

# Lyophilised Biopolymer-Clay Hydrogels for Drug Delivery

Farnoosh Kianfar<sup>1</sup>, Nicola Dempster<sup>2</sup>, Elsie Gaskell<sup>2</sup>, Matt Roberts<sup>2</sup> and Gillian A Hutcheon<sup>2\*</sup>

<sup>1</sup>Nemaura Pharma, Loughborough, LE11 3QF, UK

<sup>2</sup>School of Pharmacy and Biomedical Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK

## Article Info

### \*Corresponding author:

Gillian A Hutcheon

School of Pharmacy and Biomedical Sciences  
Liverpool John Moores University  
Byrom Street, Liverpool, L3 3AF, UK  
Tel.: + 44 (0) 151 231 2130  
Email: g.a.hutcheon@ljmu.ac.uk

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## Abstract

Clays have previously demonstrated potential as drug delivery carriers for the extended release of a variety of drugs. The objective of this study was to develop and characterise drug-containing clays in combination with natural hydrogels for the preparation of lyophilised xerogels. Sulfathiazole (STH) (a hydrophobic model drug) was intercalated within the interlayer spaces of Laponite® RDS (LAP RDS) or refined montmorillonite (MMT) and then mixed with either carageenan 812 (CAR 812) or hydroxyethyl cellulose (HEC) hydrogels prior to lyophilisation. The resulting xerogels were characterised visually, using differential scanning calorimetry (DSC) and with scanning electron microscopy (SEM). Optimal geo-polymeric wafers contained 1.5% W/W CAR 812 with 2% LAP RDS and 1% W/W intercalated STH. DSC and SEM results indicated the amorphous form of STH was intercalated in LAP RDS within the leafy structure of CAR 812. This xerogel hydrated up to 1700% within 40 minutes and released the STH by Higuchi kinetic model.

**Keywords:** Polymer; Clay, Intercalation, Xerogel, Wound delivery, Amorphous, Physicochemical characterisation, Polymers, hydrogel, drug delivery, lyophilised wafer.

## Abbreviations

STH (Sulfathiazole), LAP (Laponite), MMT (montmorillonite), CAR (carrageenan), HEC (hydroxyethyl cellulose), DSC (differential scanning calorimetry), SEM (scanning electron microscopy), polyethylene glycol (PEG).

## Introduction

Drug-delivery systems composed of natural materials have become increasingly important because of their nontoxicity and biodegradability [1]. Amongst the diverse range of natural materials investigated for this purpose, clays have demonstrated useful properties for pharmaceutical, clinical and general health applications attracting increasing interest over the last decade; although the therapeutic effects of clays have been referred to from prehistoric times [2, 3].

Montmorillonite (MMT) and refined MMT are natural clay minerals with a high internal surface area, high cation exchange capacity, high adsorption ability, and low toxicity [4]. Due to the negatively charged layers, the swelling of these clays in the presence of water is high and positively charged species can be intercalated into the interlayer spaces via electrostatic interactions. Laponite® (LAP), a synthetic layered silicate with the chemical formula  $\text{NaC}_{0.7}[(\text{Si}_8\text{Mg}_{5.5}\text{Li}_{0.3})\text{O}_{20}(\text{OH})_4]^{-}\text{K}_{0.7}$  is composed of disc-shaped nanoparticles of 25 nm diameter and 1 nm layer thickness [5]. Some octahedral magnesium ions in the octahedral sheets are replaced with lithium ions so

negatively charged layers are present which are compensated for with exchangeable sodium ions in the interlayer space. The film forming ability of these materials is a desirable property for the development of mucosal films for novel drug delivery systems [6]. Tixogel VZ and VP are synthetic organophilic clays with high thixotropic properties and can be used as anti-settling agents in low polarity systems. They can be dispersed in alcohols or ketones following a high agitation process [7].

The use of clay minerals for human health is not restricted to pharmaceutical excipients and cosmetics [8] as recently clays have demonstrated potential as carriers for the delivery and extended release of a variety of drugs [9]. Studies on the mobility of chemical elements from healing clays to the human body during topical applications and ingestion were undertaken by [6, 10, 11]. Many formulations are based on the intercalation of molecules between the interlayer spaces of the clay enabling the incorporation of either hydrophilic or hydrophobic drugs via the exchange of small two dimensional organic molecules, inorganic and organic ions or polymeric ions with the ions originally present within the clay structure [12, 13]. For example Beak, et al. [14] intercalated glutathione in montmorillonite for antioxidant delivery with the aim of protecting the drug molecules from chemical and enzymatic hydrolysis following oral ingestion. Ibuprofen, the most common medicine for rheumatoid arthritis, osteoarthritis and moderate pain treatment, was intercalated in montmorillonite to minimize side effects [15]. The intercalated formulation controls the drug release and minimizes frequent side effects within the gastrointestinal tract and the ulcerogenic effect [16].

Clay:polymer nanocomposites are widely used in the materials industry where the addition of clay can be used to enhance the physical and engineering properties of a material [17] and there is increasing interest in the use of clay-polymer composites for pharmaceutical applications such as tissue engineering and drug delivery [9, 18]. Although individually, both biopolymers and clays are present in many drug delivery systems a hybrid of the two can provide enhanced properties to a drug delivery matrix such as improved water uptake, increased mechanical strength, improved rheology and modified drug release.

Carrageenan and hydroxyethyl cellulose (HEC) are both natural products commonly used for the formulation of drugs. More recently they have been used to prepare buccal [19] and lyophilised xerogels [20] for drug delivery and wound healing [20, 21]. Lyophilised xerogels are shaped hydrophilic polymer glasses that adhere to the wound, adsorb fluid and form a viscous gel releasing any drugs contained within.

