Drug release from magnesium aluminium silicate-polyethylene oxide (PEO) nanocomposite matrices: An investigation using the USP III apparatus

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Highlights

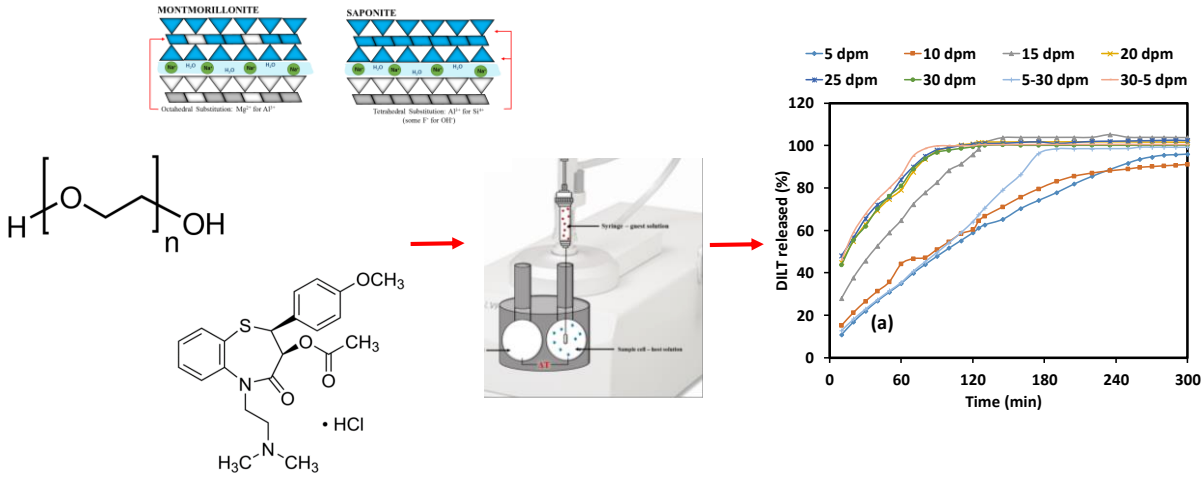
ITC results show binding between DILT and PEO was enthalpy and entropy driven

Binding between veegum and DILT in the presence of PEO shown to be enthalpy driven and entropically unfavourable

ITC results successfully explain drug release from veegum-PEO matrices

USP III used to successfully simulate fed and fasted states with matrices robust in up to 0.2 M ionic strength

Graphical abstract



ISOTHERMAL CALORIMETRY IN UNDERSTANDING DRUG RELEASE FROM COMPLEXES

Abstract

This work investigated the use of the USP III apparatus in discriminating simulated fed and fasted conditions as well as ionic strength on veegum-polyethylene (PEO) (called clay-PEO matrices hereafter) matrices. The successful formulations were characterised using differential scanning calorimetry (DSC) and evaluated for their physical properties. Isothermal calorimetry (ITC) was used to evaluate the thermodynamics of the complexation processes. The effect of agitation sequences on the matrices as evaluated from the USP III suggested an increase in polymer content to significantly decrease the burst release experienced using diltiazem hydrochloride (DILT) as a model cationic drug. The manufacturing methods showed superior performance in relation to a decrease in burst release over the physical manufactured counterparts. The clay-PEO matrices also showed robustness (no matrix failure) in up to 0.2 M ionic strength solutions mimicking the upper limit experienced in the GI tract. ITC results revealed that the binding between DILT and PEO was enthalpy and entropy-driven. Furthermore, the binding between veegum and DILT in the presence of PEO was shown to be enthalpy-driven and entropically unfavourable, which was also the case for the binding between veegum and PEO thus giving insights to how the matrices were performing on a molecular level.

Keywords: USP III apparatus; PEO, veegum; hydrophilic matrices; magnesium aluminium silicate; nanocomposites

Abbreviations: PEO, polyethylene oxide; DSC, differential scanning calorimetry; MAS, magnesium aluminium silicate; DILT, Diltiazem hydrochloride; ITC, Isothermal calorimetry; PEG, polyethylene glycol; API, active pharmaceutical ingredient; NaCMC, carboxymethylcellulose; PM, physical mixture; GI, gastrointestinal;

1. Introduction

Polyethylene oxide (PEO) (Figure 1a) is a synthetic polymer obtained commercially upon the catalytic polymerisation of ethylene oxide. It has the same chemical structure as polyethylene glycol (PEG) but a higher molecular weight, usually over 100,000. PEO is also soluble in a wide variety of solvents (ethanol, acetone, toluene, chloroform) and in water. When dissolved in water, PEO tablets hydrate, swell and form a gel layer outside the dry core. As with hydrophilic matrices, this gel layer controls the release of an active pharmaceutical ingredient (API) as the polymeric chains unfold and disentangle in the dissolution medium (Ward et al., 2019; Nokhodchi *et al*., 2012; Ma, Deng and Cheng, 2014). Its physicochemical properties such as rapid hydration and high water solubility, non-toxicity, pH insensitivity to physiological fluids and easy manufacturability make PEO an attractive polymer and as such it is widely used in the formulation of controlled drug release systems (Ma, Den and Cheng, 2014; Kim *et al*, 1995; Maggi *et al*., 2002; Shojaee *et al*., 2013a, 2013b, 2015; Kaialy *et al*., 2016). Palmer *et al.* (2013) used PEO in combination with other matrix-forming polymers such as sodium carboxymethylcellulose (NaCMC), to control the release of chlorpheniramine maleate, venlafaxine hydrochloride, propranolol hydrochloride and verapamil hydrochloride (Palmer *et al*., 2013). The authors found that a synergistic interaction between PEO and NaCMC in the tablets significantly slowed drug release when compared to the tablets containing a single polymer component (PEO or NaCMC) (Palmer *et al*., 2013; Nokhodchi *et al*., 2015).

Veegum also known as magnesium aluminium silicate (MAS) (Figure 1b and c) is a mixture of natural smectite montmorillonite and saponite clays. Veegum has a layered silicate structure, formed of one alumina or magnesia octahedral sheet, sandwiched between two tetrahedral silicate sheets (Vanderbilt 2014a and b; Kanjanakawinkul et al., 2013; Totea *et al*., 2020). MAS has become a material for the use in drug formulation due to its high surface area and good

affinity with cationic drugs which has been well documented and exploited (Rojtanatanya and Pogjanyakul., 2010; Adebisi *et al*., 2015; Okeke and Boateng, 2016, 2017; Totea *et al*., 2019). Several polymers including quaternary polymethacrylates, chitosan and alginate have also been successfully crosslinked with veegum to produce coatings, films or matrices for the successful delivery of drugs (Rongthong *et al*., 2013, 2020; Khuathan and Ponjanyakul, 2014; Khlibsuwan *et al*., 2017; Khlibsuwan *et al*., 2016). Pappa *et al.* reported the intercalation of PEO between nanolayers of sodium montmorillonite to formulate nanostructured composites, intended for the dissolution modulation of aprepitant. The authors found the PEO and clay nanocomposites were highly effective as drug carriers for sustained release (Pappa *et al*., 2018).

