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MECHANISM OF RELEASE FROM PELLETS COATED WITH AN ETHYLCELLULOSE-BASED FILM

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Studies were conducted to determine the mechanism of drug release from pellets coated with an ethylcellulose-based pseudolatex widely accepted for use as a sustained release coating for pharmaceuticals. Possible mechanisms for release include solution/diffusion through the continuous polymer phase and/or plasticizer channels, diffusion through aqueous pores and osmotically driven release through aqueous pores. To distinguish between these mechanisms, the release rate was studied as a function of coating thickness, plasticizer content, and osmotic pressure in the dissolution medium. As the coating thickness was increased from 9 to 50 μm, the rate of release fell from $9.93 \cdot 10^{-3}$ *to* $1.71 \cdot 10^{-3}$ *g phenylpropanolamine (PPA)·HCl/100 ml h in an inversely proportional manner. Release as a function of plasticizer content was studied over the range 12 to 24% dibutyl sebacate (DBS). At 18 or 24% DBS, the rates of release of PPA·HCl were virtually identical, about 50% of PPA·HCl in six hours. At 12% DBS through, over 80% was released in the first hour. Surface area measurements and scanning electron microscopy (SEM) showed that the larger surface area of the 12% DBS batch was attributable to the presence of cracks in the coating. These results indicated that while the plasticizer is important in terms of forming a continuous film, diffusion through plasticizer channels is unlikely to make a significant contribution to the overall release rate. Release was also studied as a function of the osmotic pressure in the medium. A plot of release rate vs. osmotic pressure revealed an inverse linear relationship with a nonzero intercept. The steep dependency of release rate on osmotic pressure of the medium suggested that osmotically driven release is a major mechanism for release, while the nonzero intercept indicated some contribution from diffusion mechanisms. For all batches, SEM indicated that the film exhibited pores approximately 2 μm in diameter, consistent with these mechanisms. In summary, then, the release from PPA·HCl pellets coated with an ethylcellulose-based film appears to be a combination of osmotically driven release and diffusion through the polymer and/or aqueous pores. A mathematical expression for this type of release is presented.*

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INTRODUCTION

Multiparticulate dosage forms are becoming an increasingly popular method for providing controlled release of drugs in the gastrointestinal (GI) tract, partly because they have relatively reproducible upper GI transit profiles and partly because they minimize the risk of dose dumping. These multiparticulates usually consist of a drug entrapped in a sustaining matrix, or of a drug core overcoated with a low permeability polymer film. Water insoluble film-forming agents used to create a barrier to drug release include various cellulose derivatives and polymethacrylates. Film formation can be achieved by applying the polymer from an organic solution [1–3], from a coating emulsion or from an aqueous dispersion. Traditionally the film was formed from an organic polymer solution by evaporating the solvent. Later, a coating emulsion process was developed by Bauer and Osterwald [4], in which up to 75% of the organic solvent could be saved without changing the final polymer structure. Most recently, the use of aqueous dispersions has enabled films of water insoluble polymers to be cast entirely without the use of organic solvents. This is desirable because of the hazards associated with organic solvents, which include toxicity, flammability and environmental pollution. For aqueous dispersions, the film-forming polymer latex consists of a colloidal dispersion of discrete polymer spheres. To form a continuous film, the aqueous phase is evaporated, resulting in coalescence of the spheres [5].

Aquacoat® is a pseudolatex aqueous dispersion of ethylcellulose. Dispersions are prepared by dissolving the polymer in a suitable solvent, then forming an emulsion in water. In addition to ethylcellulose, small amounts of cetyl alcohol, sodium lauryl sulfate and Anti-foam A (dimethyl polysiloxane and silica gel) are added. The first two ingredients serve as stabilizers and surfactants, respectively, during the latter stages of production. After homogenization, the solvent is removed by vacuum distillation.

This ethylcellulose-based formulation is widely accepted for use as a sustained release coating for pharmaceuticals. A knowledge of the mechanism of release from pellets coated with ethylcellulose-based pseudolatexes would help to create a model relating formulation and processing conditions to release profiles. Such a model could subsequently be used as a guide to the formulation of new sustained release dosage forms. In this paper we report studies on the mechanism of release of PPA·HCl from pellets coated with this ethylcellulose-based film.