In this present study a model drug, Sulfathiazole (STH, figure 1), was intercalated into various clays (LAP, MMT, refined MMT, Tixogel VZ and Tixogel VP) and then incorporated into a natural hydrogel consisting of either carrageenan or hydroxyethyl cellulose. The gels were subsequently lyophilised to form a dry xerogel. The composition of the xerogel was varied in terms of type and quantity of clay, polymer and drug to produce a matrix with optimal properties for wound healing and drug delivery applications. STH (pKa=7.2), an antimicrobial

drug, is a weak acid with extremely low solubility in water (LogP=0.35). Formulation methodology was developed and optimal conditions (hydration time, pH, and clay concentration) for an even distribution of the drugs and clays within the aqueous polymeric matrix were realised by intercalating STH into the interlayers of refined MMT and various grades of LAP.

Figure

1

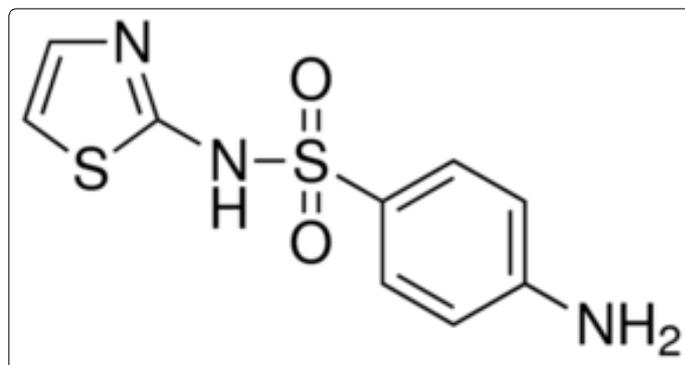


Figure 1. Chemical structure of Sulfathiazole (STH).

## Experimental and Methods

### Materials

MMT, refined MMT, various Tixogels (VP & VZ; CAS: 67479-91-8) and all LAP grades (CAS: 227605-22-3, XL21, RDS, RD and WXP) were kindly gifted from BYK(Widnes, UK). Sulfathiazole (STH; CAS: 72-14-0, batch number: 053K3451) and Chitosan medium molecular weight (CAS: 9012-76-4, batch number: MKBH1108V) were purchased from Sigma Aldrich. The PEG 1500 (CAS: 25322-68-3, batch number: ZA3726628) was purchased from BDH and Hydroxyethylcellulose (CAS: 9004-62-0, batch number: P-0189) from Aqualon Hercules. Carrageenan 812 (CAS: 9000-07-1 232, Gelcarine) was kindly gifted from FMC BioPolymer company.

### Dispersion of clays

A gradual ratio of MMT, refined MMT, Tixogels or various LAP grades [0.5-20%(w/w)] were added to 50 mL deionized water in separate beakers (200 mL) and stirred vigorously at 800rpm for 30 minutes at room temperature. The visual properties were inspected and initial pH determined before the drop wise addition of 1M NaOH or HCl while recording the pH accordingly. In order to enhance the solubility and obtain an even dispersion of 0.5-1.5% (w/w) MMT and Tixogels within the system, a gradual volume of ethanol (2-20 mL) was added while the mixture was constantly agitated. Furthermore, 0.5-1.5% (w/w) MMT or Tixogels were dispersed in 20 mL ethanol or propanol and the physical properties evaluated.

### Intercalation of STH into MMT and LAP

A 2% dispersion of clay (LAPs and MMT) was produced by adding the clay to deionized water while agitating vigorously (800rpm) at room temperature for 30 minutes. Then STH (0.2-1g) was slowly added to this dispersion with the gradual addition of 3 mL NaOH to ionize the drug with on-going agitation for a further 45 minutes. To reduce the time required for the intercalation process a second technique was employed

where the drug was ionized prior to addition to the clay dispersion; STH (0.2-1g) was dissolved in 3 mL of NaOH and the ionized drug solution added to 47ml of the 2% (w/w) refined MMT or LAP dispersion and stirred (800rpm) at room temperature for 10 min. This process was repeated at 40°C.

### Gel preparation

Polymers [1-4% PEG 1500, 1-4% Hydroxyethyl cellulose, 0.5-1.5% K-carrageenan 812 (CAR), and 0.5-2% Carbopol 940] were added to 50ml deionized water with stirring (500rpm) at 40°C for 20 minutes. The dispersion of 1-2.5% chitosan required acidic conditions so 0.5-2% medium molecular weight chitosan was added to deionized water and HCl (1M) added dropwise to pH 1-2 to obtain a transparent gel.

### Polymer-clay hydrogel preparation

Two different techniques were compared for the preparation of drug containing polymer-clay hydrogels.

1. Polymer dispersions were prepared (according to section 2.4) and solid clay added (2% w/w) with stirring at 800 rpm and 40°C until the clay was completely dispersed in the polymeric matrix. Then the ionized drug (0.2-1g in 3ml NaOH) was introduced to the system with stirring for 10 minutes.
2. A polymer dispersion was produced using half the required total volume of deionised water (gel preparation section) and a clay dispersion with intercalated drugs prepared using the other half (as described in intercalation section). Then the polymer dispersion was added to the clay dispersion with stirring hence maintaining the same final concentrations of components.
3. Finally, a gradual concentration of STH (0.2-1g) was dissolved in 2 mL ethanol and added to the 2% LAPs and refine MMT dispersions with on-going stirring.

### Formulation of drug delivery system

Following the even distribution of clay and drug within the polymeric matrices, potential forms of drug delivery systems were evaluated. The hydrogels were divided into three equal portions and treated as follows:

- a) Left as a hydrogel.
- b) Oven dried in a petri dish at 40°C for 24 hours.
- c) Lyophilised in a six-well tissue culture plate for 24 hours at -50°C (Mini-LyotrapFD/85002 freeze dryer).

