BJPS

Brazilian Journal of Pharmaceutical Sciences
vol. 47, n. 3, jul./sep., 2011

Article

Formulation of a modified release metformin.HCl matrix tablet: influence of some hydrophilic polymers on release rate and in-vitro evaluation

John Rojas*, Cesar González, Carolina Rico, Oswaldo Saez

School of Pharmaceutical Chemistry, The University of Antioquia

Metformin hydrochloride is an antidiabetic agent which improves glucose tolerance in patients with type 2 diabetes and reduces basal plasma levels of glucose. In this study, a *simplex centroid* experimental design with 69 runs was used to select the best combination of some hydrophilic polymers that rendered a 24 h *in-vitro* release profile of metformin.HCl. The Korsmeyer–Peppas model was used to model the dissolution profiles since it presented the best fit to the experimental data. Further, a cubic model predicted the best formulation of metformin.HCl containing polyvinyl pyrrolidone, ethyl cellulose, hydroxypropyl methyl cellulose, carrageenan, sodium alginate, and gum arabic at 6.26, 68.7, 6.26, 6.26, 6.26 and 6.26 % levels, respectively. The validation runs confirmed the accuracy of the cubic model with six components for predicting the best set of components which rendered a once-a-day modified release hydrophilic matrix tablet in compliance with the USP specifications.

Uniterms: Metformin/release profile. Metformin.HCl/modified release/in-vitro evaluation. Hydrophilic polymers/influence/drugs release. Korsmeyer-Peppas model/dissolution profiles.

O cloridrato de metformina é um agente antidiabético que melhora a tolerância à glicose em pacientes com diabetes tipo 2 e reduz os níveis plasmáticos basais de glicose. Neste estudo, um projeto experimental do tipo "centróide simplex" com 69 tomadas foi usado para selecionar a melhor combinação de alguns polímeros hidrofílicos que gerou um perfil de liberação da metformina.HCl de 24 horas. O modelo Korsmeyer-Peppas foi usado para modelar os perfis de dissolução, uma vez que apresentou os melhores ajustes aos dados experimentais. Além disso, um modelo cúbico previu a melhor formulação de metformina.HCl sendo aquela contendo polivinilpirrolidona, etilcelulose, hidroxipropilmetil celulose, carragena, alginato de sódio e goma arábica nos níveis 6.26, 68.7, 6.26, 6.26, 6.26 e 6.26 %, respectivamente. As corridas de validação confirmaram a precisão do modelo cúbico com os seis componentes para prever o melhor conjunto de componentes que originou uma libertação do tipo "uma vez ao dia" em conformidade com as especificações da USP, a partir de comprimidos matriciais.

Unitermos: Metformina/perfil de liberação. Cloridrato de metformina/liberação modificada/*in-vitro* evaluation. Polímeros hidrofílicos/influência/liberação de fármacos. Modelo Korsmeyer-peppas/perfil de dissolução.

INTRODUCTION

It is estimated that by 2025 around 300 million people will be diagnosed with diabetes (Ritu *et al.*, 2009; Jain, Gupta, 2009). Metformin hydrochloride (MH) is an oral anti-hyperglycemic drug used in the treatment of Type 2 diabetes in patients who cannot manage the disease with only diet and exercise (Chouldhury, Kar, 2008). It improves glucose tolerance by lowering both basal and postprandial glucose by decreasing intestinal absorption of glucose, decreasing hepatic gluconeogenesis, increasing glycogenesis, lipogenesis and glucose uptake by adipocytes and muscle cells (Choudhury *et al.*, 2008; Stepensky *et al.*, 2002). MH is a highly water soluble drug

***Correspondence:** T. P. John Rojas. School of Pharmaceutical Chemistry, The University of Antioquia, Cll 65 # 53-108 Office 1-157, Medellin, Colombia. E-mail: jrojasca@gmail.com

(0.5 g/mL) administered up to 2.5 g/day in three separate doses given with meals to minimize possible gastrointestinal side effects such as anorexia, abdominal discomfort, nausea, and diarrhea (Gouldson, Deasy, 1997). However, food also decreases the absorption of the drug (Hu *et al.*, 2006). The presence of side effects and the need for three-times-a-day administration could reduce patient compliance and hinder successful treatment (Mandal *et al.*, 2007).

MH does not produce lactic acidosis as seen in other biguanide drugs such as phenformin and buformin (Tucker *et al.*, 1981). Further, MH does not bind to plasma proteins and the elimination of the unchanged drug mainly occurs by active tubular secretion through the kidneys. A single dose of 500 mg of an immediate and modified release MH showed higher plasma concentrations for the latter in the steady-state (Karttunen *et al.*, 1983). A single immediate release dose of MH exhibits a flip-flop model and a bioavailability of about 61%. The t_{max} and $t_{1/2}$ of MH after a single immediate release oral dose of 500 mg was ~2 h and 2.6 h, respectively (Pentikainen *et al.*, 1979). However, a 250 mg sustained-release MH pellet showed a t_{max} of 7.3 h and $t_{1/2}$ of 8.3 h and a 165% increase in bioavailability in comparison to the immediate release formulation and thus, t_{max} depended on the dose. For instance, t_{max} was 2.2 h and 1.5 h for an immediate release dose of 0.5 and 1.5 g, respectively (Tucker, 1981). Further, ~20% of the single immediate release dose is recovered in faeces, indicating saturable absorption and low absorption in the terminal segment of the colon (Lian-Dong *et al.*, 2006; Gusler *et al.*, 2001; Pentikainen, 1986). This problem creates the need for a modified release device to modulate the release and hence, the absorption of MH. Thus, a modified release system allows for achieving an optimal therapy, improving patient compliance and safety, reducing dose dumping, plasma fluctuations and the incidence of side effects. Corti and collaborators achieved a sustained-release MH matrix based on Eudragit L100-55, HPMC and β-cyclodextrin which released up to 60% of the drug within 5 h (Corti *et al.*, 2008).

