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Three-layer matrix tablets and simple approach of drug release programming

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A face-centered central composite experimental design was applied in programming the sustained drug release from three-layer matrix tablets. Xanthan gum (XG), sodium alginate (SA) and their 1:1 mixture were employed as the matrix former controlling the release of diltiazem HCl (DH). Mass fraction of DH in the intermediate layer (X_1) and percentage of XG in the matrix former of the intermediate and outer layers (X_2 and X_3, respectively) were the independent experimental variables (formulation factors). Cumulative percent release at 2 and 12 h (rel_{2h}, rel_{12h}), shape parameter of the release profiles in Weibull function (b), and exponent in the power law model of Peppas (n), were selected as dependent variables and related to the formulation factors via multiple linear regression analysis using second order polynomial equations including two-factor interaction terms. Simplified equations were derived and response surface analysis enabled the formulation factor effects and interactions to be visualized. It was found that different shapes of release profiles can be obtained corresponding to Weibull shape parameter (b) between 0.311 and 1.247. In general, increased incorporation of DH in the intermediate layer or of XG in the outer layers reduced the drug release because of restricted and delayed exposure to the dissolution medium or formation of a stronger diffusion barrier, respectively. Highly significant linear correlation ($r = 0.894$, $p < 0.001$) was found between the values of b and the exponent in the power law model of Peppas (n). Good agreement between the predicted, on the basis of the simplified equations (regression models), and the experimental values of three control formulations confirmed the validity of the suggested models in programming the release behavior by the proposed three-layer tablet system within the experimental domain.

Key words: Three-layer matrix tablets – Xanthan gum – Sodium alginate – Drug release – Weibull equation – Face center cube design – Multiple regression.

Sustained-release oral dosage forms have become popular for the administration of many drugs because they give more consistent blood levels and the tablet matrices of water-swellable polymers (hydrophilic colloids) are the simplest and least expensive systems [1]. Their mechanism of release control is based on the polymer swelling due to hydration by the gastrointestinal fluids and formation of a high viscosity gel layer, which retards the diffusion of dissolved drug [2]. A major disadvantage of these diffusion-controlled matrix devices is the non-linear release and multi-layered matrix tablets comprising an intermediate layer containing most of the active drug(s), and two outer barrier layers have been suggested as zero-order sustained release systems [3-6]. Furthermore, various release profiles other than constant such as delayed release, pulsatile or multimodal delivery profiles may be achieved by the design of multi-layer tablets differing in the geometry, the composition or combination (arrangement) of layers [7].

Since the system of multi-layered matrix tablets is a recognized flexible technology for modifying release of drugs and statistical experimental design methodologies are systematic efficient tools for optimizing pharmaceutical formulations, their combined application was thought to be of interest. In the present work, a system of three-layer matrix tablet is evaluated as a simple approach of drug release programming, by altering the drug (diltiazem HCl, DH) distribution and the composition of the hydrophilic matrix former (xanthan gum, XG, and sodium alginate, SA) in the intermediate and outer layers. Statistical significance of the main effects and two-way interactions is quantified in order to derive simplified equations as a tool of drug release programming.

I. MATERIALS AND METHODS

1. Materials

Diltiazem HCl fine powder (particle size < 180 μm) was kindly offered by the United Pharmaceutical Manufacturing (UPM) Co., Amman, Jordan. Xanthan gum (80.2% < 180 μm, 19.8% 180-400 μm) and sodium alginate (90.4% < 180 μm, 9.6% 180-400 μm) were purchased from Sigma, USA, and BDH, UK, respectively. The viscosity of 0.67% w/v polymer solution in distilled water at 25°C and shear rate 30 s^{-1} was determined using the Cup and bob method on Physica MCR 301 rheometer (Anton Paar, Austria) and was found to be 0.396 and 0.012 Pa.s for xanthan gum and sodium alginate, respectively. All materials were used as received.

2. Methods

2.1. Preparation of three-layer tablets

Fifteen batches of different three-layer matrix experimental tablets comprising a 400-mg intermediate layer and two 200-mg outer layers of identical composition were prepared. All the tablets contained a fixed amount (300 mg) of diltiazem HCl (DH) distributed in the intermediate and the outer layers by using appropriate physical mixtures with xanthan gum (XG), sodium alginate (SA) or a binary mixture of them (1:1). The composition of the tablets is described in *Table I* as the mass fraction of DH incorporated in the intermediate layer (X_1) acquiring levels 0.2, 0.6 and 1.0 and the percentage of XG in the matrix former of the intermediate (X_2) and outer (X_3) layers, acquiring levels 0, 50 and 100%. Physical mixing was applied in a small mortar with a spatula for 15 min. For the preparation of tablets, a 13-mm flat-faced punch and die set and a hand-operated hydraulic press (Shimadzu,

Table I - Composition and drug release parameters of the experimental three-layer matrix tablets [cumulative percent release at 2 and 12 h (rel_{2h}, rel_{12h}), correlation coefficients (r), shape parameter (b) and time for 63.2 % release (t_d) in the Weibull release function, and release rate constant (K_p) and exponent (n) in the power law model of Peppas].