### Differential Scanning Calorimetry (DSC)

Samples were analysed using a PE DSC8000 (Perkin Elmer, Bucks., UK) and Pyris software to investigate the stability of the materials during the gel formation and lyophilisation processes. The DSC was calibrated using standard reference materials of indium (melting temperature 156.6°C,  $\Delta H_f$  28.45 J g<sup>-1</sup>) and zinc (melting temperature 419.47°C).

Samples of 3 - 10 mg were accurately weighed into standard aluminium sample pans, crimped and placed into the DSC with a blank crimped standard pan as reference. The samples were analysed using a cool-heat cycle with a scan rate of 10°C min<sup>-1</sup> throughout and a 20 ml min<sup>-1</sup> nitrogen

purge. The method was as follows for MMT, HEC, CAR 812 and LAP RDS: i) initial temperature 25°C, hold for 1 minute, ii) cool to -50°C, hold for 1 minute iii) heat to 350°C, hold 1 minute, iv) re-cool to -50°C, hold for 1 minute v) final re-heat to 350°C, hold for 1 minute. The method was modified using a maximum temperature of 205°C for analysis of STH and 200°C, for the optimal xerogels.  $T_m$  and  $T_g$  values were calculated using extrapolated onset values from endotherms or exotherms and extrapolated half cp values, respectively.

### Scanning electron microscopy

Scanning electron microscopy (SEM) was used to evaluate the topographic characteristics and morphology of the xerogels. The analyses were carried out using a JeolJSM-6490LV Instrument (Tokyo, Japan) with back-scattered electrons and artificial shadowing ability for uncoated samples at low vacuum (520 Pa) and an accelerating voltage of 20 kV.

### Hydration and swelling studies

This study was conducted to investigate the maximum time required for complete hydration as well as the maximum swelling capacity of the xerogel using phosphate buffer solution (pH=7.5) to mimic wound fluid. Samples were cut to 2 cm×2 cm pieces, weighed and placed in 50 mL of the buffer media. The weight change in the sample was measured by removing the sample, blotting, then weighing every 10 minutes until a constant weight was maintained. The % swelling (% weight change) for the polymeric matrices was calculated using equation 1 where  $W_0$  and  $W_t$  are the weights of the xerogel initially and at time t respectively. Each data point represents the mean ( $\pm$  s.d), of three replicates.

$$\% \text{ Swelling} = (W_t - W_0) / W_0 \times 100 \quad \text{Eqn 1}$$

### Drug release studies

STH release studies were performed at 37°C using phosphate buffer (pH = 7.2) in a dissolution bath. Approximately 0.2-0.3g of lyophilised xerogels were placed in 50 mL phosphate buffer to simulate the wound surface fluid secretion and dispersed for 4 hours. Dissolution media samples were taken at 2 min intervals from time zero. The amount of STH released (mg) was calculated by UV spectrometry ( $\lambda=283$  nm) and cumulative percentage release versus time profiles plotted. The kinetics of STH release from the geo-polymeric xerogel was assessed by fitting the dissolution data (percentage cumulative release against time) to the Higuchi, Hixon-Crowell, Korsmeyer-Peppas, first or zero order equations in order to determine the drug release mechanism. As a model-dependent approach, the dissolution data was fitted to five common release models i.e. zero order, first-order, Higuchi, Hixon-Crowell and Korsmeyer-peppas equations. The kinetic model with the highest coefficient correlation (r) was assumed to be the most appropriate model for the dissolution data.

## Results and Discussion

### Visual evaluations

Preliminary visual observations were performed on the initial clay dispersions, polymeric gel, dried films and lyophilised

xerogels to evaluate them in terms of; ease of pouring, stability, flexibility and the even distribution of the components within the matrix with no air bubbles in the films. The fragility and brittleness of a matrix impacts on the physical and mechanical stability during handling and storage. For wound healing applications, a xerogel must also be soft and flexible to provide the desirable mechanical strength during handling and comfort upon the application without potential irritation [22]. In addition, an ideal xerogel should have an optimum thickness of less than 1mm as thicker preparations maybe difficult to apply without disturbing the wound surface. Thickness also affects both the rate of hydration and the diffusion distance of the drug through the resulting swollen gel which can have significant effects on drug release profiles [20, 21].

The maximum concentration of the different clays which could be dispersed evenly in deionized water is shown in table 1 and the highest ratio achieved was 20% LAP RDS. However at these concentrations, the viscosity of the hydrogels increased dramatically resulting in thick gels containing air bubbles that were not easy to pour. The optimum concentration of refined MMT and LAPs that could be dispersed in water with the desirable viscosity was determined to be 2% (figure 2). Interestingly, during the dispersion process applying heat reduced the dispersion time and produced LAPs hydrogels with a more desirable transparency and flow-ability. Therefore, for the next stage the various grades of LAPs and refined MMT were assessed for drug intercalation and incorporation into hydrogels.

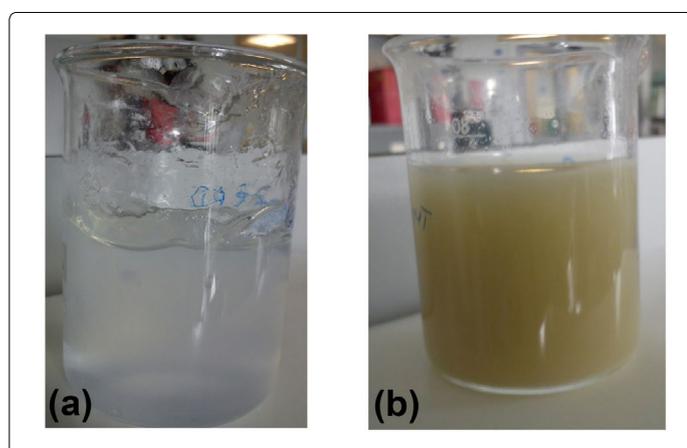


Figure 2. 2% pure (e) Laponite and (f) refine MMT dispersion.

The Tixogels (VZ and VP) which are organic in nature and MMT did not disperse in aqueous media (table 1) but dispersed in pure organic solvents such as ethanol or isopropyl alcohol. However, for pharmaceutical applications this is not acceptable as a consequence of potential toxicity or irritations. Furthermore,

the addition of a small quantity of deionised water resulted in the precipitation of the clays producing two separated phases.

All the clays assessed were basic in nature and the initial pH of the aqueous dispersions was approximately pH=9. STH is also a weak acid so ionization required basic conditions to feasibly accommodate it between the interlayer spaces of clays via ion exchange. The addition of STH shifted the pH to around 11. This basic pH of the clay-drug combination had a direct impact on the miscibility within the polymeric matrixes. It was also observed that increasing the pH of the clay dispersion increased the viscosity, whereas in acidic condition the reverse occurred (table 1) and this impacted on the stability of the hydrogel during storage and the lyophilisation process.

A range of polymers were selected for the preliminary hydrogel formulation studies (table 2). Carbopol 940 and low MW chitosan required acid conditions to fully disperse in water which disintegrate the clay-drug dispersion. Table 2 demonstrates that HEC, Carrageenan and PEG 1500 all produced transparent hydrogels within a pH range of 6-7 so it was concluded that basic or neutral polymers would be the most compatible clay-containing matrices for future studies. The viscosity of the hydrogel is also very important and very low viscosity polymeric hydrogels are not desirable as they can show phase separation during storage at room temperature. For example, the gel comprising of 10% PEG 1500, 2% LAP and 1% STH separated due to the low viscosity of PEG 1500 which enabled the clay and drug to drift to the bottom of the container. This also occurred when the concentration of HEC was 1%, producing a gel with low viscosity which also phase separated. The viscosity of the polymeric matrix needs to be high enough to entrap the clay and drug providing an even distribution of all the components during storage.

From the preliminary studies, the hydrogel systems with the most desirable properties consisted of either 3% HEC, 2% LAP or MMT or 1.5% CAR and 2% LAP or MMT in combination with 1% drug. These were remade and split into 3 portions; a hydrogel, a dryfilm and a lyophilised xerogel. In both cases, the hydrogel system remained stable after 1 month storage at room temperature with an even distribution of the components (Figure 3a and b). The dried film was extremely brittle and hence did not meet the criteria which is a soft and robust texture to be mechanically stable and convenience for wound healing applications. So it was not considered further as a potential drug delivery system (Figure 3c and d).

Table 1. Physico-chemical characteristics of clays' dispersions in deionized water also basic and acidic condition (pH=1-2& pH=13-14).

| Maximum clay (% w/w) | Initial pH | Initial characteristics            | Acidic pH characteristics | Basic pH characteristics  |
|----------------------|------------|------------------------------------|---------------------------|---------------------------|
| 5 % Laponite RD      | 9.21       | Transparent, viscose gel           | Transparent, viscose gel  | Transparent, viscose gel  |
| 0.5% Tixogel VZ      | NA         | Suspension, quickly separated      | Sit on the aqueous phase  | Sit on the aqueous phase  |
| 4% Refined MMT       | 9.32       | Stable suspension, not transparent | Stable suspension, opaque | Stable suspension, opaque |
| 0.5% MMT             | NA         | Suspension, quickly separated      | Sit on the aqueous phase  | Sit on the aqueous phase  |
| 20% Laponite RDS     | 9.2        | Transparent solution               | Transparent solution      | Transparent solution      |
| 4% Laponite WXFP     | 9.59       | Viscose gel, transparent           | Viscose gel, transparent  | Viscose gel, transparent  |
| 4% Laponite XL21     | 9.39       | Transparent solution               | Transparent solution      | Transparent solution      |
| 0.5% Tixogel VP      | NA         | Suspension, quickly separated      | Sit on the aqueous phase  | Sit on the aqueous phase  |

Table 2. Characteristics of polymers in aqueous media

| Maximum (%w/w) Polymers   | pH    | pH stability | Characteristics                                   |
|---------------------------|-------|--------------|---|
| 2% Carbopol 940           | 4-5   | 3.5-10       | Yellowish transparent, good viscosity gel         |
| 3% Hydroxyethyl Cellulose | 6-8.5 | 3-10         | Clear and transparent gel, high viscosity         |
| 1.5% K-Carageenan 812     | 5-6   | 4.3-12       | Yellowish transparent gel, good viscosity gel     |
| 10% PEG 1500              | 5-7   | 4-9          | Transparent, very low viscosity gel               |
| 2% Chitosan Medium MW     | 4-6   | 2.3-6.3      | Yellowish transparent, good viscosity gel at pH=2 |

