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# Release characteristics of some bronchodilators from compressed hydrophilic polymeric matrices and their correlation with molecular geometry

S.K. Baveja, K.V. Ranga Rao, Amarjit Singh and V.K. Gombar

*Department of Pharmaceutical Sciences, Panjab University, Chandigarh (India)*

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## Summary

For a series of structurally related water-soluble bronchodilators namely ephedrine hydrochloride, phenylpropanolamine hydrochloride, salbutamol sulphate, terbutaline sulphate, reproterol hydrochloride and aminophylline, the release rates from compressed matrices of hydroxypropylmethylcellulose (HPMC) were investigated. On varying the drug tracer it was observed that despite almost identical aqueous solubilities different drug molecules show different release rates from matrix tablets. The release rates through HPMC matrices of different viscosity grades were found to be highly correlated ($r > 0.95$) with the accessible surface area (ASA) of the drugs; indicating the importance of geometrical features like shape and size of the solute molecules in release rates through HPMC matrices. The predictive capability of the correlations was tested for orciprenaline sulphate, outside the training sample. The agreement between the experimental and the predicted release rates was found to be within experimental uncertainty ($\pm 5\%$). The internal consistency of the quantitative relationship was established by the 'hold-one-out' procedure.

## Introduction

One of the well-known methods of formulating controlled-release dosage forms is by creating a physical barrier to the release of water-soluble drugs (Lee and Robinson, 1978). Christenson and Dale (1962) introduced a method of incorporating the drug in a matrix tablet of hydrophilic polymers to achieve controlled release. This has attracted considerable attention (Korsmeyer et al., 1983a) and has been described by several workers (Huber et al., 1966; Lapidus and Lordi, 1966, 1968; Huber and Christenson, 1968; Buri and Doelker, 1980). The drug release profiles have been analyzed using equations that were derived by T. Higuchi (1963) and W. Higuchi (1962) and adapted by Lapidus and Lordi (1968). The equations have been further modified (Bamba et al., 1979a and b; Korsmeyer and Peppas, 1983; Korsmeyer et al., 1983a) and reviewed (Buri, 1984; Peppas, 1985; Gander et al., 1986a and b). The effects of several factors related to formulation, fabrication and physicochemical characteristics of drugs on the release rates have been studied extensively (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Salomon et al., 1979a and b; Korsmeyer et al., 1983a and b; Daly et al., 1984; Ford et al., 1985a and b; Baveja and Ranga Rao, 1986).

*Correspondence:* S.K. Baveja, Department of Pharmaceutical Sciences, Panjab University, Chandigarh 160014, India.

We have been engaged in formulation of prolonged-release matrix tablets of certain bronchodilator drugs. We have selected 6 structurally related water-soluble bronchodilators namely, phenylpropanolamine hydrochloride, ephedrine hydrochloride, salbutamol sulphate, terbutaline sulphate, reproterol hydrochloride and aminophylline, and determined their release rates from compressed matrices of hydroxypropylmethylcellulose (HPMC). It was observed that although all the drugs have similar aqueous solubilities (freely soluble) yet their release rates are different. Korsmeyer et al. (1983a) studied the release of potassium chloride, phenylpropanolamine hydrochloride and bovine serum albumin through polyvinylalcohol matrices and observed that as the molecular size of the drug increases the release rate falls. The phenomenon was attributed to decreased diffusivity. However, molecular weight was taken as the criterion of molecular size and the study was not aimed at establishing any explicit relationship. In the present paper an attempt has been made to correlate the release rates of the above-mentioned drug molecules diffusing out of swollen matrices of HPMC K4M, HPMC K15M and HPMC K100M with their molecular shape and size. Molecular connectivity indices (Kier and Hall, 1976a) and accessible surface area (ASA) (Pearlman, 1980) of drug molecules have been taken as the parameters for quantification of molecular shape and size. Connectivity indices, ${}^{m}\chi_t^l$, of different order (Kier et al., 1975), type (Kier and Hall, 1976b) and complexity (Jain et al., 1984) quantify molecular size and shape at the topological level whereas ASA is based upon the 3-dimensional geometry of a molecule.

