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# COMMUNICATIONS

## STUDIES ON DRUG RELEASE KINETICS FROM CARBOMER MATRICES

Manzer J. Durrani, Audrey Andrews, Roy Whitaker, and S.C. Benner
Pharm. Technology Section, The B.F. Goodrich Company, Brecksville, Ohio 44141



### ABSTRACT

The objective of this study is to gain a mechanistic understanding of drug release kinetics from directly compressed tablets containing Carbopol 934P and 974P resins. Carbopol resins belong to a family of carbomers which are synthetic, high molecular weight, non-linear polymers of acrylic acid, crosslinked with polyalkenyl polyether. They are currently being used as polymeric matrices for controlling drug release in pharmaceutical tablets. This investigation focuses on the influence of the type of drug and the pH of the dissolution media, along with other factors on the drug release kinetics from carbomer matrices. Directly compressed tablets were prepared using a Stokes single station laboratory press and blends of polymers and lactose with drugs like theophylline, norephedrine HCl, and chlorpheniramine maleate. In vitro drug release studies from the tablets were performed according to USP method II. Drug release rates were obtained by plotting the fraction released versus time and data fitted to the equation:

$$M_t/M_\infty = kt^n$$

The k and n values at pH 1.2 (SGF) and pH 6.8 (SIF) for theophylline, norephedrine hydrochloride, and chlorpheniramine maleate were determined. Our results demonstrate that, even though the tablet formulations were the same, the diffusion processes were different for these drugs. Depending on the type of drug and the pH of the media, the diffusion process occurs as either Fickian, non-Fickian or Case II transport.

### INTRODUCTION

Carbopol® 934P and 974P resins are the oral pharmaceutical grades of polymers generically known as the carbomers. These are synthetic, high molecular weight crosslinked polymers of acrylic acid. Carbopol 974P resin is a newer addition to the carbomer family. It is polymerized in ethyl acetate and is slightly treated with a potassium base.

These polymers when incorporated in pharmaceutical tablets have shown a tendency to linearize the drug release curves and give zero or near zero order drug

release(1,2). S.B.Bhardwaj et al. (3) have studied the sustained release properties of verapamil HCl from directly compressible polymer matrix tablets using blends of Carbopol 934P, channelling agents, and binders. They found that these matrices exhibited a zero-order drug release at several different concentrations of polymers. There are several novel applications of these polymers in such drug delivery areas as topical (4), transdermal (5), buccal (6), nasal(7), ophthalmic (8), intestinal or rectal(9).

The present study focuses on the mechanistic aspects of polymer controlled drug release kinetics from pharmaceutical tablets. In an aqueous dissolution medium, Carbopol® polymers absorb water and swell to form a gelatinous network or barrier layer, which acts as a diffusional barrier to drug molecules (10). The drug release mechanism from such polymers has been described as a swelling - controlled system. The swelling of drug/polymer tablets is due to the diffusion of water into the polymer matrix, which results in the lowering of the glass transition temperature (Tg) of the polymer. At a macromolecular scale, the presence of water causes stresses within the glassy polymer matrix due to the relaxation of the polymer chains. These stresses are compensated by an increase in the radius of gyration and end-to-end distance of polymer molecules. Macroscopically, the polymer relaxation response is manifested as the swelling of the polymer matrix (11). This transition of the hydrophilic polymer chains from a glassy to a dynamic rubbery state, influences drug diffusion through the rubbery state (12).

In this report we apply the simple exponential model $M_t/M_\infty = kt^n$ to describe this swelling controlled diffusion mechanism. The model drugs for this study are theophylline, chlorpheniramine maleate, and norephedrine HCl, incorporated in tablets containing either Carbopol 934P or Carbopol 974P.

## MATERIALS AND METHODS

Tablets containing 100 mg of theophylline (32.9 %, Sigma Chemical Co.); 8.1 mg of chlorpheniramine maleate (2.7 % , Sigma Chemical Co); or 50.0 mg of norephedrine hydrochloride (16.5 % , Aldrich Chemical Co.) were prepared using a Stokes single station laboratory press employing manual power feed. Formulations also contained Cab-o-Sil® 0.4 % ; magnesium stearate (0.7 % , Synthetic Products Co.) ; polymer (Carbopol 934P resin or 974P resin, B.F. Goodrich Co) 10 %; and sufficient anhydrous lactose (USP, Sheffield Products.) to bring the composition to 100 percent.