Diltiazem hydrochloride (DILT) (Figure 1d) is a non-dihydropyridine calcium channel blocker with molecular weight and pKa of 450.98 g/mol and 7.8 respectively. DILT inhibits the calcium channels in the blood vessels which leads to vasodilatation and, hence lower blood pressure (Padial *et al*., 2016). DILT has an elimination half-life of 3.2 ± 1.3 h following oral administration with a bioavailability of 42 ± 18 % following first-pass metabolism (Herman *et al*., 1983) therefore making it an ideal candidate for extended release (Qazi *et al*., 2013; Li *et al*., 2016) hence its use as the model cationic drug.

Although multiple studies have reported the efficient use of PEO as an excipient in the formulation of controlled release systems on its own or in combination with other polymers or materials such as clay, the effect of the polymer on the clay adsorption capacity has not been previously explored at a molecular level. This experiment therefore aims to understand the interactions between the model drug DILT, PEO and veegum at the molecular level and how the interaction can potentially impact on the drug release from the clay-PEO matrices. This is primarily investigated using isothermal calorimetry (ITC). Secondly, a more biorelevant dissolution methodology (USP III) is utilised in conducting the dissolution studies using a range of dip per minute (dpm) as well as dpm in ascending and descending order as reported

elsewhwere (Asare-Addo et al., 2013a and b) to mimic the potential effect of food as well as ionic strength on DILT release from the manufactured matrices. To the best of the author's knowledge, this is the first of such a study. Hence, the information reported in this study will allow a formulator to draw conclusions on parameters that may need to be manipulated in order to improve drug release modulation.

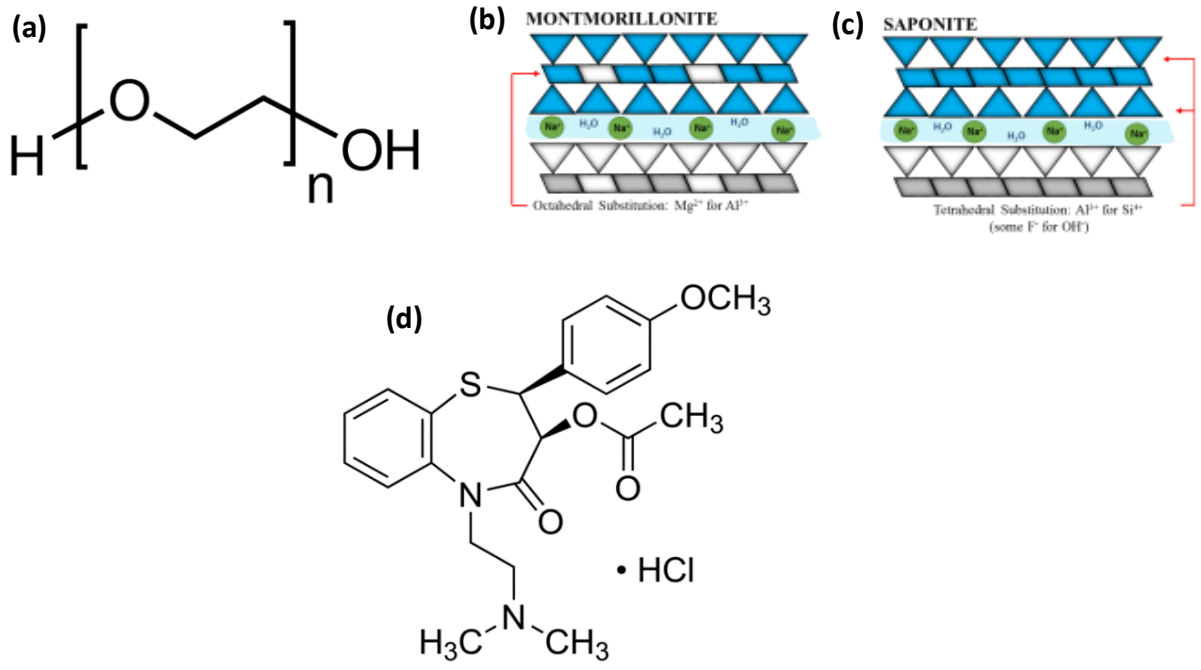


Figure 1. Chemical structures of material used (a) Polyethylene oxide (PEO), (b) Magnesium aluminium silicate (Veegum) and (c) Diltiazem hydrochloride.

2. Materials and methods

2.1 Materials

The hydrophilic matrix tablets were prepared using DILT as the model drug. DILT was purchased from TCI chemicals, UK. The PEO (Polyox WSR 301, with a molecular 4,000,000) polymer was a kind gift from Colorcon, Ltd, UK. Veegum F was a kind gift from Lake Chemical UK. The dissolution media used was prepared according to the USP 2003 method of preparing buffers using potassium chloride (Acros Organic, UK), hydrochloric acid (Fisher

Scientific, UK) for pH 1.2 and 2.2, and potassium phosphate monobasic-white crystals (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for pH 5.8, 6.8, 7.2 and 7.5 media.

When investigating the effect of ionic strength on the drug release, sodium chloride (Fisher Scientific, UK) was used to adjust the ionic strength of each pH buffer.

2.2 Tablet preparation and mechanical strength test

Six formulations in total were prepared in three distinct ways to aid comparisons. The first two formulations (F1 and F2) were prepared by measuring out the components as in Table 1 and mixed in the Turbula blender (Type T2C, Switzerland) for 10 min (these two formulations are classified as the physical mixtures (PM)). For formulations F3 and F4, the drug (DILT) was firstly dissolved in deionised water (5 mL) after which it was added to the veegum in a ball mill (10 min at 400 rpm). After this was air-dried, it was mixed with the appropriate amount of PEO in the turbula mix for 10 min. Formulation F5 and F6 were prepared by physically mixing the veegum and DILT in the turbula mix for 10 min, introducing the clay-drug mix into the ball mill (10 min at 400 rpm) then adding deionised water (5 mL) to the milling process. After the drying process, the appropriate amount of PEO was again added and mixed on the turbula mix for 10 min (Table 1). Round cylindrical tablets with a diameter of 9.6 mm (obtained using an electronic digital calliper) with a target weight of 250 mg were then prepared (Table 1) using a single punch tableting machine at 1500 psi (5.5 kN) (Model MTCM-1, Globe Pharma, US). The die wall was lubricated each time before tablet compression using a 2 % suspension of magnesium stearate in acetone to enable the easy removal of the tablets from the die.