## Materials and Methods

*Materials*

Ephedrine hydrochloride IP. (Warner, India), phenylpropanolamine hydrochloride USP (Eskayef, India), salbutamol sulphate BP (Cipla, India), terbutaline sulphate BP (Ranbaxy, India), reproterol hydrochloride (Schering, U.K.) aminophylline BP (Boehringer Ingelheim, U.K.) and orciprenaline sulphate BP (Boehringer Ingelheim, U.K.) were used. Hydroxypropylmethylcellulose (Colorcon Ltd., U.K.) of 3 viscosity grades was used, i.e., Methocel K4M, Methocel K15M and Methocel K100M. All the materials were sieved and the fraction passing through 100-mesh screen (British Standard Sieve) with particle size range 5–50 $\mu$m were used for the study.

*Tablet formulae*

All the tablets contained 50 mg of the drug. Compaction was accomplished using the direct compression technique. The drug and HPMC (1 : 1) were thoroughly blended and passed through a 100-mesh screen to achieve uniformity. The mixture was compressed into tablets with 6 mm flat-faced punches on Manesty single-punch hand-operated tabletting machine. The compaction pressure was kept constant by monitoring the hardness of tablets (5–6 kg/cm$^2$).

*Dissolution studies*

The dissolution rates of tablets at 37 °C were monitored using Thermonik dissolution rate test equipments (Campbell, Bombay, India) as per USP XXI specification with 900 ml of distilled water as the dissolution medium. The USP 1 dissolution method was used at a basket rotation speed of 100 rpm. The dissolution rates of aminophylline, salbutamol sulphate and reproterol hydrochloride tablets were calculated by recording the absorptions at 270 nm, 277 nm and 273 nm, respectively, using a Lambda 3 UV-VIS spectrophotometer (Perkin Elmer). The dissolution samples of terbutaline sulphate and orciprenaline sulphate tablets were analysed colorimetrically at 680 nm by the method described by Kamalapurkar and Priolkar (1983). The samples of ephedrine hydrochloride and phenylpropanolamine hydrochloride tablets were analyzed by the periodate–oxidation method at 247 nm (Chafetz, 1963). The dissolution studies were performed in triplicate for each batch of the tablets and the results were reproduced within $\pm 5\%$ of the mean value.

*Calculation of connectivity indices*

Connectivity indices, ${}^{m}\chi_t^l$, of order $m$ (Kier et al., 1975), type $t$ (Kier and Hall, 1976a and b) and complexity level $l$ (Jain et al., 1984) are unitless

structure descriptors which can uniquely and unambiguously quantify salient topological features like number and types of atoms and bonds, extent of branching, cyclisation etc., depending upon two-dimensional connectedness of non-hydrogen atoms in a molecule. The calculation of these indices begins with drawing a hydrogen-suppressed graph (HSG) whose vertices and edges represent non-hydrogen atoms and bonds, respectively. To every vertex is then assigned a numerical quantity, called $\delta$ value, depending upon the chosen level of complexity. Corresponding to each of the subgraphs, ${}^{m}g_t$, of order $m$ and type $t$ contributing to the index ${}^{m}\chi_t^l$ is then computed the quantity $C_i$:

$$C_i = \prod_{j=1}^{m+1} \left(\delta_j^l\right)_i^{-1/2} \qquad (1)$$

Here $m + 1$ is the number of vertices constituting the $i^{\text{th}}$ subgraph as embedded in the molecule. The $C_i$ values are then summed up (Eqn. 2) to yield the desired connectivity index.

$${}^{m}\chi_t^l = \sum_{i=1}^{{}^{m}g_t} C_i \qquad (2)$$

In the present work valence connectivity indices have been employed and the $\delta^v$ values of various atoms have been taken from Kier (1980). The HSG was numerically transformed into an adjacency matrix and input to a FORTRAN computer program VG0386 (Gombar et al., unpublished work), capable of computing all types of indices (Jain et al., 1984) upto seventh order. In the present work only ${}^{0}\chi^{v}$, ${}^{1}\chi^{v}$, ${}^{2}\chi^{v}$, ${}^{3}\chi^{v}$ and ${}^{3}\chi_1^{v}$ indices were calculated.

*Calculation of ASA*

Different measures of surface area viz. cavity surface area (CSA) or ASA, surface area (SA) and smoothed surface area (SSA) or contact surface area appeared in the literature (Hermann, 1972; Pearlman, 1980) depending upon the definition of molecular surface. When a "solvent sphere" is rolled over the Van der Waals surface generated by the intersection of all the "atomic spheres" in a molecule, the surface traced out by the centre of the solvent sphere is termed ASA. The ASA represents the two-dimensional space available to a solvent molecule in contact with a given tracer. Any changes in the molecular conformation are significantly reflected in the magnitude of ASA.