The recipe was structured according to the drug requirements. All drugs and excipient were blended geometrically with mortar and pestle; then placed in a V-mixer for 25 minutes. The lubricant magnesium stearate was added and blending continued for another five minutes. One hundred tablets were then made from each formulation. These tablets were analyzed for hardness, friability, and disintegration time.

Dissolution testing was carried out with the USP Apparatus II, paddle method (dissolution test station, Sitco-Pharma), with a Perkin-Elmer Lambda 3 UV/Vis Spectrophotometer interfaced with a Perkin-Elmer Data Station. All tests were done at 37°

and 50 rpm paddle speed, in 900 ml of either 0.2M HCl (pH 1.2) or 0.2 M Potassium Phosphate Monobasic buffer adjusted to pH 6.8 to simulate gastric fluid (SGF) or intestinal fluid (SIF), respectively. Six uniform tablets of each drug were simultaneously tested in the dissolution cells. Drug dissolution profiles were obtained by plotting the fraction of drug released versus time.

## RESULTS AND DISCUSSION

The interaction of solute(drug)/polymer/solvent (aqueous media) systems was investigated in terms of the type of drug diffusion mechanism . The drug release data from 90 % of the release curve were fitted to the exponential release model equation.

$$\frac{M_t}{M_\infty} = kt^n$$

where $M_t/M_\infty$ is the fractional solute release into the penetrating solvent (dissolution medium), k is a constant which incorporates the properties of the macromolecular polymeric system and the drug; and n is the diffusional exponent, which characterizes the drug transport mechanism (13). When the exponent n=0.5, the drug diffuses through and is released from the polymer with a quasi-Fickian diffusion mechanism, even though there is swelling of the polymer and dynamic macromolecular relaxations. For n>0.5, an anomalous, non-Fickian solute diffusion is observed . The special case of n = 1 has gained importance due to its potential application in the development of swelling-controlled drug delivery systems with zero-order kinetics. This mechanism of solute transport is known as pseudo-case-II solute transport (12).

The mathematical models were developed using a non-linear regression technique with the SAS software available on the VAX computers. The summary tables (Tables 1,2) for each dissolution curve investigated in this study show the model parameters for k and n as well as statistics for Prediction Error($S_{y,x}$), % variation explained, and 95% confidence limits for the equation. The $S_{y,x}$ is a statistic which indicates the fit of the model based on residuals about the dissolution curve. The percent variation explained is a comparison on the residuals of the curve compared to the total variation in the data. The 95% confidence limits indicate the accuracy of the estimates for each of the coefficients in the non-linear model.

Perez-Marcos et al. (14,15) have shown that drug solubility can influence the mechanism of drug release. Atenolol, a highly water soluble drug demonstrated a square-root time dependent drug release. While, furosemide, poorly water soluble drug gave a zero-order release. In the present study Table 3 and 4 show that, although there are differences in polymer controlled drug release rates, the release mechanisms are quite similar for tablets

| DRUG TYPE | PREDICTION ERROR(Sy.x) | %VARIATION EXPLAINED | LOWER 95% CONF LIMIT | SLOPE K | UPPER 95% CONF LIMIT | LOWER 95% CONF LIMIT | EXPONENT n | UPPER 95% CONF LIMIT |
|---|---|---|---|---|---|---|---|---|
| THEOPHYLLINE | 0.00998 | 99.85 | 0.009516 | 0.010488 | 0.011460 | 0.713504 | 0.729766 | 0.746028 |
| CHLORPHENIRAMINE | 0.01766 | 99.42 | 0.019388 | 0.024124 | 0.028859 | 0.591554 | 0.629699 | 0.667844 |
| NOREPHEDRINE | 0.01489 | 99.70 | 0.042719 | 0.048935 | 0.055151 | 0.512221 | 0.537359 | 0.562498 |
| INTESTINAL FLUID | | | | | | | | |
| THEOPHYLLINE | 0.01937 | 99.90 | 0.001572 | 0.001723 | 0.001874 | 0.910891 | 0.925337 | 0.939783 |
| CHLORPHENIRAMINE | 0.03685 | 98.40 | 0.001277 | 0.002669 | 0.004063 | 0.927358 | 1.023809 | 1.120261 |
| NOREPHEDRINE | 0.01999 | 99.40 | 0.063038 | 0.073637 | 0.084235 | 0.425252 | 0.453308 | 0.481363 |

