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RELATIONSHIP BETWEEN FILM PROPERTIES AND DRUG RELEASE FROM ACRYLIC FILMS

M. Dittgen

University of Greifswald, Section of Pharmacy,
GDR 2200 Greifswald, Jahnstr. 17

ABSTRACT

An in vitro technique was used to determine the release rates of drugs from different acrylic copolymers as carrier systems. The drugs used in this investigation were pilocarpine, streptomycine, isosorbide salts and nitroglycerol. By applying the Higuchi equations the diffusion coefficients of the drugs were calculated. A tensile stress test was used to examine certain mechanical properties of the films.

It was found that the incorporation of drugs into acrylic films by different techniques allowed the facile preparation of various compositions with diffusion coefficients in a relativly large range ($10^{-8}..10^{-15} cm^2 s^{-1}$). The choice of the physico-chemical state of the drug and the film composition can significantly affect drug release. The strain of the films depended on the tensile stress, the water and additives content.

It was examined that the drug release depended on the mechanical properties of the films. In general the drug release was faster from the lower viscosity grades and higher humidity contents of the films. This can be done

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by modifying the chemical structure of the used polymer system or by making use additives with alcoholic groups.

INTRODUCTION

Different techniques and polymers have been used for preparing drug loaded films (5,8,10,14,16,17,19). One way to get such films is to use acrylic polymers and to prepare the films by a solvent cast technique (10,19). However, an use of solvents has its own particular problems and can be restrictive to manufacture.
The mechanism of the drug release has been investigated by in vitro methods and the diffusion coefficient can be calculated by Higuchi equation (9,10,19). On the other hand it is clear that brittleness and elasticity are major mechanical properties connected with drug loaded films in therapy. Two methods have been used to evaluate these properties of films served for film coating (3,13,15): identation and tensile stress testing.
The aim of this work is to examine the effects that certain additives and drugs have on the mechanical properties of aqueous based acrylic films and to investigate wheter or not the modification of these properties afford in fact certain diffusion coefficients of drugs. In addition to reporting the fabrication technique to prepare the drug loaded films, this paper also deals with the release profile of four drugs from the films. The nature of the used polymer, the physico-chemical state of the drug and the influence of additives affecting the drug release from films are discussed as well.

MATERIALS AND METHODS

Chemicals

The drugs used in this investigation were Pilocarpine hydrochloride and Streptomycine sulphate (VEB Jenapharm,

Jena, GDR), Nitroglycerol (VEB Sprengstoffwerk, Schönebeck, GDR) and Isosorbide dinitrate (LEK, Ljubljana, Jugoslavia). Following pharmakopoe (1) grades additives with alcoholic groups were used: Ethylene glycol, propylene glycol, glycerol and in producer quality: glycol monoethylether (VEB Laborchemie, Apolda, GDR). Two different acrylic copolymers served as film forming materials: Eudragit E 30 D (Röhm Pharma GmbH, Darmstadt, FRG) and Scopacryl D 340 (VEB Chemische Werke Buna, Schkopau, GDR).

Preparation of Films

The drugs were dissolved in water or in a water-ethanol mixture. Whilst stirring the drug solution, the desired amount of the acrylic copolymer (suspension in water) was added. The mixture was stirred until complete homogeneity was effected. Any desired additives were added at this stage and best results were achieved if the mixture was immediately cast on an aluminium foil. After the drying process (30 h at 25...30 °C) a homogenous film resulted, with a thickness of about 0,4 mm. The films were stored at room temperature and defined humidity (58 ± 2 % R.H.).

Tensile Stress Test

The films were cut using a stainless steel template (test section 10·65 mm) and scalpel. Each sample was stored for 48 h at 20 °C ± 2 K and 58 ± 2 % R.H. before testing. The samples were labelled and their thickness measured using a micrometer in three places along the middle of the 65 mm section. The mean of these readings was used in the calculation of c_0 and tensile strength. Three samples of each formulation were tested using an apparatus described by Eichhorn and Dittgen (6). The time-strain curve was recorded directly and from this the ultimate time at 10 % elongation t_{10} was estimated.

