, and thus drug release. However in this case, the high concentrations of starch may potentially have generated a very viscous solution around the matrix tablets leading to a slow penetration of dissolution media into the tablet hence, its relatively slower dissolution profiles as compared to B1.

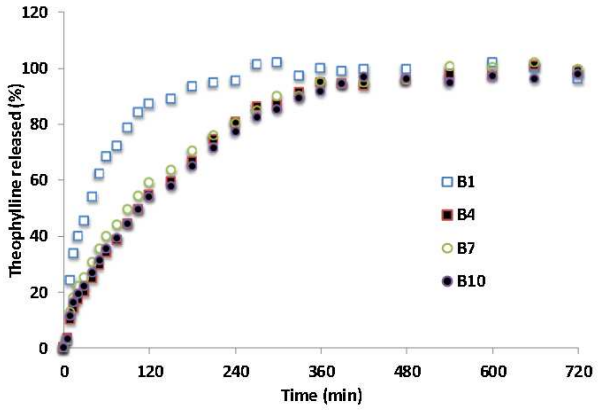

Figure 6. Effect of starch concentration on theophylline release

3.6. DSC hydration

The hydration values were determined at 10 min to coincide with the first sampling time in the release studies. The DSC scans obtained from the hydration studies were integrated to determine the average amount of bound water present in the tablet matrices (Table 2). In comparing the first four formulations, MAS as a single excipient binds more to water than the other three

excipients used (29 %). MCC as a single excipient however contained the lowest amount of bound water with a value of 19 %. Binary mixtures of the excipients in different concentrations as depicted in Table 1 from B5-10, renders different bound water percentages in the various tablet matrices with the highest of 25 % for B5 and the lowest 21 % for B9. It proved difficult in trying to establish a trend as was done in Asare-Addo *et al*. [27] where the percentage bound water was successfully used to explain drug release from theophylline HPMC tablet matrices. They however observed in a more recent publication [31] that this was dependant on the nature of drug used as this same methodology proved unsuccessful in explaining drug release for a very soluble cationic drug. This may be due to the nature of MAS and, as such, warrants further research.

4. Conclusion

Theophylline tablet matrices were produced and the influence of the fillers used was investigated. MAS at 49 % with theophylline did not prolong the drug release as compared to the other tablet formulations and also produced the compacts with the lowest mechanical strength. The results generally showed that MAS does not contribute to sustaining the release of theophylline from its matrices. This may be due to the nature of the model drug used. DSC hydration showed the states of water in the hydrated compact but failed to make a link as to how the drug was released. The results therefore show that the dominant factor in controlling drug release is interaction or intercalation of the drug with the clay. This is usually by the use of cationic drugs. In the absence of this, other excipients can play a role in controlling drug release.

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