As an additional investigation, the hardness of the compressed tablets was explored to aid comparisons between the various formulations. Using a tablet hardness tester (Model 8M),

150 tablets were fractured diametrically with the result displayed in Newton (N) on the screen and
151 recorded. All experiments were conducted in triplicate

152 Table 1. Composition for each formulation (values are per tablet)

Formulation code	Initial process	Diltiazem HCl (mg)	Veegum (mg)	PEO 301 (mg)	Nominal weight (mg)
F1	Simple physical mixture of all components in turbular blender	200	25	25	250
F2	Simple physical mixture of all components in turbular blender	200	16.7	33.3	250
F3	Drug was dissolved in water and mixed with veegum in ball mill. After drying, the mixture was mixed with PEO	200	25	25	250
F4	Drug was dissolved in water and mixed with veegum in ball mill. After drying, the mixture was mixed with PEO	200	16.7	33.3	250
F5	Drug and veegum was mixed uniformly following by grinding in ball mill in the presence of water. After drying the mixture was mixed with PEO	200	25	25	250
F6	Drug and veegum was mixed uniformly following by grinding in ball mill in the presence of water. After drying the mixture was mixed with PEO	200	16.7	33.3	250

153

154 **2.3 Carr's Index**

155 The tap and bulk densities were determined according to the method of Nep et al., 2017 for the
156 formulations produced (F1-F6) to allow the determination of their Carr's Compressibility
157 Index (%) (Equation 1). In brief, 10 g of each of the formulation was introduced into a 100 mL
158 measuring cylinder. Taking care not to disturb the cylinder, the volume was read to give the
159 bulk volume of the powder tested. The measuring cylinder was then tapped until the volume

of powder was constant representing the tapped volume. The bulk or tapped density was then calculated. experiments were conducted in triplicates.

$$CI = \left(\frac{Pt-Pb}{Pt}\right) x100 \qquad \text{Equation 1}$$

where;

CI = Carr's Index, Pb = Bulk Density and Pt = Tapped Density

2.4 Differential Scanning Calorimetry (DSC)

DSC was used as an investigation to evaluate the composition of the formulation to see if there were any interactions between the drug and polymers after mixing and heating. Samples of each formulation, as well as samples of the pure materials only (DILT, PEO and Veegum), were placed in a standard 40 µm aluminium crucibles and sealed. These aluminium crucibles were heated from 25 to 300 °C at a scanning rate of 10°C/min under nitrogen gas using a Mettler Toledo DSC equipment. The software provided by the instrument was used to evaluate the melting point and enthalpy were recorded.

2.5 Dissolution studies

2.5.1 Effect of dip rate on the release of DILT from the clay-PEO matrices

An automated USP type III Bio-Dis (Varian, US) was used to carry out the dissolution tests. For the first two formulations (F1 and F2), agitation rates of 5, 10, 15, 20, 25, 30, 5-30 (ascending order) and 30-5 dpm (descending order) were evaluated as shown in Table 2 (Asare-Addo et al., 2010). The transit times in Table 2 represents the period of time the tablet matrix stays in a particular vial before transferring to the next vessel. The changes in pH as in Table 2 were used to simulate the digestive tract (Klein et al., 2002). Following this, for the remaining

formulations (F3-F6) was evaluated at a dip rate 20 dpm only for comparison. The dissolution vessels contained 250 mL of the appropriate medium and the temperature of the medium was kept constant at 37 ± 0.5 °C. DILT release was measured using a UV/visible spectrophotometer at a wavelength of 240 nm.

2.5.2 Effect of ionic strength on the release of DILT from the clay-PEO matrices

To investigate the effect of ionic strength on DILT release from the matrices, sodium chloride was used to regulate the ionic strength at 0.2 M in buffers with pH of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5 (Asare-Addo et al., 2011). All formulations (F1-F6) were tested using this methodology to investigate potential differences between the formulations as they were subjected to the different ionic strength conditions.

Table 2. Transit times, pH values and agitations applied during dissolution testing of DILT clay-PEO matix tablets

		Applied Agitation (dpm)							
Media pH	Transit time (min)	Constant						Ascending	Descending
1.2	60	5	10	15	20	25	30	5	30
2.2	60	5	10	15	20	25	30	10	25
5.8	10	5	10	15	20	25	30	15	20
6.8	120	5	10	15	20	25	30	20	15
7.2	30	5	10	15	20	25	30	25	10
7.5	30	5	10	15	20	25	30	30	5

2.5.3 Mathematical modelling of drug release

There have been several equations reported in literature used in mathematical modelling to define the mechanisms of drug relase (Bruschi 2015; Gonçalves-Araújo et al., 2010). Two different models namely, Higuchi and the Korsmeyer–Peppas model (Power Law) (Equations 1 and 2 respectively) are adopted here to aid in defining the mechanisms arising as a result of the varying agitiation or increased ionic strength.

$Q = K_H t^{0.5}$ Equation 1

$Q = K_K t^n$ Equation 2

In these equations, Q is the amount of the drug dissolved in time t; K_H is the Higuchi rate constant; K_K is the release constant and n is diffusional exponent. As the compacts produced were cylindrical, n values of up to 0.45 suggest Fickian diffusion, and values of above 0.89 suggest Case-II transport. Value between these two suggests anomalous transport (Ford et al., 1991; Siahi-Shadbad et al., 2011). For a detailed review of these processes, readers are referred to the following citations (Siepmann and Peppas 2001, 2012; Bruschi, 2015).

2.6 Isothermal calorimetry (ITC) - effects of PEO on the adsorption of DILT onto veegum

The molecular interactions between DILT and veegum has been recently explored and published by the authors (Totea *et al*., 2020). The authors of the current research therefore focused on understanding the interactions between DILT, veegum and PEO in this manuscript. To this end, calorimetric studies were carried out at 25 °C and pH 5, to study the effects of PEO on veegum-DILT binding. Experiments were undertaken between PEO and veegum, PEO and DILT, as well as DILT and veegum-PEO mixture. Control binding studies were also performed. The binding isotherm was studied in 30 – 35 injections of 8 – 10 µL each into the sample cell every 550 – 1500 seconds. Veegum dispersion (0.037 % w/v) and DILT solution (0.090 % w/v (2 mM)) were prepared. PEO dispersion (0.020 – 0.037 % w/v) was also prepared. The veegum-PEO mixture was prepared using a 1:1 v/v mixture of separately

prepared veegum dispersion (0.074 % w/v) and PEO dispersion (0.040 % w/v). A competitor binding model (Figure 2) was fitted to the data to determine thermodynamic parameters using AFFINImeter (AFFINImeter, Spain).

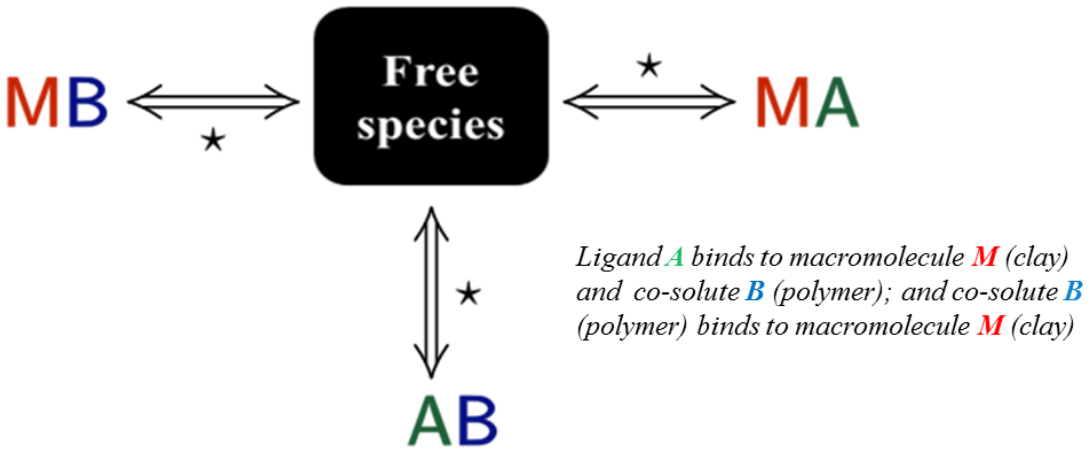


Figure 2. Competitive ligand binding where A is the ligand in the syringe (DILT) and M and B are the macromolecule and co-solute respectively (Veegum and PEO respectively), both present in the sample cell.