THEORETICAL

There are several possible mechanisms by which release from multiparticulate dosage forms coated with water insoluble polymers may occur (**a**) solution/diffusion through the continuous plasticized polymer phase, (**b**) solution/diffusion through plasticizer channels, (**c**) diffusion through aqueous pores and (**d**) osmotically driven release.

(a) Solution/diffusion through continuous plasticized polymer phase

This mechanism assumes the polymer to be a continuous phase in which the plasticizer and other additives are dispersed homogeneously (Fig. 1). The polymer film has molecular sized openings between the cross-linked polymer chains [6]. Most likely, the drug molecules diffuse through these openings in a process known as hindered molecular diffusion. The openings must be wetted for drug molecules to diffuse; a process which is effected by the plasticizer and other additives. The additives also influence interchain dimensions by changing the cross-linking properties of the polymer chains. Another, less likely, mechanism for release is the movement of the drug molecules on the polymer chains, known as configurational diffusion.

The solution/diffusion mechanism has been demonstrated for many polymer films prepared from organic solvents [7–10]. Therefore, it is a likely mechanism for ethylcellulose films prepared from organic solvents, and may also be applicable for dosage forms coated with a pseu-

dolatex formulation when the plasticizer content is low and the film is complete.

The release rate for such a model can be described by:

$$J=\frac{P_m}{\delta}(C_s-C_b) \quad (1)$$

where J is the flux (release rate per unit surface area of film), C_s and C_b are the concentration of drug at the drug-film interface and the bulk, respectively, and δ is the thickness of the film. The permeability coefficient P_m can be written as

$$P_m=\frac{D\epsilon}{\tau\beta}K \quad (2)$$

where D is the molecular diffusivity of the drug, K is the distribution coefficient of the drug between the polymer membrane and water, ϵ is the volume fraction of the openings, β is a chain immobilization factor reflecting the degree of cross-linking of crystallites in the polymer, and τ is the tortuosity factor [6].

Reasonable values for permeability coefficients in complete polymer films have been reported on the order of 10^{-8}–10^{-9} cm^2/s [7–10].

(b) Solution/diffusion through plasticizer channels

When the plasticizer is not uniformly distributed in the film, and when the plasticizer content is high, the plasticizer could conceivably take the form of a continuous phase in the form of patched channels. If the solubility of the drug in the plasticizer is higher than that in water, it is possible that the drug would be preferentially transported through such plasticizer channels (Fig. 2).

The release rate for this model can be described by an equation analogous to eqn. (2), but with the permeability coefficient, P_{pl} represented as,

$$P_{pl}=\frac{D_{pl}\epsilon_{pl}}{\tau_{pl}}K_{pl} \quad (3)$$

In this case, K_{pl} is the distribution coefficient of drug between plasticizer and water, τ_{pl} is the tortuosity of the plasticizer channels and ϵ_{pl} is the volume fraction of plasticizer channels.

There has not been any study in the literature surveyed which observed this mechanism for films cast from either organic solvents or aqueous dispersions, most likely because a localization of the plasticizer phase to form continuous channels represents an extreme con-

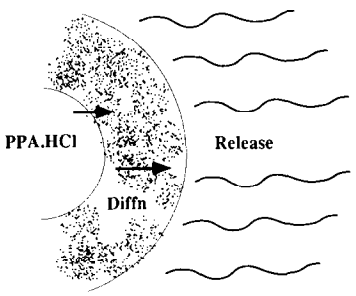

Fig. 1. Mechanism (**a**): Solution/diffusion through continuous plasticized polymer phase.

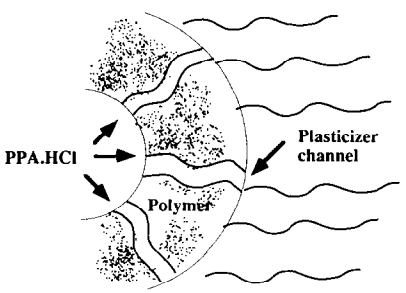

Fig. 2. Mechanism (**b**): Solution/diffusion through plasticizer channels.

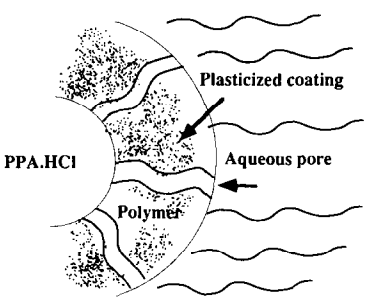

Fig. 3. Mechanism (**c**): Diffusion through aqueous pores.