TABLE II CARBOPOL 974P - MATHEMATICAL MODELING OF DISSOLUTION DATA

| DRUG TYPE | PREDICTION ERROR(Sy.x) | %VARIATION EXPLAINED | LOWER 95% CONF LIMIT | SLOPE K | UPPER 95% CONF LIMIT | LOWER 95% CONF LIMIT | EXPONENT n | UPPER 95% CONF LIMIT |
|---|---|---|---|---|---|---|---|---|
| GASTRIC FLUID | | | | | | | | |
| THEOPHYLLINE | 0.00503 | 99.96 | 0.016347 | 0.017126 | 0.017905 | 0.656665 | 0.664881 | 0.573096 |
| NOREPHEDRINE | 0.01809 | 99.56 | 0.034170 | 0.042503 | 0.050836 | 0.542016 | 0.582908 | 0.623801 |
| INTESTINAL FLUID | | | | | | | | |
| THEOPHYLLINE | 0.02222 | 99.53 | 0.002238 | 0.003980 | 0.005722 | 0.991028 | 1.083151 | 1.175274 |
| CHLORPHENIRAMINE | 0.03638 | 98.59 | 0.003201 | 0.005819 | 0.008437 | 0.829810 | 0.914915 | 1.000020 |
| NOREPHEDRINE | 0.02523 | 99.33 | 0.026983 | 0.037505 | 0.048027 | 0.572742 | 0.632058 | 0.591374 |

## TABLE III

**Drug Release Kinetics from Tablets using Carbopol 934P resin.**

| Polymer | Carbopol 934P | | | Carbopol 934P | | |
|---|---|---|---|---|---|---|
| Medium | SGF | | | SIF | | |
| Parameter | k | n | Mech. | k | n | Mech |
| Theophylline | 0.0105 | 0.73 | Anom.[3] | 0.0017 | 0.93 | Casell |
| CPM[1] | 0.0241 | 0.63 | Anom. | 0.0027 | 1.02 | Casell |
| NOR[2] | 0.0490 | 0.54 | Fick.[4] | 0.0736 | 0.45 | Fick. |

Abbrev. [1]Chlorpheniramine maleate, [2]Norephedrine HCl, [3]Non-Fickian-Anomalous, [4]Fickian.

## TABLE IV

**Drug Release Kinetics from Tablets using Carbopol 974P resin.**

| Polymer | Carbopol 974P | | | Carbopol 974P | | |
|---|---|---|---|---|---|---|
| Medium | SGF | | | SIF | | |
| Parameter | k | n | Mech. | k | n | Mech |
| Theophylline | 0.0171 | 0.67 | Anom. | 0.0040 | 1.08 | Casell |
| CPM | 0.0333 | 0.57 | Fick. | 0.0058 | 0.92 | Casell |
| NOR | 0.0425 | 0.54 | Fick. | 0.0375 | 0.63 | Anom. |

containing Carbopol 934P and 974P resins. For a highly water soluble drug like norephedrine HCl, the drug release was quasi-Fickian for both the carbomers, independent of the composition or the pH of the dissolution fluid. In the case of Carbopol 974P the n = 0.63 suggests a slight shift towards the anomalous release mechanism. However, Carbopol 934P resin containing norephedrine HCl tablets show a Fickian release; a classical Higuchi-type square-root time dissolution controlled drug release. In the case of a highly water soluble drug like norephedrine HCl, it is postulated that drug dissolution may control the mechanism of drug release from these crosslinked polyacrylic matrices. This drug, due to its high aqueous solubility, may tend to partition through the regions of low microviscosity (water-filled pores or microvoids) present in the gel microstructure of the hydrated tablet. Lockhead et al. (16) have postulated the existence of such regions of low microviscosity, based on their quasi-elastic light scattering studies to determine the Stokes-Einstein microdiffusion coefficient of colloidal gold-sol particles immersed within polyacrylic acid gels.