Both non-computational and computational methods (Harris et al., 1973; Pearlman, 1980; Lande et al., 1985) are available for the estimation of ASA associated with a molecule. In this study the algorithm according to Hermann (1972) using 180 cutting planes arranged in 1° increments about the axis of each "atomic sphere" is used. A microcomputer version of the FORTRAN program by Pearlman (1981) was employed to compute ASA on an in-house 8-bit machine (ESPL Super-MICRO 8). For ephedrine hydrochloride, phenylpropanalamine hydrochloride, salbutamol sulphate, terbutaline sulphate, reproterol hydrochloride and aminophylline the X-ray diffraction data (Phillips, 1954; Kier, 1968; Beale and Stephenson, 1972; Leger et al., 1978; Hickel et al., 1982; Sutor, 1958; Beale and Grainger, unpublished work) were used to define the input conformations. In the instance of non-availability of X-ray diffraction data of any molecule or part of a molecule standard geometry (Kennard, 1977) in the staggered conformation was assumed. The solvent radius for water has been taken to be 0.15 nm and the values of van der Waals radii used for atoms C, H, N and O are 0.17, 0.12, 0.15 and 0.14 nm, respectively (Pearlman, 1981).

*Regression analysis*

The program listed by Purcell et al. (1973) was used for linear multiple regression analysis. The set of independent variables included ASA, ${}^{0}\chi^{v}$, ${}^{1}\chi^{v}$, ${}^{2}\chi^{v}$, ${}^{3}\chi^{v}$ and ${}^{3}\chi_1^{v}$. All possible combinations of connectivity indices were used to develop the correlations. In view of the small sample size the analysis was terminated after two-variable correlations.

## Results and Discussion

The experimentally measured percentages of drugs released through the matrices of HPMC

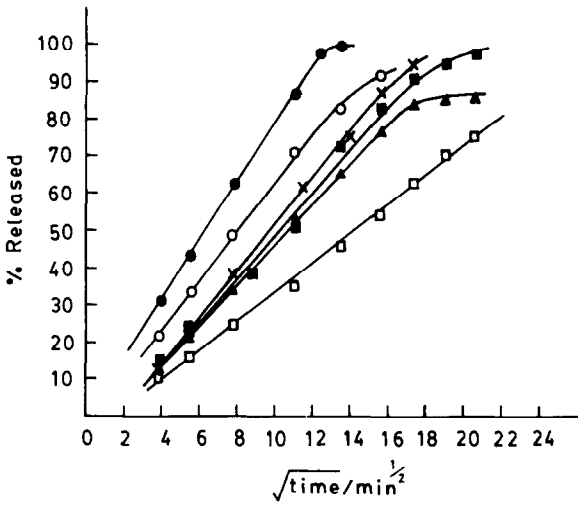


Fig. 1. Drug release profiles (●, phenylpropanolamine hydrochloride; ○, ephedrine hydrochloride; ×, aminophylline; ■, terbutaline sulphate; ▲, salbutamol sulphate; □, reproterol hydrochloride) through HPMC K4M matrices.

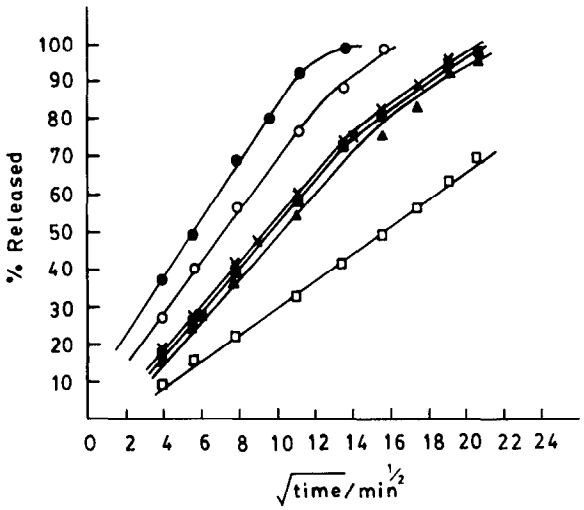


Fig. 2. Drug release profiles (●, phenylpropanolamine hydrochloride; ○, ephedrine hydrochloride; ×, aminophylline; ■, terbutaline sulphate; ▲, salbutamol sulphate; □, reproterol hydrochloride) through HPMC K15M matrices.