Hydrophilic matrices are composed of hydrophilic polymers, an active ingredient and other excipients homogeneously distributed in a three dimensional network. Several factors affect the drug release from a hydrophilic matrix (Conte *et al.*, 1988; Colombo *et al.*, 1999). These factors are the drug solubility, polymer swelling, polymer erosion, drug dissolution/diffusion characteristics, distribution of drug within the polymer matrix and proportion and geometry of the system (Wu, Zhou, 1998; Zhou, Wu, 1997; Adrover *et al.*, 1996). The absorption of solvent, as well as the drug release, also depends on the viscoelastic properties of the polymer (Crank, 1975).

If the network of the matrix is seen as a mesh, large spaces can be defined as access points for the diffusion of drugs (Maulin, Ben-Avhraham, 1987). In non-porous matrices, swelling occurs first, moving and expanding the dry glassy core portion of the swollen matrix (Crank, 1975; Colombo *et al.*, 1999). However, for porous systems, drug release also depends on the porosity of the matrix and drug dissolution/diffusion through the pores. This behavior is prevalent in hydrophobic porous matrices (Barry *et al.*, 1979; Colombo *et al*., 1999). Non-porous systems have no defined pores and the molecules diffuse through the mesh of the matrix (Robert *et al.*, 1985). In the case of poorly soluble drugs, the diffusion front may appear between the outside of the swollen matrix, where the drug is completely dissolved, and the inside, where the drug is still undissolved. Drug release in swellable matrices is controlled by the diffusion coefficient and the swelling process (Grassi, 2003).

In a swellable matrix, swelling of the polymer matrix and drug loading affect the drug release kinetics (Grassi *et al.*, 2003). The swelling behavior depends largely on the number of intermolecular bonds per volume of polymer. For neutral polymers, the amount of solvent absorbed depends on the chemical affinity of the polymer for the solvent and on the elastic properties of the swollen polymer network. In the case of charged polymers, swelling depends on the ionic strength (Ricka, Tanaka, 1984; Okazaki *et al.*, 1996). In fact, the chains of a cross-linked polyelectrolyte assume a modified conformation in pure water, while this conformation is precluded in aqueous salt solutions, due to the electrostatic interactions between polymer charges and mobile ions present in the solution (Tanaka *et al.*, 1986).

In the present study, formulations of hydrophilic matrixes composed of MH, ethylcellulose, HPMC, carrageenan, sodium alginate, gum arabic and PVP were prepared by wet granulation followed by tableting to achieve a once-a-day controlled release preparation. This provides a lower but controlled drug concentration over an extended period of time (24 h). The resulting dissolution profiles and release kinetics of the matrices were also evaluated.

MATERIAL AND METHODS

Material

Ethylcellulose standard 7 with ethoxyl content of 48-49.5% (lot TS051977) was donated by Colorcon, Inc. Harleysville, PA, USA. HPMC Type 2919 with methoxyl content of 28–30% and hydroxypropyl content of 7–12% (lot 506825) was obtained from Dow Wolff Cellulosics

Midland, MI, USA). K-carrageenan (lot 217882), and gum Arabic (lot 104K0151) were purchased from Bell Chem Corp., Longwood, FL, USA. Sodium alginate (lot 990972) and PVP K-30 (lot 0911106) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Monobasic potassium phosphate (lot 8N117059B) and NaOH (lot B0244398) were obtained from Carlo Erba, Milan, Italy and Merck, Darmstadt, Germany, respectively.

Methods

Preparation of Matrix Compacts

Powder mixtures of ~10 g were prepared in a mortar a pestle using a 70% ethanol solution as a wetting agent. The wet samples were then granulated on an oscillating granulator equipped with a size 40 mesh (*Riddhi Pharma Machinery, Gulabnagar, India)*, followed by drying at room temperature for 14 h until reaching a moisture content of less than 3%. The dry samples were then granulated on an oscillating granulator using a size 40 and 60 mesh, consecutively. Cylindrical compacts, each Weighing ~1750 mg were then made on a rotary tablet press (512-1, FJ Stokes Manufacturer Corporation, Philadelphia, PA, USA) equipped with a 13 mm diameter concave punches and die set. The compression force was controlled to give a compact porosity of ~ 0.3 (compact solid fraction of 0.7). The uniformity of the dose (Table I) was assessed on three compacts of each formulation by grinding 3 compacts from each formulation in a mortar, followed by dispersing the powder in distilled water and filtering through a 0.45 μm membrane. Dilutions of this solution were conducted to achieve a concentration of 8 μg/mL. The absorbance of this solution was measured at 232 nm and the resulting concentration was interpolated from a calibration curve. The United States Pharmacopoeia (USP34/NF29) specification for uniformity of dose is from 90 to 100%.

In-vitro dissolution studies

Matrixes containing 750 mg of MH were agitated at 100 rpm in 1000 mL of phosphate buffer pH 6.8 at 37 °C in a dissolution basket assembly (VARIAN dissolutor, VK7000, Palo Alto, CA, USA). Five milliliter aliquots were withdrawn periodically with immediate replacement of the dissolution medium and subsequent filtration through a 0.45 μm filter. Samples were analyzed by UV spectroscopy (Shimadzu UV-1700, Kyoto, Japan) at 232 nm (USP34/NF29).

Simplex centroid mixture design

A "simplex centroid" experimental mixture design with 6 components (ethyl cellulose, HPMC, PVP, carrageenan, sodium alginate and gum arabic) and 69 runs was employed (Table I). The two dependent variables were release rate (k) and release order (n). The non-linear fitting model was conducted by using the Statgraphics software (StatPoint, Inc. Warrenton, VA). The coefficients of the model estimate the variation in the experimental parameters. The results were analyzed either as an analysis of the coefficients of the various polymers, or as an analysis of variance (ANOVA). Preliminary fitting of the data to the zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas (KP) determined the latter as the most suitable release model based on the comparison of the relevant correlation coefficients and thus, only results from this model were included in this study.