In the case of theophylline and chlorpheniramine maleate, there is a shift from an anomalous mechanism towards a Case II type release mechanism for tablets containing both Carbopol 934P and 974P resins. This shift is dependent on the pH of the dissolution media. A pH dependent swelling of of these anionic polymers occurs as the pH is raised from 1.2 to 6.8. In SGF (pH 1.2), the polymers are not fully swollen and there are larger regions of low microviscosity. As the pH is increased to SIF conditions (6.8 pH), the ionization of the carboxylic acid groups causes maximum swelling, resulting in fewer and smaller regions of low microviscosity. In this case, drug release is controlled by the degree of swelling of the polymer, and therefore the release kinetics profile shift towards a swelling-controlled, Case II mechanism. It has also been demonstrated by Durrani et al. (17) that increasing the amount of Carbopol 934P in tablets results in a reduction in the drug release rate and a linearization of the drug release curve leading to a shift towards a Case II type mechanism. This may be due to the closing of the micropores and a reduction in regions of low microviscosity in the swollen tablet. The swelling of the tablet is due to the hydration of the polymers, which results in a rapid decrease in their Tg to the temperature of the dissolution solvent. Microscopically, there is a relaxation response of the polymer chains due to stresses introduced by the presence of the dissolution solvent; which results in an increase in the radius of gyration and end-to-end distances of the polymer chains (18). There is a significant increase in the molecular volume of the hydrated polymer. This reduces the free volume due to the presence of the micropores. This effect may manifest itself as a shift in the drug release mechanism.

Kopecek et al.(19) have suggested that in pH-sensitive hydrogels the equilibrium swelling degree is influenced by such factors as charge of the ionic monomer, pKa of the ionizable group, degree of ionization, concentration of the ionizable monomer in the crosslinked matrix, and pH, ionic strength, and composition of the dissolution medium. In the case of these carbomers, the rates of drug release from Carbopol 974P are higher than Carbopol 934P. This is consistent with the presence of the potassium in Carbopol 974P. Monovalent salts generally reduce the swelling of polyacrylic acids. Therefore, at equal concentrations, Carbopol 974P will have lesser degree of swelling than Carbopol 934P, which may result in the formation of more areas or regions of low microviscosity in the gel

microstructure for the drug to channel through, resulting in faster drug release. This effect is greater in simulated intestinal fluid, since the pH of this medium is above the pKa of Carbopol 974P. The shielding effect of potassium ion would also reduce the swelling due to the repulsion of negatively charged carboxylic groups. The differences in the drug release rates from these ionic hydrogels may also be due to their unbound water content (20).

Another factor for the shift towards zero order for the less water soluble drugs theophylline and chlorpheniramine maleate, may be that less water soluble drugs must also go through the polymer matrix. These drugs are more soluble in the organic interior domain of the polymer than in water. The potassium in the Carbopol 974P may reduce the tendency for these drugs to partition into the polymer. The potassium will occupy a large area near the carboxylic acid groups and make the interior domain of the polymer more inorganic from a solubility parameter viewpoint. Further, if any drug interaction with the carboxyl groups acts as a driving force by increasing drug partitioning into the polymer, the strong base potassium, would displace the weakly basic drug. Work by Graf et al.(21) suggests that, at least for the cases of the dexchlorpheniramine maleate and diphenhydramine HCl, complexation with polymers like Carbopol 934P is not likely. This suggests that the effect of potassium on equilibrium swelling and on drug solubility within the interior domain of a polymer may define the key differences between these two carbomers; and that polymer composition, gel microstructure, and drug solubility play a major role influencing the drug release from matrix tablets.

## CONCLUSIONS

Drug release from carbomers like Carbopol 934P and C974P resins can occur both by diffusion through low microviscosity pores (polymer hydrofusion), and by a swelling-controlled mechanism. Highly water soluble drugs show Fickian release by dissolution through the low microviscosity voids. Factors which reduce the number and size of these voids, such as increasing pH, which increases polymer swelling and decrease drug solubility, or increasing polymer concentration, tend to shift the release profile towards swelling-controlled, Case II (zero-order) type release mechanism. Factors such as the presence of potassium or any other monovalent cation, would tend to reduce polymer swelling and increase the rate of drug release. Also, both these carbomers can be used to obtain zero-order release profiles from controlled release tablets; but the exact result would depend upon the drug type and dissolution fluid.

Other factors, which may influence the drug release from these pH-sensitive hydrogels include their equilibrium degree of swelling, affected by the charge of the ionic monomer and their rates of hydrations; pKa of the ionizable group (Carbopol resin pKa $\approx$ 6.0 $\pm$ 0.5), degree of ionization, concentration of the ionizable group in the network; and the pH, ionic strength and the composition of the swelling medium.

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