DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(2), 347-360 (1990)

AN APPROACH FOR THE PREDICTION OF THE INTRINSIC DISSOLUTION RATES OF DRUGS UNDER UNBUFFERED CONDITIONS

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ABSTRACT

Predicted intrinsic dissolution rates were obtained under unbuffered conditions for ionizable and unionizable drugs employing a simple approach based on the diffusion layer theory. These rates correlated well with experimentally determined values for Cromakalim, Diproteverine HCl and Ephedrine thereby substantiating the applicability of the approach for these molecules. For ionizable molecules, the pH at the surface of the dissolving particles rather than the bulk pH, in addition to the other parameters of the Noyes-Whitney equation, determine the intrinsic dissolution rates. For unionizable drugs, the rate is primarily determined by the original Noyes-Whitney equation. The model could be employed in the selection of an appropriate chemical or physical form of a drug for development.

INTRODUCTION

A generally useful rule of thumb is that if the in vitro intrinsic dissolution rate of a drug substance, at ∞ rotation speed, is < 1 mg.cm^{-2}.min^{-1} then it could exhibit dissolution rate limited bioavailability[1,2].

Determination of the intrinsic rate of dissolution is time consuming, requiring the production of compacts and the dissolution testing of these compacts in a specially designed holder/stirrer at various rotation speeds[1,3-10]. In addition, compaction can in certain cases cause polymorphic transformation[11] leading to the generation of erroneous data.Mooney et al.[12] developed a model, based on the diffusion layer theory, to characterise the initial steady-state dissolution of carboxylic acids. These workers employed intrinsic solubility, pKa and diffusion coefficient to accurately predict the initial intrinsic dissolution rates of acids as a function of pH. Oravec and Parrott[13] found good agreement between experimentally determined dissolution rates of p-amino benzoic acid and those calculated from the original two zone model[14] and the Higuchi et al. model[15].

The purpose of the present work was to investigate a simple approach for predicting the intrinsic dissolution rates of various forms of drugs (i.e. acids, bases, salts and unionizable molecules) in unbuffered media. This could be an added tool to aid the selection of an appropriate crystal or salt form of the drug during preformulation screening.

THEORY

The case for the dissolution of a monobasic acid is presented as an example. Similar arguments and derivations will

apply when considering other forms. The method is based on the diffusion layer model first described by Nernst and Brunner[14] and later elaborated on by Higuchi et al.[15] and Mooney et al.[12,16-17]. Using this model of simultaneous diffusion and chemical reactions (the former being the slowest and hence dissolution rate determining), equation 1 was derived to calculate the pH at the surface of the dissolving particles, pH_s[12]:

$$pH_s=-\log[[-1.68 \times 10^{-3}([H^+]_h-[OH^-]_h)-(2.82 \times 10^{-6}([H^+]_h-[OH^-]_h)^2 + 6.72 \times 10^{-3}(3.86 \times 10^{-17} + Dk_a[HA]_o))^{0.5}]/-3.36 \times 10^{-3}] \quad ...1$$

where D and K_a are the diffusion coefficient and the dissociation constant of the drug respectively. It was assumed in deriving equation 1 that the diffusion coefficients of H^+ and OH^- are equal at $1.68 \times 10^{-3} cm^2.min^{-1}$ [15,18] and that the ionization constant of water at 37°C is 2.30×10^{-14} [19].

As an approximate value for the diffusion coefficient of the drug a simplified version of the Stokes-Einstein equation could be used:

$$D = K/M^{0.333} \quad .....2$$

where K is a constant and M is the molecular weight of the diffusant. Comparison of experimental D values and molecular weights for a variety of compounds can be shown to yield an approximate K value of $2.40 \times 10^{-3} cm^2.min^{-1}$. Therefore

$$D = 2.40 \times 10^{-3}/M^{0.333} \ (cm^2.min^{-1}) \quad ..... 3$$

and substitution of equation 3 into equation 1 yields equation 4.