Humidity

The films were conditioned at certain humidity (% R.H.) using chambers filled with saturated solutions of salts as shown in Table 1.

Drug Release

To follow the release of the drugs the Sartorius liberation chamber (Sartorius, Göttingen, FRG), a modificated Strickers Resorption model was used. 40 ml Aqua destillata (32 °C ± 1 K) was employed as acceptor medium. Acceptor medium pours over one side of the film (5,3 ml min^{-1}). 20 ml samples were removed at 30 (first) and 60 min intervals, fresh Aqua added and the released drug amount assayed as follows: pilocarpine according to Beyrich (4) catalymetrically at 366 nm, streptomycine acc. to Ashton, Forster and Fatherley (2) at 525 nm and nitroglycerol acc. to Ermer (7) at 530 nm both colorimetrically and isosorbide acc. to Mc Niff, Yap and Ho-Leung Fung (12) at 290 nm spectrophotometrically. The amount of drug released from the films was calculated and plotted as a function of square root of time (s)

TABLE 1
Salts using for humidity conditioning according to Nikolski (11)

Salt	% R.H. at 20 °C
$LiCl \cdot H_2O$	15
$Zn(NO_3)_2 \cdot 6\ H_2O$	42
$NaBr \cdot 2\ H_2O$	58
$(NH_4)_2SO_4$	81
$CaSO_4 \cdot 5\ H_2O$	98

on a personal computer (HP 85, Hewlett Packard, Corvallis, Oregon 97339, USA).
Utilizing the slope of the straight line of this plot the apparent diffusion coefficient D was determined by a modificated Higuchi equation (9):

$$D = \frac{a^2 \pi}{(2c_0)^2 A^2} \qquad \text{(Eq.1)}$$

c_0 = initial drug concentration (0,00025 mol/cm^3)
A = film area (38,5 cm^2)

RESULTS AND DISKUSSION

Knowing that the results of tensile strain study could be dependent upon the water content chosen, it was first necessary to investigate the effect of the humidity on the water content of the films. The conditioning of the polymeric films at certain humidity resulted in significant changes in water content. The water content of film without additives decreases by less than 40 % R.H. slight and increases by more than 60 % R.H. strongly. Figure 1 shows that changes in water content seems to be dependent of the drugs and additives. It is obvious as the concentration of glycerol is increased there are significant changes in water content measured. Compared to the unloaded films the absolute altitude of the water content of the streptomycine loaded films was changed dramatically when glycerol added.
These results are in general agreement with the work of Turner (18). It was concluded that the remainder of the studies should be conducted with films stored at about 58 % R.H.
A follow-up to this part of the experiment the mechanical properties of the films was determined by means of a tensile stress test. Figure 2 shows the effect of

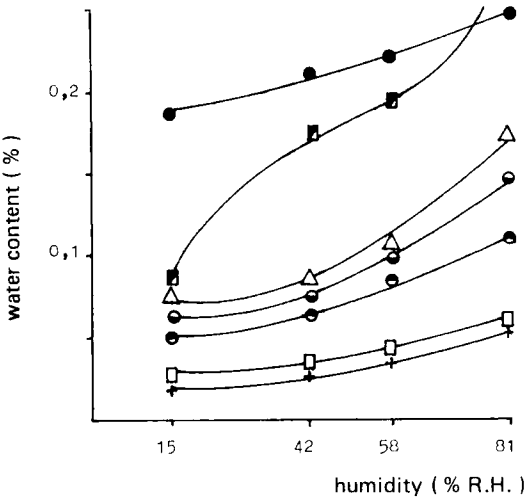

FIGURE 1

Percent water content of scopacryl films vs. humidithy as a function of drug loading and glycerol content

+scopacryl
Δ pilocarpine(0,125 g/cm^3)
□ streptomycine(0,125 g/cm^3)
◪ streptomycine(0,125 g/cm^3)and glycerol(0,01 g/cm^3)
◓ glycerol(0,01 g/cm^3)
◒ glycerol(0,03 g/cm^3)
● glycerol(0,09 g/cm^3)