Tablet composition				rel_{2h} (%)	rel_{12h} (%)	Weibull parameters			Power law parameters		
	X_1	X_2	X_3			b	t_d (h)	r	n	K_p (h^{-n})	r
1	1.0	100	100	7.9	17.5	0.311	5186.1	0.962	0.367	0.062	0.952
2	1.0	100	0	16.1	91.5	1.173	6.4	0.987	1.228	0.078	0.998
3	1.0	0	100	4.8	13.2	0.398	2969.1	0.972	0.303	0.040	0.990
4	1.0	0	0	15.9	83.5	1.208	7.7	0.994	1.098	0.079	0.997
5	0.2	100	100	21.9	70.1	0.665	17.1	0.979	0.498	0.146	0.997
6	0.2	100	0	21.9	62.9	0.786	11.4	0.999	0.673	0.138	0.999
7	0.2	0	100	36.2	97.0	0.954	3.9	0.991	0.658	0.223	0.999
8	0.2	0	0	36.6	100.0	1.176	3.8	0.998	0.916	0.184	0.998
9	0.6	50	50	22.4	92.5	1.178	5.9	0.997	1.028	0.110	0.999
10	0.6	100	50	16.1	55.5	0.819	17.5	0.998	0.707	0.094	0.998
11	0.6	0	50	32.4	93.8	1.127	5.1	0.999	0.945	0.142	0.999
12	1.0	50	50	10.2	80.4	0.955	13.9	0.956	1.169	0.045	0.995
13	0.2	50	50	20.8	88.5	1.038	6.8	0.992	0.920	0.114	0.999
14	0.6	50	100	9.0	34.6	0.872	17.3	0.988	0.637	0.101	0.988
15	0.6	50	0	29.7	92.9	1.247	4.5	0.998	1.056	0.139	0.999

X_1: mass fraction of diltiazem hydrochloride (DH) incorporated in the intermediate layer. X_2 and X_3: percentage of xanthan gum in the mixture of hydrophilic polymers used as matrix former of the intermediate and the outer layers, respectively.

Japan) were used. Two hundred milligrams of accurately weighted mixture of outer layer was transferred into the die cavity and slightly compressed by hand for uniform spreading. The upper punch was lifted and 400 mg of intermediate layer mixture was placed over the first outer layer and again slightly compressed for uniform spreading. Another 200 mg of outer layer mixture was poured and then 10 MPa pressure was applied for 30 s, resulting in saturated (zero porosity) three-layer compacts (matrix tablets).

2.2. *In vitro* drug release

The release rate of DH from the matrix tablets was determined using USP Apparatus II paddle dissolution system (Pharma Test PTW 2, Hainburg, Germany), at 100 rpm, with 900 mL of distilled water as dissolution medium. The paddle instead of the basket system was used in order to avoid possible interference with the swelling of the three-layer matrix tablets and the release process, since the tablets are relatively large and contain highly-swellable xanthan gum [8]. At certain time intervals, 10-mL samples were taken and the volume of water was replaced. The samples were filtered through 0.45-μm cellulose acetate syringe filter and the concentration of DH dissolved was determined, after suitable dilution, by UV spectroscopy (Spectronic 601, Milton Roy, USA) at a wavelength corresponding to maximum absorbance (237 nm). All tests were performed in triplicate and the percent drug release was determined from the mean concentration.

The effects of formulation variables on the release profile were evaluated with the aid of MS Excel by fitting the cumulative Weibull distribution function to the release results employing the linearized form [9 -11]:

$$\log[-\ln(1-m)] = b \log (t - T_i) - \log a \qquad \textbf{Eq. 1}$$

where m is the cumulative drug release at time t, T_i is the lag time before the onset of dissolution or release process that in most cases will be zero, b is the shape parameter and a is the time scale of the process. From a and b the time for 63.2% release, t_d, can be calculated [12]: $t_d = a^{1/b}$. This Weibull function was selected as being capable of dealing with dissolution profiles corresponding to an initial release phase followed by either a faster or slower one. More specifically, when b = 1, the curve is exponential and *Equation 1* reduces to the simple first order model. For b > 1, the release profile is sigmoid, while for b < 1 it is parabolic corresponding to fast initial release slowing gradually. In extreme cases, where $b \rightarrow 0$, *Equation 1* yields a straight line and when $b \rightarrow \infty$, the curve degenerates to a step function [13]. The linearized form is equivalent and provides almost identical results to non-linear fit [14].

In order to characterize the release mechanism, the power law model of Peppas was fitted by non-linear regression to the release data (for the first 60% dissolved) [15]:

$$M_t/M_\infty = K_p . t^n \qquad \textbf{Eq. 2}$$

where M_t/M_∞ represents the fractional release of drug at time t, K_p is the release rate constant and the exponent n is indicative of the release mechanism. In the example of cylindrical tablets, a value of $n \approx 0.45$ indicates Fickian diffusion, while higher values of n (between 0.45 and 0.9) indicate non-Fickian diffusion and a value of n = 0.9 is indicative of erosion controlled and zero-order release kinetics. The non-linear regression was applied using the program Sigma Plot 10.0 for Windows (Systat Software, San Jose, CA, USA) and in all experiments of the present work time (t) was expressed in identical quantity (e.g. time in hours/1 h). Thus, the dimensionality of a and K_p do not depend on b and n, respectively, and this enabled t_d to be expressed in hour units.

2.3. Experimental design and statistical analysis

A face centered cubic experimental design (a central composite design with $\alpha = 1$) reducing the number of runs (15 instead of 27 for a 3^3 full factorial design) was applied [16]. Moreover, this design allows sequential experimentation by first using a full 2^3 factorial design and then seven additional experimental points at intermediate levels of the independent experimental variables (formulation factors) in order to study the curvature.

The levels (low, medium and high) of the formulation factors X_1 (0.2, 0.6 and 1.0), X_2 and X_3 (0, 50 and 100%) are presented in *Table I*, for the fifteen experimental batches of three-layer matrix tablets. The responses characterizing: i) the initial and final stages of drug release (% release at 2 and 12 h, rel_{2h} and rel_{12h}), ii), the overall release profile (shape parameter in the Weibull function, b) and iii) the release mechanism (exponent in the power law model of Peppas, n), were related with the independent experimental variables (formulation factors) by applying multiple linear regression and fitting of second order polynomial equations including two-factor interaction terms: