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*Full Length Research Paper*

# Assessment of a modified release verapamil hydrochloride (HCl) matrix compacts: Effect of formulation composition on the *in vitro* release kinetic

**J. Rojas[1]*, J. Aristizabal and J. Sanchez**

Department of Pharmacy, School of Pharmaceutical Chemistry, The University of Antioquia, Medellin, Colombia.

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**Verapamil hydrochloride is a drug used to treat arrhythmias. In this study, a D-optimal mixture design with 16 runs was used to select the best combination of three polymers into a matrix that rendered an 8 h *in vitro* release profile of verapamil. hydrochloride (HCl) which fulfill a once-a-day modified release in compliance with the United States Pharmacopeia (USP) specifications. The Korsmeyer-Peppas model was used to fit the dissolution data since it presented the best fitting characteristics. A cubic model predicted the best formulation of verapamil.HCl containing carnauba wax, hydroxypropyl methyl cellulose and Avicel_PH101 at the 40, 20 and 40% levels, respectively. Validation runs confirmed the accuracy of the cubic models which include these three components.**

**Key words:** Verapamil, controlled-release preparations, non-linear models, experimental design.

## INTRODUCTION

The number of United States (US) adults with some form of heart disease is expected to increase to 110 million by 2030. This is translated in a 37.3 and 9.3% of adults with hypertension and coronary disease, respectively. Obese people with a sedentary lifestyle are the most vulnerable group to acquire these diseases (Mathers and Loncar, 2006). Conventionally, verapamil.HCl (V.HCl), administered in the form of an immediate release dosage form has been the main drug used for the treatment of heart disease, especially that related with supraventricular tachyarrhythmias. On the other hand, V.HCl suffers from a first pass effect, has a short biological half-life (4 to 6 h), a low bioavalability, and requires a high frequency of administration (3 times per day) to maintain effective plasma levels. As a result, the incidence of side effects such as constipation, dizziness and headache is boosted, leading to patience incompliance and hence, therapeutic ineffectiveness (Deshmane et al., 2009).

In order to solve these problems, modified release dosage forms have been attempted to provide a lower but controlled drug concentration. In one study, chitosan was employed to create a 6 h-release gastro-retentive beads, but the drug loading efficiency was only 42% (Yassin et al., 2006). A different approach employed melt granulation of synthetic waxy materials such as glyceryl monostearate and stearic acid to achieve an 8 h sustained release matrix. However, the resulting compacts were difficult to swallow (Bhagwat et al., 2008). Further, transdermal drug delivery systems have been attempted with hydroxypropyl methycellulose (HPMC), but large drug loads and high pHs were needed to enhance drug release and absorption through the skin (Ramírez and Villafuerte, 2004). Likewise, a 6 h sustained released buccal patch with chitosan and PVP K-30 has been reported

*Corresponding author. E-mail: jrojasca@gmail.com.

K-30 has been reported. Nonetheless, this dosage form could be uncomfortable in the mouth for an extended period of time. Further, a 12 h matrix compacts made of carbopol and Eudragit NE30D has been reported. However the oral administration of carbopol is questionable (Elkheshen, 2001; Khamanga and Walker, 2011).

A modified release of a drug could be achieved through the development of a matrix composed of a polymer and other excipients homogeneously distributed in a three dimensional network. Soluble active ingredients such as V.HCl when released are first wet, dissolved and disseminated in the matrix, whereas insoluble excipients remain in place until the surrounding matrix is eroded or dissolved (Chouldhury et al., 2008). Other factors affecting the release kinetics are the polymer swelling coupled with chain relaxation, erosion, drug dissolution/ diffusion characteristics, homogeneity of the drug within the polymer matrix and geometry of the system (Wu and Zhou, 1998). However, the occurrence of multicomponent transport processes, composition, device geometries, drug loading and solubility in the matrix make the release mechanism more complex.

Currently, mixture designs are widely used to analyze a set of formulation components to render the desirable response. Mixture factors stand for the amounts of ingredients in a mixture. They are part of a formulation and add up to a value of 100%. In some cases, a D-optimal mixture design is employed if the components are used in a short range, giving a small number of experimental runs. Replication is used to measure the experimental error and it is usually done on the center point run. These runs are also used for curvature checking and error variance estimation (Montgomery, 2012).

In this study, V.HCl was selected as a model drug for designing a modified release matrix. This formulation was composed of carnauba wax, HPMC and microcrystalline cellulose (Avicel_PH101) prepared by direct compression. These components were crucial to achieve a combined hydrophilic and lipophilic mechanism. Preliminary studies with the pure components failed to render an 8 h modified release. The resulting dissolution profiles and release kinetics of the matrices were also evaluated.

## EXPERIMENTALS

Verapamil Hydrochloride (lot YR3110) was donated from ECAR laboratories. Avicel_PH101 (particle size, 43.5 µm; lot 1430) was obtained from FMC BioPolymers. Hydroxymethylpropylcellulose (HPMC Type 2919 with methoxyl content of 28 to 30% and hydroxypropyl content of 7 to 12%, lot 506825) was obtained from Dow Wolff Cellulosics, and Carnauba Wax lot 07110 was purchased from Carnauba do Brazil. Monobasic potassium phosphate (lot 8N117059B) and concentrated hydrocloric acid (37%, lot 2612KLHV) were purchased from Carlo Erba and Mallinckrodt Specialty Chemicals Co., respectively.

### D-optimal mixture design

A D-optimal mixture design with 3 components (Carnauba wax, HPMC and Avicel_PH101) and 16 runs was employed. The selected dependent variables were release rate (k) and release order (n). The non-linear fitting model was conducted using the software Statgraphics (StatPoint, Inc. Warrenton, VA). The coefficients of the model estimated the variation in the experimental parameters. The results were analyzed by performing an analysis of the coefficients of the various polymers, and by the analysis of variance (ANOVA). Preliminary fitting of the data to the Higuchi, Hixson-Crowell, Baker and Lonsdale, Jorgensen and Christensen 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 the results and discussion from this model were included in this study. Restrictions of the components were set up from preliminary studies in order to obtain an 8 h release of V.HCl. These constrains ranged from 0.3 to 0.6 for carnauba wax and Avicel_PH101 and from 0.1 to 0.4 for HPMC, respectively.

### Preparation of matrix compacts

Dry powder mixtures of ~10 g each were prepared on a mortar and pestle (Table 1). Powder mixtures were then passed through a 250 µm sieve. Cylindrical compacts, each weighing ~1,240 mg were then made on a single punch tablet press (060804 Compac, Indemec, Itagüí, Columbia) using a 13 mm cylindrical punches and die set at a pressure of 150 MPa at a dwell time of 1 s. The porosity of the resulting compacts was ~20%. The upper punch was equipped with a load cell (LCGD-10K, Omega Engineering, Inc., Stamford, CT) and a strain gauge meter (DPiS8-EI, Omega Engineering, Inc., Stamford, CT).

### *In vitro* dissolution studies

Matrixes containing 240 mg of V.HCl were agitated at 50 rpm in a 900 ml dissolution type II apparatus (DT6-K, Erweka GmbH, Milford, CT) at 37°C. The first treatment employed a simulated gastric fluid (0.01 N) for 1 h, followed by treatment with a simulated intestinal fluid (pH of 6.8) for 7 h according to the USP specifications. Five milliliter aliquots were withdrawn periodically and immediately replaced by a fresh dissolution medium. Aliquots were then filtrated through a 0.45 µm filter and diluted using a dilution factor of 1/10. Samples were analyzed by ultra violet (UV) spectroscopy (HACH DR500, HACXH Company, Loveland, CO) at 280 nm. The V.HCl concentration was determined by interpolation from a calibration curve built using 10, 20, 30 40 and 80 µg/ml concentrations. The uniformity of content was determined on three individual compacts and analyzed for drug content as described.

### Dissolution profile models

The release models of Higuchi, Hixon and Crowell, Baker and Korsmeyer-Peppas were used to analyze the *in vitro* data to find the model that best represents the data. The Korsmeyer-Peppas model was employed due to the best fit to the experimental data:

$$F=k*t^n \quad (1)$$

Where F is the fraction of drug released within the range of 0.1 to 0.60 at a time t, k is the release rate constant which incorporates structural and geometric factors. On the other hand, n is the exponent

**Table 1.** D-Optimal mixture design matrix.

| Batch | CW | HPMC | AV | V.HCl | UC (%) |
|---|---|---|---|---|---|
| F1 | 0.45 | 0.1 | 0.45 | 0.24 | 101.2±1.2 |
| F2 | 0.45 | 0.25 | 0.3 | 0.24 | 104.2±0.8 |
| F3 | 0.6 | 0.1 | 0.3 | 0.24 | 100.8±2.1 |
| F4 | 0.3 | 0.1 | 0.6 | 0.24 | 98.9±1.8 |
| F5 | 0.4 | 0.3 | 0.3 | 0.24 | 100.7±2.4 |
| F6 | 0.45 | 0.1 | 0.45 | 0.24 | 102.3±1.2 |
| F7 | 0.3 | 0.1 | 0.6 | 0.24 | 101.6±0.9 |
| F8 | 0.6 | 0.1 | 0.3 | 0.24 | 103.6±1.3 |
| F9 | 0.4 | 0.2 | 0.4 | 0.24 | 104.2±0.9 |
| F10 | 0.3 | 0.25 | 0.45 | 0.24 | 100.9±2.4 |
| F11 | 0.3 | 0.1 | 0.6 | 0.24 | 99.1±3.3 |
| F12 | 0.35 | 0.15 | 0.5 | 0.24 | 98.8±1.9 |
| F13 | 0.5 | 0.2 | 0.3 | 0.24 | 102.1±1.1 |
| F14 | 0.3 | 0.3 | 0.4 | 0.24 | 101.6±2.1 |
| F15 | 0.3 | 0.4 | 0.3 | 0.24 | 101.3±1.8 |
| F16 | 0.3 | 0.4 | 0.3 | 0.24 | 100.5±2.3 |

CW = carnauba wax; HPMC= hydroxypropylmethylcellulose, AV = avicel_PH101, V.HCl = verapamil.HCl; UC = uniformity of content.

exponent that characterizes the process of drug transport mechanism. If "n" is equal to 0.45; 0.45 < n < 0.89; and >0.89 the diffusion process is Fickian, non-fickian, and zero order, respectively for a cylindrical matrix (Ritger and 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 and 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 non-Fickian or anomalous (Grassi et al., 1998).

**Validation of the model**

A cubic model including interaction terms were generated for "k" and "n" using the multiple linear regression analysis obtained from the Design Expert software (Stat-Ease, Inc, Minneapolis, MN). The statistical validity of the model was established on the basis of the ANOVA test. Further, the grid search from the contour plots was used to find the optimal formulation composition. Two check points were also selected to validate the model. Subsequently, the experimental data of the check points were quantitatively compared with that of the predicted values.

## RESULTS

Table 1 lists the experimental matrix composed of three independent factors and the uniformity of content of each batch. Further, Table 2 shows the parameters and correlation coefficient of all the release models used. The Korsmeyer-Peppas (KP) model was selected for the release analysis since in most cases it rendered the best fit to the experimental data. Table 3 shows the analysis of variance for the two responses (release rate and release order) obtained from the KP model. The first column present the terms of the fitted cubic models. The p-values determined the cubic models as significant, indicating that the relative composition of all factors had a strong effect on the two responses. The goodness of fit statistic of the mixture design was examined by the coefficient of determination ($r^2$), which indicates how much variation in the responses was explained by the cubic models. The higher the $r^2$, the better the model fits the data. The fitted cubic models for the release rate and release order are:

**Ln(k)** = +1159.6* **CW**-670.3***HPMC** -899.8* **AV** -1128.9* **CW*HPMC** -460.6***CW*AV** +2255.3* **HPMC *AV**+1648.4* **CW * HPMC*AV**-341.6***CW*HPMC*(CW-HPMC**)-5247.9* **CW*AV*(CW-AV**) +2468.0* **HPMC*AV*(HPMC-AV)**

**n** =-181.6***CW**+120.9***HPMC**+139.6***AV**+139.3***CW*HPMC**+72.4***CW*AV**-373.6* **HPMC * AV**-221.1***CW*HPMC*AV**+92.0***CW*HPMC*(CW-HPMC)**+815.6***CW *AV*(CW-AV)** -395.7***HPMC*AV*(HPMC-AV)**

Figure 1a and b shows the contour plots for the release rate and release order, respectively. The lowest values are depicted with a blue color font and the highest values with a red color font, respectively. In general, HPMC and Avicel_PH101 levels between 0.3 and 0.4 rendered high values of release rates. Likewise, high levels of Avicel_PH101 (> 0.5) rendered high release rates. Conversely, formulations that possessed a large level of carnauba wax such as F1, F2, F3, F5, and F6 exhibited the slowest release rates. The optimal range of the desired 8 h drug release rate is depicted in the contour plot in green color and ranged between 0.0006 and 0.0054. This area is composed of HPMC, carnauba wax and Avicel_PH101 at ranges of 0.3 to 0.4, 0.4 to 0.5 and 0.35 to 0.4, respectively.