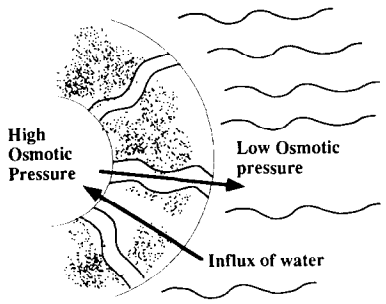

Fig. 4. Mechanism (**d**): Osmotically driven release.

dition. Normally, as is the case for other additives, the plasticizer is expected to be more or less uniformly distributed in the film.

(c) Diffusion through aqueous pores

In this model, the coating is not homogeneous and continuous, but punctuated with pores. These pores fill with solution when the dosage form comes in contact with an aqueous medium, and thereby facilitate the diffusion of the drug (Fig. 3). The transport mechanism in these pores can range from pure molecular diffusion to convection, depending on the pore size. Pores, and sometimes even cracks, can occur as a result of processing conditions under which coalescence of the pseudolatex particles is incomplete or defects are produced.

In this case, the permeability coefficient, P_p is given by,

$$P_p = \frac{D_p \epsilon_p}{\tau_p} \tag{4}$$

K is unity, as there is no partitioning between the channels and the aqueous environment in the bulk, ϵ_p is the volume fraction of the aqueous channels and τ_p is the tortuosity of the aqueous channels.

Relevant studies in the literature indicate that this mechanism is often accompanied by other mechanisms [7,10–12]. The most usual combination is diffusion through the continuous polymer phase in parallel with diffusion through aqueous channels. Assuming that two mechanisms operate independently, the resultant permeability is given by

$$P_a = P_m + P_p = \frac{D\epsilon}{\tau\beta}K + \epsilon_p D_p/\tau_p \tag{5}$$

where P_m and P_p are the permeabilities in the polymer and the aqueous phases respectively.

(d) Osmotically driven release

A different mechanism occurs when release is driven by osmotic pressure (Fig. 4). This is a well known process for porous membranes [13,14], when there is sufficient osmotic pressure generated by the core material. Sucrose is widely used as a core material (in the form of Nu-Pareils) in ethylcellulose coated sustained release formulations. Furthermore, if the drug applied to the core material is of low molecular weight and is water soluble, the release may be driven by the combined osmotic pressures of the drug and the sucrose core material.

Osmotically driven release for coatings similar to the ethylcellulose-based films considered here, but in which pores were deliberately created by adding water-soluble excipients to the film formulation, has been demonstrated previously [14–16]. Each study used urea to increase the osmolarity of the dissolution medium. When the urea concentration in the dissolution medium was increased, the release rate decreased, consistent with an osmotically driven release mechanism which predicts a lower release rate when a lower osmotic pressure difference is present across the coating.

The release rate for osmotically driven release may be described by:

$$J = \alpha\Delta\Pi(C_i - C_b) = \kappa\sigma\Delta\Pi(C_i - C_b) \tag{6}$$

where α equals $\kappa\sigma$ is the osmotic driving force parameter (κ is the filtration coefficient, σ is the reflection coefficient), $\Delta\Pi$ is osmotic pressure difference across the coating, and C_i and C_b are the core and bulk drug concentrations, respectively [15].

Calculations

Diffusivity

The Wilke–Chang eqn. (6) was used to estimate the diffusivities in the aqueous channels and the plasticizer according to

$$D_{AB} = 7.4 \cdot 10^{-8} [(\phi M_B)^{1/2} \frac{T}{\mu_B v_A^{0.6}}] \quad (7)$$

where D_{AB} is the diffusivity of species A in medium B (in cm^2/s), ϕ is the association constant ($\phi=1$ for organic solvents, $\phi=2.6$ for water), M_B is the molecular weight of the medium (18 and 316.6 g/mol for water and dibutyl sebacate (DBS), respectively), T is temperature (310 K for the experiments described), μ_B is the viscosity of the diffusion medium (1 mPa·s for water and 7.9 mPa·s for DBS), and v_A is the molal volume of diffusing species (190 cm^3/mol for PPA·HCl). Using the equation above, diffusivities for PPA·HCl were calculated at $6.74 \cdot 10^{-6}$ cm^2/s in water and $2.22 \cdot 10^{-6}$ cm^2/s in DBS.