3. Results and discussion

3.1 Solid-state properties and physical properties of the starting materials and formulated blends

The DSC thermograph of the pure drug DILT exhibited a sharp endothermic melting peak at ~ 209 °C (Table 3). Prasad *et al*., 2013, however, reported the melting peak of DILT to be around ~ 215 °C. This difference may have to do with the manufacturing and purity of the drug as they were sourced from different suppliers. The veegum exhibited a broad endothermic peak at ~ 70 °C, which was attributed to the dehydration of free water residues within the clay (Figure 3a) which has also reported elsewhere (Rojtanatanya and Pongjanyakul, 2010). PEO exhibited a broad melting peak at ~ 66 °C due to its crystalline structure (Figure 3a) (Ozeki *et al*., 1999;

242 Crowley *et al*., 2002). All formulations exhibited the crystalline peak for PEO, however, there
243 was a slight decrease in the melting point of the DILT present therein. The melting points of
244 DILT in the formulations ranged between 204 - 206 °C (Table 3). These deviations in the
245 melting point in the formulations coincided with significant decreases in the enthalpy of the
246 DILT in the formulations. Pure DILT had an enthalpy of ~ 106 J/g which dropped to range
247 from 79 – 85 J/g (Table 3) suggesting a decrease in the crystallinity of DILT in the various
248 formulations. This behaviour has been observed and reported for propranolol hydrochloride, a
249 cationic drug used in the liquisolid preparation for veegum-polysaccharide matrices (Ward *et*
250 *al*., 2020). The preparation methods for the formulation (F3-F6) where the DILT drug was
251 mixed with the veegum in the presence of water or DILT dissolved in water first and mixed
252 with the veegum (Table 1) causes an intercalation of the cationic drug between the layers of
253 the veegum (Rojtanatanya and Pogjanyakul., 2010). This process molecularly disperses some
254 of the drug which may also be accountable for the reduction in the observed enthalpy. For the
255 physical formulations (F1 and F2), it is also possible that the observed decrease in the enthalpy
256 for the DILT peak may be caused by a solubilisation of the DILT crystals in the melted PEO
257 which may also cause some of the DILT to be in amorphous form (Kaialy et al., 2016; Alhijjaj
258 et al., 2015).
259 The Carr's index for flowability did not show any real trends with values ranging from 22 – 30
260 indicating fair to poor flowability for the formulations (Table 3). This, however, did not impact
261 on the tabletting process as a single punch tabletting instrument was used. It was also
262 interesting to note that processing associated with the manufacture of the formulation F3-F6
263 did not impact greatly on the hardness of the compacts produced.

264 Table 3. Carr's index, formulation compact hardness and DSC traces for enthalpy and melting
265 of DILT in each manufactured formulation.

Formulation code	Carr's index (%)	Hardness (N)	Enthalpy (J/g)	Melting (°C)
DILT	-	-	106.2±1.6	208.9±0.8
F1	24.3±4.7	28.0±1.0	81.4±1.6	206.0±0.8
F2	29.4±1.0	31.3±1.5	84.1±5.0	204.6±0.4
F3	29.5±1.1	34.6±1.5	82.0±8.9	205.3±0.1
F4	28.0±2.4	29.6±0.6	80.2±11.5	204.1±0.9
F5	21.9±1.0	31.0±1.7	84.7±4.6	205.8±0.9
F6	25.2±1.0	36.6±0.6	79.3±3.9	205.8±0.4

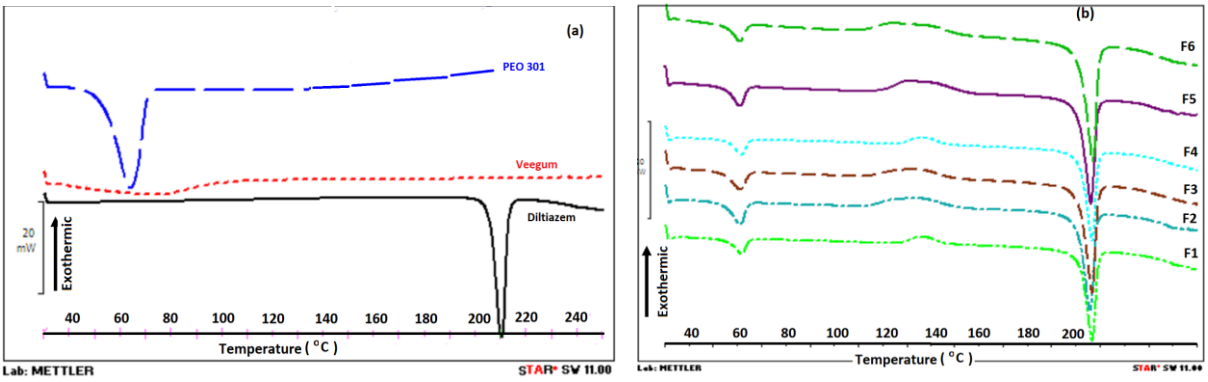


Figure 3. DSC thermographs of (a) starting materials, PEO, veegum and DILT drug, (b) manufactured formulations for making compacts for dissolution testing. For an understanding of the formulation code, please refer to Table 1. Note: Black arrow indicates exothermic direction.

3.2 Effect of agitation on DILT release

The method of increasing agitation (dpm) to mimic different food effect on matrices as developed by Asare-Addo *et al*., (2010) was used in discriminating against the clay-PEO matrices. It was interesting to note from Figure 4 where the physical mixtures are investigated that generally, the lower agitations (5 and 10 dpm) showed similarity. Similarly, the higher agitations (20 – 30 dpm) were similar. This may seem to suggest that the hydrodynamics produced and the effects on the matrices at that set dpm could be similar. This may, however, require further studies to establish this fact around the influence of hydrodynamics. It is also

280 important to note that this behaviour may be polymer dependent (Asare-Addo *et al*., 2013). Of
281 interest also is the profiles of the ascending order (where agitation is increased by 5 dpm every
282 time the cylinder containing the formulation is moved from one vial to the other. This means
283 in pH 1.2, the agitation is 5 dpm, 10 dpm in pH 2.2, 15 dpm in pH 5.8, 20 dpm in pH 6.8, 25
284 dpm in pH 7.2 and finally 30 dpm in pH 7.5) and descending order (where the reverse
285 experimentation was conducted i.e. agitation was decreased by 5 dpm every time the cylinder
286 containing the formulation moved from one vial to the other meaning in pH 1.2, agitation was
287 kept at 30 dpm, in pH 2.2, agitation was kept at 25 dpm and so forth) of agitations. Here it was
288 observed that at the descending order of agitation, the drug release profile was similar to that
289 of the higher agitation (20-30 dpm) profiles with the drug all going into solution around 90-
290 100 min (Figure 4a) or around 130-145 min (Figure 4b). Where the ascending order of agitation
291 is concerned, the lower agitation profiles of 5 and 10 dpm is followed closely till around the
292 120 min mark where agitation is set to now move to 15 dpm (indicated by the red arrow in
293 Figure 4). Here, it is possible that the gel layer formed is **de**creasing **as** a greater level of
294 agitation is applied and therefore erosion increased hence the sudden increase in drug release.
295 The different profiles obtained can, therefore, give an indication as to how different food effects
296 can influence drug release without the laboursome and often expensive methods of using actual
297 food in the dissolution testing method. In Table 4, the Higuchi and the Peppas (Power Law)
298 are applied to the release profiles. With the exceptions of drug release profiles from F2 at 10
299 and 15 dpm where the mathematical models suggested first order and the Higuchi as the
300 kinetics of release, all the dpms explored for both formulations (F1 and F2) had the Peppas
301 (Power Law) as the dominant kinetics of drug release. For the F1 matrices, the n values, where
302 the lowest agitation of 5 dpm was applied, anomalous transport was suggested to be occurring
303 with a value of 0.69. An increase in agitation or the dpm displayed a decrease in the value of n
304 up to the 20 dpm mark. This also suggested an increase in the contribution of Fickian diffusion