Surprisingly, the regions of the contour plot that showed

**Table 2.** Parameters and correlation coefficients obtained from the different release models.

| Batch | Higuchi model | | Hixon-Crowell model | | Baker model | | Korshmeyer-Peppas model | | |
|---|---|---|---|---|---|---|---|---|---|
| | $k_H$ | r | $k_{HC}$ | r | $k_B$ | r | $k_{kp}$ | n | r |
| F1 | 0.024 | 0.9403 | 0.0004 | 0.8644 | 0.0001 | 0.9558 | 0.04 | 0.483 | 0.953 |
| F2 | 0.0144 | 0.8403 | 0.0002 | 0.7179 | $3\times10^{-5}$ | 0.7642 | 0.035 | 0.338 | 0.932 |
| F3 | 0.0156 | 0.4237 | 0.0001 | 0.4971 | 0.00003 | 0.9441 | 0.076 | 0.216 | 0.883 |
| F4 | 0.0271 | 0.9814 | 0.0005 | 0.9442 | 0.0002 | 0.9854 | 0.025 | 0.515 | 0.982 |
| F5 | 0.0153 | 0.7256 | 0.0002 | 0.7145 | $4\times10^{-5}$ | 0.7084 | 0.072 | 0.233 | 0.966 |
| F6 | 0.0185 | 0.9786 | 0.0003 | 0.9452 | $7\times10^{-5}$ | 0.9759 | 0.02 | 0.486 | 0.979 |
| F7 | 0.032 | 0.9757 | 0.0007 | 0.9857 | 0.0003 | 0.965 | 0.017 | 0.614 | 0.991 |
| F8 | 0.0403 | 0.9334 | 0.001 | 0.9231 | 0.0004 | 0.978 | 0.035 | 0.524 | 0.934 |
| F9 | 0.0292 | 0.8628 | 0.0008 | 0.9030 | 0.0004 | 0.978 | 0.003 | 0.921 | 0.956 |
| F10 | 0.0199 | 0.6579 | 0.0005 | 0.7662 | 0.0001 | 0.5829 | $3\times10^{-6}$ | 1.996 | 0.865 |
| F11 | 0.0528 | 0.7699 | 0.0014 | 0.7642 | 0.001 | 0.8234 | 0.065 | 0.461 | 0.804 |
| F12 | 0.0528 | 0.8012 | 0.0015 | 0.7860 | 0.001 | 0.814 | 0.071 | 0.446 | 0.775 |
| F13 | 0.0402 | 0.9192 | 0.001 | 0.9529 | 0.0005 | 0.9681 | 0.021 | 0.616 | 0.939 |
| F14 | 0.0221 | 0.7894 | 0.0005 | 0.9098 | 0.0001 | 0.797 | 0.001 | 0.996 | 0.913 |
| F15 | 0.013 | 0.8214 | 0.0001 | 0.8418 | $3\times10^{-5}$ | 0.9113 | 0.04 | 0.299 | 0.982 |
| F16 | 0.0122 | 0.9197 | 0.0001 | 0.8590 | $3\times10^{-5}$ | 0.9441 | 0.029 | 0.348 | 0.987 |

$k_h$,$k_{hc}$, $k_b$ and $k_{kp}$ corresponds to release constants of the different models and n is the release order of the Korshmeyer-Peppas model

showed a high release rate also exhibited non-Fickian release orders (< 0.4). On the contrary, the F11 and F12 experimental batches composed of ~0.3, 0.1 and 0.6 of carnauba wax, HPMC and Avicel PH_101, respectively exhibited a Fickian-like release with an "n" value of ~0.45 (Figure 2). The optimal range of an 8 h modified release formulation is shown in Figure 3. F9 was the only formulation that falls under the specifications. It is composed of 0.4, 0.2 and 0.4 levels of carnauba wax, HPMC and Avicel PH101, respectively.