Permeability coefficients

The permeability coefficients can be calculated from the above diffusivities using the appropriate permeability equation for each mechanism if the distribution coefficient K, volume fraction ϵ, the tortuosity τ, and the parameter β are known. The distribution coefficient K in the plasticizer channels was estimated by dividing the solubility of PPA·HCl in DBS (1.89 g/100 ml) into the solubility of PPA·HCl in water (40 g/100 ml). Using these values, the DK product of PPA·HCl was calculated to be $5.39 \cdot 10^{-6}$ cm^2/s for aqueous channels and $2.09 \cdot 10^{-8}$ cm^2/s for plasticizer channels.

In the USP #1 dissolution apparatus the following expression can be used to represent the release rate:

$$V\frac{dC_b}{dt} = n4\pi r_0 r_1 \frac{P}{r_0 - r_1}(C_i - C_b) \quad (8)$$

where V is the bulk liquid volume 900 ml, C_b is the concentration in the bulk (assumed 0), t is time, n is the number of microcapsules used (for 16% coating loading, 1125 beads/g; for 10% drug loading, 1476 beads/g; and for 5% coating loading, 1153 beads/g), r_0 and r_1 are the outer and inner radius of the capsule, respectively, P is the permeability coefficient, and C_i is the drug solubility given in Table 1.

TABLE 1

PPA·HCl solubility in various plasticizers and in water at 25 °C

Solubility	Medium				
	DBS	Triacetin	Myvacet	TEC	Water
PPA·HCl (g/100 ml)	1.89	1.694	3.954	2.97	40

Experimental permeability coefficients were calculated for all batches on which the dissolution tests were run using this analysis. These permeability coefficients were compared with the estimated parameters for each mechanism and their reasonableness considered.

Osmotic pressure

Osmotic pressures were calculated using the equation [15]:

$$\Pi = \Pi_{ideal}\phi \quad (9)$$

where $\Pi_{ideal} = CRT$ and ϕ is the factor related to the deviation from ideality. The values of ϕ can be calculated using:

$$\phi = 1 - \frac{0.042783m}{(1+0.15m)} - \frac{0.0004198m^2}{(1+0.15m)^2} \quad (10)$$

where m is the molality of urea solution.

Osmotic pressure calculations for PPA·HCl and Nu-Pareils were carried out using the model equations given by Zentner et al. [15]. For PPA·HCl at saturation, the concentration, C is 2.12 mol/l, leading to an osmotic pressure of 54.4 bar, while for Nu-Pareils the sucrose concentration at saturation is 5.85 mol/l, leading to an osmotic pressure of 150.1 bar. Total osmotic pressure is calculated from these contri-

butions of Nu-Pareils and PPA·HCl as 204.5 bar. So, for PPA·HCl loaded onto Nu-Pareils seeds, both materials will contribute significantly to the osmotic pressure generated.

EXPERIMENTAL

Solubility of PPA·HCl in various plasticizers

The solubilities of PPA·HCl in different plasticizers and in water were measured after 24 hours at 25°C. Concentrations were determined by UV spectrophotometry (Perkin Elmer, Model $\lambda 7$) at 257 nm, using standard curves prepared in each solvent.

Dissolution test

Dissolution tests were performed in standard USP basket type dissolution apparatus. In these tests, baskets were immersed into vessels containing 900 ml medium. A waterbath was used to keep the temperature constant at 37°C. The spindle rotation rate was adjusted to 100 rpm. Samples were taken every hour, and their concentrations were measured by UV spectroscopy at 257 nm. All dissolution tests were run in triplicate.

The effect of coating loading on the release of PPA·HCl. Pellets consisting of Nu-Pareil cores loaded with 40% PPA·HCl (IP 58064) and coated with Aquacoat (Lot #J 8281) were obtained from FMC Corporation (Princeton, NJ) at three different coating loadings: 5% (Batch #5851-138), 10% (Batch #5851-135), and 16% (Batch #5851-137). Dibutyl sebacate (Union Camp Corporation, Jacksonville, FL) was used as a plasticizer at 24% level. Dissolution experiments were performed for at least 6 h at 37°C in standard USP basket dissolution apparatus using water as the dissolution medium. Ten milliliter samples were taken every hour and replaced by 10 ml distilled water. These samples were filtered through filters (Millipore, Bedford, MA, pore size 0.2 μm) prior to analysis.