K4M, HPMC K15M and HPMC K100M are plotted against $\sqrt{\text{time}}$ in Figs. 1, 2 and 3, respectively. It can be seen, in all the cases, that the drug release follows a Higuchian pattern (Higuchi, 1963). The absence of positive deviation indicates that the drug is released primarily by diffusion and that attrition contributes negligibly (Lapidus and Lordi, 1968). The release rates (RR) were calculated by subjecting the points representing up to 75% release to least-square linear fitting. The values are collected in Table 1. It can be seen

TABLE 1

*ASA and experimental, calculated and predicted RR of some bronchodilator drugs through HPMC matrices*

| Drug | ASA ($nm^2$) | RR/% · $min^{-1/2}$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | HPMC K4M | | | HPMC K15M | | | HPMC K100M | | |
| | | Experimental | Calculated (Eqn. 9) | Predicted (hold-one-out) | Experimental | Calculated (Eqn. 10) | Predicted (hold-one-out) | Experimental | Calculated (Eqn. 11) | Predicted (hold-one-out) |
| Phenylpropanolamine hydrochloride | 3.579 | 7.520 | 7.251 | 7.144 | 8.060 | 7.762 | 7.566 | 7.970 | 7.587 | 7.377 |
| Ephedrine hydrochloride | 3.854 | 6.460 | 6.854 | 7.054 | 6.980 | 7.262 | 7.370 | 6.680 | 7.072 | 7.240 |
| Aminophylline | 4.611 | 6.230 | 5.896 | 5.880 | 6.030 | 6.055 | 6.062 | 6.020 | 5.828 | 5.814 |
| Terbutaline sulphate | 4.658 | 5.904 | 5.841 | 5.875 | 5.940 | 5.986 | 5.995 | 5.720 | 5.757 | 5.790 |
| Salbutamol sulphate | 4.709 | 5.504 | 5.784 | 5.871 | 5.900 | 5.914 | 5.917 | 5.450 | 5.682 | 5.746 |
| Reproterol hydrochloride | 6.708 | 3.900 | 3.892 | 3.990 | 3.600 | 3.530 | 3.320 | 3.310 | 3.224 | 3.020 |

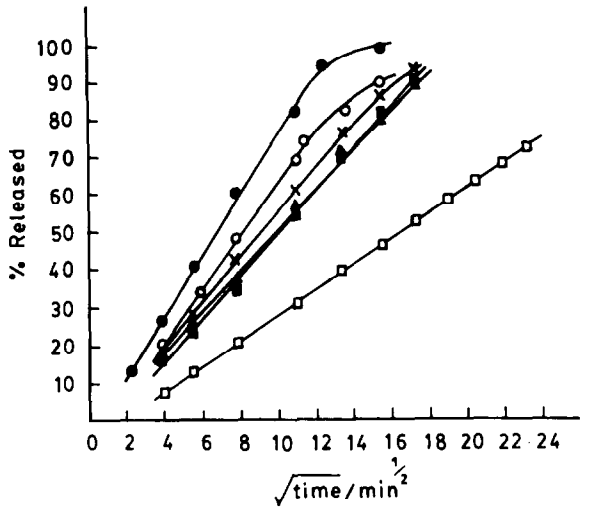


Fig. 3. Drug release profiles (●, phenylpropanolamine hydrochloride; ○, ephedrine hydrochloride; ×, aminophylline; ■, terbutaline sulphate; ▲, salbutamol sulphate; □, reproterol hydrochloride) through HPMC K100M matrices.

that release rates (RR/%. $min^{-1/2}$) through different matrices for a given drug do not vary significantly even though the viscosity grade of HPMC matrices is changed from 4 M through 100 M. This is in agreement with the earlier observations made by Salomon et al. (1979a) and Ford et al. (1985a).

The slopes of the lines in Figs. 1–3 reveal that the release rate falls with increase in molecular bulk (size and shape) of the drug. In order to rationalize this trend quantitatively, the release rates were regressed against valence connectivity indices, ${}^{m}\chi_t^v$, of different orders and types as these indices can quantify shape and size of a molecule at the topological level.