$$pH_s = -\log[[-1.68 \times 10^{-3}([H^+]_h - [OH^-]_h) - (2.82 \times 10^{-6}([H^+]_h - [OH^-]_h)^2 + 6.72 \times 10^{-3}(3.86 \times 10^{-17} + 2.40 \times 10^{-3} K_a [HA]_o / M^{0.333}))^{0.5} / -3.36 \times 10^{-3}] \quad \ldots\ldots 4$$

The only requirements to solve equation 4 are the pH of the medium, the solubility of the unionized form of the drug and the ionization constant. pH_s, the surface pH, is an important parameter which determines the dissolution rate of drugs and could be unrelated to the pH of the bulk of the medium depending upon the solubility and the degree of ionization[20-21]. Only for the case of unionizable drugs dissolving under sink conditions is the original form of the Noyes-Whitney equation is applicable.

$$R = D[HA]_o M/h \quad \ldots\ldots 5$$

where R is the intrinsic dissolution rate in $mg.cm^{-2}.min^{-1}$.

The film thickness, h, can be calculated from knowledge of the diffusion coefficient, viscosity and rotation speed according to Levich[22]

$$h(cm) = 1.61\ D^{0.333}\ V^{0.166}/W^{0.5} \quad \ldots\ldots 6$$

where V is the kinematic viscosity of the medium in $cm^2.min^{-1}$ (0.42 $cm^2.min^{-1}$ for water at 37°C) and W is the angular velocity in $rad.min^{-1}$ (1 rpm = 6.3 $rad.min^{-1}$). It should be noted that the Levich model predicts varying film thicknesses, depending on $(D)^{0.333}$ of the diffusant, in a multidiffusant system. However, the differences between these thicknesses are dampened by the one-third power dependence of the thickness on the diffusion coefficient[12]. Therefore, in order to simplify the computations involved it can be assumed that there is only a

single boundary layer of a thickness determined by the diffusion coefficient of the drug, the viscosity of the medium and the rotation speed. This assumption was found valid by Mooney et al.[12] for the purpose of generating dissolution rates.

Substitution of equation 6 into equation 5 and rearranging gives:

$$R = 1.56\, D^{0.666}\, [HA]_o\, M\, S^{0.5}/V^{0.166} \quad \ldots\ldots 7$$

where S is the rotation speed in rpm.

Equation 7 reduces to equation 8 for dissolution in water

$$R = 1.80\, D^{0.666}\, [HA]_o\, M\, S^{0.5} \quad \ldots\ldots 8$$

For acidic drugs of unknown diffusion coefficients dissolving in water equation 8 can be rewritten as follows

$$R = 3.24 \times 10^{-2}\, [HA]_o M^{0.778}\, S^{0.5} \quad \ldots\ldots 9$$

Equations 7, 8 and 9 are only applicable to dissolution of unionizable molecules or when dealing with unreactive media. Dissolution of unionizable molecules is not influenced by the pH at the surface of the dissolving particles. However, for the general case where ionization and chemical reactions are taking place an extended form of the Noyes-Whitney equation is required based on the reactive model and the boundary conditions given earlier [12,15]. These extended equations for acids are equation 10 for the general case, equation 11 for dissolution in water and equation 12 for dissolution in water where the diffusion coefficient is unknown.

$$R = (1.56\ S^{0.5}M/D^{0.333}\ V^{0.166})[D[HA]_0 + 1.68 \times 10^{-3} (10^{-pHs} - 10^{-pHb}) + 1.68 \times 10^{-3} (10^{pHb-pKw} - 10^{pHs-pKw})] \quad ..10$$

$$R = (1.80\ S^{0.5}M/D^{0.333})[D[HA]_0 + 1.68 \times 10^{-3} (10^{-pHs} - 10^{-pHb}) + 1.68 \times 10^{-3} (10^{pHb-pKw} - 10^{pHs-pKw})] \quad ...11$$

$$R = 13.43\ S^{0.5}M^{1.111}\ [(2.40 \times 10^{-3}[HA]_0/M^{0.333}) + 1.68 \times 10^{-3} (10^{-pHs} - 10^{-pHb}) + 1.68 \times 10^{-3} (10^{pHb-pKw} - 10^{pHs-pKw})] \quad ..12$$

where pHb is the pH of the bulk solution and pKw is the ionization product of water.

Similar set of equations can be derived for the dissolution of bases. Dissolution of salts can be treated as acids or bases depending on the nature of these salts.

MATERIALS AND METHODS

The two research compounds Cromakalim (BRL 34915-a novel potassium channel activator) and Diproteverine HCl (BRL 40015A-a calcium antagonist) were from Beecham Research Laboratories and are currently being evaluated clinically. (+)- Ψ-Ephedrine was obtained from Sigma Chemical Company Ltd.

The solubility of the drugs in distilled water was determined at 37±1°C. Quantification was carried out using uv spectrophotometry. The pH of the saturated filtrate was recorded using a direct reading pH meter (C.P. Instruments Co.Ltd.).

The pKa values were determined by potentiometric titrations at 37°C[23].

Compacts of each of the drugs were made on an IR KBr press (Beckman) using 13.0 mm diameter flat faced punches and die. All compacts were made at 20 KN force and the die wall and punches were lubricated with 5% w/v magnesium stearate in absolute ethanol after each compaction. Measurements of compact dimensions after 24 hours at 20°C showed no significant expansion or contraction.

Nujol mull IR scans of Cromakalim and Diproteverine HCl, which are known to exist in different polymorphic forms, showed no polymorphic transformation following compaction.

The intrinsic dissolution testing was carried out using apparatus 2 of the USP XXI (Prolabo Dissolutest) in 1000 ml of distilled water for Cromakalim and in 500 ml distilled water for Diproteverine HCl and Ephedrine. The paddle stirrer of apparatus 2 of the USP XXI was replaced by a specially constructed compact holder/stirrer. The compact was inserted in the holder/stirrer exposing a surface area of $\pi r^2 = 1.327$ cm^2 to the dissolution medium. Dissolution was followed to < 50% dissolved making sure that the same surface area remained at the end of the experiment. For quantification, filtered samples (Technicon reagent filter) were pumped (Watson Marlow peristaltic pump) to a u.v./vis. spectrophotometer (LKB Biochrom Ultraspec II). The absorbances, at 253 nm for Cromokalim, at 244 nm for Diproteverine HCl and at 257 nm for Ephedrine, were recorded at suitable time intervals.

RESULTS AND DISCUSSION

Cromakalim

Cromakalim has the following properties which are relevant to intrinsic dissolution: molecular weight = 286.3, solubility

TABLE 1

Intrinsic Dissolution Rates of Cromakalim in Water at 37°C ($mg.cm^{-2}.min^{-1}$)

Rpm	Cromakalim x 10^{+2}		Diproteverine HCl		Ephedrine	
	exp.[a]	pred.	exp.[a]	pred.	exp.[a]	pred.
25	2.27(0.14)	2.25	-	-	-	-
50	3.36(0.28)	3.56	3.28(0.11)	3.28	0.69(0.02)	0.68
75	4.19(0.04)	4.36	-	-	-	-
100	4.66(0.16)	5.04	4.59(0.12)	4.64	0.96(0.08)	0.96
150	-	-	5.52(0.26)	5.68	1.21(0.06)	1.18
200	5.95(0.29)	7.13	7.02(0.36)	6.55	1.42(0.04)	1.36

a. Mean of 3 determinations

in water at 37°C = 0.55 $mg.ml^{-1}$ and pKa = undetermined due to unionizability in the pH range 0 - 14. The intrinsic dissolution rates of Cromakalim were determined at five rotation speeds and the results are given in TABLE 1. The experimentally determined intrinsic dissolutions rates were obtained by linearly regressing the quantity of the drug dissolved (ordinate) versus time (abscissa).

The slopes of the resulting rectilinear plots ($p<0.001$), when divided by the surface area of the compact (1.327 cm^2), represent the zero order intrinsic dissolution rate at a particular rotation speed. Furthermore, and in order to obtain a single intrinsic dissolution parameter, plots of the

reciprocal of the intrinsic dissolution rates (ordinate) versus the reciprocal of rotation speed (abscissa) were constructed according to Nicklasson et al.[2]. The reciprocal of the intercepts of these rectilinear plots are the single intrinsic dissolution rates at infinite rotation speed (i.e. at zero diffusion layer thickness).

