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In vitro drug release from chitosan membranes

Study of the mechanisms of permeation

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SUMMARY

In vitro studies of controlled release from chitosan membranes were carried out using drugs of different molecular weight. The release rate was measured in water at 37º ± 0.5º C by determining the amount of drug released by spectrophotometric analysis. It was found that release of acetamide, nicotinamide, sodium benzoate, sodium salicylate, phenobarbital sodium and sodium cefazoline followed zero-order kinetics. The relation between molecular weight and diffusion coefficient was established.

INTRODUCTION

Among all the new controlled release technologies, the use of membranes is the most promising due to their ability to maintain constancy in the drug delivery profiles.

Solute transport through polymeric membranes is generally described in terms of two mechanisms (1,2): the pore mechanism and the solution-diffusion or partition mechanism. In the first type, the diffusion rate is controlled primarily by the pore size of the membrane and the molecular volume of the solute. In the other mechanism, the physical-chemical properties of the solute and the membrane play dominant roles. These two mechanisms represent the extreme types of permeation and drugs probably permeate by both mechanisms, one of them being predominant.

In previous studies (3) we used a reservoir-type device in an in vitro assay for controlled release of sodium salicylate employing a chitosan membrane. The results showed that sodium salicylate release followed zero order kinetics. In the present study the permeation of acetamide, nicotinamide, sodium benzoate, sodium salicylate, phenobarbital sodium and sodium cefazoline through a chitosan membrane was determined and the results were interpreted in terms of the mechanisms of drug permeation through chitosan films.

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EXPERIMENTAL

Chemical and Reagents: The chitosan (Sigma) was purified by dissolving it in aqueous acetic acid, filtering, precipitating with sodium hydroxide, and washing with deionized water. The degree of N-acetylation (4) was 14.5 % and the relative molecular mass (5,6) was 5.90×10^5. Acetamide, nicotinamide, sodium benzoate, sodium salicylate, phenobarbital sodium and sodium cefazoline of analytical grade were used without further purification. The water used was deionized.

Apparatus: Spectrophotometric studies were carried out on a Shimadzu UV 260 spectrophotometer. A constant-temperature bath which was regulated by a thermostat (Haake E2) with ± 0.5 ºC precision was used.

Preparation of chitosan membrane: The chitosan samples were dissolved in acetic acid solution 1 M at a concentration of 1 %. The chitosan solution was filtered and cast on a Petri dish. The dish was kept at 60 ºC until the solvent was completely removed. The chitosan membrane thus obtained was immersed in aqueous NaOH solution 1 M at room temperature for 24 hours and then was washed with abundant deionized water. The thickness of the membrane swollen in water was determined with an optical microscope.

Measurement of water content (W) of the membrane: A weighed sample of the membrane, without drug, was immersed in deionized water and swollen in a vessel thermostated at 37º ± 0.5º C. The swollen sample was removed from the water at regular time intervals and the excess solution on the swollen sample was absorbed by gentle tamping between filter papers. The sample was weighed, and the procedure was repeated until a constant weight was obtained. Measurements were performed in triplicate. The swelling degree was calculated from the following equation (7):

$$(W) = 100 \left(\frac{\textit{Weight of swollen sample - Weight of dry sample}}{\textit{Weight of swollen sample}} \right)$$

Measurement of release rates: The release studies were carried out with a reservoir-type device which was placed into a tube containing 30 ml of water and then stored at 37 ± 0.5 ºC with continuous stirring during the experiment. Samples were withdrawn at suitable time intervals. The drug concentration was determined spectrophotometrically at the analytical wavelength. The release medium was completely removed after every measurement. All experiments were in triplicate and the average values were plotted.

RESULTS AND DISCUSSION

The diffusion studies were carried out using a reservoir-type device (3) under the following conditions: container of saturated drug, continuous stirring and periodical renewal of the release medium.

Table 1: Molecular Weight (Mol.Wt.), Water Solubility (Cs), Analytical Wavelength (λ max) and Molar Absorptivity Coefficients (ϵ) of the Studied Drugs.

Drug	Mol.Wt.	Cs (mg/ml)	λmax	ϵ (l/mol.cm)
Acetamide	59	2000	209.6	133
Nicotinamide	122	1000	261.0	2872
Sodium Benzoate	144	556	224.0	7456
Sodium Salicylate	160	1111	294.0	3620
Phenobarbital Sodium	254	1000	238.0	8620
Sodium Cefazoline	476	1000	270.0	12242

A chitosan membrane, prepared by solvent evaporation, with a total water content at equilibrium of 50.7 % was used. The thickness of the membrane swollen in water was 304 μ.