Table 3. Visual characteristics of clays' dispersions in the polymers' matrices

| 2% (w/w) clay | Polymers (%w/w) | Characteristics  |
|---------------|-----------------|--|
| Laponite RD   | 2% HEC          | Transparent, low viscosity gel                         |
| Refined MMT   | 2% HEC          | Yellow cloudy gel, low viscosity                       |
| Laponite RDS  | 2% HEC          | Transparent, low viscosity gel                         |
| Laponite WXFP | 2% HEC          | Transparent, low viscosity gel                         |
| Laponite XL21 | 2% HEC          | Transparent, low viscosity gel                         |
| Laponite RD   | 3% HEC          | Transparent, good viscosity                            |
| Refined MMT   | 3% HEC          | Yellow cloudy gel, good viscosity                      |
| Laponite RDS  | 3% HEC          | Transparent, good viscosity                            |
| Laponite WXFP | 3% HEC          | Transparent, good viscosity                            |
| Laponite XL21 | 3% HEC          | Transparent, good viscosity                            |
| Laponite RD   | 1.5% CAR        | Transparent, good viscosity                            |
| Refined MMT   | 1.5% CAR        | Yellow cloudy gel, good viscosity                      |
| Laponite RDS  | 1.5% CAR        | Transparent, good viscosity                            |
| Laponite WXFP | 1.5% CAR        | Transparent, good viscosity                            |
| Laponite XL21 | 1.5% CAR        | Transparent, good viscosity                            |
| Laponite RD   | 2% CAR          | Transparent, high viscosity, trapped air bubbles       |
| Refined MMT   | 2% CAR          | Yellow cloudy gel, high viscosity, trapped air bubbles |
| Laponite RDS  | 2% CAR          | Transparent, high viscosity, trapped air bubbles       |
| Laponite WXFP | 2% CAR          | Transparent, high viscosity, trapped air bubbles       |
| Laponite XL21 | 2% CAR          | Transparent, high viscosity, trapped air bubbles       |

However, the lyophilised xerogels, in particular the HEC based ones, showed good physical properties in terms of softness and flexibility (Figure 4 a, b and c). A wound delivery system should be soft and flexible enough to prevent discomfort and potential damage to the wound surface while possessing sufficient stability to remain durable during the application. The CAR based xerogels were dried completely after 24 hours freeze-drying but the rigidity was high and would require the addition of a plasticizer to be appropriate as a desirable wound delivery system (Figure 4d and e).

**Differential scanning calorimetry (DSC)**

DSC traces for the raw materials showed that no melting endotherms were detected for CAR 812, LAP RDS, refined MMT or HEC, although broad endotherms between 50° C-150° C indicated moisture loss. The large exothermic event at 214° C observed for CAR 812 confirmed the onset of degradation. During the first heating cycle three sharp endothermic peaks with extrapolated onset temperatures at 166.51° C, 173.66° C and 201.08° C were observed from STH (form III (T<sub>m</sub>), transition of form III and form I(T<sub>m</sub>)), respectively. However, after quench cooling these crystalline forms became amorphous due to the instability of polymorphs and a glass transition temperature (T<sub>g</sub> at half cp) was detected at 63.29° C (figure 5a).

The optimal xerogels were also analysed by DSC (figure 5b-5e). The DSC thermograms from 3% HEC, 2% LAP RDS and 1% STH- 3% HEC, 2% MMT, 1%STH- 1.5% CAR, 2% LP RDS, 1%STH as well as 1.5% CAR, 2% MMT, 1%STH showed only moisture loss indicating that the STH was in the amorphous form in all of them.

The absence of STH melting peaks in DSC thermograms of xerogels showed that during the formulation process including intercalation, heating, stirring, mixing with hydrogels or lyophilisation, all the STH polymorphs were converted to the amorphous form of the drug.

In figure 5b & 5c, the glass transition point may be masked by the broad endotherm peak due to moisture loss from the MMT and HEC.

Additionally, the thermograms in figures 5d & 5e are demonstrating the broad endotherm peak due to moisture loss from the LAP and MMT and a sharp peak endothermic superimposed with onset around 87° C, followed by an exothermic event at around 160° C indicating that the matrix stability has decreased and the geo-polymeric xerogel degraded, probably due to the presence of the CAR 812.