## DISCUSSION

Batches that had a high HPMC and low carnauba wax composition presented a high swelling. On the other hand, matrices with a low HPMC loads and high Avicel PH101 levels showed more erosion. Swelling is caused by the overlap of the polymer chains and intermolecular entanglement leading to a three dimension (3D) network structure. As a result, the mobility of polymer chains is reduced, leading to an increase of viscosity of the polymeric matrix. On the other hand, batches containing a high level of carnauba wax did not show swelling, but partial erosion.

The multiple regression coefficients indicate that 98.3 and 97.6% of the experimental variance for "k" and "n," respectively were explained by the fitted cubic models. The other variability (1.7 and 2.4%, respectively) was due to a random error as demonstrated by the lack of fit test. The latter evaluates whether the variation due to the lack of fit of the model is small enough to be accepted as a negligible portion of the pure error. In this case, the null hypothesis established the lack of fit error as zero. These results show that the experimental variations observed for the release rate and release order could be attributed to randomized errors.

Formulations with a high composition of Avicel_PH101 (> 0.5) rendered high release rates. This is explained by its high hydrophilicity. On the other hand, batches containing high levels of HPMC in the matrix system increased the swelling tendency and hence, increased the rapid V.HCl release. Further, a large amount of Avicel_PH101 and a low level of HPMC made the matrix more erodible and hence, increased the release rate. In most cases, high values of carnauba wax and low values of HPMC made hydrophobicity more prevalent than swelling, resulting in a decrease of drug release rate. The optimal range of the desired 8 h drug release rate is depicted in the contour plot in green color and ranged between 0.0006 and 0.0054. This area is composed of HPMC, carnauba wax and Avicel_PH101 at ranges of 0.3 to 0.4, 0.4 to 0.5 and 0.35 to 0.4, respectively. In this area, a combination of the swelling and erosion mechanisms was predominant. Most batches had a release order different from 0.5 for indicating that a non-Fickian release kinetics predominated and the drug release mechanism involved a combination of erosion and matrix swelling by water filled pores (polymer chain-relaxation). Thus, results showed that swelling and erosion phenomena

**Table 3.** ANOVA table of the release rate (k) and release order (n).

| Source | Sum of Squares | DF | Mean square | F-value | p-value (α=0.05) |
|---|---|---|---|---|---|
| Model | 92.15 | 9 | 10.24 | 39.37 | 0.0001 |
| Linear mixture | 10.01 | 2 | 5.01 | 19.25 | 0.0025 |
| AB | 0.021 | 1 | 0.021 | 0.081 | 0.7859 |
| AC | 0.16 | 1 | 0.16 | 0.60 | 0.4683 |
| BC | 69.69 | 1 | 69.69 | 267.97 | <0.0001 |
| ABC | 1.95 | 1 | 1.95 | 7.50 | 0.0338 |
| AB(A-B) | 0.88 | 1 | 0.88 | 3.40 | 0.1147 |
| AC(A-C) | 23.36 | 8 | 23.36 | 89.83 | <0.0001 |
| BC(B-C) | 13.40 | 3 | 13.40 | 51.51 | 0.0004 |
| Residual | 1.56 | 6 | 0.26 | - | - |
| Lack of Fit | $3.991\times10^{-3}$ | 1 | $3.991\times10^{-3}$ | 0.013 | 0.9143 |
| Pure error | 1.56 | 5 | 0.31 | - | - |
| SD=0.51 | $r^2$ | 0.9833 | - | - | - |
| | | **Release order (n)** | | | |
| Model | 2.73 | 9 | 0.30 | 27.59 | 0.0003 |
| Linear mixture | 0.27 | 2 | 0.14 | 12.47 | 0.0073 |
| AB | $3.429\times10^{-3}$ | 1 | $3.429\times10^{-3}$ | 0.31 | 0.5967 |
| AC | $1.574\times10^{-3}$ | 1 | $1.574\times10^{-3}$ | 0.14 | 0.7181 |
| BC | 2.04 | 1 | 2.04 | 185.17 | <0.0001 |
| ABC | 0.04 | 1 | 0.04 | 3.19 | 0.1242 |
| AB(A-B) | 0.064 | 1 | 0.064 | 5.84 | 0.0522 |
| AC(A-C) | 0.56 | 1 | 0.56 | 51.32 | 0.0004 |
| BC(B-C) | 0.34 | 1 | 0.34 | 31.32 | 0.0014 |
| Residual | 0.066 | 6 | 0.011 | 0.62 | 0.5750 |
| Lack of Fit | $5.650\times10^{-3}$ | 1 | $5.650\times10^{-3}$ | 0.47 | 0.5242 |
| Pure error | 0.060 | 5 | 0.012 | - | .- |
| SD=0.10 | $r^2$ | 0.9764 | - | - | - |

A = carnauba wax; B = HPMC; C = Avicel_PH101; DF = degrees of freedom.

dictated the kinetics and mechanism of drug release from modified release formulations, but one process predominated over the other because of different excipient characteristics.