The best one-variable correlation was obtained with the zero-order index, ${}^{0}\chi^{v}$. Eqns. 3–5 represent the correlations between ${}^{0}\chi^{v}$ and release rates through HPMC K4M, HPMC K15M and HPMC K100M matrices, respectively.

$$\mathrm{RR}/\% \cdot \mathrm{min}^{-1/2}(\mathrm{HPMC\ K4M}) \quad (3)$$

$$= 9.018 - \ 0.317\ {}^{0}\chi^{v}$$

$$(\pm 0.539)\ (\pm 0.053)$$

$$r = 0.948,\ S = 0.403,\ F_{1,4} = 35.7,\ P < 0.25$$

$$\mathrm{RR}/\% \cdot \mathrm{min}^{-1/2}(\mathrm{HPMC\ K15M}) \quad (4)$$

$$= 9.622 - \ 0.359\ {}^{0}\chi^{v}$$

$$(\pm 0.855)\ (\pm 0.084)$$

$$r = 0.905,\ S = 0.639,\ F_{1,4} = 18.1,\ P < 0.25$$

$$\mathrm{RR}/\% \cdot \mathrm{min}^{-1/2}(\mathrm{HPMC\ K100M}) \quad (5)$$

$$= 9.778 - \ 0.402\ {}^{0}\chi^{v}$$

$$(\pm 0.802)\ (\pm 0.079)$$

$$r = 0.930,\ S = 0.599,\ F_{1,4} = 25.8,\ P < 0.25$$

Here $r$ is the correlation coefficient, $S$ is the standard error of the estimate and $F$ is the F-ratio. Standard error of the regression coefficients is given in parenthesis. The inclusion of ${}^{0}\chi^{v}$ in the regression indicates the role of molecular size in drug release. However, as this structure descriptor cannot completely quantify the extent of branching, and thus shape, correlations were attempted forcing cluster-type connectivity indices in the regression. The best two-variable correlations were

TABLE 2

*ASA and predicted RR of the drugs in prediction set through HPMC matrices*

| Drug | ASA ($nm^2$) | Predicted RR/% · $min^{-1/2}$ | | |
|---|---|---|---|---|
| | | HPMC K4M (Eqn. 9) | HPMC K15M (Eqn. 10) | HPMC K100M (Eqn. 11) |
| Orciprenaline sulphate | 4.493 | 6.035 | 6.223 | 6.006 |
| Phenylephrine hydrochloride | 3.869 | 6.835 | 7.235 | 7.044 |
| Fenoterol hydrobromide | 5.665 | 4.796 | 4.667 | 4.396 |

TABLE 3

*Predicted and experimental RR of orciprenaline sulphate through HPMC matrices*

| Matrix tablet | $RR/\% \cdot min^{-1/2}$ | | | |
|---|---|---|---|---|
| | Experimental | Predicted | Equation used | $\lvert\Delta\rvert\%$ |
| HPMC K4M | 6.301 | 6.035 | (9) | 4.22 |
| HPMC K15M | 6.240 | 6.223 | (10) | 0.27 |
| HPMC K100M | 6.150 | 6.006 | (11) | 2.34 |

obtained with ${}^3\chi^v$ and ${}^3\chi_1^v$, (Eqns. 6–8).

$$RR/\% \cdot min^{-1/2}(\text{HPMC K4M}) \quad (6)$$

$$= 8.690 - \underset{(\pm 0.429)}{0.776\ {}^3\chi^v} - \underset{(\pm 0.277)}{0.740\ {}^3\chi_1^v}$$

$$(\pm 0.131)$$

$$r = 0.969,\ S = 0.359,\ F_{2,3} = 23.4,\ P < 0.05$$

$$RR/\% \cdot min^{-1/2}(\text{HPMC K15M}) \quad (7)$$

$$= 9.292 - \underset{(\pm 0.703)}{0.905\ {}^3\chi^v} - \underset{(\pm 0.455)}{0.803\ {}^3\chi_1^v}$$

$$(\pm 0.215)$$

$$r = 0.940,\ S = 0.588,\ F_{2,3} = 11.5,\ P < 0.10$$

$$RR/\% \cdot min^{-1/2}(\text{HPMC K100M}) \quad (8)$$

$$= 9.393 - \underset{(\pm 0.637)}{0.991\ {}^3\chi^v} - \underset{(\pm 0.413)}{0.947\ {}^3\chi_1^v}$$

$$(\pm 0.195)$$

$$r = 0.959,\ S = 0.533,\ F_{2,3} = 17.3,\ P < 0.10$$

An improvement in all the statistical parameters is observed in these correlations. The correlations, however, were not found to be internally consistent when tested by the hold-one-out procedure. Also, in view of low observation-to-variable ratio of 3, these relationships have a high probability of chance correlation. In spite of limited data the two-variable regression can be retained as an indication in the light of its high significance.