Effect of urea (osmotic pressure experiments). To test the hypothesis that release occurs via an osmotically driven mechanism, we performed dissolution tests into urea solutions at various concentrations. Water, 4*M* and 8 *M* urea were used as the dissolution media. Batches tested are listed in (i) above.

The effect of plasticizer content. To test the effect of the plasticizer level, three batches with 12% (Batch #E6264-61), 18% (Batch #E6264-60), 24% (Batch #E6264-59) DBS which had been oven (60°C for 2 h) or column dried after coating with a 10% loading of Aquacoat (Lot #J 7221) were prepared. Dissolution was tested at 37°C for 6 hours as described previously.

Microscopy measurements

Scanning electron microscopic measurements. Samples taken at 1 and 3 hours, and at the end of the test on the 5%, 10% and 16% coating loading batches were dried at 60°C for 10 min. These and predissolution samples were then sputter coated at 20 mA for 90 s with Au/Pt under Ar plasma (E 5100 Sputter coater Polaron, Hatfield, PA) from both above and the side to prepare them for SEM (Model DS-130, International Scientific Instruments, Milpitas, CA).

Diameter measurements with light microscope. Predissolution, 1 h, 3 h and 5 h dissolution test samples were prepared for batches with coating loadings of 5%, 10% and 16%. Photographs of each sample were taken using a Leitz Orthoplan 35 mm Vario-Orthomat camera (Wild Leitz USA, Inc., Rockleigh, NJ). A magnification ratio of 6.3 was used to calculate the diameter from positive enlargements. Diameters of 10 beads were measured for each sample, and the average diameter was calculated for both the predissolution and the dissolution test samples.

Surface area measurement

To determine the relationship between drug release and surface area, surface area measurements on batches which had different permeabilities and lag times were made. To relate permeability to surface area, the surface areas of two batches were measured; a column-dried batch containing 18% DBS with a 10% coating loading (Aquacoat Lot #J 7221, 40% PPA·HCl, Batch #6264-60), and a column dried batch containing 12% DBS with a 10% coating loading (Aquacoat Lot #J 7221, 40% PPA·HCl, Batch #6264-61). Neither of these batches exhibited a lag time, but the release rate of the 12% DBS batch was much faster than that of the 18% DBS batch. To relate lag time to surface area, the surface areas of two further batches were measured: a batch which had been heat treated at 60°C (Aquacoat Lot #J 7302, 10% coating loading, 24% DBS, 76% PPA·HCl, Batch #E 5851-111) which had no lag time, and a corresponding batch which had not been heat treated (Aquacoat Lot #J 7302, 10% coating loading, 24% DBS, 76% PPA·HCl, Batch #E 5851-111), and which had a lag time of 4.5 hours. These measurements were carried out using Digisorb 2600 equipment for surface area measurement with Krypton as the adsorbing gas, at Micromeritics (Norcross, GA).

RESULTS AND DISCUSSION

Solubility of PPA·HCl

Solubilities of PPA·HCl in various plasticizers and water are given in Table 1. Notice that the solubility of PPA·HCl is much greater in water than in the plasticizers studied. Using the solubility ratio as a first approximation to the distribution coefficient, it appears that partitioning into and transport via the plasticizer channels would be inefficient relative to release mechanisms utilizing aqueous channels, for PPA·HCl.

At 24% DBS, the pore volume fraction would be 0.24, the K value is 0.0474 (from the solubility ratio) and the diffusivity in DBS is estimated as $2.22 \cdot 10^{-6}$ cm^2/s. For a permeability coefficient of $3 \cdot 10^{-9}$ cm^2/s, this would require the tortuosity to be a maximum of 8.4, which is not an unreasonable value.

Plasticizer effect on mechanism of drug release

Dissolution test results with drug which had different plasticizer contents showed that lowering the amount of plasticizer increased the release rate dramatically (Fig. 5). For both of the samples containing 12% DBS in the film, drug release was almost complete by the end of the first hour. This result is in general agreement with measurements reported by Steuernagel [5], who reported that the cumulative percentage release of theophylline was almost linear over the 6 h dissolution test at DBS levels of 20 and 24%, but exhibited exponential profiles with much faster release at 16% and 18% DBS level [5]. Goodhart et al. [17] and Sutter [18] observed similar trends in release characteristics as a function of plasticizer level. Goodhart et al. found that PPA·HCl release rates are inversely proportional to plasticizer concentration [17]. Sutter observed that the film tends to stick if the plasticizer exceeds a level of 35% DBS, whereas films containing 9% DBS will be