Formulations that showed a high release rate also exhibited low release orders (< 0.4), indicating a fast disruption of the eroding excipient matrix leading to a non-Fickian release profile. Batches F11 and F12 presented a rapid release in the intestinal medium due to the high water wicking power of Avicel_PH101 (Figure 2). This is due to the large formation of hydrogen bonds of cellulose upon water contact which counteracted the hydrophobic and swelling effect of carnauba wax and HPMC, respectively. The grid search within the contour plots was employed to select the optimal region that presented an “n” value between 0.86 and 1.19 and is shown in green color. This area also matches the region of Figure 1a which had the optimal values of release rate. This region was composed of HPMC (0.3 to 0.4), carnuba wax (0.4 to 0.5) and Avicel (0.35 to 0.4). Matrices produced in this study are considered porous systems and thus, drug release also depended on the drug dissolution/diffusion rate through the pores. Since drug loading was constant (240 mg), polymer swelling also affected the drug release kinetics.

The *in vitro* dissolution profiles shown in Figure 2 simulate the gastrointestinal transit of the drug at a pH of 1 for 1 h followed by treatment at pH of 6.8 for 7 h. It is evident that the drug release increased with time, but a larger dissolution was achieved mainly at a pH of 6.8 due to the larger residence time. The increase in dissolution rate with increasing pH could be attributed to the ions of the buffer which enhanced the hydration properties of the drug. The hydrodynamic particle consists of the solute and solvent molecules bound or adsorbed to the surface. The molecule transport takes place through interstices of polymer chains filled with the solvent.