Modeling of dissolution profiles

The Korsmeyer-Peppas model was employed (Ritger, Peppas, 1987):

$$M/M\infty = k*t^n \quad (1)$$

where $M\infty$ is the amount of drug released at infinite time, k is the rate constant of drug release and n is the exponent that characterizes the process of release. If the diffusion process is Fickian, n is equal to 0.5, 0.45 and 0.43 for thin films, cylindrical and spherical matrices, respectively. When n exceeds these thresholds, the release is non-Fickian (Ritger, Peppas, 1987). The release mechanism is given once the polymer chains contact the solvent and the chains are reoriented to achieve a new equilibrium condition (Siepman, Peppas, 2001). The time required for this reorganization is called polymer relaxation time (t_r). If t_r is much smaller than the diffusion time t_d required for the release, the process is then Fickian. When $t_r \cong t_d$, solvent absorption is not Fickian or anomalous (Grassi *et al.*, 1998).

Validation of optimization model

A cubic model including interaction terms were generated for k and n using the multiple linear regression analysis of the Minitab software (State College, PA). Statistical validity of the model was established on the basis of the ANOVA test. Further, the feasibility and grid search were used to find the composition of the optimum formulations. Ten check points were also selected based on the criteria of optimum formulation by intensive grid search to validate the experimental design and the model. The formulations corresponding to the optimal formulation were prepared and evaluated for the two responses. Subsequently, the experimental data of the ten check points and the optimal formulation were quantitatively compared with that of the predicted values.

RESULTS AND DISCUSSION

In-vitro dissolution studies

Table I lists the composition of 69 trial formulations prepared with different combinations of polymers such as ethyl cellulose, HPMC, PVP, carrageenan, sodium alginate, and gum arabic. The data obtained were modeled according to the KP model because it was the only model that rendered the best fit (R^2> 0.9991) to the release data of MH except for formulation 40 (R^2> 0.8753). Preliminary fitting to other models such as zero order, first order, Hixson-Crowell and Higuchi failed to give R^2 higher than 0.85. The parameters k and n obtained from the KP model are also shown in Table I.

TABLE I - Simplex centroid matrix and responses obtained according to the Korsmeyer-Peppas (KP) model

F	PVP	EC	HPMC	C	SA	GA	K	N	R^2	UD(%)
F1	0.25	0.25	0.00	0.25	0.00	0.25	0.335	0.340	0.9505	102.1
F2	0.00	0.25	0.25	0.25	0.25	0.00	0.289	0.402	0.9708	97.6
F3	0.58	0.08	0.08	0.08	0.08	0.08	0.844	0.073	0.9861	95.6
F4	0.00	0.25	0.25	0.00	0.25	0.25	0.304	0.396	0.9775	91.8
F5	0.33	0.00	0.00	0.33	0.00	0.33	0.335	0.369	0.9793	102.6
F6	0.17	0.17	0.17	0.17	0.17	0.17	0.291	0.414	0.9683	101.4
F7	0.50	0.00	0.00	0.00	0.00	0.50	0.287	0.411	0.9576	100.4
F8	0.00	0.00	0.00	0.50	0.00	0.50	0.297	0.396	0.9631	100.5
F9	0.25	0.00	0.00	0.25	0.25	0.25	0.206	0.497	0.9906	98.3
F10	0.00	0.00	0.25	0.25	0.25	0.25	0.282	0.391	0.976	100.2
F11	0.00	0.00	0.33	0.33	0.00	0.33	0.244	0.445	0.9941	100.1
F12	0.25	0.25	0.00	0.25	0.25	0.00	0.702	0.129	0.9412	93.7
F13	0.50	0.00	0.00	0.50	0.00	0.00	0.821	0.042	0.9792	96.5
F14	0.00	0.33	0.33	0.00	0.33	0.00	0.257	0.435	0.9908	95.2
F15	0.00	0.00	0.50	0.00	0.00	0.50	0.254	0.442	0.976	94.3
F16	0.00	0.00	0.50	0.50	0.00	0.00	0.260	0.435	0.985	98.7
F17	0.20	0.20	0.00	0.20	0.20	0.20	0.396	0.317	0.9306	101.3
F18	0.00	0.33	0.33	0.00	0.00	0.33	0.170	0.505	0.9891	99.2
F19	0.00	0.33	0.33	0.33	0.00	0.00	0.186	0.529	0.9975	94.9
F20	0.25	0.25	0.25	0.25	0.00	0.00	0.251	0.452	0.9753	100.4
F21	0.25	0.00	0.25	0.25	0.25	0.00	0.368	0.314	0.9976	95.2
F22	0.20	0.20	0.20	0.00	0.20	0.20	0.213	0.487	0.996	98.1
F23	0.00	0.25	0.00	0.25	0.25	0.25	0.238	0.451	0.9994	95.9
F24	0.00	0.50	0.50	0.00	0.00	0.00	0.198	0.510	0.9992	93.4
F25	0.25	0.00	0.25	0.00	0.25	0.25	0.274	0.408	0.9882	92.1
F26	0.00	0.33	0.00	0.00	0.33	0.33	0.175	0.548	0.9985	96.1
F27	0.33	0.33	0.00	0.00	0.00	0.33	0.362	0.348	0.9837	95.8
F28	0.08	0.08	0.08	0.08	0.58	0.08	0.359	0.322	0.9929	105.7
F29	0.00	0.00	0.33	0.33	0.33	0.00	0.241	0.447	0.9939	99.5
F30	0.33	0.00	0.00	0.00	0.33	0.33	0.195	0.514	0.9996	94.8
F31	0.00	0.00	0.33	0.00	0.33	0.33	0.282	0.402	0.9956	97.8
F32	0.08	0.08	0.08	0.08	0.08	0.58	0.291	0.387	0.9977	98.1

