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Sequential design of a novel PVA-based crosslinked ethylenic homopolymer for extended drug delivery

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Abstract

A Box–Behnken Design was employed to study the influence of boric acid, sodium sulfate, ammonia and *n*-propanol in the formulation of crosslinked ethylenic homopolymeric (CEH) gelispheres from native polyvinyl alcohol (PVA). The dependent variables studied included the size of the spherical gelispheres, drug encapsulation efficiency, in vitro dissolution after 30 min and textural parameters, namely fracture force and matrix rupture energy. Based on these responses, an optimized CEH gelisphere matrix was formulated and thereafter incorporated as a powder into a candidate crosslinked zinc–pectinate multiple-unit device to assess its effect on modifying drug release. In the case of the CEH-loaded zinc–pectinate gelispheres, it was determined via constrained optimization that a maximum drug encapsulation efficiency of 28.63% could be obtained under the conditions of 0% (w/v) CEH, 13 h of crosslinking and drying temperature of 60 °C. On the other hand, initial drug release could be significantly retarded when 0.10% (w/v) of CEH was included in the formulation and crosslinked for 24 h at 40 °C. In this regard, CEH induced a 4 h lag phase. Furthermore, zero-order drug release was produced and could be maintained over several weeks. Kinetic analysis of drug release further supported that CEH inhibits polymer relaxation ($k_2 \ll k_1$), and hence slows down drug diffusion. Based on these results, the CEH-zinc–pectinate drug delivery system appears to be a suitable carrier that may be employed for long-term administration for, e.g. via subcutaneous implantation.

Keywords: Polyvinyl alcohol; Crosslinked ethylenic homopolymeric gelispheres; Experimental Design

1. Introduction

Polyvinyl alcohol (PVA) and its copolymers have found various applications in controlled drug release (Diluccio et al., 1994; Orienti et al., 2000, 2001; Soppimath et al., 2000; Doria-Serrano et al., 2001; Yin Win and Feng, 2005). Despite their high water con-

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tent, PVA hydrogels have been reported to be useful for the release of both hydrophobic and hydrophilic drugs (Shaheen and Yamaura, 2002; Kuntsche et al., 2004; Moretto et al., 2004). Since PVA is hydrophilic and easily swells upon hydration, some grades (based on molecular weight) have shown volume expansion up to 500% at 37 °C (Morita et al., 2000). However, this expansion can be inhibited by swelling controlling agents such as electrolytes. Based on this unique property of PVA, different types of controlled release systems could be developed, whereby the release rate is controlled by the content of PVA, the content of swelling controlling agent incorporated into the matrix core and the application of film coatings (Morita et al., 2000; Hsu et al., 2001; Kwok et al., 2004). During the initial stage of drug release, the rate is determined by water permeation through the film coating. However, when the film bursts as a result of swelling, the release rate is controlled by the matrix, which typically produces traditional first-order or square root kinetics.

To prolong drug release from the inherently hydrophilic network, PVA may be crosslinked to reduce its macromolecular pore size available for diffusion. The crosslinking process can be carried out either before or after drug loading, the former process being preferred since further possible side reactions between the drug and crosslinking agent may additionally reduce its diffusion (Korsmeyer and Peppas, 1981; Ahlin et al., 2002; Huang et al., 2002).

The crosslink density affects the size of the macromolecular pores of the hydrogel network and thus the water content, which is responsible for the transport (efflux) of solute molecules (Kotha et al., 1998; Pillay et al., 2002; Ostroha et al., 2004). The diffusion coefficient can be linearly increased for solute molecules by increasing water content in the hydrogel, thereby indicating that diffusion occurs primarily through hydration of the network (Burczak et al., 1994; Katzhendler et al., 2000).

It is well known that the reaction between PVA and boric acid results in an incompatibility which is manifested as a polymeric “sludge”. However, to date, this reaction has not been fully explored to synthesize a “useful sludge” for oral drug delivery, and hence became the objective of this study. The overriding motive was to optimize the sludge in a way such that a crosslinked ethylenic homopolymer (CEH) could be synthesized from native PVA. In order to assess the effectiveness of the newly synthesized CEH polymer as a release rate-modifying excipient, a zinc–pectinate system was formulated. The CEH polymer was incorporated into the zinc–pectinate system to study any changes induced in drug release. Ideally this study is aimed at achieving zero-order drug release over an extended period of time with the option of inducing a lag phase. Theophylline was employed as the model drug.

2. Materials and methods

2.1. Materials

Theophylline was purchased from Fluka Chemicals (Buchs, Switzerland), PVA from Aldrich Chemical Company (MO, USA) and boric acid, sodium sulfate, ammonia and *n*-propanol were obtained from Rochelle Chemicals (Johannesburg, South Africa). Low methoxyl citrus pectin (DE ≈ 34–38%) was donated by Herbstreith and Fox (Neuenburg/Wurttemberg, Germany). Zinc sulfate ($ZnSO_4$) and Zn gluconate ($C_{12}H_{22}ZnO_{14}$) USP were purchased from Spectrum (NJ, USA).