Formulations F7 and F9 fall within the desirable limits

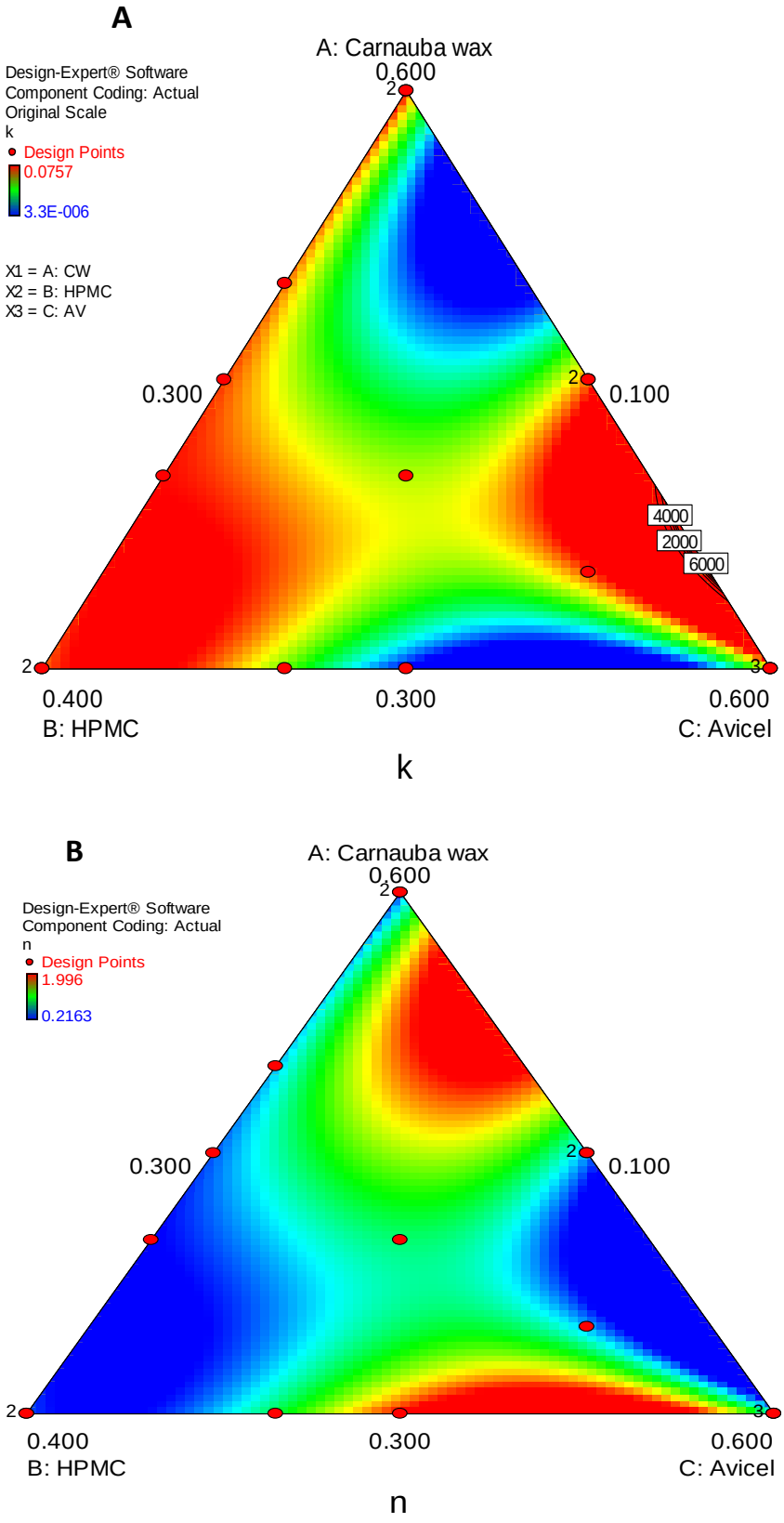


**Figure 1.** Contour plot for (A) the "k" release rate and (B) the "n" release order.

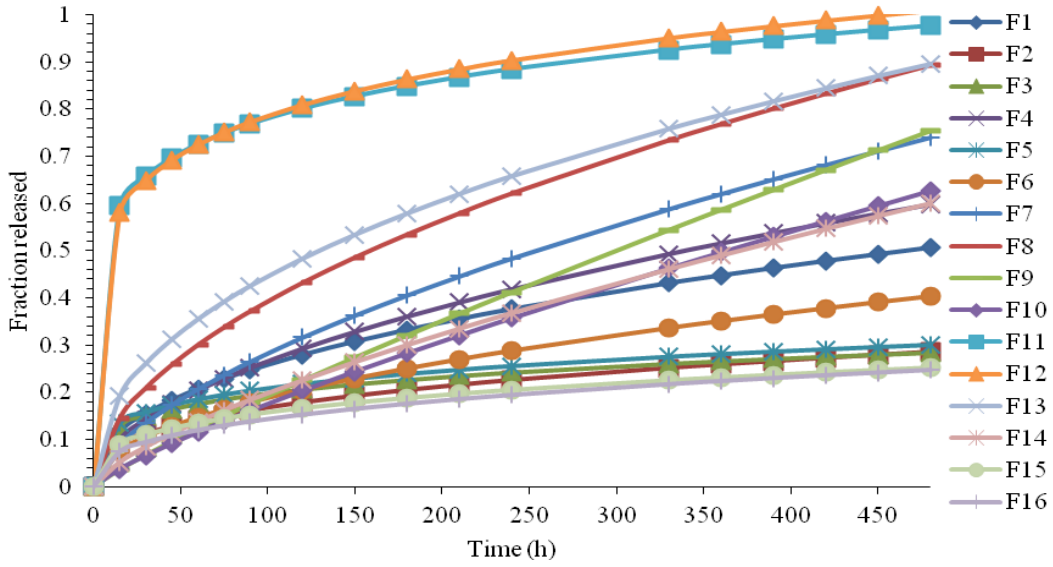


**Figure 2.** Release profiles obtained from the 16 formulations of the mixture design.

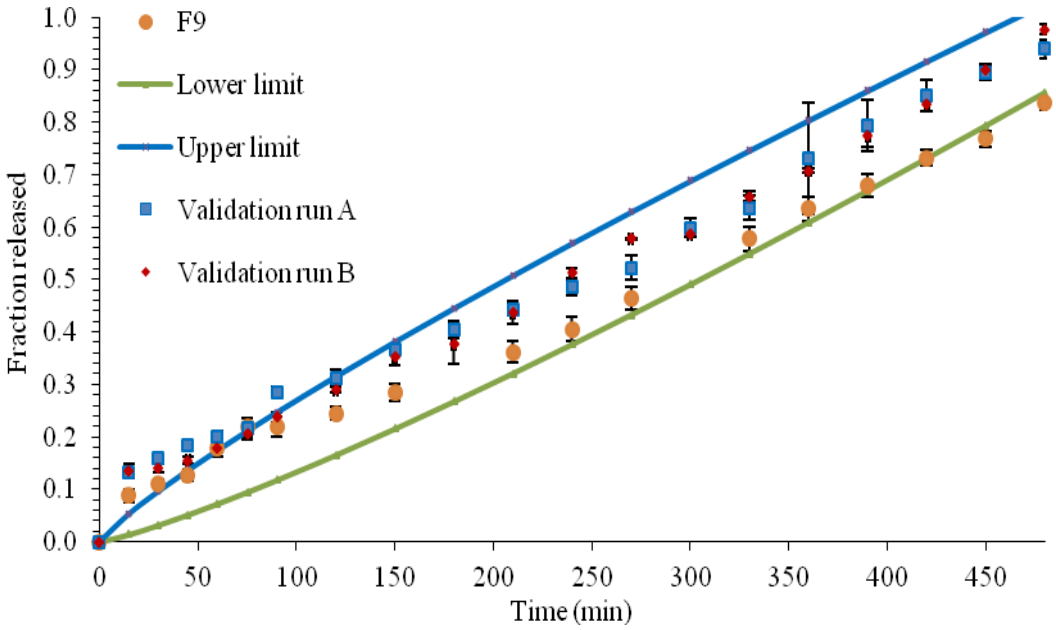


**Figure 3.** Validation runs of formulation 9 compared to the limits established by the USP.

for an optimal 8 h release profile. However, the cubic models presented F9 as the most optimal formulation composed of carnauba wax, HPMC and Avicel_PH101 at the 0.4, 0.2 and 0.4 levels, respectively. Two more experimental runs of a formulation with this composition were conducted to assess the validity of the cubic models and results are depicted in Figure 3. This composition fall within the USP specifications and hence, was selected to achieve the desired 8 h release profile of V.HCl.

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**REFERENCES**

Bhagwat DA, Kawtikwar PS, Sakarkar DM (2008). Sustained release matrices of verapamil HCl using glyceryl monosterate and stearic acid. Res. J. Pharm. Tech. 1:405-409.

Chouldhury PK, Kar M, Chauhan CS (2008). Cellulose acetate microspheres as a floating depot system to increase gastric retention of antidiabetic drug: formulation, characterization and *in vitro- in vivo* evaluation. Drug Dev. Ind. Pharm. 34:349-354.