The pooled experimental data gave a predicted intrinsic dissolution rate at ∞ rotation speed of 7.36 (s.d.=0.39) x 10^{-2}mg. cm^{-2} min^{-1} for Cromakalim in distilled water. The predicted values (see TABLE 1), which were obtained using equation 9, when plotted as above to yield the intrinsic dissolution rate at ∞ rotation speed gave a value of 8.09 (s.d.=0.76) x 10^{-2}mg. cm^{-2} min^{-1}. The agreement between the latter value and that obtained through experiments at various rotation speeds is close enough to validate the applicability of equation 9. As Cromakalim does not ionize in the pH range 0-14, no change in the intrinsic dissolution rate was observed while changing the pH of the bulk solution. Moreover, the pH at the surface of the dissolving particles closely followed that of the bulk medium reflecting the neutral reaction of Cromakalim molecules, due to unionizability, and low aqueous solubility. The pH at the surface of the dissolving particles at any given bulk pH should be similar to those of saturated solutions having the same initial pH as that of the bulk solution [20-21,24-25]. Experimental observations confirmed that no significant pH change occured after saturating aqueous solutions, at varying initial pH values, with Cromakalim.

Diproteverine HCl

Diproteverine HCl has the following properties which are relevant to intrinsic dissolution : molecular weight = 462.0,

solubility in water at 37°C = 55.80 $mg.ml^{-1}$ and pKa at 37°C = 7.00. The intrinsic dissolution data for Diproteverine HCl are given in TABLE 1. The experimental data were treated in a similar way to Cromakalim to yield a predicted intrinsic dissolution rate at infinite rotation speed of 9.48 (s.d.=0.68)$mg.\ cm^{-2}\ min^{-1}$. The latter value is well above the limit of $1mg.\ cm^{-2}\ min^{-1}$ below which one could anticipate possible bioavailability problems.

The predicted data in TABLE 1 were obtained using an equation appropriately derived for an ionizable weak base-strong acid salt. Intrinsic dissolution rates collected from the use of such an equation gave a predicted dissolution rate at ∞ rotation speed of 9.17 (s.d. = 0.75)$mg.\ cm^{-2}\ min^{-1}$ which is in a good agreement with the same parameter when obtained from experiments at varying rotation speeds.

The model also predicts no significant change in the intrinsic dissolution rate while varying the bulk pH between 1 and 7. This could be attributed to the pH reduction in the diffusion layer caused by the solubility of the acidic salt, Diproteverine HCl. The pH around the dissolving particles was kept, as predicted by the model, to below pH 4.5 even though the bulk pH exceeds this value. Below pH 4.5 no significant change in the proportion of the ionized and unionized forms of the drug could take place (pKa=7) and hence no change in the dissolution rate is to be expected. Diproteverine, as a base, is practically insoluble in aqueous solutions and is likely to precipitate if the surface pH approaches the pKa. However, Diproteverine HCl reduces the pH of the diffusion layer to a value of <4.5, even when the bulk pH exceeds the pKa by one unit, hence favouring the existence of the ionized and the more soluble HCl salt in the diffusion layer. Measurements of the pH