2.2. Methods

2.2.1. Formulation of the CEH gelispheres

Various 2:1 aqueous PVA:theophylline suspensions were made up to 100 mL (0.25–6%, w/v, PVA). Each suspension was titrated into a separate crosslinking solution composed of different concentrations of boric acid and sodium sulfate (5–15%, w/v), and ammonia and *n*-propanol (10–70 mL). These lower and upper limits were selected based on the formation of suitable surface and structural morphology of the gelispheres, i.e. rigid and spherical multiple-units within the operating concentration range. The resulting gelispheres were allowed to gently stir in the crosslinking solution for a further 30 min, after which they were stored in a dark area to cure for a period of 24 h. At the end of this period, the CEH gelispheres were washed with 3× 500 mL deionized water and air-dried under an extractor for 48 h.

In order to quantitatively understand the dynamics of the crosslinking process of native PVA, we

Table 1
Box–Behnken Design to optimize the physicochemical and physicomechanical properties of the CEH gelispheres

Formulation number	Boric acid (%, w/v)	Sodium sulfate (%, w/v)	Ammonia (mL)	*n*-Propanol (mL)
1	10	10	5	10
2	5	5	10	70
3	10	10	10	40
4	10	10	5	40
5	10	10	10	40
6	5	5	15	40
7	10	10	10	10
8	10	10	5	70
9	15	15	10	70
10	15	15	10	40
11	15	15	15	40
12	10	10	10	40
13	10	10	5	40
14	15	15	5	40
15	10	10	10	10
16	5	5	10	40
17	5	5	10	10
18	15	15	10	40
19	15	15	10	10
20	10	10	15	40
21	10	10	15	70
22	10	10	15	10
23	10	10	10	40
24	10	10	15	40
25	5	5	10	40
26	10	10	10	40
27	5	5	5	40
28	10	10	10	70
29	10	10	10	70

opted to build a Box–Behnken Experimental Design (Table 1).

The general quadratic function (Eq. (1)) for the design encompassed 15 terms with 4 factors and 5 center points:

$$\begin{aligned}\text{Response} = {} & b_0 + b_1 * A + b_2 * B \\ & + b_3 * C + b_4 * D + b_5 * A * A \\ & + b_6 * B * B + b_7 * C * C \\ & + b_8 * D * D + b_9 * A * B \\ & + b_{10} * A * C + b_{11} * A * C \\ & + b_{12} * B * C + b_{13} * B * D \\ & + b_{14} * C * D \end{aligned} \quad (1)$$

where A, B, C and D represent the concentrations (%, w/v) and volumes (mL) of boric acid, sodium sulfate, ammonia and *n*-propanol, respectively. b_0–b_{14} are the regression coefficients.

The responses that were measured included gelisphere size (mm), drug encapsulation efficiency (%), dissolution after 30 min ($t_{30\,\text{min}}$) (%), matrix rupture energy (J) and fracture force (N).

2.2.2. *Formulation of zinc–pectinate gelispheres containing CEH*

For this purpose, a separate Box–Behnken Design was employed with factors depicted in Table 2. Drug-free CEH gelispheres (as in Section 2.1, except without drug) were triturated to a fine powder and incorporated into 100 mL of an aqueous solution composed of 2% (w/v) pectin and 1% (w/v) theophylline. This dispersion was then crosslinked in a 2% (w/v) combination of zinc sulfate and zinc gluconate using peristaltic titration.

Table 2
Box–Behnken Design for the CEH-zinc–pectinate gelispheres

Formulation number	Crosslinked ethylenic homopolymer (CEH) concentration (%, w/v)	Crosslinking reaction time (CRT) (h)	Drying temperature (dT) (°C)
1	0.05	24	40
2	0.10	24	60
3	0.00	13	40
4	0.05	13	20
5	0.00	2	20
6	0.10	2	60
7	0.10	13	40
8	0.05	13	40
9	0.05	13	40
10	0.00	2	60
11	0.05	13	60
12	0.10	2	20
13	0.00	24	60
14	0.00	24	20
15	0.05	13	40
16	0.05	2	40
17	0.05	13	40
18	0.05	13	40
19	0.10	24	20

The quadratic model for this design comprised 3 factors and 5 center points with 10 terms as shown below:

$$\begin{aligned}\text{Response} = {} & b_0 + b_1 * \text{CEH} + b_2 * \text{CRT} + b_3 * \text{dT} \\ & + b_4 * \text{CEH} * \text{CEH} + b_5 * \text{CRT} * \text{CRT} \\ & + b_6 * \text{dT} * \text{dT} + b_7 * \text{CEH} * \text{CRT} \\ & + b_8 * \text{CEH} * \text{dT} + b_9 * \text{CRT} * \text{dT} \qquad (2)\end{aligned}$$

where CEH: crosslinked ethylenic homopolymer, CRT: crosslinking reaction time and dT: drying temperature. b_0–b_9 are the regression coefficients.

2.2.3. Size analysis of gelispheres

The size of the gelispheres ($N = 10$) was determined using a digital micrometer which had a measurement range of 0–25 mm and resolution of 0.001 mm (Digitonic Micrometer, Moore & Wright, Birmingham, England).