The drugs (Table 1) were chosen taking into account their molecular weight, water solubility and suitability in visible-ultaviolet absorption.

Figures 1 and 2 show plots of the total amount (mg) of the drug released versus time for each drug. In all the plots a non-linear zone (not shown) was observed. This zone corresponds to the time lag before establishment of the steady-state concentration profile. The parameters for the linear ratio were calculated by means of a standard technique of linear regression. The line regression, the variances and the correlation coefficients are listed in Table 2.

Table 2: Line regression, variance and correlation coefficients (r) of amount of drug released as a function of time profile for all the studied drugs.

Drug	Line regression	Variance	r
Acetamide	$-1.58 + 4.27\times10^{-1} \cdot X$	1.11	0.997
Nicotinamide	$-7.06 + 2.13\times10^{-1} \cdot X$	2.97	0.998
Sodium Benzoate	$-35.4 + 4.01\times10^{-1} \cdot X$	1.69	0.982
Sodium Salicylate	$-14.4 + 7.42\times10^{-2} \cdot X$	1.41	0.986
Phenobarbital Sodium	$-11.2 + 9.87\times10^{-2} \cdot X$	0.07	0.999
Sodium Cefazoline	$-88.3 + 1.10\times10^{-1} \cdot X$	1.67	0.996

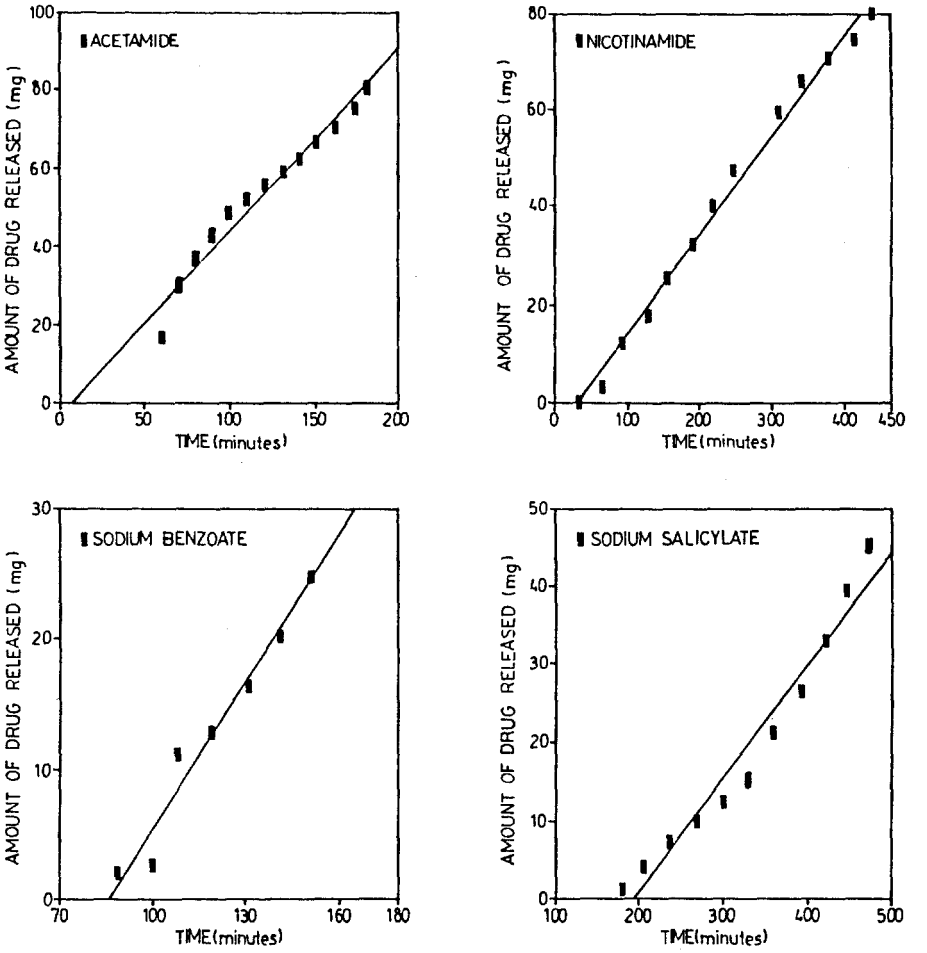

Figure 1: Total amount of drug released versus time.