Deshmane SV, Channawar MA, Chandewar AV, Josh UM (2009). Chitosan based sustained release mucoadhesive buccal patches containing verapamil HCl. Int. J. Pharm. Pharm. Sci. 1:216-239.

Elkheshen A (2001). Interaction of verapamil hydrochloride with carbopol 934P and its effect on the release rate of the drug and the water uptake of the polymer matrix. Pharm. Dev. Ind. Pharm. 27:925-934.

Khamanga SD, Walker RB (2011). Drug transport mechanisms from carbopol/Eudragit verapamil sustained-release tablets. Dissol. Technol. 1:30-38.

Mathers CD, Loncar D (2006). Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 3:e442.

Montgomery DC (2012). Design and Analysis of Experiments, 7th Edition. Wiley, NY. 680p

Ramírez M, Villafuerte L (2004). Effect of formulation variables on verapamil hydrochloride release from hydrated HPMC matrices. Rev. Soc. Quím. Méx. 48:326-331.

Ritger PL, Peppas NA (1987). A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J. Control Release 5:37-42.

Siepman J, Peppas NA (2001) Modeling of drug release from delivery systems based on hydroxypropylmethylcellulose (HPMC). Adv. Drug Rev. 48:139-157.

Wu XY, Zhou Y (1998). Finite element analysis of diffusional drug release from complex matrix systems II. Factors influencing release kinetics. J. Control Release 51:57–71.

Yassin AE, Alsarra IA, Al-Mohizea AM (2006). Chitosan beads as a new gastroretentive system of verapamil. Sci. Pharm. 74:175-188.