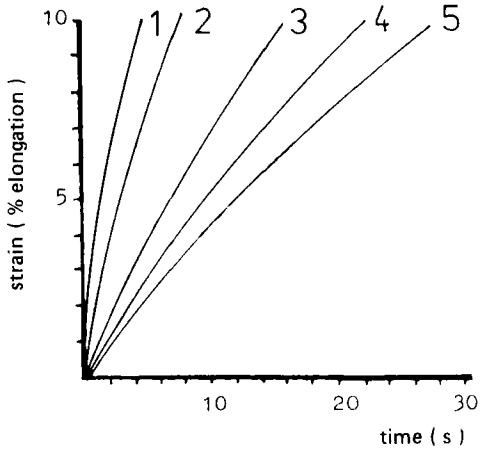

FIGURE 2

Strain-time curves of scopacryl films containing different additives

1 glycol monoethylether
2 propylene glycol
3 glycerol
4 ethylene glycol
5 unloaded scopacryl film

different glycols on the elongation of the scopacryl film.

Generally the lower molecular weight, the greater the plasticising action. These results are in agreement with the investigations of Aulton and Abdul-Razzak (3). The athors have looked at the influece of PEG on the relevant properties of HPMC films. It is obvious that the differences noted in the strain-time curves are dependent on the chemical structure of additives. At first the number of hydroxyl groups and their position plays a certain role. At second the degree of etherizing can be modified the plasticising action. The monoethylether of glycol was most effective as plasticiser. This can be explained that it will be more reduce the number of active centres available and contacts between polymer molecules (3). Furthermore it is interesting to note that the presence of drugs (Figure 3) in the acrylic films had different effect. Three drugs did act as plasticiser. This effect is independent of the film forming material. In general the eudragit films are more plastic. Streptomycine has a negative effect on these film properties. The streptomycine films are brittle and can be easily broken in the fingers and the eudragit films are absolute instabile. The drug release were evaluated for the pilocarpine, isosorbide and nitroglycerol films formed with scopacryl and eudragit as well as for the streptomycine films formed with scopacryl (Figure 4 and 5).

It can be seen that in the time period from 30 to 330 minutes, there is in all cases a linear relationship between the amount of drug released (mol) and $\sqrt{t}$ as in the model proposed by Higuchi (9). Generally speaking, it was found that the drug release was faster from the scopacryl films. It can be seen from

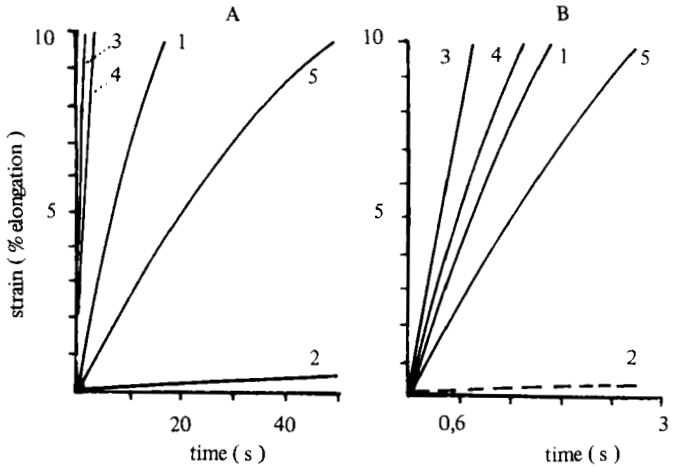

FIGURE 3

Strain-time curves of scopacryl(A) and eudragit(B) films containing 0,25 • 10^{-3}mol/cm^3 of different drugs