to accompany the increased agitation (Table 4). The ascending and descending order of agitiation had a significant impact on the n values (0.64 and 0.36 respectively). These values suggested that when agitation is started of slowly (5 dpm), anomalous transport dominated whereas when agitation is faster initially (30 dpm), Fickian diffusion dominates (Table 4).

Figure 4 also signifies the phenomena where an increase in polymer content (PEO in this case) significantly reduces the burst release. This observation has been recorded by several authors for hydrophilic polymers (Ebube et al., 1997; Velasco et al., 1999; Mason et al., 2015). Doubling the polymer content reduces the burst release experienced by the higher dpm profiles (20-30 dpm), where over 40 % of the drug is released immediately (Figure 4a) to less than 30 % for these same dpm experiments (Figure 4b). This is indicated by dashed red lines in Figure 4b. This observed decrease is also explained further with the ITC data in section 3.4 where the interactions between PEO, DILT and veegum is thought to have a contributory factor. Here also (F2), there was a decrease in the n value that accompanied an increase in the level of agitation from 5 dpm – 20 dpm (Table 4). In this case however, the increase in the polymer content meant there was more of a contribution of swelling as indicated by their increased n values (Table 4). The ascending and descending order of agitiation both displayed anomalous transport with n values of 0.67 and 0.52 respectively suggesting that when agitation is started of slowly, swelling tends to contribute a lot more than when agitation is faster initially (Table 4).

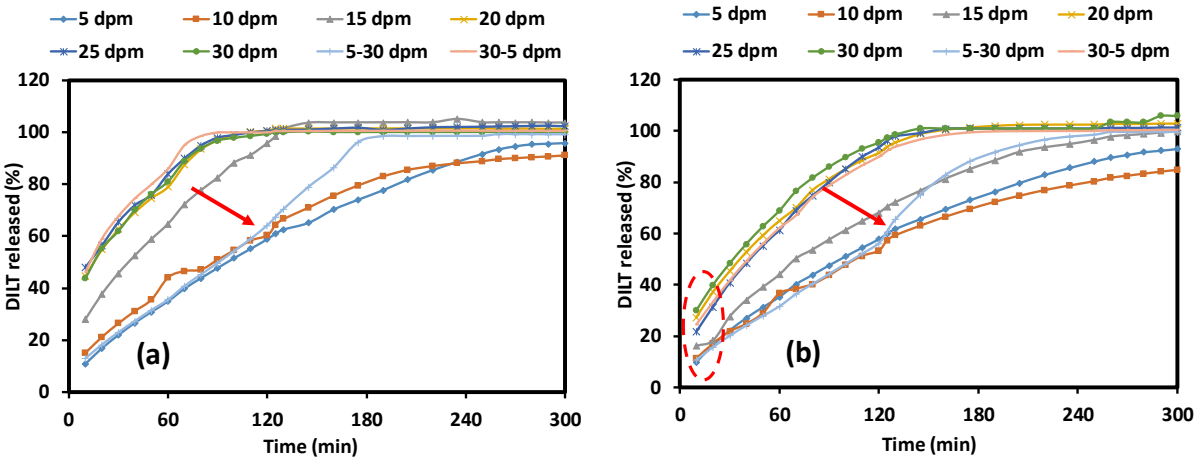


Figure 4. Dissolution profiles of DILT from the physical mixture formulations (PM) (a) F1-containing veegum:PEO in a 1:1 ratio respectively, (b) F2 - containing veegum:PEO in a 1:2 ratio respectively assessing the effects of agitation (dpm) on the manufactured matrices

Table 4. Mathematical models used in evaluating drug release profiles from the formulations at the varying agitations

Formulation and dipping speed (dpm)	Mathematical model				Formulation and dipping speed (dpm)	Mathematical model		
		RSQ	k	n		RSQ	k	n
F1-5dpm	Higuchi	0.9949	0.0647		**F2-5dpm**	0.9955	0.0619	
	Peppas (Power Law)	0.9987	0.0216	0.69		0.9996	0.0192	0.71
F1-10dpm	Higuchi	0.9777	0.0573		**F2-10dpm**	0.9888	0.0551	
	Peppas (Power Law)	0.9925	0.0389	0.57		0.9940	0.0245	0.65
F1-15dpm	Higuchi	0.9971	0.0898		**F2-15dpm**	0.9836	0.0642	
	Peppas (Power Law)	0.9988	0.0957	0.46		0.9672	0.0333	0.63
F1-20dpm	Higuchi	0.9944	0.0822		**F2-20dpm**	0.9980	0.0835	
	Peppas (Power Law)	1.0000	0.2286	0.29		0.9986	0.0890	0.48
F1-25dpm	Higuchi	0.9517	0.0760		**F2-25dpm**	0.9964	0.0938	
	Peppas (Power Law)	0.9987	0.0730	0.53		0.9987	0.0555	0.59
F1-30dpm	Higuchi	0.9656	0.0708		**F2-30dpm**	0.9961	0.0864	
	Peppas (Power Law)	1.0000	0.2012	0.34		0.9979	0.1061	0.45
F1-5-30dpm	Higuchi	0.9471	0.0708		**F2-5-30dpm**	0.9621	0.0736	
	Peppas (Power Law)	0.9895	0.0270	0.64		0.9925	0.0210	0.67
F1-30-5dpm	Higuchi	0.9695	0.0782		**F2-30-5dpm**	0.9787	0.0784	
	Peppas (Power Law)	1.0000	0.2034	0.36		0.9958	0.0728	0.52

In Figure 5, the PM formulations F1 and F2 are compared to formulations F5 and F6 where the DILT and veegum were mixed together in a turbula mixer before being ground together in a ball mill in the presence of water, dried and finally mixed with PEO. In the case of F1 and F5 where the veegum and PEO are in the 1:1 ratio, it was evident that the processing of F5 brought about a significant decrease in the burst release profiles at 20 dpm. The burst release experienced by F1 at 45 % was reduced to 24 %. Although a decrease was also observed by the F6 formulation in comparison to its PM counterpart F2, it was not as poignant as the effects of the increased polymer content come to effect here. Further explanation as to the behaviour observed as a result of the processing parameters will be explored in section 3.4.