2.2.4. Drug encapsulation efficiency

The drug encapsulation efficiency (DEE) of both CEH gelispheres and CEH-zinc–pectinate gelispheres was determined by dissolving 50 mg of each sample in 100 mL phosphate buffer, pH 7.4. Upon dissolution, 5 mL of each sample was withdrawn and filtered through a 0.45 μm membrane filter (Millipore, Billerica, MD, USA) and analyzed by UV at the wavelength maximum for theophylline (271 nm). Based on the experimental and theoretical drug loadings, the encapsulation efficiency was computed using Eq. (3).

$$\text{DEE}\,(\%) = \left(\frac{\text{experimental loading}}{\text{theoretical loading}}\right) \times 100 \qquad (3)$$

2.2.5. In vitro dissolution studies

Drug release studies on the CEH-gelispheres and CEH-zinc–pectinate gelispheres were conducted using a modified method of the USP 25 employing a ring mesh assembly (Pillay and Fassihi, 1998) in deionized water at 50 rpm ($N = 3$). At pre-determined time intervals, samples were removed by an automated system via a 0.45 μm membrane filter (Millipore) and analyzed by UV at 271 nm for theophylline. Deionized water was selected as the dissolution medium so as to account for the sole behavior of the CEH system in the absence of any interfering ions (e.g. phosphate buffer ions). In cases where samples had to be diluted, an appropriate correction factor was employed.

Table 3
Textural parameters employed for calculation of matrix rupture energy and fracture force

Parameters	Settings
Pre-test speed (mm/s)	1
Test speed (mm/s)	0.2
Post-test speed (mm/s)	0.2
Compression force	95% stress
Trigger type	Auto
Trigger force (g)	0.5
Load cell (kg)	5

2.2.6. *Textural profiling studies*

To determine the matrix rupture energy and fracture force, a TA.XT*plus* Texture Analyzer (Stable Micro Systems, Surrey, England) fitted with a 36 mm cylindrical steel probe and 5 kg load cell was used. The textural parameters employed are listed in Table 3. At each sampling time point, a quantity of 10 gelispheres of each formulation was analyzed. The fully integrated data acquisition, analysis and display software, i.e. Texture Exponent Version 3.2, was employed to acquire data at 200 points/s.

Fig. 1 depicts typical force–distance profiles used to determine the parameters outlined in Table 3.

The graph in Fig. 1a is used to calculate the matrix rupture energy, which is the total area under the curve (AUC) for a force–distance profile (i.e. AUC between anchors 1 and 2). The units would therefore be Newton meter, which is equivalent to Joules. The first break in the upward gradient (Fig. 1b) is indicative of a primary facture phase which is associated with a fracture force (Newton).

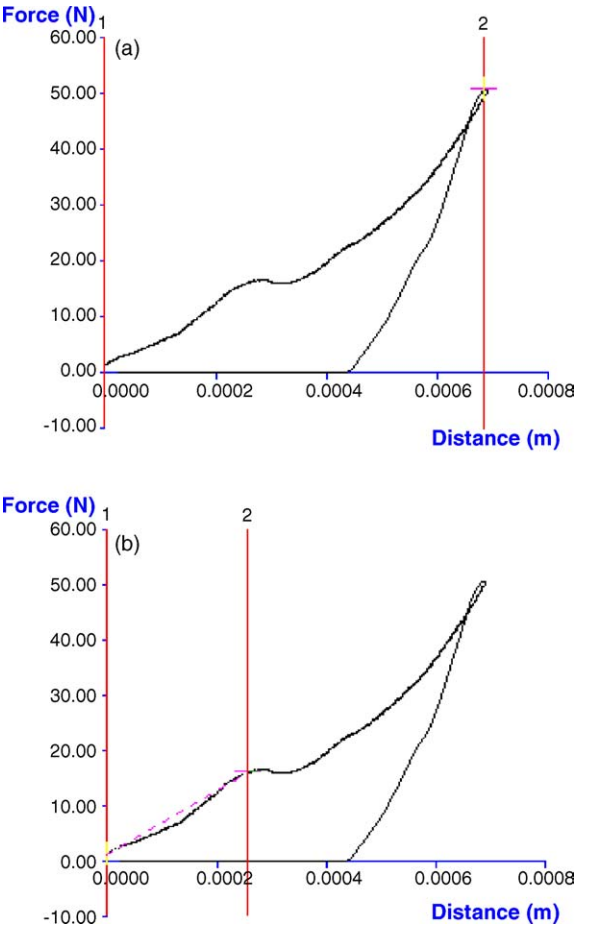

Fig. 1. Typical textural analysis force–distance profiles of crosslinked matrices for the determination of: (a) matrix rupture energy and (b) fracture force (in all cases, it was observed that S.D. < 0.03 was obtained, $N = 10$).

3. Results and discussion

3.1. *Influence of different concentrations of boric acid and sodium sulfate*

In order to explore the crosslinking phenomenon of PVA in the presence of boric acid and sodium sulfate, gelispheres were formed by the titration of aqueous PVA solutions (0.25% (w/v)–6% (w/v)) into different crosslinking solutions within a concentration range of 0.25% (w/v)–15% (w/v), as illustrated in Table 4. Based on preliminary studies, various concentrations of each component were selected to provide significantly different results.