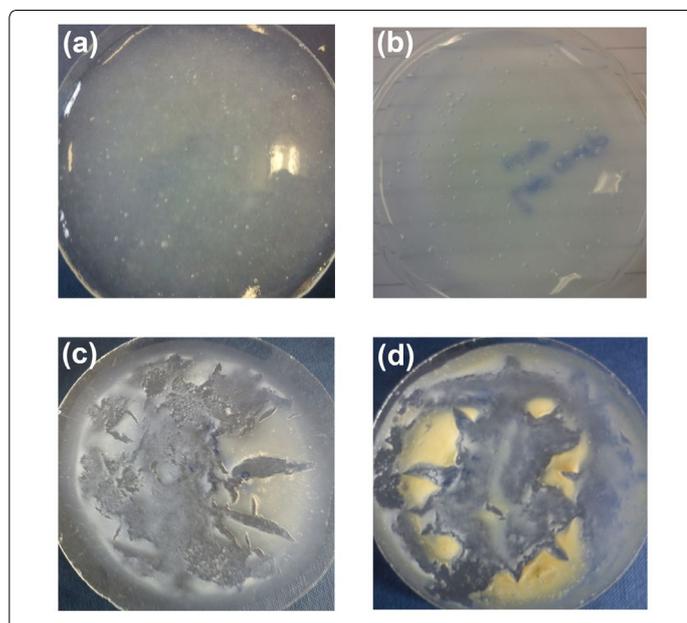
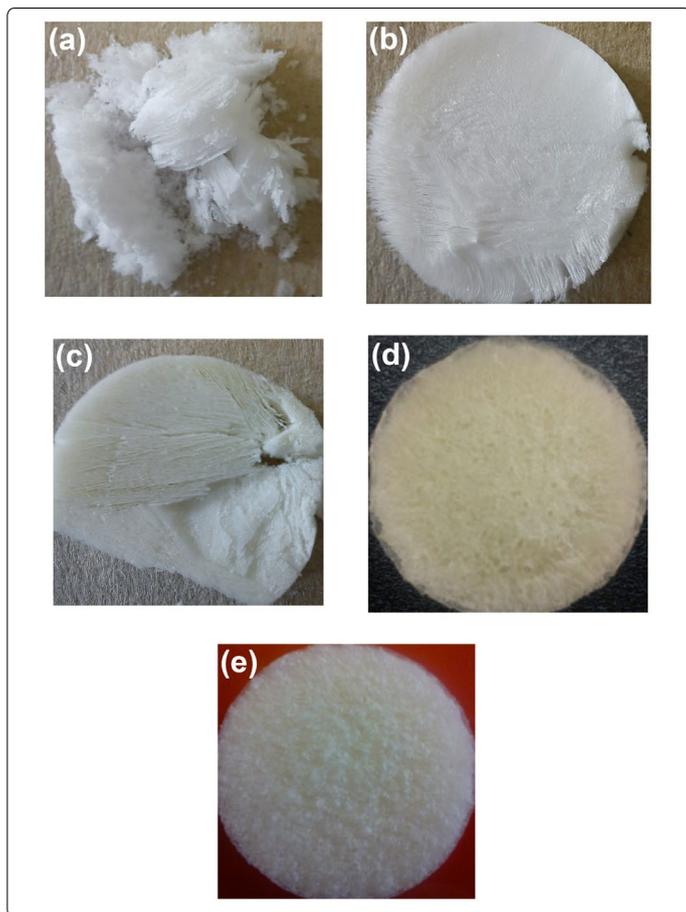
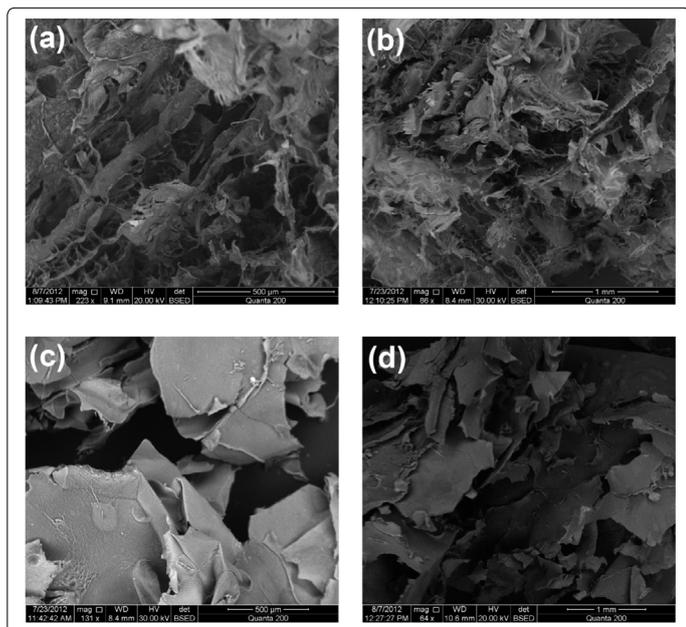


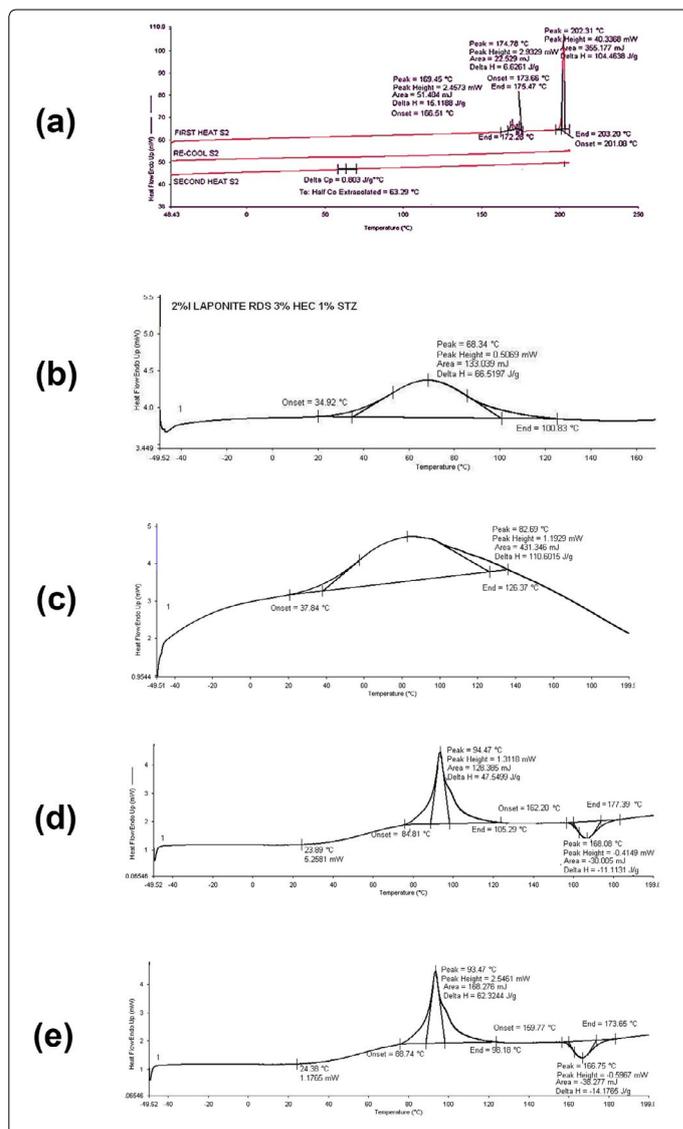
Figure 3. Demonstrate the images of hydrogels contain (a) 3% w/w HEC + 2% w/w Laps + 1%w/wSTH, (b) 3% w/w HEC + 2% w/w refine MMT + 1% w/w STH and dried film of (c) 3% w/w HEC + 2% w/w Laps + 1% w/w STH (d) 3% w/w HEC + 2% w/w MMT + 1% w/w STH



**Figure 4.** Representative digital images of xerogel prepared from hydrogels comprising (a) 3% w/w HEC + 2% w/w Laps + 1% w/w STH, (b) 3% w/w HEC + 2% w/w refine MMT + 1% w/w STH, (c) 3% w/w HEC + 2% w/w refine MMT + 1% w/w STH, (d) 1.5% w/w CAR + 2% w/w refine MMT + 1% w/w STH, (e) 1.5% w/w CAR + 2% w/w LAP RDS + 1% w/w STH