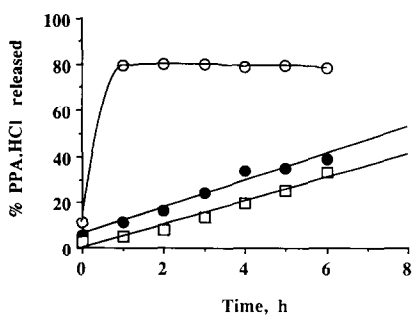

Fig. 5. Effect of plasticizer level on drug release (column dried sample, 10% coating loading, 40% PPA·HCl. Legend: ○ 12% DBS, ● 18% DBS, and □ 24% DBS.

fragmented [18]. In our experiments, nonlinearity in the release profile was observed at 12% DBS level but release was linear at 18% or 24% DBS. The fast release observed at low plasticizer content (associated with a high surface area, shown by SEM to result from major flaws in the film) indicates the need to have a minimum level of plasticizer to form a complete film. The decrease in release rate between 12 and 18% DBS and the lack of difference in release profile between 18 and 24% DBS suggest that despite the reasonable value calculated for tortuosity, diffusion through plasticizer channels is an improbable mechanism of release through ethylcellulose-based films.

Release as a function of coating loading

The release profiles of PPA·HCl for the three batches are given in Fig. 6. It is seen that a linear release profile is obtained during the first 50% of drug release. Film thicknesses (measured by SEM), release rates obtained and calculated permeabilities are presented in Table 2. From data in Table 2 it is clear that the release rate is decreased by increasing the coating loading, indicating that the film is controlling the release process. Also, the same mechanism appears to be operating for all three coatings loadings, since the relationship between film thickness and release rate is linear (Fig. 7).

TABLE 2

Release rates of PPA·HCl from pellets coated with an ethylcellulose-based film at three different coating loadings

Coating loading (% w/w)	Film thickness (μm)	Release rate (g/100 ml·h)	Permeability coefficient (10^{-10}, cm^2/s)
5	9.2	0.0099	36.8
10	22.5	0.0038	34.5
16	49.2	0.0017	33.9

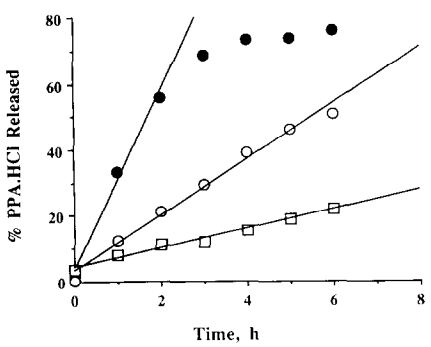

Fig. 6. Effect of coating loading on PPA·HCl release profiles pellets coated with an ethylcellulose-based film. Legend: ● 5% coating, ○ 10% coating, and □ 16% coating.

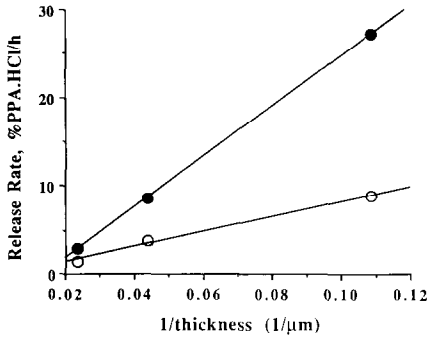

Fig. 7. Effect of coating thickness on PPA·HCl release rate. Legend: ● water, and ○ 4 *M* urea.

For a measured permeability coefficient of $3 \cdot 10^{-9}$ cm^2/s and predicted diffusivity of $7 \cdot 10^{-6}$ cm^2/s, the ratio of $K\epsilon/\tau\beta$ needs to be greater than $4.3 \cdot 10^{-4}$ for the solution/diffusion mechanism be operative. Since $\tau\beta$ must be greater than unity, and assuming an ϵ value on the order of 0.01 this mechanism would require K, the partition coefficient between the polymer and aqueous phases, to be at least 0.043.