TABLE I - continuation

F	PVP	EC	HPMC	C	SA	GA	K	N	R^2	UD(%)
F33	0.08	0.08	0.08	0.58	0.08	0.08	0.334	0.344	0.9842	100.4
F34	0.00	0.50	0.00	0.50	0.00	0.00	0.659	0.126	0.9919	103.1
F35	0.20	0.00	0.20	0.20	0.20	0.20	0.248	0.443	0.9948	102.3
F36	0.00	0.00	1.00	0.00	0.00	0.00	0.243	0.446	0.9904	105.2
F37	0.25	0.00	0.25	0.25	0.00	0.25	0.312	0.356	0.9823	97.3
F38	0.00	0.20	0.20	0.20	0.20	0.20	0.263	0.423	0.996	104.5
F39	0.20	0.20	0.20	0.20	0.20	0.00	0.277	0.391	0.993	99.2
F40	0.50	0.00	0.50	0.00	0.00	0.00	0.527	0.222	0.8753	106.8
F41	0.33	0.00	0.33	0.00	0.33	0.00	0.290	0.400	0.9919	100.1
F42	0.33	0.33	0.00	0.00	0.33	0.00	0.907	0.026	0.9656	105.2
F43	0.33	0.33	0.33	0.00	0.00	0.00	0.359	0.346	0.9441	102.1
F44	0.00	0.00	0.50	0.00	0.50	0.00	0.269	0.400	0.9936	104.3
F45	0.00	0.33	0.00	0.33	0.00	0.33	0.338	0.346	0.9965	101.6
F46	0.50	0.50	0.00	0.00	0.00	0.00	1.000	0.002	0.9998	101.2
F47	0.00	0.50	0.00	0.00	0.50	0.00	0.368	0.313	0.9732	99.5
F48	0.00	1.00	0.00	0.00	0.00	0.00	0.629	0.160	0.9389	103.8
F49	0.00	0.33	0.00	0.33	0.33	0.00	0.949	0.022	0.9924	102.2
F50	0.00	0.25	0.25	0.25	0.00	0.25	0.288	0.411	0.9841	106.5
F51	0.00	0.00	0.00	0.00	1.00	0.00	0.313	0.363	0.983	105.3
F52	0.25	0.25	0.25	0.00	0.00	0.25	0.294	0.388	0.997	103.1
F53	0.33	0.00	0.00	0.33	0.33	0.00	0.927	0.017	0.9989	104.8
F54	0.33	0.00	0.33	0.00	0.00	0.33	0.513	0.232	0.9563	98.2
F55	1.00	0.00	0.00	0.00	0.00	0.00	0.985	0.000	0.9976	106.1
F56	0.00	0.50	0.00	0.00	0.00	0.50	0.320	0.380	0.9727	104.2
F57	0.33	0.33	0.00	0.33	0.00	0.00	0.917	0.044	0.9882	104.9
F58	0.20	0.20	0.20	0.20	0.00	0.20	0.309	0.382	0.9858	103.5
F59	0.00	0.00	0.00	0.00	0.50	0.50	0.286	0.411	0.9851	94.9
F60	0.00	0.00	0.00	1.00	0.00	0.00	0.792	0.067	0.9821	102.5
F61	0.00	0.00	0.00	0.00	0.00	1.00	0.316	0.383	0.9837	106.1
F62	0.25	0.25	0.00	0.00	0.25	0.25	0.718	0.117	0.9746	104.1
F63	0.00	0.00	0.00	0.33	0.33	0.33	0.365	0.339	0.984	102.3
F64	0.00	0.00	0.00	0.50	0.50	0.00	0.524	0.206	0.9962	96.4
F65	0.08	0.58	0.08	0.08	0.08	0.08	0.313	0.380	0.9905	99.8
F66	0.33	0.00	0.33	0.33	0.00	0.00	0.891	0.036	0.9938	105.7
F67	0.50	0.00	0.00	0.00	0.50	0.00	0.733	0.107	0.9707	107.3
F68	0.25	0.25	0.25	0.00	0.25	0.00	0.433	0.290	0.9125	97.4
F69	0.08	0.08	0.58	0.08	0.08	0.08	0.285	0.398	0.9926	99.3

F = formulation; E = ethyl cellulose; SA = sodium alginate; GA = gum arabic; C = carrageenan; HPMC = hydroxypropyl methyl cellulose; PVP = Polyvinyl pyrrolidone; k = drug release constant; n = release type; UD = uniformity of the dose

The release profile of MH from the single polymers is shown in Figure 1. PVP caused the fastest release of MH and when this component was present at a high level, drug release was also fast. PVP is very soluble in water and wets easily when its matrixes come into contact with water, leading to quick dissolution and erosion of the matrix. By contrast, the HPMC matrix alone rendered the slowest drug release. The HPMC matrix hydrates rapidly on contact with water to form a gel on the surface of the tablet. Soluble drugs such as MH are released primarily by diffusion through the gel layer. The matrix compacts containing ethyl cellulose in combination with hydrophilic polymers presented the mechanism of swelling and erosion, whereas ethyl cellulose alone has a diffusion through the pores mechanism. The formulation containing MH and pure carrageenan formed a fast eroding gel which could have increased the medium viscosity.

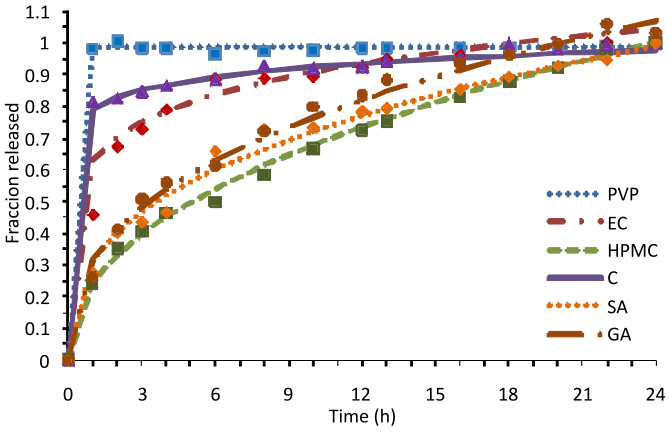

FIGURE 1 - Release profiles of metformin.HCl from the single polymers.