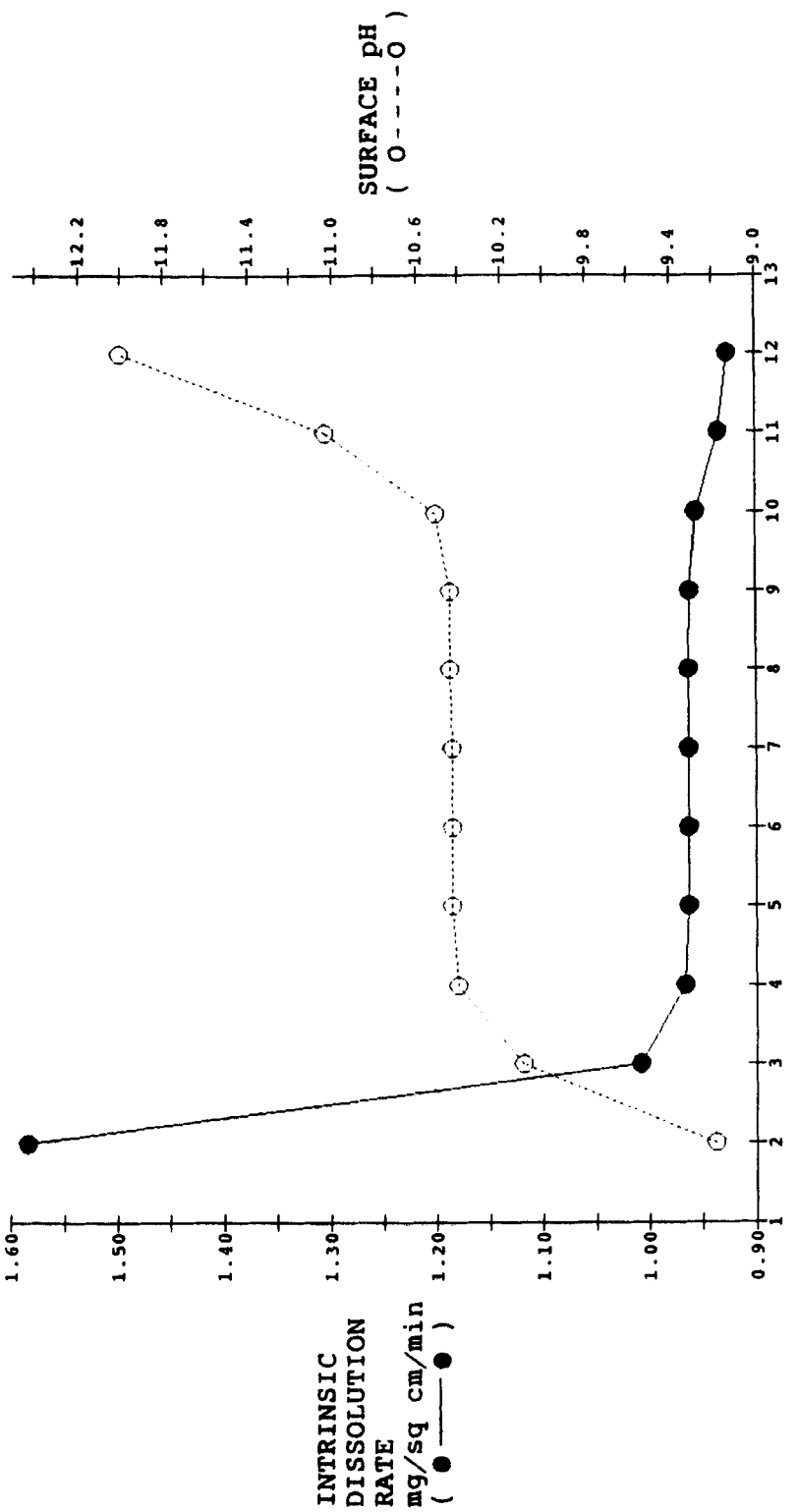

FIGURE 1

Intrinsic dissolution of Ephedrine at 37°C and 100 rpm

of saturated aqueous solutions, having different initial pH values, showed a similar pattern of behaviour to that exhibited in the relationship between surface pH and bulk pH.

Ephedrine

Ephedrine has the following properties which are relevant to intrinsic dissolution : molecular weight = 165.2, solubility in water at 37°C = 8.95 $mg.ml^{-1}$ and pKa at 37°C = 9.04. The intrinsic dissolution data of Ephedrine are shown in TABLE 1. The predicted intrinsic dissolution rate at infinite rotation speed, from experimental data, was 1.96 (s.d.=0.14)mg. $cm^{-2}.min^{-1}$ which is once again in a good agreement with a value of 1.91 (s.d.=0.12)mg. $cm^{-2}.min^{-1}$ obtained through using an appropriately derived equation for bases. The derived equation also predicts three separate segments in the dissolution rate versus bulk pH curve as illustrated in FIGURE 1. Below a bulk pH of 3, the pH at the surface of the particles is kept below pH 10.2 with a significant proportion of the ionized Ephedrine (the more soluble and the faster dissolving form). The proportion of ionized Ephedrine increases as the pH around the particles decreases. In the bulk pH region 4 to 10, the model predicts no significant change in the surface pH leading to an essentially constant intrinsic dissolution rate within this range. This could be attributed to the presence of the predominantly unionized Ephedrine which saturates the film around the particles and keeping the film pH constant at approximately 10.5. This predicted saturated film pH is identical with the measured pH of a saturated solution in distilled water. Above bulk pH 10.5, the medium alkalinity which is in excess of the pH of a saturated solution dictates the final surface pH. Once more, measurements of the pH of saturated Ephedrine solutions, from various initial pH values, yielded a pattern

similar to that describing the variability of surface pH with bulk pH depicted in FIGURE 1.