**Figure 6.** Demonstrating SEM images of xerogel prepared from hydrogels comprising (a) 3% w/w HEC + 2% w/w refined MMT + 1% w/w STH, (b) 3% w/w HEC + 2% w/w refine MMT + 1% w/w STH, (c) 1.5% w/w CAR + 2% w/w LAP RDS + 1% w/w STH, (d) 1.5% w/w CAR + 2% w/w LAP RDS + 1% w/w STH



**Figure 5.** Representative DSC thermograms of xerogel prepared from hydrogels comprising (a) Sulfathiazole (STH), (b) 3% w/w HEC + 2% w/w LAP RDS + 1% w/w STH, (c) 3% w/w HEC + 2% w/w refine MMT + 1% w/w STH, (d) 1.5% w/w CAR + 2% w/w LAP RDS + 1% w/w STH, (e) 1.5% w/w CAR + 2% w/w refine MMT + 1% w/w STH

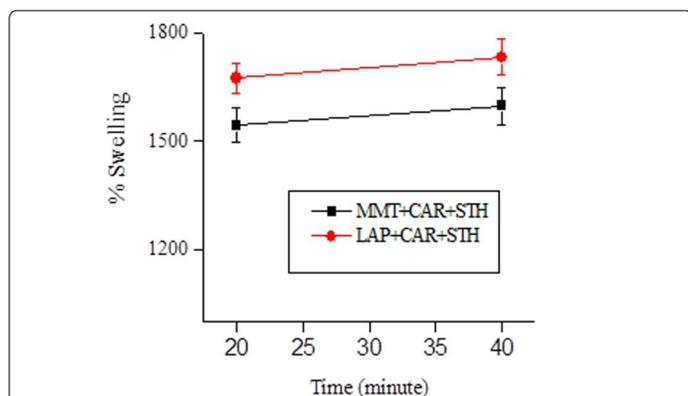
The results illustrate the effect of either formulation process or the amorphous nature of CAR or LAP RDS on transformation of crystalline STH to amorphous form which needs to be investigated. This can accelerate the release of STH from the matrix due to its higher solubility over crystalline form [23, 24].

### Scanning electron microscopy (SEM)

SEM was employed to assess the surface morphology of the lyophilised geo-polymeric xerogels and observe the effect of the microstructure on the swelling properties. According to the SEM data (Figure 6a-d), the presence of CAR 812 resulted in a more compact, leafy structure with smaller pores compared to the larger pores in observed in the HEC materials. These pores potentially provide extra spaces for occupation by the active compounds, increasing drug loading and also enabling faster water ingress consequently affecting the release of the drug after administration [19].

**Hydration and swelling studies**

It was observed that when the geo-polymeric xerogels comprising HEC were immersed in buffer (pH=7.2) they swelled vigorously within 10 min (figure 7). The complete demolition of the xerogel structure and resultant dispersion of fine pieces within the media made the measurement of weight gain impossible. The complete hydration of CAR 812 based xerogel occurred over 40 minutes and the discs remained intact due to their morphology and more impenetrable structure. The overall weight gain after 40 min reached 1700% and 1550% of initial weight for CAR based xerogels comprising LAP RDS and MMT respectively.



**Figure 7.** Swelling graph of xerogel comprising 3% w/w HEC+ 2% w/w refined MMT + 1% w/w STH, and 1.5% w/w CAR+ 2% w/w LAP RDS + 1% w/w STH

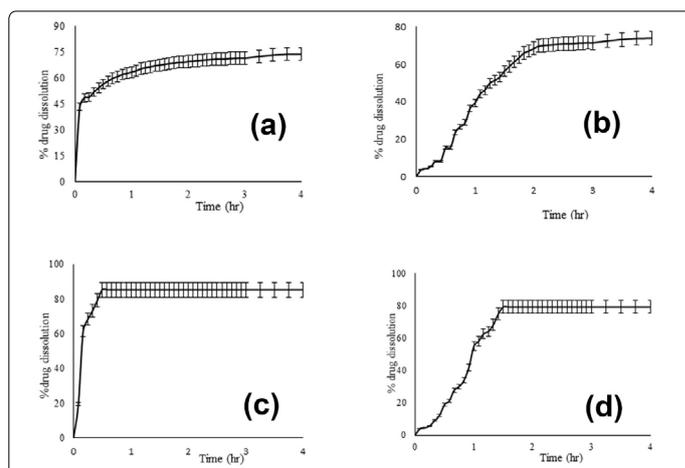
Following the placement of a polymeric xerogel matrix in a moist environment (such as the wound mucosa), the swelling process begins by the ingress of water or body fluids. In the early stages, water penetrates into the xerogel due to a concentration gradient which results in mobility enhancement of the polymer chains and hydration of the clays. This phenomenon increases the macromolecular mobility at a specific clay-polymer-water concentration. Subsequently the clay's hydration and polymer chains relaxation (hydration) increase the water content and mesh size of the clay: polymer network within the formulation. The relaxation step for CAR 812 based systems will be accelerated as the polymer's  $T_g$  of CAR is below the temperature of the swelling media.

In addition, the effect of CAR 812 on hydration profiles was more dominant compared to HEC which is attributed to differences observed in the micro-structure observed in the SEM images. According to the SEM results (Figure 6a-6d) the presence of CAR 812 resulted in xerogels with smaller pores and therefore, less capacity for water ingress and consequently they were hydrated to a lesser extent.