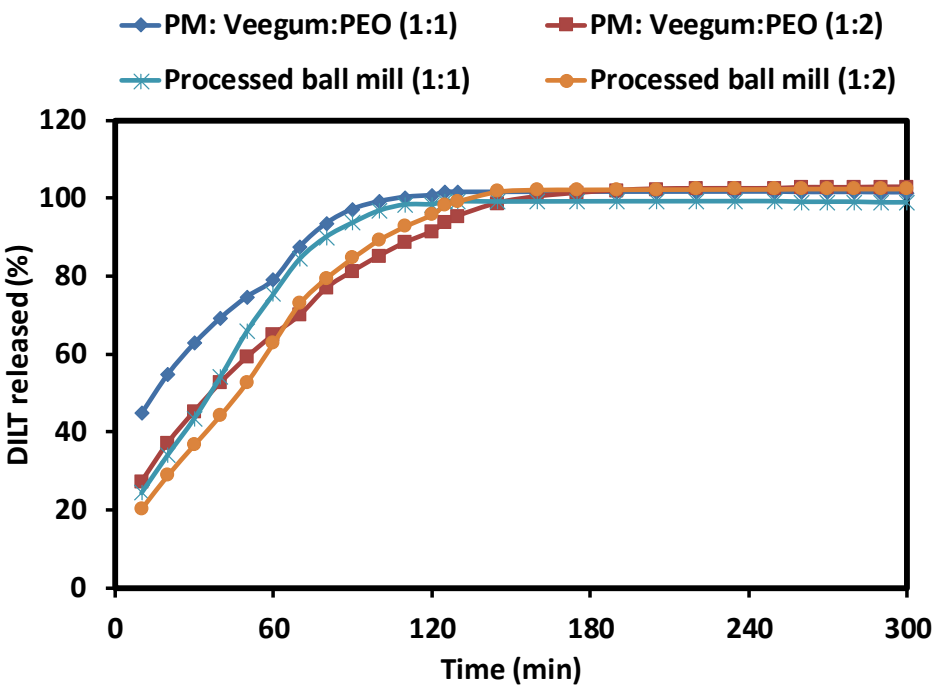


Figure 5. Dissolution profiles of DILT from the physical mixture formulations (PM) F1 and F2 being compared to the processed balled milled samples. Note: processed ball milled samples here refer to formulation F5 and F6 and dissolution was conducted at an agitation of 20 dpm

3.3 Effect of ionic strength on DILT release

pH and ionic strength are two of the major properties of the gastrointestinal (GI) fluids and are reported to vary greatly along the GI tract under fasting and fed conditions (Charman *et al*., 1997, Wilson and Washington, 1989). It has been estimated that in a fasted stomach, ionic concentration strength is approximately 0.11 M (Lindahl *et al*, 1997). As a result, ionic concentrations of up to 0.2 M is tested to determine the robustness of the clay-PEO matrices. Figure 6 depicts the effect of ionic strength on the PM formulations F1 and F2. Here, Figure 6b shows a reduction in the burst release experienced by the clay:PEO in the 1:1 ratio. This in fact, is also experienced by the formulation F3-F6 (Figure 7) although formulation F3 and F5 experience reduced burst effect in comparison to their PM counterpart F1 due to their manufacturing process. Here also, a further increase in the polymer content brings about a further decrease in burst release. The similarity in release profiles also suggests that these matrices are robust to the effect of ionic strength.

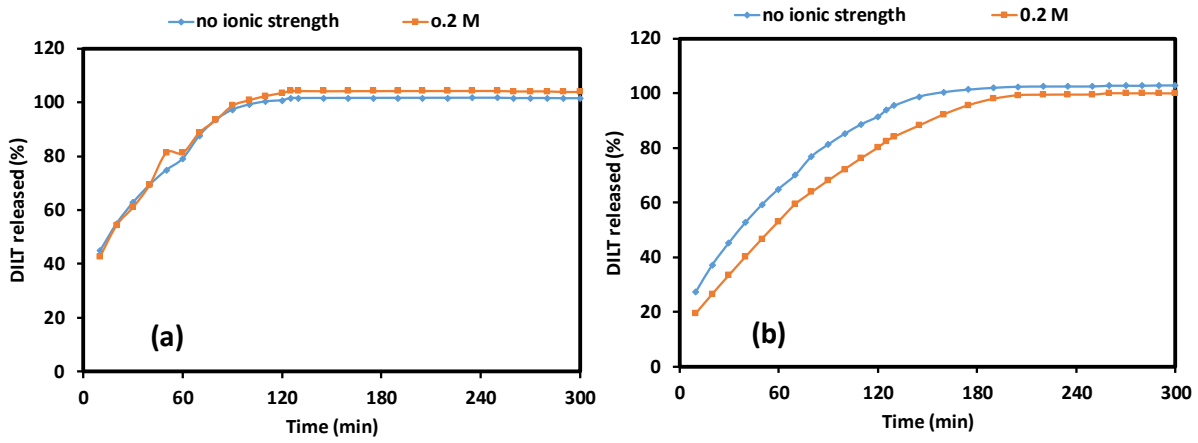


Figure 6. Dissolution profiles of DILT from the physical mixture formulations (PM) (a) F1-containing veegum:PEO in a 1:1 ratio respectively, (b) F2 - containing veegum:PEO in a 1:2 ratio respectively assessing the effects of ionic strength at an agitation of 20 dpm

Table 5 displays the mathematical models used in the analysis of the release profiles in ionic media of 0.2 M NaCl. The physical mixture formulation show that F1 has Fickian diffusion as a dominant mechanism whereas the increased polymer content for the F2 formulation suggests

anomalous transport as the dominat mechanism. It was also interesting to note that F3 and F5 both had the Peppas (Power Law) as the main dominant mechanism whereas the F4 and F6 formulation (increased polymer content) had Higuchi as the dominant mechanism. The reported values of n however when the Peppas model is applied (0.53 and 0.62) depicts how a small change in the formulation process can significantly impact the kinetics of release suggesting care and consideration being given to these investigated parameters (Table 5).