Based on these experiments, the following concentrations of PVA and crosslinking agents were selected for further investigation: 6% (w/v) PVA and 15% (w/v) each of boric acid and sodium sulfate. Using this solution as the primary crosslinking combination, separate volumes of 10, 40 and 70 mL each of ammonia and *n*-propanol were individually added in combinations to the 15% (w/v) boric acid and sodium sulfate solution in order to assess their ability to reinforce the crosslinked gelispheres. It was established that a minimum of 10 mL each of both ammonia and *n*-propanol was adequate to prevent dissolution of the gelispheres within the crosslinking solution, and consequently maintain their rigidity and sphericity.

Table 4
Preliminary selection of concentrations of PVA and primary crosslinking solution combination composed of boric acid and sodium sulfate for the formation of CEH gelispheres

Components	Concentrations (%, w/v)			
Polymer: PVA	0.25	1	4	6
Aqueous crosslinking solution				
Boric acid	0.25	1	5	15
Sodium sulfate	0.25	1	5	15
	Physical observation			
	No gelispheres formed	No gelispheres formed	Aggregated weak gelispheres formed. Dissolved in crosslinking solution within 2 h	No aggregation, irregularly shaped, weak, gelispheres formed. Dissolved in crosslinking solution within 2 h

Table 5
Experimental responses for the 29 statistically formulated CEH gelispheres

Formulation number	Experimental response values				
	Size (mm)	DEE (%)	Fracture force (N)	Matrix rupture energy (J)	Fractional dissolution ($t_{30\,min}$)
1	1.99	9.83	49.91	0.014	0.647
2	2.00	11.72	45.57	0.017	0.784
3	2.02	13.57	75.57	0.021	0.769
4	2.40	35.43	38.54	0.018	0.248
5	1.66	73.60	45.13	0.013	0.322
6	2.28	9.77	12.64	0.001	0.747
7	1.77	8.28	16.00	0.006	0.726
8	1.39	8.11	41.19	0.006	0.658
9	1.97	18.09	24.33	0.005	0.206
10	1.94	10.65	53.65	0.011	0.533
11	1.13	9.77	34.72	0.004	0.868
12	1.17	7.30	48.16	0.006	0.662
13	0.99	9.93	36.09	0.016	0.936
14	1.36	11.84	35.10	0.010	0.903
15	2.31	61.34	25.06	0.013	0.423
16	2.50	22.47	31.02	0.008	0.565
17	1.00	14.51	66.48	0.020	1.057
18	1.10	7.76	46.07	0.006	0.760
19	2.50	48.97	32.86	0.016	0.199
20	2.50	11.69	17.52	0.001	0.527
21	3.00	64.37	36.40	0.012	0.373
22	2.50	15.02	23.12	0.002	0.604
23	2.50	8.65	26.98	0.003	0.638
24	2.00	5.81	95.54	0.023	0.471
25	2.10	4.60	86.11	0.029	0.491
26	3.00	46.25	37.71	0.020	0.448
27	2.00	53.38	29.17	0.010	0.306
28	Irregular	2.50	–	0.045	0.031
29	Irregular	2.00	–	0.034	0.014

$t_{30\,min}$ indicates fractional dissolution after 30 min. DEE: drug encapsulation efficiency.