**Drug release**

The release profile of STH from 2% MMT, 3% HEC, 1% STH also 2%MMT, 1.5% CAR, 1%STH and 2% LAP RDS, 1.5% CAR, 1% STH as well as 2% LAPS, 3% HEC, 1% STH samples are demonstrated in Figure 8. The mechanism of STH release from hydrophilic polymeric matrices (CAR or HEC) involves solvent penetration, hydration and swelling of the CAR or HEC, diffusion of the dissolved STH from the geo-polymeric matrices, and erosion of the hydrogel layer. Primarily, the

diffusion coefficient of drug in the dehydrated CAR or HEC matrix is low but it rises considerably as time progresses and the CAR and HEC imbibe more water and form gels.



**Figure 8.** Dissolution graph of xerogel comprising (a) 3% w/w HEC+ 2% w/w refine MMT + 1% w/w STH, (b) 1.5% w/w CAR+ 2% w/w LAP RDS + 1% w/w STH (c) 3% w/w HEC + 2% w/w LAP RDS + 1% w/w STH and d)1.5% w/w CAR + 2% w/w refine MMT + 1% w/w STH.

Various parameters such as hydrogel composition (type of polymer, type of drug and excipients), geometry (size and shape), preparation technique and the drug release conditions affect the kinetics of drug release [25]. These phenomena stimulate the wetting of the drug delivery system to facilitate the ingress of the medium. The degradation of the polymer promotes diffusion of drug through the polymer matrix, hence CAR with more cross-links and higher density absorbs less water and subsequently releases the STH considerably slower than the HEC matrix.

The coefficient ( $r^2$ ) value for 5 different kinetic models is shown in table 4. A comparison of the  $r^2$  values confirm that STH is released from the 3% HEC, 2%MMT and 1.5% CAR 812, 2% LAP matrices according to the Hixson-Crowellkinetic model (eqn 2) whereas the Higuchi kinetic model (eqn 3) determines the release of STH from 1.5% CAR 812, 2% MMT and 3%HEC, 2% LAP RDS samples.

**Table 4.**  $r^2$  value for the variousKinetic model of STH release from geo-polymeric matrixes

| Release kinetic | S1    | S2    | S3    | S4    |
|-----------------|-------|-------|-------|-------|
| Zero order      | 0.692 | 0.943 | 0.924 | 0.809 |
| First order     | 0.771 | 0.915 | 0.873 | 0.595 |
| Higuchi         | 0.870 | 0.982 | 0.824 | 0.933 |
| Hixson- Crowell | 0.975 | 0.971 | 0.976 | 0.634 |
| Peppas          | 0.634 | 0.869 | 0.734 | 0.835 |

S1:2% MMT, 3% HEC, 1% STH; S2:2%MMT, 1.5% CAR, 1%STH; S3: 2% LAP RDS, 1.5% CAR, 1% STH

S4: 2% LAPS, 3% HEC, 1% STH

$$3\sqrt{Q_0} + 3\sqrt{Q_t} = M_{HC} t \quad \text{Equation2: Hixson-Crowell}$$

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \quad \text{Equation3: Higuchi}$$

It is assumed in Hixson-Crowell release kinetics that the release rate is limited by the dissolution rate of the drug particles and not by diffusion through the polymeric matrix; this model describe the release profile considering the diminishing surface

of the drug particles during the dissolution [26]. The Hixson-Crowell cube root law describes the release of the STH from xerogels where the surface area and diameter of delivery system is critical. The dissolution rate of STH from the surface of geo-polymeric systems is proportionally to diminishing polymers (CAR or HEC), in such a manner that the initial geometrical form remains constant [27].

The Higuchi kinetic model however describes the STH release as a diffusion process based in the Fick's law, square root time dependent [28]. Fickian diffusion refers to the STH transport process where the polymer relaxation time ( $t_r$ ) is much greater than the characteristic solvent diffusion time ( $t_d$ ). This equation has been used successfully to describes the experimentally observed in vitro release STH from polymers (HEC and LAP RDS or CAR 812 and MMT) where erosion or swelling of the polymeric matrix does not contribute to drug release during the short time period [29, 30].

Overall, in both kinetic models, the release of STH from CAR and HEC involves water diffusion and chain disentanglement at the final stage. Though the polymer dissolution does not result in the scission of polymer chains, it results in the loss of bulk material. CAR 812 and HEC experience dissolution in the aqueous medium due to water penetration effect, swelling, and polymer chain disentanglement and relaxation. The fractional release of STH from xerogels consisting of HEC and CAR 812 matrices corresponded well with the fractional release of HEC and CAR812, indicating drug release is primarily driven by dissolution and followed by erosion [31].

## Conclusion

These results demonstrate that due to strong cross-linked polymer chains CAR 812 sustains the release of STH from the geo-polymeric matrices for up to 2 h due to the prolonged hydration of the matrix. This favours the delivery of STH to wound surfaces from CAR 812 matrices over the extremely fast hydration and drug release from the HEC based geo-polymeric matrices which would also be displaced from the wound surfaces due to the generation of a slippery residue following the fast polymer degradation.

Overall, a comparison of the four optimized xerogels demonstrated that the matrix comprising 1.5% CAR 812, 2% LAP RDS and 1% STH possessed the most desirable stability, swelling and drug release for wound deliver applications. The DSC results confirmed that any STH present was in an amorphous form, which supports data from dissolution studies that confirmed the effect of the drug dissolution rate on release kinetic. The presence of the STH in amorphous form increased the dissolution rate which can be advantageous where the purpose of the application is obtaining the fast release of antibiotic from the wound delivery system. However it might be not desirable if the drug release should be prolonged and over a longer period of time. Ideally, the most efficient system in order to deliver the antibiotic to the wound surfaces should be capable to release the drug rapidly after the application followed by a gradual release over the time [32]. This will be obtained by designing the most optimised combination of hydrogel polymer and clay to develop a stabilized geo-polymeric matrix.

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