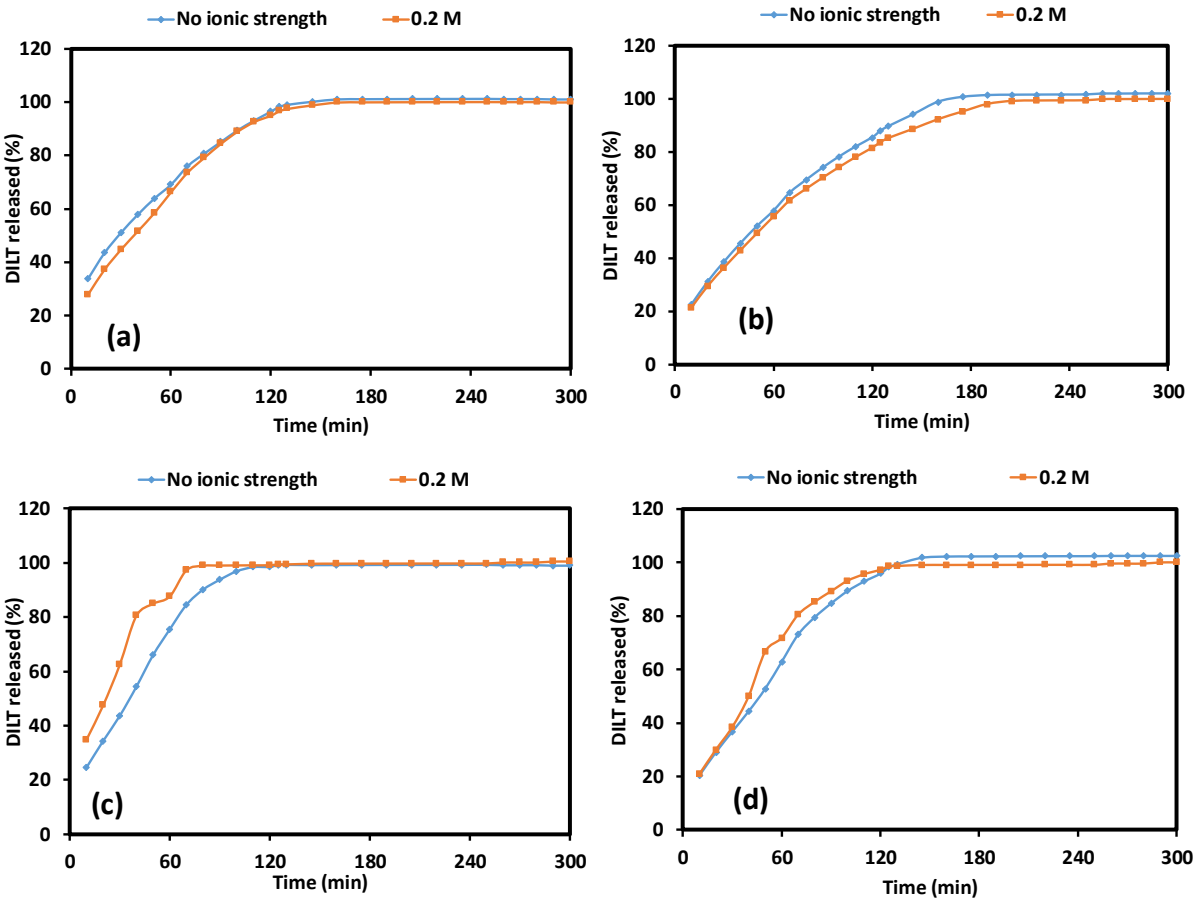


Figure 7. Dissolution profiles of DILT from the formulations (a) F3 - containing veegum:PEO in a 1:1 ratio respectively, (b) F4 - containing veegum:PEO in a 1:2 ratio respectively (c) F5 - containing veegum:PEO in a 1:1 ratio respectively, (d) F6 - containing veegum:PEO in a 1:2 ratio respectively assessing the effects of ionic strength at an agitation of 20 dpm

Table 5. Mathematical models used in evaluating drug release profiles from the formulations in the ionic strength media (0.2 M) at 20 dpm only.

Formulation	Mathematical model				Formulation	Mathematical model		
		RSQ	k	n		RSQ	k	n
F1	Higuchi	0.9911	0.0892		**F2**	0.9969	0.0822	
	Peppas (Power Law)	1.0000	0.1900	0.35		0.9912	0.0524	0.56
	Higuchi	0.9929	0.1005			0.9963	0.0809	
F3	Peppas (Power Law)	0.9990	0.1068	0.45	**F4**	0.9958	0.0635	0.53
	Higuchi	0.5452	0.0224			0.9814	0.1299	
F5	Peppas (Power Law)	0.9867	0.0921	0.52	**F6**	0.9859	0.0534	0.62

3.4 ITC in understanding the effects of PEO on the adsorption of DILT onto MAS

It has been reported that cationic drugs intercalate between the layers of veegum or MAS (Rojtanatanya and Pongjayakul 2010). This property has been exploited in the modulation of drug release as well as in the preparation of nanocomposites for film coatings (Rongthong et al., 2020; Pongjanyakul et al., 2013). Totea et al., 2019 and 2020 recently detailed the thermodynamics of two cationic drugs binding to veegum. The authors found using propranolol hydrochloride as a model drug that the overall change in enthalpy was exothermic with a comparatively small entropic contribution to the total change in Gibbs free energy (Totea et al., 2019). This suggested that the binding process was enthalpically driven and entropically unfavourable meaning hydrogen bonding and electrostatic interactions dominating the interaction. For DILT, the same authors found that a competitor binding model was needed and therefore proposed one which suggested from the thermodynamics that DILT binding to veegum was thought to enthalpy driven and entropically unfavourable (Totea et al., 2020).

From the ITC studies conducted, the interaction between veegum and PEO at 25 ºC was shown to be exothermic in nature. The non-constant heats and non-sigmoidal curve suggested that PEO can weakly bind to veegum and form a complex by intercalation of PEO particles between the veegum platelets (Figure 8) (Gao, 2004). The binding isotherm showed non-constant heats at the end of titration in the presence of excess PEO. This could be due to the aggregation of

the PEO-veegum mixture or a contribution of the PEO self-aggregation in water at pH 5. PEO dilution into water at pH 5 (25 °C) (Figure 8) showed a monotonous decrease of ITC heat signals without a sigmoidal behaviour, suggesting that PEO self-associates weakly in aqueous solution. Due to its amphiphilic structure (hydrophobic backbone and hydrophilic side groups), PEO may show a tendency to self-aggregate in aqueous solution, even at a very low concentration.

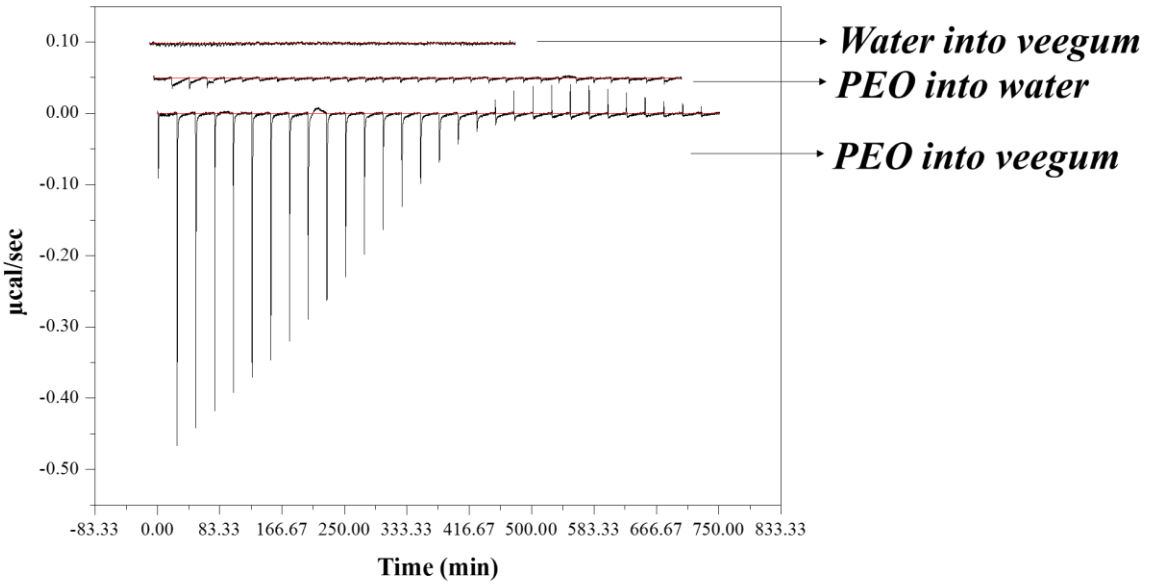


Figure 8. Raw data for titration of 0.037 % w/v PEO dispersion (pH 5) into 0.037 % w/v veegum dispersion (pH 5) at 25 °C; Control run between 0.037 % w/v PEO dispersion solution (pH 5) and water (pH5) at 25 °C and between 0.037 % w/v veegum dispersion solution (pH 5) and water (pH5) at 25 °C.