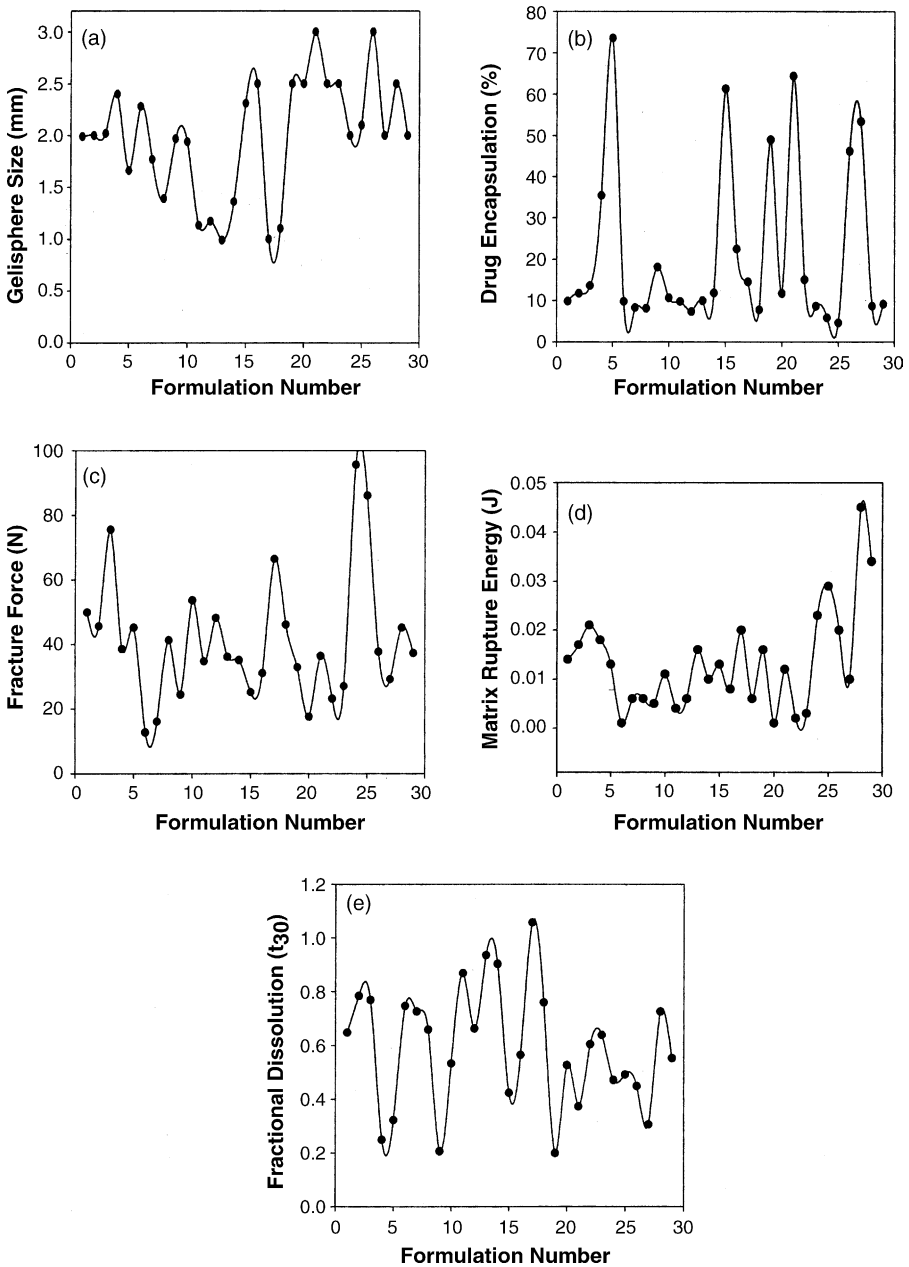

Fig. 2. Inter-formulation variations in responses for the CEH gelispheres: (a) size, (b) drug encapsulation efficiency, (c) fracture force, (d) matrix rupture energy and (e) fractional dissolution after 30 min ($t_{30\,\mathrm{min}}$) (in all cases, it was observed that S.D. < 0.07 was obtained, $N = 10$ except for dissolution where $N = 3$).

Table 6
Constraints for optimization of the combined quadratic model

Parameters	Constraints
Boric acid (%, w/v)	5–15
Sodium sulfate (%, w/v)	5–15
Ammonia (mL)	10–70
n-Propanol (mL)	10–70
Size (mm)	1.8–3.8
Drug encapsulation efficiency (%)	90
Dissolution ($t_{30\,min}$)	10
Fracture force (N)	≥96
Matrix rupture energy (J)	≥0.031

Table 7
Efficiency of the quadratic model

Parameters	Goodness-of-fit
Average leverage	0.517
Maximum prediction variance	0.583
Average prediction variance	0.517
G-efficiency (%)	88.70
Scaled D-optimality criterion	5.153
Condition number	1.933

3.2. Variability in the physicochemical and physicomechanical properties of the CEH gelispheres

Table 5 and Fig. 2 indicate the different experimental values derived for the selected responses.

3.3. Statistical optimization of the CEH gelispheres derived from native PVA

Using constrained settings outlined in Table 6, the CEH gelisphere formulations were optimized on Design Expert Version 6 (Stat-Ease, Minneapolis, USA). Table 7 depicts the stability indicators for the generated quadratic response model.

Based on the statistical desirability function, it was found that a maximum level of predictability of 89.10% could be achieved, whereby the optimized quantities of boric acid and sodium sulfate were theoretically confirmed to be 15% (w/v) each, and ammonia and *n*-propanol were 10 mL each (Section 3.1). This combination theoretically produced a gelisphere size of 3.6 mm, drug encapsulation efficiency of 89%, drug dissolution of 12% after 30 min, fracture force of 93 N and rupture energy of 0.051 J. An experimental CEH gelisphere formulation was accordingly prepared and the responses were measured (Table 8). No statistical differences were observed ($p > 0.05$) between the predicted and experimental values.

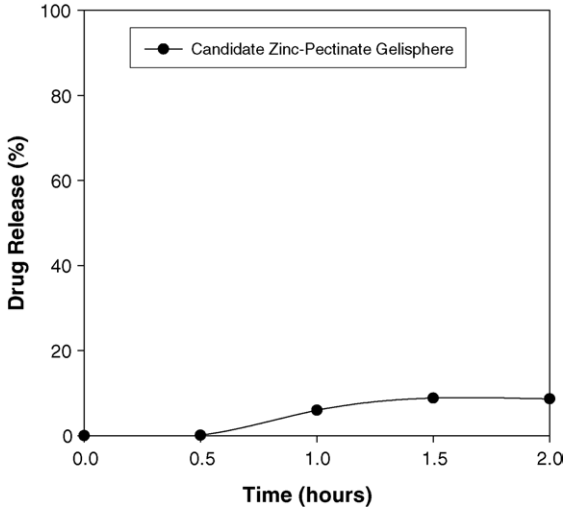

Fig. 3. Dissolution profile of theophylline from candidate native zinc–pectinate gelispheres (i.e. without CEH). Note the zinc–pectinate matrix is composed of 2% (w/v) pectin and crosslinked in a 2% (w/v) combination of zinc sulfate and zinc gluconate.