The diffusion coefficient for each drug was determined from steady-state diffusion experiments using the following equation (2):

$$M_t = \frac{S\,P\,C}{l}\left(t - \frac{l^2}{6\,D}\right)$$

where M_t is the total amount of drug released, S the membrane surface area, P the membrane permeability, C the drug reservoir concentration, l the thickness of the membrane, t the time and

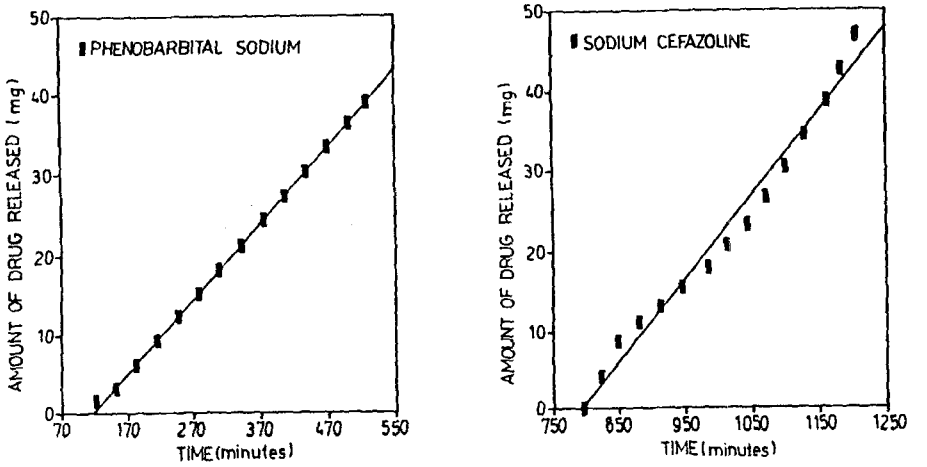

Figure 2: Total amount of drug released versus time.

D the diffusion coefficient.

As shown in Figure 1, by plotting M_t versus t, the intercept of the steady-state portion on the time axis is $l^2 / 6\ D$, which corresponds to the time lag (t_l) (8).

The time lags were calculated from the line regression equation where

$$M_t = a + b\ .\ t$$

where a is the intercept of lines of regression and b is the slope.

Extrapoling this to $M_t = 0$ gives $t = t_1$ or

$$t_1 = \frac{a}{b}$$

In this way, the time lag for each drug was used to calculate the diffusion coefficients using

$$D = \frac{l^2}{6\ t_1}$$

The time lags and the diffusion coefficients for all the studied drugs are shown in Table 3.

Figure 3 shows a plot of the diffusion coefficients versus molecular weights.

The diffusion coefficients are relatively independent for drugs of molecular weights between 476 and 144. Therefore the dominant mechanism for the permeation of these solutes is a solution-diffusion mechanism.

Table 3: Time lags and diffusion coefficients for all the studied drugs.

Drug	t_l (min)	D (cm^2/min)
Acetamide	3.7	4.18×10^{-5}
Nicotinamide	33.1	4.68×10^{-6}
Sodium Benzoate	88.3	1.75×10^{-6}
Sodium Salicylate	194.1	7.98×10^{-6}
Phenobarbital Sodium	113.5	1.36×10^{-6}
Sodium Cefazoline	802.7	1.93×10^{-7}

The abrupt change of the slope in the plot shown in Figure 3 suggests that a modification in the permeation mechanism occurs for the low molecular weight drugs with a prevailing pore mechanism.

In the change zone, both mechanisms of solute permeation probably contribute to the observed permeability.

In conclusion, these results would confirm that chitosan membranes can be employed as controlled-release devices for drugs using a reservoir-type device. The relationship between molecular weight and diffusion coefficient enabled us to determine the dominant permeability mechanism through chitosan membranes. This mechanism is valid for single and monovalent drugs where complex interactions of drug-membrane are minimum.

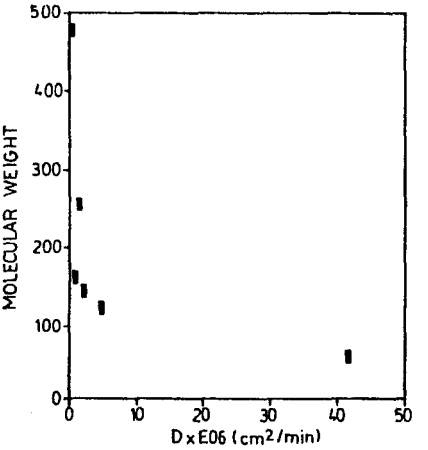

Figure 3: Molecular weight versus diffusion coefficient.

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