The connectivity indices have the disadvantage that they provide incomplete quantification of molecular size and shape as, in the first place, these are calculated from HSGs, and secondly, there is no consideration of interatomic distances, angles and torsional angles. On the other hand, ASA is a structure descriptor derived from the 3-dimensional geometry of all the atoms including hydrogens. This parameter quantifies molecular structure with respect to the molecular surface which can be accessed by a solvent. Therefore, an attempt was made to develop correlations between ASA and release rates. The correlations in case of HPMC K4M, HPMC K15M and HPMC K100M matrices are given in Eqns. 9–11.

$$RR/\% \cdot min^{-1/2}(\text{HPMC K4M}) \quad (9)$$

$$= 38.687 - \underset{(\pm 4.079)}{5.346 \cdot \ln(ASA)}$$

$$(\pm 0.665)$$

$$r = 0.970,\ S = 0.324,\ F_{1,4} = 64.58,\ P < 0.10$$

$$RR/\% \cdot min^{-1/2}(\text{HPMC K15M}) \quad (10)$$

$$= 47.363 - \underset{(\pm 2.626)}{6.735 \cdot \ln(ASA)}$$

$$(\pm 0.428)$$

$$r = 0.992,\ S = 0.208,\ F_{1,4} = 247.32,\ P < 0.05$$

$$RR/\% \cdot min^{-1/2}(\text{HPMC K100M}) \quad (11)$$

$$= 48.424 - \underset{(\pm 3.966)}{6.945 \cdot \ln(ASA)}$$

$$(\pm 0.647)$$

$$r = 0.983,\ S = 0.315,\ F_{1,4} = 115.28,\ P < 0.10$$

It can be seen that all these correlations are more significant in all the statistical tests than the corresponding one-variable and two-variable correlations with topological indices. This confirms the expectation that ASA carries better quantification regarding size and shape of a molecule than the connectivity indices. The release rates predicted from Eqns. 9–11 are compared with the experimental values in Table 1. The absolute average deviations of 3.56%, 1.85%, 3.56%, observed with HPMC K4M, HPMC K15M, &HPMC K100M matrices, respectively, are of the order of experimental error.

The true test of any structure–property correla-

tion is the confidence with which it can predict the magnitude of property, particularly of compounds outside the training sample. Therefore, ASA was computed for 3 drugs, namely orciprenaline sulphate, phenylephrine hydrochloride, and fenoterol hydrobromide which belong to the same class. They have comparable aqueous solubilities and are structurally related to the 6 drugs in the training set.

Their release rates were predicted from Eqns. 9–11 and are given in Table 2. During the course of study, however, it was possible to procure orciprenaline sulphate for confirmation of the predicted release rates. The release rates through compressed matrices of HPMC K4M, HPMC K15M and HPMC K100M were determined under similar conditions as for the training sample. The predicted and experimental values are compared in Table 3.

The agreement between the values is within the experimental uncertainties (5%). This shows high predictive capability of the correlations in all the cases with maximum deviation of 4.2% in the case of HPMC K4M.

The reliability of these correlations was further established by including orciprenaline sulphate in the training sample and predicting release rates of all the drugs by the 'hold-one-out' procedure. The results are summarized in Table 1. From the fact that the absolute average deviation is still in the order of experimental error, it can be concluded that the correlations are internally consistent and can be employed for prediction of release rates with confidence. An attempt was made to develop a single relationship applicable to predict the release rates through HPMC matrices of different viscosity grades. It can be seen from the regression coefficients of Eqns. 9–11 that the slopes and intercepts of the correlations for HPMC K15M and HPMC K100M are almost the same whereas for HPMC K4M they are quite different. This difference can be attributed to the lower viscosity grade HPMC K4M matrices which are more prone to erosion than the HPMC K15M and HPMC K100M matrices. The release rate data for HPMC K15M and HPMC K100M matrices was combined and regressed against ln(ASA). The correlation thus obtained (Eqn. 12) can be regarded to have more significance

$$RR/\% \cdot \min^{-1/2} = 48.286 - 6.908 \cdot \ln(ASA) \quad (12)$$
$$(\pm 2.494)\ (\pm 0.407)$$

$r = 0.983,\ S = 0.277,\ F_{1,10} = 288.19,\ P < 0.05$

as for an increased degree of freedom the correlation coefficient remains almost the same.

The work regarding synthesis/procurement of other structurally related drugs is currently being undertaken to further test the reported correlations.

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