The formulation containing MH and sodium alginate also formed a gel when placed in contact with the medium, but eroded slowly. The formulation containing only gum arabic also formed a gel, but it was less viscose than that produced by carrageenan and sodium alginate. For swelling and gelling polymers such as HPMC, the viscosity of the gel layer around the compact increases at higher hydrogel concentration, slowing the release of MH because the gel is formed by closely-packed swollen particles. In general, the release rate (k) of the pure polymers with the drug followed the trend:

PVP> Carrageenan> ethylcellulose>sodium alginate ≅gum arabic> HPMC. It is observed that formulations containing sodium alginate (F51) and gum arabic (F61), which were the most gelling materials, had similar release rates (0.313 and 0.316, respectively). By contrast, the formulation containing only MH and HPMC (F36) yielded the slowest release profile. The value of n of this formulation indicates that it follows a Fickian release (n = 0.45) which coincides with that expected for cylindrical matrices. This is the major reason why this polymer is widely used for modified release of drugs. Conversely, most formulations had an anomalous release which comprises swelling, erosion and disintegration of the matrix.

Formulations such as F3, F12, F13, F42, F46, F53, F57, F62, F66, and F67 containing considerable levels of PVP or carrageenan and very low levels of highly gelling polymers such as HPMC, exhibited an initial burst of the matrix releasing the drug quickly as seen by the high k values. This is attributed to the dissolution of the drug present initially at the surface of the matrices followed by a fast penetration of dissolution media to the matrix causing a disruption of its structure. By contrast, sodium alginate and gum arabic (which gel and form a halo around the area of contact with the aqueous medium) release the drug more slowly and their profiles fall within the USP range.

For gum arabic, HPMC and ethylcellulose, the presence of cross-links among polymer chains is responsible for the wetting of the polymer with the liquid, resulting in the expansion of the network resembling a sponge soaked in water. If cross-linking among the polymer chains have a covalent nature the network does not change with time. On the contrary, if the interactions are Van der Waals, dipole-dipole, hydrophobic or hydrogen bonding type, the polymer chains are not rigidly connected, resulting in polymer burst/erosion as occurred for PVP and carrageenan (Barry, Meyer, 1979). Since the method of preparation of these matrices involves wet granulation and tableting, the resulting matrixes can be considered porous systems and MH which is a water soluble drug is more likely to diffuse through the pores, rather than through the mesh of the matrix.

The USP gives the specifications for the range of percentage of MH released in a 24 h profile. This profile range is between 20-40%, 35-55%, 75-85%, and 85-100% at 1, 4 10 and 24 h, respectively. These values are reflected in a k value from 0.23 to 0.39 and n value from 0.3 to 0.43. For matrix tablets, an n value close to 0.5 indicates a diffusion control mechanism and n close to 1.0, erosion or relaxation control. The range for n values suggests that formulations with diffusion as the dominant mechanism of drug release is desirable. Formulations which rendered k and n parameters within the USP range and having the best fit to the non-linear KP model ($R^2 > 0.9990$) were selected as appropriate and shown in Figure 2. Since the USP gives a broad range of drug release, 10 formulations fulfilled the specifications out of the 69 formulations studied. For

example, formulations 21, 28, 31, 32, 39, 44, 45, 52, 65 and 69 had low levels of highly hydrophilic polymers such as PVP and carrageenan and high levels of swelling and gelling polymers such as ethyl cellulose, sodium alginate, HPMC and gum arabic.

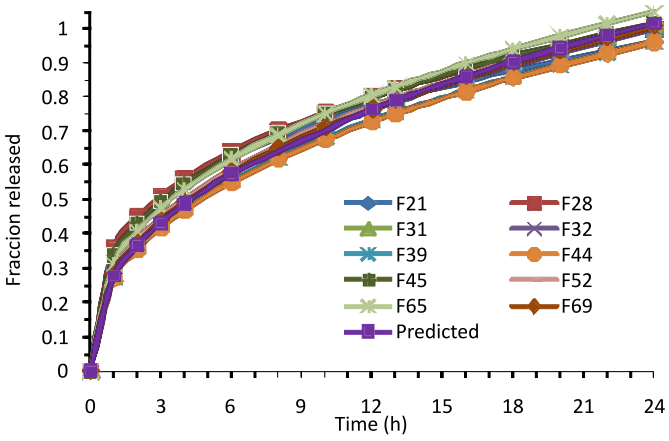

FIGURE 2 - Release profiles of metformin.HCl for formulations which fulfilled USP34/NF29 specifications.

Mathematical modeling

The least squares method rendered a cubic model for the mixture design with the best fit for k and n. Thus, the results of the model statistics show R^2 values of 0.9645 and 0.9664 for both response models, which indicate a good correlation between the experimental and predicted responses (Table II). The ANOVA test conducted on the cubic regression models indicates that the mixture design developed for the two responses were significant and adequate.

The cubic model fitting evaluates the effect of the polymers to obtain an estimate of the coefficients. These coefficients and their significance are shown in Table III. The cubic equations comprise the coefficients for first order main effects and their interaction terms. The sign and magnitude of the main effects signify the relative influence of each factor on the response, i.e., average result of changing one factor at a time from its low to high value. The interaction terms show how the response changed when two factors were simultaneously changed.

In the coefficients table a negative sign signifies an antagonistic effect, while a positive sign signifies a synergistic effect to the responses. It can be observed in Table III that the release rate increased greatly with increasing levels of PVP and carrageenan, whereas it decreased with increasing levels of sodium alginate, whereas gum arabic had a minor effect. Most of the second and third order interaction terms had a negative effect on release rate especially if PVP was present.

On the other hand, the release order (n) was found be positively influenced by increasing levels of the polymers studied, especially for HPMC. If this material is formulated alone with the drug a Fickian diffusion mechanism is expected. Conversely, if the matrix is mainly composed of PVP or carrageenan an anomalous release is expected.

Figure 3A and B show the mixture surface plots for k and n of three components at a time, while keeping the other three components constant. The k parameter increases when the PVP component increases, whereas for EC and HMPC it fluctuates showing a saddle shape. The n parameter on the other hand, increased with increasing amount of EC and HPMC, yet decreased with increasing amounts of PVP. Figure 3C shows the surface plot for k having the components C, SA and AG. Overall, it had a butterfly shape. In this case, the k parameter increased when the amount of GA increased, whereas it decreased forming a valley and then increased when the amount of C and SA increased. Figure 3D shows the surface plot for the n parameter having a saddle shape. This parameter remained virtually unchanged with increasing amounts of GA. However, when the amount of C and SA increased, n reached a saddle point followed by a sharp decrease.