1 pilocarpine
2 streptomycine
3 isosorbide
4 nitroglycerol
5 unloaded film

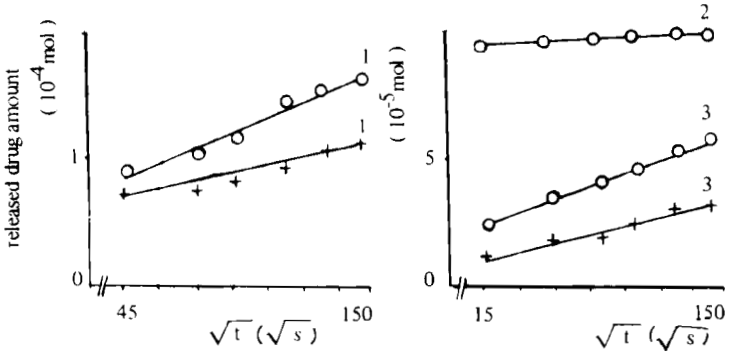

FIGURE 4

Drug release from scopacryl(o) and eudragit(+) films
1 pilocarpine, 2 streptomycine, 3 isosorbide

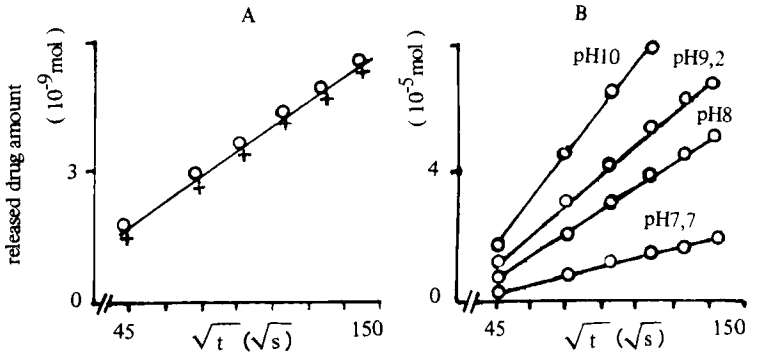

FIGURE 5
Nitroglycerol(A) and streptomycine(B) release from scopacryl(o) and eudragit(+) films

Figure 5 that the release rate of nitroglycerol from scopacryl film is nearly equal to this from eudragit film and verry small.

The apparent diffusion coefficients are variable in a relativly large range from $1,07 \cdot 10^{-8}$(pilocarpine) to $1,4 \cdot 10^{-15} cm^2 s^{-1}$(nitroglycerol).

A change of physico-chemical state of sthe drug in the acrylate film can be done by modifying the pH inside the film (Figure 5). In this way the apparent diffusion coefficient of streptomycine from scopacryl film was modulated from about 4.10^{-8}(pH 10) to 9.10^{-9}(pH 7,7) and $0,2 \cdot 10^{-10}$(pH 7,4).

The primary purpose of this studies was apparent diffusion coefficients calculated to compare with the mechanical properties of the films (Table 2).

A comparative evaluation of the apparent diffusion coefficients and the t_{10}-values shows in all cases the same effect. The film with the lowest diffusion coefficient (eudragit) is the same with the lowest mechanical stability. But the change from one drug to an other did not a change in mechanical proper-

TABLE 2

App. diff. coefficients D ($10^{-12}cm^2s^{-1}$) and t_{10} (s at 2,5 N/mm^2) of scopacryl(A) and eudragit(B) films

drug	D^A	t_{10}	D^B	t_{10}
unloaded	-	51	-	2
pilocarpine	10650	15,5	1730	1,3
streptomycine	21	-	-	-
isosorbide	1050	0,8	309	0,5
nitroglycerol	0,0015	1,3	0,0014	1,0

ties in correlation with the diffusion coefficients. In this case the influence of drug properties (e.g. partition coefficient, corresponding solubility) was dominated in relation to drug release.

CONCLUSION

The use of strain-time test allowed the classification of drug loaded films. But the study showed that the change in drug loading can affect strongly the drug release from acrylic films. Follow-up studies are being designed to further characterize and quantitate the influence of drugs as well as additives on the mechanical properties of drug loaded films such as scopacryl and eudragit.

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