3.4. Responses of the 19 zinc–pectinate gelisphere formulations containing CEH

The candidate theophylline-loaded native zinc–pectinate matrices (i.e. without CEH) produced a dissolution profile depicted in Fig. 3.

In order to modify this profile, triturated drug-free CEH was incorporated into the zinc–pectinate matrices as per Box–Behnken Design to form a crosslinked

Table 8
Theoretical and experimental response values generated from the CEH-gelispheres

Formulation	Responses from predicted solution and experimental study				
	Size (mm)	DEE (%)	Dissolution ($t_{30\,min}$)	Fracture force (N)	Matrix rupture energy (J)
Predicted statistical solution	3.60	89	12	93	0.051
Experimental solution	3.72	92.95	8.60	82.39	0.032

DEE: drug encapsulation efficiency.

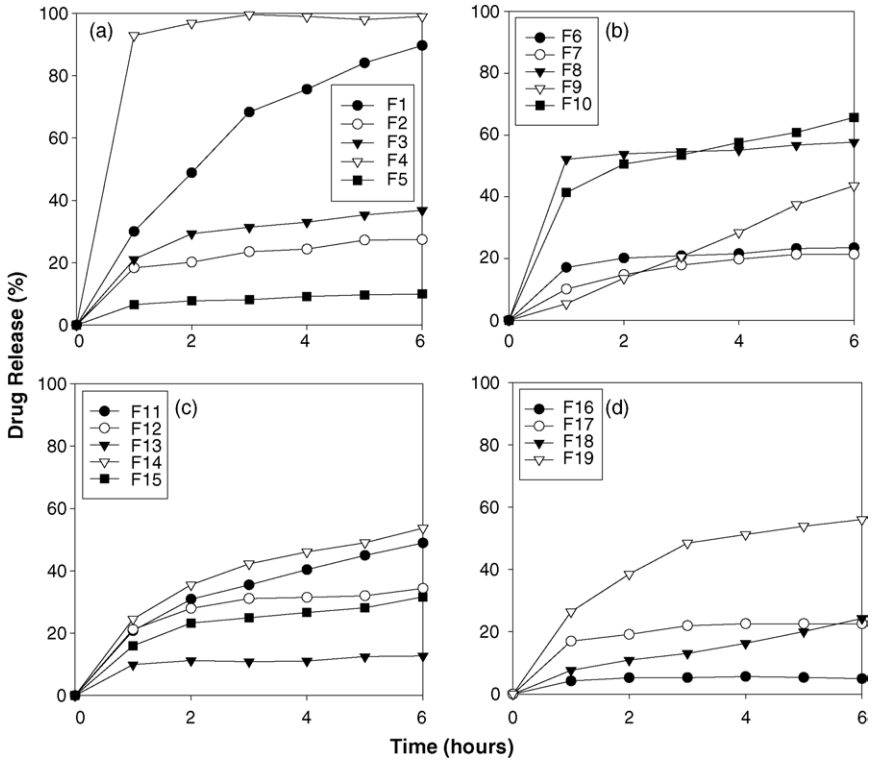

Fig. 4. Dissolution profiles for: (a) Formulations 1–5, (b) Formulations 6–10, (c) Formulations 11–15 and (d) Formulations 16–19 (in all cases, it was observed that S.D. < 0.02 was obtained, $N = 3$).

CEH-zinc–pectinate system (see Section 2.2). Fig. 4 indicates the dissolution profiles for the 19 statistical formulations up to 6 h of drug release. Our intention was to use the $t_{6\,h}$ value as a marker to indicate the degree of drug release suppression. We postulated that on the basis of the plastically deforming nature of CEH, considerable variation in drug release may be achieved based on the concentration of CEH used in the zinc–pectinate formulation.

Table 9 details the drug encapsulation efficiency and 6-h dissolution values ($t_{6\,h}$).

3.5. Statistical optimization of the zinc–pectinate gelispheres containing CEH

The objectives used for the optimization of the CEH-zinc–pectinate gelispheres included the following:

(i) maximization of the drug encapsulation efficiency based on an economic perspective;

(ii) minimization of dissolution up to 6 h ($t_{6\,h}$) such that the early phase of drug release can be suppressed.

Objective (ii) was intended to enhance the lag phase observed in Fig. 3. This may be beneficial in applications such as: (a) targeted drug delivery to the proximal and distal intestine, particularly if drugs are sensitive to the acidic gastric juice, and (b) delivery of drugs which demonstrate enhanced absorption in the intestine or are intended for the treatment of colonic disorders.