TABLE II - ANOVA table for k and n as result of cubic model

Response	Source	Sum of squares	Degrees of freedom	Mean squares	F-ratio	p-value
k	Cubic model	7.42915	55	0.135075	39.63	<0.01
	Error total	0.27947	82	0.003408		
	Total (corregido)	7.70862	137		R^2	0.9637
n	Model	3.07841	55	0.055971	43.89	<0.01
	Error total	0.10457	82	0.001275		
	Total (corregido)	3.18297	137		R^2	0.9671

k= release rate constant; n= release order

TABLE III - Cubic model fitting results for k and n

Parameter	K				N			
	Coeff.	SE	t statistic	p-value	Coeff.	SE	t statistic	p-value
PVP	0.98	0.1	9.80	<0.01	0.004	0.06	0.07	<0.01
EC	0.62	0.1	6.20	<0.01	0.16	0.06	2.67	<0.01
HPMC	0.24	0.1	2.40	<0.01	0.45	0.06	7.50	<0.01
C	0.79	0.1	7.90	<0.01	0.07	0.06	1.17	<0.01
AS	0.31	0.1	3.10	<0.01	0.37	0.06	6.17	<0.01
GA	0.31	0.1	3.10	<0.01	0.39	0.06	6.50	<0.01
PVP*GA	-1.27	0.2	-6.33	0.00	0.77	0.1	6.35	<0.01
PVP*EC	0.95	0.2	4.75	<0.01	-0.39	0.1	-3.18	<0.01
PVP:SA	0.51	0.2	2.54	0.01	-0.40	0.1	-3.29	<0.01
EC*HPMC	-1.26	0.2	-6.33	0.00	0.75	0.1	6.12	<0.01
EC*GA	-0.47	0.2	-2.35	0.02	0.37	0.1	2.97	<0.01
HPMC:C	-0.99	0.2	-4.92	0.00	0.70	0.1	5.67	<0.01
C:GA	-0.96	0.2	-4.80	0.00	0.64	0.1	5.22	<0.01
PVP*EC*HPMC	-9.71	1.3	-7.34	0.00	4.82	0.8	5.96	<0.01
PVP*EC*C	-5.04	1.3	-3.81	0.00	3.15	0.8	3.89	<0.01
PVP*EC*SA	7.64	1.3	6.00	0.00	-5.61	0.8	7.20	<0.01
PVP*HPMC*SA	-9.42	1.4	6.51	0.00	6.86	0.9	7.75	<0.01
PVP*HPMC*GA	4.26	1.4	2.96	0.00	-2.12	0.9	-2.41	0.02
PVP*C*GA	-4.80	1.4	-3.33	0.00	2.84	0.9	3.23	<0.01
EC*HPMC*C	-6.98	1.4	-4.95	0.00	6.68	0.9	7.73	<0.01
EC*HPMC*GA	4.89	1.6	3.06	0.00	-2.95	1.0	-2.35	0.02
HPMC*C*GA	5.05	2.2	2.30	0.02	-0.34	1.0	-0.35	0.73
HPMC*SA*GA	-4.46	2.1	-2.09	0.04	1.57	1.3	1.21	0.23
C*SA*GA	-9.89	2.1	-4.64	0.00	8.93	1.3	6.85	<0.01

SE = standard error; Coeff. = Coefficient

Validation of the cubic model results

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. The optimization was done with the constraints for n of 0.36 and k of 0.31 as the goals to find the optimum composition of polymers in the new formulation. Further, check points of the 10 formulations which fulfilled the USP requirements were conducted. The experimental responses were compared to those predicted by the cubic models and the results are shown in Table IV. A high correlation was observed between the predicted and observed response variables (> 98%). The optimized formulation is composed of 68.7% ethylcellulose and ~6.3% of all other polymers, rendering k and n values of 0.28 and 0.41, respectively.

CONCLUSION

The magnitude of release rate and release order depended on the interactions between the drug, polymers and the medium employed. Hydrophilic matrixes of MH were successfully prepared by wet granulation followed by tableting. The effect of type of polymer and its concentration was evaluated using a mixture design. Formulations containing high levels of PVP presented a burst effect on the release rate and the release mechanism was anomalous. Conversely, high levels of HPMC and ethylcellulose were desirable to achieve the desirable once-a-day modified release profile. Further, high levels of HPMC shifted the release mechanism towards a Fickian type. The cubic model was accurate for predicting the release rate and order of release of MH.