CONCLUSIONS

Using data normally generated during preformulation characterisation, it is possible, using this model, to predict with a reasonable degree of accuracy the intrinsic dissolution rate of new chemical entities. The intrinsic dissolution rate could then be used, in conjunction with other parameters, to select the most suitable crystal or salt form of the drug for further progression.

ACKNOWLEDGMENTS

The author would like to express his appreciation of the technical assistance given by Miss Wendy Pennington and the advice of the other staff members of the Formulation Development Department at Great Burgh.

REFERENCES

1. S.A.Kaplan, Drug Metab.Rev.,1,15(1972)

2. M.Nicklasson, A.Brodin and H.Nyqvist, Acta Pharm.Suec., 18,119(1981).

3. G.Levy and B.A.Sahli,J.Pharm.Sci.,51,58(1962).

4. G.Levy and J.A.Procknal,J.Pharm.Sci.,53,656(1964).

5. G.Levy and W.Tanski,J.Pharm.Sci.,53,679(1964).

6. W.I.Higuchi, N.A.Mir, A.P.Parker and W.E.Hamlin, J.Pharm.Sci.,54,8(1965).

7. J.H.Wood, J.E.Syarto and H.Letterman,J.Pharm.Sci.,54, 1068(1965).

8. K.G.Nelson and A.C.Shah,J.Pharm.Sci.,64,610(1975).

9. A.C.Shah and K.G.Nelson,J.Pharm.Sci.,64,1518(1975).

10. A.Tsuji, E.Nakashima, S.Hamono and T.Yamana, J.Pharm.Sci.,67,1059(1978).

11. H.K.Chan and E.Doelker,Drug Dev.and Ind.Pharm.,11, 315(1985).

12. K.G.Mooney,M.A.Mintun,K.J.Himmelstein and V.J.Stella, J.Pharm.Sci.,70,13(1981).

13. P.L.Oravec and E.L.Parrott,Drug.Dev.and Ind.Pharm.,11,1467(1985).

14. W.Nernst and E.Brunner,Z.Physik.Chem.,47,52(1904).

15. W.I.Higuchi,E.L.Parrott,D.E.Wurster and T.Higuchi,J.Am.Pharm.Assoc.Sci.Ed.,47,376(1958).

16. K.G.Mooney,M.A.Mintum,K.J.Himmelstein and V.J.Stella,J.Pharm.Sci.,70,22(1981).

17. K.G.Mooney,M.Rodriguez-Gaxiola,M.Mintun,K.J.Himmelstein and V.J.Stella,J.Pharm.Sci.,70,1358(1981).

18. R.H.Stokes,J.Am.Chem.Soc.,72,2243(1950).

19. H.S.Harned and B.B.Owen, "The Physical Chemistry of Electrolyte Solutions",3rd.Ed.,Rienhold Publishing Corp.,New York,1958.

20. A.T.M.Serajuddin and C.I.Jarowski, J.Pharm.Sci.,74,142(1985).

21. A.T.M.Serajuddin and C.I.Jarowski, J.Pharm.Sci.,74,148(1985).

22. V.G.Levich, "Physico-Chemical Hydrodynamics", Prentice-Hall,New Jersey,1962.

23. A.Albert and E.P.Serjeant,"The Determination of Ionization Constants",2nd.Ed.,Chapman and Hall Ltd.,London,1971.

24. E.Nelson,J.Am.Pharm.Assoc.Sci.Ed.,46,607(1957).

25. E.Nelson,J.Am.Pharm.Assoc.Sci.Ed.,47,297(1958).