Employing a stepwise forward and backward regression technique, the following equations were derived for drug encapsulation efficiency and 6-h dissolution:

$$\begin{aligned}\text{DEE}\,(\%) = {} & b_0 + b_1 * \text{CEH} + b_2 * \text{CRT} + b_3 * \text{dT} \\ & + b_4 * \text{CEH} * \text{CEH} + b_5 * \text{CRT} * \text{CRT} \\ & + b_6 * \text{dT} * \text{dT} + b_7 * \text{CEH} * \text{CRT} \\ & + b_8 * \text{CEH} * \text{dT} + b_9 * \text{CRT} * \text{dT} \qquad (4)\end{aligned}$$

Table 9
Responses of the 19 CEH-zinc–pectinate gelispheres

Formulation number	Drug encapsulation efficiency (%)	Dissolution (%) at $t_{6\,h}$
1	4.56	89.69
2	23.59	28.42
3	34.3	36.77
4	28.71	90.72
5	24.43	8.35
6	21.46	23.48
7	16.24	21.39
8	35.2	57.7
9	19.42	43.52
10	32.08	58.66
11	22.27	48.94
12	33.21	34.37
13	24.09	12.68
14	21.33	53.69
15	14.59	31.64
16	22.02	4.96
17	32.85	22.59
18	10.56	24.29
19	5.98	56.04

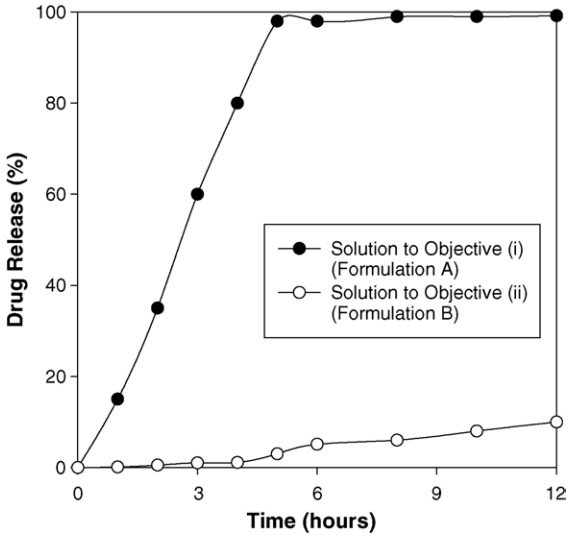

Fig. 5. Dissolution profiles derived from optimization objectives for the CEH-zinc–pectinate matrices (Table 10) (In all cases, it was observed that S.D. < 0.14 was obtained, $N = 3$).

$$\begin{aligned}\text{Dissolution at } t_{6\,h}\,(\%) &= b_0 + b_1 * \text{CEH} + b_2 * \text{CRT} \\ &\quad + b_3 * \text{dT} + b_4 * \text{CEH} * \text{CEH} + b_5 * \text{CRT} * \text{CRT} \\ &\quad + b_6 * \text{dT} * \text{dT} + b_7 * \text{CEH} * \text{CRT} \\ &\quad + b_8 * \text{CEH} * \text{dT} + b_9 * \text{CRT} * \text{dT} \qquad (5)\end{aligned}$$

Table 10 indicates the necessary formulation parameters in order to achieve the solutions to objectives (i) and (ii) using a solver function (Frontline Systems, NV, USA). Note that overall, there were no statistical significances ($p > 0.05$) between the predicted and experimental responses.

Based on the above optimization objectives, the corresponding experimental dissolution profiles were obtained (Fig. 5).

From the above profiles, it was apparent that with the appropriate concentration of CEH, crosslinking reaction time and drying temperature, a range of drug release profiles may be tailor-made. In all cases, zero-order drug delivery at different rates was produced. More interestingly, it was observed that as the concentration of CEH was increased, a larger lag time was introduced (4 h), hence enabling prolonged delivery over several days to weeks. This was a major improvement from the original zinc–pectinate profile depicted in Fig. 3 (0.5 h lag phase). It is postulated that the CEH polymer interpenetrates with other polymeric materials such as zinc–pectinate and subsequently retards swelling and reduces the inward diffusion of water, thereby inhibiting drug release (see Section 3.6). In this regard, we propose that the CEH-zinc–pectinate gelisphere system may be suitable for site-specific colonic

Table 10
Formulation parameters to obtain selected drug encapsulation efficiency and dissolution properties

Optimization objective	Solver-predicted formulation parameters			Solution (%)	
	CEH (%, w/v)	CRT (h)	dT (°C)	Predicted response	Experimental response
(i)	0	13	60	35.84 (DEE)	28.63
(ii)	0.10	24	40	2.31 (dissolution after $t_{6\,h}$)	5.1

Objectives (i) and (ii) produced Formulations A and B, respectively. DEE: drug encapsulation efficiency.

drug delivery. In addition, based on the potential controlled release of the drug over several weeks, the system may be suitable as a subcutaneous carrier for small bioactive molecules.