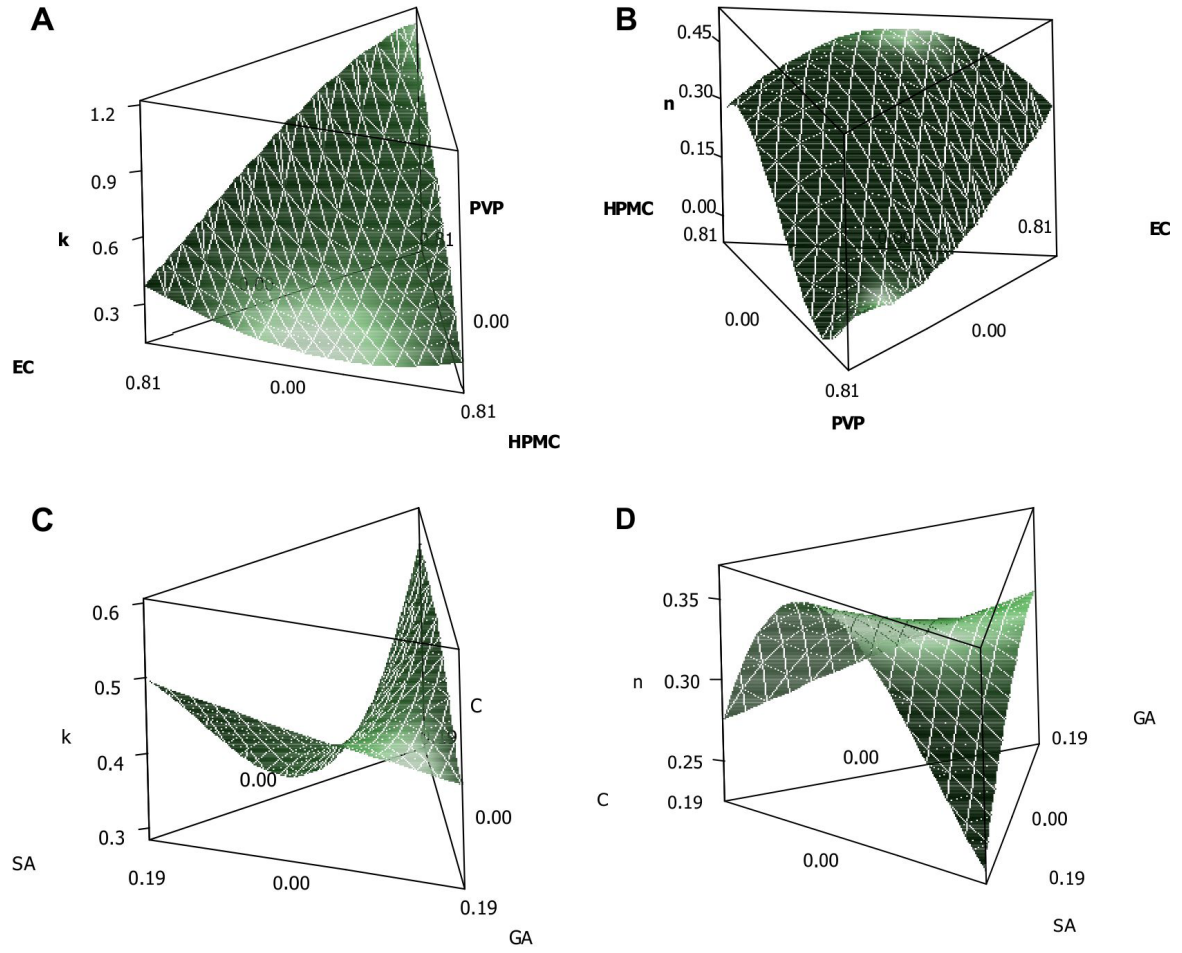

FIGURE 3 - Mixture surface plots for k and n. **A.** and **B.** SA, C and GA are held at 0.0626. **C** and **D**. PVP, HPMC and EC are held at 0.0626, 0.0626 and 0.687, respectively.

TABLE IV – Validation runs for k and n

Formulation	Experimental values		Predicted values		R^2
	k	n	k	N	
Target*	0.310	0.360	0.276	0.410	0.9826
F21	0.359	0.309	0.312	0.360	0.9954
F28	0.359	0.322	0.312	0.362	0.9973
F31	0.282	0.402	0.308	0.36	0.9977
F32	0.291	0.387	0.309	0.360	0.9990
F39	0.277	0.391	0.312	0.360	0.9987
F44	0.269	0.400	0.308	0.366	0.9985
F45	0.338	0.346	0.311	0.360	0.9994
F52	0.294	0.388	0.314	0.360	0.9989
F65	0.313	0.380	0.312	0.360	0.9995
F69	0.285	0.398	0.306	0.360	0.9981

*The target formulation was that which renders k and n values of 0.31 and 0.36, respectively

ACKNOWLEDGMENTS

The authors would like to thank Professors Ana Giraldo and Constain Salamanca for their technical support. The authors also thank the Pharmacy department for financing this project.

REFERENCES

ADROVER, A.; GIONA, M.; GRASSI, M. Analysis of controlled release in disordered structures: a percolation model. *J. Membrane Sci.*, v.113, p.21-30, 1996.

BARRY, B. W.; MEYER, M. C. The rheological properties of carbopol gels I. Continuous shear and creep properties of carbopol gels. *Int. J. Pharm.*, v.2, p.1-25, 1979.

CHOULDHURY, P.K.; KAR, M; CHAUHAN, C.S. Cellulose acetate microspheres as a floating depot systems to increase gastric retention of antidiabetic drug: formulation, characterization and in vitro – in vivo evaluation. *Drug Dev. Ind. Pharm*. v.34, p.349-354. 2008.

CHOUDHURY, P.K.; KAR, M. Controlled release metformin hydrochloride microspheres of ethyl cellulose prepared by different methods and study on the polymer affected parameters. *J. Microencapsul*., v.26, p.46-53, 2009.

COLOMBO, P.; BETTINI, R.; CASTELLANI, P. L.; SANTI, P.; PEPPAS, N. A. Drug volume fraction profile in the gel phase and drug release kinetics in hydroxypropylmethyl cellulose matrices containing a soluble drug. *Eur. J. Pharm. Sci.,* v.9, p.33-40, 1999.

COLOMBO, P.; BETTINI, R.; PEPPAS, N. A. Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug. *J. Control. Release*, v.61, p.83-91, 1999.

CONTE, U.; COLOMBO, P.; GAZZANIGA, A.; SANGALLI, M. E.; LA MANNA, A. Swelling-activated drug delivery systems. *J. Biomaterials*, v.9, p.489-493, 1988.

CORTI, G.; CIRRI, M.; MAETRELLI, F.; MENNINI, N.; MURA, P. Sustained-release matrix tablets of metformin hydrochloride in combination with triacethyl-β-cyclodextrin, *Eur. J. Pharm. Biopharm.,* v. 68, p.303-309. 2008.

CRANK, J. *The mathematics of diffusion*. 2.ed. Oxford: Clarendon Press, 1975. 414 p.

GOULDSON, M.P.; DEASY, P.B. Use of cellulose ether containing excipients with microcrystalline cellulose for the production of pellets containing metformin hydrochloride in the process of extrusion-spheronization. *J. Microencapsul*., v.14, p.137-153, 1997.