To study the effects of PEO on veegum-DILT binding, the simple binding experiment between DILT and PEO (Figure 9) was linked to the data showing the effects of PEO on DILT adsorption onto veegum (Figure 10). Hence, a competitive binding model was fitted to the data showing the binding between veegum, DILT and PEO, using the parameters obtained following the fitting of a one set of sites model to the data showing DILT and PEO binding.

Results showed that the binding between DILT and PEO was enthalpy and entropy driven (Table 6). Furthermore, the binding between veegum and DILT in the presence of PEO was shown to be enthalpy driven and entropically unfavourable, which was also the case for the binding between veegum and PEO (Table 6). This behaviour suggests that the entropic effects observed in the simple veegum-DILT binding experiment (negative -TΔS) are reduced upon the addition of the polymer to the mixture.

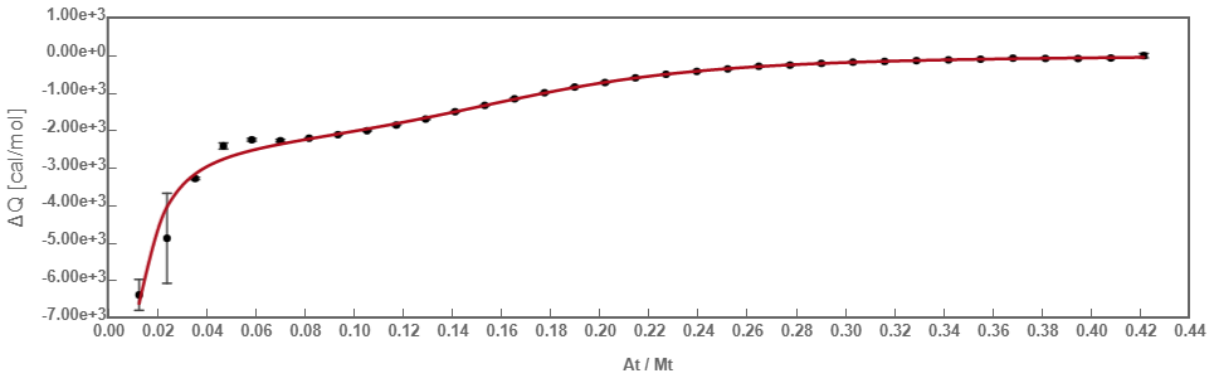


Figure 9. Thermodynamic profile through a competitive curve fitting model for adsorption of DILT solution (0.090 % w/v (2 mM)) pH 5 onto veegum-PEO mixture (0.037 % w/v veegum and 0.020 % w/v PEO mixed together at a ratio of 1:1 v/v) pH 5 at 25 °C

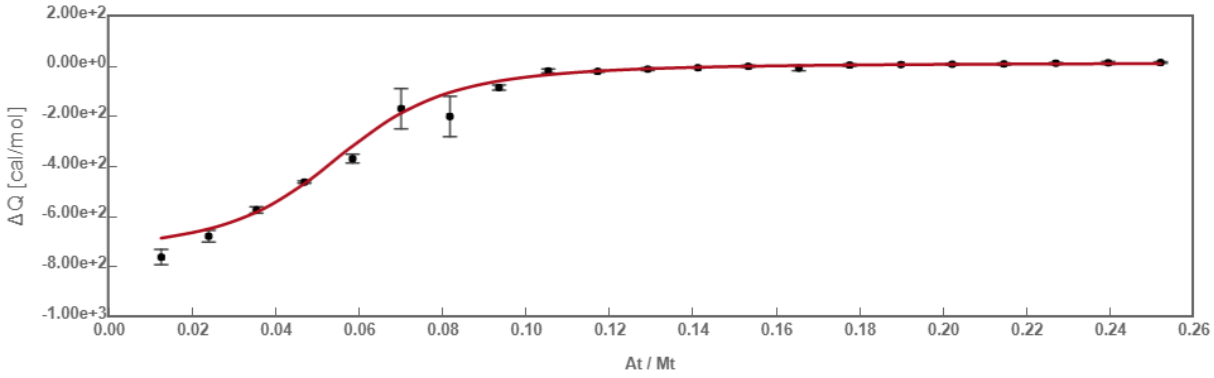


Figure 10. Thermodynamic profile through a one set of sites curve fitting model for adsorption of DILT solution (0.090 % w/v (2 mM)) pH 5 onto PEO dispersion (0.020 % w/v) pH 5 at 25 °C

Table 6. Calorimetric binding studies evaluating the adsorption of DILT (0.090 % w/v (2 mM)) onto veegum (0.036 % w/v) at 25°C (pH 5). Data analysed through a competitive curve fitting model to calculate affinity (K) and changes in enthalpy (ΔH) and entropy (-TΔS).

Reaction	**r**	**K_a [M^{-n}]**	**H [cal/mol]**	**-TΔS [cal/mol]**
M + A ↔ MA	0.06	5.2897E+5 ± 4.7516E+4	-6.9949E+4 ± 7.8197E+3	6.23E+04
*A + B ↔ AB	0.05	1.7682E+5 ± 1.9010E+3	-8.6260E+2 ± 5.4944E+0	-6.19E+03
M + B ↔ MB	0.06	8.7715E+5 ± 1.1242 E+5	-6.8785E+4 ± 7.8152E+3	6.08E+04

*binding parameters for DILT binding to PEO

The findings therefore imply that both veegum and PEO will compete for the binding with DILT which, in turn, will have effects on DILT release from the veegum-PEO matrices in slowing DILT release. Furthermore, due to the interaction observed between PEO and MAS it is expected that during DILT dissolution from veegum-PEO matrices, some of the sites on veegum would become saturated with PEO, which would prevent readsorption of DILT on both veegum and PEO.

4. Conclusions

Veegum-PEO matrices were successfully manufactured using different manufacturing techniques. The effect of agitation sequences on the matrices suggested an increase in polymer content to significantly decrease the burst release experienced using diltiazem hydrochloride as a model cationic drug. The manufacturing methods showed superior performance in relation to a decrease in burst release over the physical manufactured counterparts. The veegum-PEO matrices also showed resilience or robustness in up to 0.2 M ionic strength solutions mimicking

the upper limit experienced in the GI tract. ITC results revealed that the binding between DILT and PEO was enthalpy and entropy-driven. Furthermore, the binding between veegum and DILT in the presence of PEO was shown to be enthalpy-driven and entropically unfavourable, which was also the case for the binding between veegum and PEO thus giving insights to how the matrices were performing on a molecular level.

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Author Contributions

Kofi Asare-Addo: Conceptualisation; Writing—Original Draft; Writing—Review & Editing; Data curation

Ana-Maria Totea: Data curation; Formal analysis; Methodology; Investigation

Ali Nokhodchi: Conceptualisation; Data curation; Methodology; Investigation; Writing—Review & Editing

Conflicts of Interest

The authors declare no conflict of interest.

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