3.6. Kinetic modeling of release data from the optimal formulations

Various kinetic models were employed to identify the mechanism of drug release from the optimized CEH-zinc–pectinate gelispheres using data derived from in vitro dissolution studies (Fig. 5). Profiles from both Formulations A and B (i.e. without and with 4-h lag phase) were analyzed. All least squares analyses employed to determine the release mechanism of theophylline were performed on WinNonlin® Version 4.1 (Pharsight, USA) using the Gaussian–Newton (Levenberg–Hartely) approach.

The authors will not describe the equations below in detail as this information can be found elsewhere (Pillay and Fassihi, 1999). Kinetic modeling was applied using the Power Law equation (Eq. (6)), its expanded form (Eq. (7)) and the Hopfenberg model (Eq. (8)). Note that in the case of analyzing data pertaining to the dissolution profile exhibiting the 4-h lag phase, an additional component, t_L, was included in the equations to account for this phenomenon. In the absence of a lag phase, t_L equals to 0.

$$\frac{M_t}{M_\infty} = k_1(t - t_L)^n \quad (6)$$

where M_t is the amount of drug released at time t, M_∞ the total amount of drug encapsulated within the gelispheres, k_1 the Fickian kinetic constant, t_L the 4-h lag-time prior to release of the drug and n is a release exponent.

Alternatively, Fickian diffusion and matrix relaxation/dissolution were analyzed using an expanded version of the Power Law equation:

$$\frac{M_t}{M_\infty} = k_1(t - t_L)^n + k_2(t - t_L)^{2n} \quad (7)$$

where, in this case, k_2 is the relaxation/diffusion rate constant.

Hopfenberg's (1976) proposed model is either applicable to a slab, cylinder or sphere showing heterogeneous erosion.

$$\frac{M_t}{M_\infty} = 1 - [1 - k_1(t - t_L)]^n \quad (8)$$

where, in this case, k_1 is the erosion rate constant and $n = 1$, 2 and 3 for a slab, cylinder and sphere, respectively.

Kinetic analysis of dissolution data revealed that drug release from Formulation A was predominately modulated by polymeric relaxation ($k_2 = 35.89$) rather than simple diffusion ($k_1 = 0.004$) (Table 11). Statistically, this was supported by the lowest AIC and SBC values obtained for data fitted to Eq. (7) as compared for Eqs. (6) and (8). Furthermore, the highest degree of correlation (0.93 versus 0.86 and 0.49) was obtained when data were modeled to Eq. (7). Note that Formulation A did not contain CEH (Table 10).

Analysis of data for Formulation B indicated that simple diffusion regulated drug release ($k_1 = 0.87$). Statistically, the lowest AIC (19.24) and SBC (19.85), and the highest degree of correlation (0.99) were obtained when data were fitted to the Power Law equation (Table 11). Note that Formulation B contained CEH (Table 10). Drug release from both Formulations A and B did not appear to be significantly controlled by matrix erosion (in Hopfenberg model, comparatively higher

Table 11
Release kinetics obtained from the various diffusion, relaxation and erosion models

Model (M_t/M_∞)	k_1	k_2	n	AIC[a]	SBC[b]	Correlation[c]
($t_L = 0$) $k_1(t - t_L)^n$	(0.001)[d] 0.87	(–) –	(0.95) 0.94	(114.04) 19.24	(114.64) 19.85	(0.86) 0.99
($t_L = 0$) $k_1(t - t_L)^n + k_2(t - t_L)^{2n}$	(0.004) 1.01	(35.89) 0.001	(0.94) 0.93	(80.84) 26.04	(81.74) 26.94	(0.93) 0.98
($t_L = 0$) $1 - [1 - k_1(t - t_L)]^n$	(0.52) 0.10	(–) –	(3) 3	(106.40) 54.79	(106.70) 55.09	(0.49) 0.87

[a] Akaike Information Criterion.
[b] Schwartz's Bayesian Criterion.
[c] Correlation between experimental and predicted dissolution data.
[d] Values in parentheses indicate the comparative kinetic statistics for Formulation A, i.e. without a lag phase in drug release (i.e. $t_L = 0$). Values below this indicate those for Formulation B, i.e. with lag phase in drug release.

values for AIC and SBC were obtained, and lower value for the degree of correlation was observed).

This analysis illustrates that the inclusion of CEH in the formulation inhibits matrix swelling (relaxation) and chain disentanglement, thereby maintaining a strong diffusion gradient for drug release. Hydration of the matrix is slower; hence, drug dissolution and subsequent diffusion is slower, and reflected as a lag time. On the other hand, in the absence of CEH, polymer swelling (relaxation) is facilitated, leading to faster chain disentanglement, and consequently faster drug release (Fig. 5).

4. Conclusions

This work has shown the sequential steps for the transformation of PVA polymeric sludge into a useful material through the application of Experimental Design. The optimized product of this synthesis, a crosslinked ethylenic homopolymeric material, appears to be promising in modifying drug release rates over an extended period of time. However, one of the concerns is over the residual amount of ammonia and *n*-propanol remaining within the CEH matrix. An investigation to purify and sterilize CEH will be useful. Nonetheless, this work should be of interest to polymer scientists involved in the area of novel drug delivery systems design.

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