GRASSI, M.; LAPASIN, R.; PRICL, S. Modeling of drug release from a swellable matrix. *Chem. Eng. Commun.*, v.169, p. 79-109, 1998.

GRASSI, M.; VOINOVICH, D.; MONEGHINI, M.; FRANCESCHINIS, E.; PERISSUTTI, B.; FILIPOVIC-GRCIC, J. Theoretical and experimental study on theophylline release from stearic acid cylindrical delivery systems. *J. Control. Release*., v.92, p.275-289, 2003.

GRASSI, M.; VOINOVICH, D.; MONEGHINI, M.; FRANCESCHINIS, E.; PERISSUTTI, B.; FILIPOVIC-GRCIC, J. Preparation and evaluation of a melt pelletized paracetamol/stearic acid sustained release delivery system. *J. Control. Release*, v.88, p.381-391, 2003.

GUSLER, G.; GORSLINE, J.; LEVY, G.; ZHANG, S.Z.; WESTON, I.E.; NARET, D.; BERNET, B. Pharmacokinetics of metformin gastric-retentive tablets in healthy volunteers. *J. Clin. Pharmacol.,* v.41, p.655-661. 2001.

HAVLIN, S., BEN-AVRAHAM, D. Diffusion in Disordered Media. *Advanced Physics*, v.36, p.695-798, 1987.

HU, L.D.; LIU, Y.; TANG, X.; ZHANG, Q. E. Preparation and in vitro/in vivo evaluation of sustained release metformin hydrochloride pellets. *J. Pharm. Biopharm.,* v.64 p.185-192, 2006.

JAIN, S.K.; GUPTA, A. Development of Gelucire 43/01 beads of metformin hydrochloride for floating delivery. *AAPSPharmSciTech*., v.10, p.1128-1136, 2009.

KARTTUNEN, P.; UUSITUPA, M.; LAMMINSIVU, U. The pharmacokinetic of metformin: a comparison of the properties of a rapid-release and sustained-release preparation. *Int. J. Clin. Pharmacol. Ther. Toxicol*, v.21, p.31-36, 1983.

KYDONIEUS, A., (Ed.). *Treatise on controlled drug delivery*. New York: Marcel Dekker, Inc., 1992. 568 p.

LIAN-DONG, H.; LIU, Y.; TANG, X.; ZHANG, Q. Preparation and in vitro/in vivo evaluation of substained-release metformin hydrochloride pellets. *Eur. J. Pharm. Biopharm.,* v.64, p.185-192, 2006.

MANDAL, U.; GOWDA, V; GHOSH, A.; SELVAN, S.; SALOMON, S.; PAL, T.K. Formulation and optimization of sustained release matrix tablet of metformin.HCl using response surface methodology. *Yakugaky Zasshi*., v.127, p.1281-1290, 2007.

OKAZAKI, Y.; ISHIZUKI, K.; KAWACHI, S.; KOMIYAMA, J. Ion-specific swelling and deswelling behaviors of ampholytic polymer gels. *Macromolecules*, v.29, p.8391-8399, 1996.

PENTIKAINEN, P.J. Bioavailability of metformin. Comparison of solution, rapidly dissolving tablet, and three sustained release products. *Int. J. Clin. Pharmacol. Ther. Toxicol*, v.24, p.213-220, 1986.

PENTIKAINEN, P.J., NEUVONEN, P.J., PENTILLA, A. Pharmacokinetics of metformin after intravenous oral administration to man. *Eur. J. Clin. Pharmacol,* v.16, p.195-202, 1979.

PHARMACOPOEIAL CONVENTION AND THE NATIONAL FORMULARY, "U.S. Pharmacopeia. The Standard of Quality," USP34/NF29, United States Pharmacopeial Convention, New York, 2010.

RICKA, J.; TANAKA, T., Swelling of ionic gels: quantitative performance of the Donnan theory. *Macromolecules*, v.17, p.2916-2926, 1984.

RITGER, P.L.; PEPPAS, N. A. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J. Control. Release*, v.5, p.37-42, 1987.

RITU, B.; DIXIT, R.R.; GUPTA, H.V.; PATEL, P.S. Formulation and characterization of sustained release matrix tablet of metformin hydrochloride. *Int. J. Pharm. Recent Res.*, v.1, p.49-53, 2009.

ROBERT, C. C. R.; BURI P. A.; PEPPAS N. A. Effect of degree of crosslinking on water transport in polymer microparticles. *J. Applied Pol.Sci.*, v.30, p.301- 306, 1985.

SIEPMAN, J.; PEPPAS, N. A. Modeling of drug release from delivery systems based on hydroxypropylmethylcellulose (HPMC). *Adv. Drug Rev.*, v.48, p.139-157, 2001.

STEPENSKY, D.; FRIEDMAN, M.; RAZ, I.; HOFFMAN, A. Pharmacokinetic-pharmacodynamic analysis of the glucose-lowering effect of metformin in diabetic rats reveals first-pass pharmacodynamic effect. *Drug. Metab. Dispos.,* v.30, p.861-868, 2002.

TANAKA, T.; FILLMORE, D.; SUN, S.; NISHIO, I.; SWISLOW, G.; SHAH, A., Phase-transitions in ionic gels. *Phys. Rev. Lett.,* v.45, p.1636-1651, 1980.

TUCKER, G.T.; CASEY, C.; PHILLIPS, P.J.; CONNOR, H.; WARD, J.D.; WOODS, H.F. Metformin kinetics in healthy subjects and in patients with diabetes mellitus. *Br. J. Clin. Pharmac.,* v.12, p.235-246. 1981.

WU, X. Y.; ZHOU, Y. Finite element analysis of diffusional drug release from complex matrix systems. - II. Factors influencing release kinetics. *J. Control. Release*., v.51, p.57-71, 1998.

ZHOU, Y.; WU, X. Y. Finite element analysis of diffusional drug release from complex matrix systems. i. complex geometries and composite structures. *J. Control. Release*., v. 49, p.277-288, 1997.

Received for publication on 22nd December 2010
Accepted for publication on 30th May 2011