Scanning electron microscopy to evaluate porosity

Scanning electron micrographs of PPA·HCl pellets coated with 10% ethylcellulose, sampled before and after dissolution testing are shown in Fig. 8. Pores on the order of 2 μm in diameter were observed on the surface of the control pellets at all three coating loadings and appeared to be more numerous after dissolution, when the surface of the pellets also acquired a dimpled appearance. This would be consistent with mechanisms (**c**) and (**d**), diffusion through

aqueous pores and osmotically driven release. The porosity was also evident in the cross-sections used to measure the coating thickness in the controls (not shown). Based on these and the surface area results, the volume fraction for aqueous pores, ϵ, was estimated to be 0.02. With this value of ϵ, a permeability value of $3 \cdot 10^{-9}$ cm^2/s, and diffusivity of $7 \cdot 10^{-6}$ cm^2/s, we calculate a pore tortuosity τ_p, of 2. This number is reasonable, though rather low, so diffusion through aqueous pores is a potential mechanism for release.

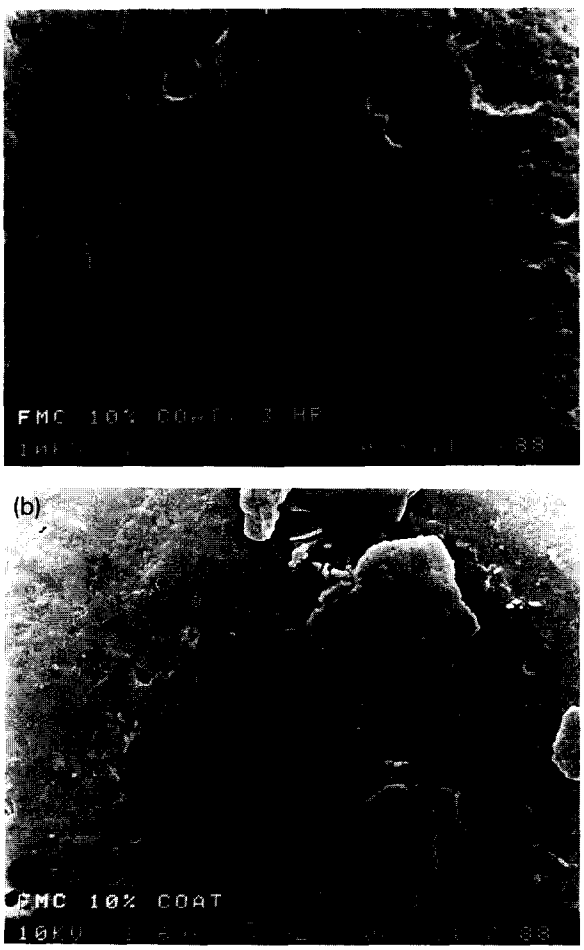

Fig. 8. SEM of coated pellets (Batch #5851-135). (A) Surface at a 10% coating loading before dissolution test. (B) Surface at a 10% coating loading after 3 h of dissolution testing.

Effect of urea on release rate

To test the hypothesis that release occurs via an osmotically driven mechanism, we performed dissolution experiments in urea solutions with different osmolarities (Table 3). The release data is summarized in Figs. 9 and 10 and in Table 4. Since increasing the osmotic pressure in the dissolution medium caused a decrease in the rate of release by about a factor of

TABLE 3

Osmotic pressures of different urea solutions

Urea M	Urea (molal)	ϕ	Π_{ideal} (bar)	Π (bar)	$\Delta\Pi$ (bar)
0	0	–	0	0	20.5
4	4.86	0.876	10	90	11.1
8	12.40	0.806	205.4	166.7	37.4

TABLE 4

Permeability coefficients for PPA·HCl release in different urea solutions, expressed in 10^{-10} cm^2/s

Urea M	Coating loading		
	5%	10%	16%
0	36.8	34.5	33.9
4	13.64	16.4	12.56
8	–	7.44	–

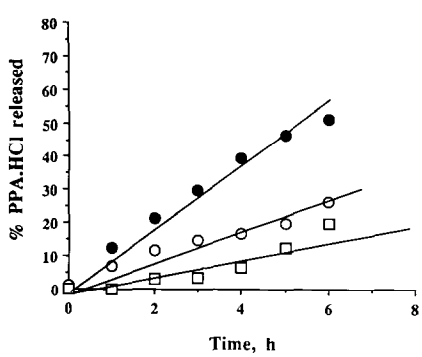

Fig. 9. Effect of osmotic pressure on PPA·HCl release profiles (at a 10% coating loading). Legend: ● 0 M urea, ○ 4 M urea, and □ 8 M urea.

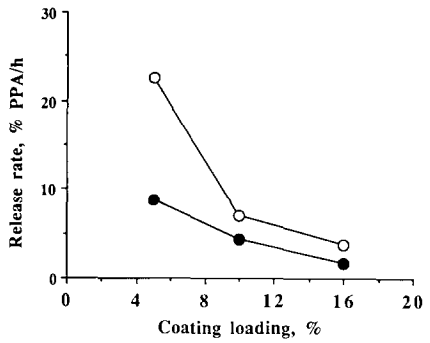

Fig. 10. Osmotic pressure experiments: PPA·HCl release rate at different coating loadings. Legend: ○ water, and ● 4 *M* urea.

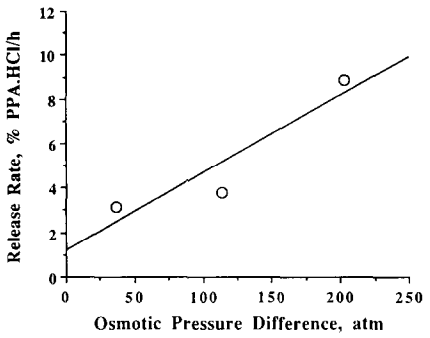

Fig. 11. Effect of osmotic pressure difference on PPA·HCl release rate at a 10% coating loading (1 atm = 1.01325 bar).

2.5 at each coating loading, it appears that osmotically driven release is an important mechanism at all coating loadings studied. When the release rates are plotted against the osmotic pressure difference in Fig. 11, a linear dependence was found. Note that there is a non-zero intercept indicating a minor contribution of solution/diffusion through the polymer continuum and/or diffusion through aqueous pores.

Surface area measurement

It was determined that the sample which had a lag time had a slightly smaller surface area (0.0060 m^2/g, with an average pore diameter of 1.27 μm) than the surface area of sample that had no lag time (0.0077 m^2/g with an average pore diameter of 1.25 μm). The surface area of samples with different permeability coefficients were 0.2184 (average pore diameter of 0.627 μm) for the higher release rate and 0.0065 m^2/g (average pore diameter of 0.79 μm) for the lower release rate. Calculations of the average pore diameters are in good agreement with SEM observations. These results are consistent with a mechanism associated with aqueous pores, either (**c**) or (**d**), since greater porosities should be associated with faster release rates if these mechanisms are operative.

Swelling of pellets during dissolution

Phase contrast light microscopy was used to determine whether any swelling of pellets occurred during the release process. Average pellet diameter was found 0.653 ± 0.029 mm before and 0.696 ± 0.034 (s.d.) mm after the dissolution test, respectively ($n = 10$ per sample). The unpaired t-test indicated that the pellets swelled significantly ($P < 0.05$) during the release process to an extent of about 7%. Since SEM indicated that coating thickness remained unchanged, the swelling most likely corresponded to an imbibement of water into the core. Again, this is consistent with a mechanism involving aqueous pores.

CONCLUSIONS

Release of PPA·HCl from pellets coated with the ethylcellulose-based pseudolatex formulation is mainly driven by osmotic pressure, with a minor contribution by diffusion through aqueous pores and perhaps solution/diffusion through the polymer membrane. Osmotic pressure measurements showed that the osmotic pressure generated by both PPA·HCl and the Nu-Pareils would contribute significantly to establishing the driving force for release. Solution/diffusion through the plasticizer is considered to be of negligible contribution for these systems. Assuming that these mechanisms operate independently and in parallel, the release

from PPA·HCl pellets coated with the ethylcellulose-based film can be mathematically described by an equation which combines mechanisms (**a**), (**c**) and (**d**) as follows:

$$J = [\alpha \Delta \Pi + \frac{P_p + P_m}{\delta}](C_s - C_b) \qquad (11)$$

where α is the osmotic driving force, $\Delta\Pi$ is osmotic pressure difference across the coating, P_p and P_m are the permeability coefficient for aqueous pores and membrane, respectively, δ is the film thickness, and C_i and C_b are the core surface and bulk drug concentrations, respectively.

The same mechanism is operative over a coating range of 5–16%, so the film thickness may be used as a means of modifying the release rate, without changing the release mechanism (within the range 10–50 μm). Important factors in determining the release rate from these systems include the volume fraction and size of pores generated during processing, the permeability of the film to water, rate of core dissolution and the ability of the core constituents and drug to generate osmotic pressure.

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