DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(5), 663-682 (1982)

Drug Release from Compression Molded Films: Preliminary Studies with Pilocarpine

Richard J. Harwood[+] and Joseph B. Schwartz*

[+]Merck Sharp and Dohme Research Laboratories
Department of Pharmaceutical Research and Development
West Point, PA 19486

*Present Address
Philadelphia College of Pharmacy and Science
Philadelphia, PA 19104

ABSTRACT

It was found that the incorporation of pilocarpine into a hydrophilic thermoplastic matrix such as hydroxypropyl cellulose by the compression molding technique allowed the facile preparation of various pilocarpine salt/hydroxypropyl cellulose compositions.

The pilocarpine release characteristics were evaluated for several compositions of this type. This study showed that the choice of pilocarpine salt and the hydroxypropyl cellulose molecular weight can significantly affect pilocarpine release from the polymer matrix. It was found that from the highest molecular weight grade of hydroxypropyl cellulose pilocarpine release was faster for the more soluble

hydrochloride salt than for the nitrate salt. In addition, when a new pilocarpine salt, pilocarpine pamoate, was incorporated into the same matrix, a dramatic decrease in pilocarpine release was exhibited. When pilocarpine pamoate was incorporated into three different molecular weight grades of hydroxypropyl cellulose, dramatic differences in pilocarpine release rate were observed. In general, it was found that pilocarpine release was faster from the lower vscosity grades of hydroxypropyl cellulose.

This manuscript discusses the method of preparation for compression molded films, the release rate testing procedure, the effects of agitation and temperature, and variations in the drug salts and the matrix composition.

INTRODUCTION

Major improvements in ophthalmic medication systems can be realized by providing for the controlled release of drug in the eye subsequent to the instillation of the medication in the eye (1-7). In principle, the medication should be released from the ophthalmic drug delivery system to the lacrimal fluid at a rate which minimizes wastage and which will still provide for a therapeutic level of medication in the eye (8,9).

The use of water-soluble gums to decrease the rate of drug release from a matrix has been reported in the literature (10-13). The

same principles should apply to other drug delivery systems and this seemed to be an ideal starting point in an effort to identify a system which would release an ophthalmic drug, such as pilocarpine from a solid matrix over a prolonged period of time. The incorporation of drugs into water-soluble matrices has been achieved by solvent casting of films (10) and by tablet compression (11-13). A freeze-drying technique (14) has been used for preparing drug loaded films using an ethylene-vinyl-acetate matrix. However, each of these techniques has its own particular problems and can be very tedious to manufacture.

One way to avoid such preparation problems is to use compression molding. Compression molding, a fabrication technique commonly used to mass produce articles of a planar configuration, is a process whereby a thermoplastic substance can be formed into a desired configuration by application of heat and pressure. This fabrication technique allows facile preparation of thin flat films without the long time periods required to prepare solvent cast films or matrix films by the freeze-drying technique. These considerations led to the concept that this fabrication technqiue could be used in a pharmaceutical research laboratory to prepare precise films of drug and a thermoplastic polymer without using any other additives. Hydroxypropyl cellulose was identified as a water-soluble, non-ionic cellulose ether which is themoplastic and amenable to this process (15). In addition to reporting on the fabrication technique to prepare the test samples, this paper also deals with the release profile of pilocarpine from the polymer matrix.

Factors affecting pilocarpine release from the matrix are discussed as well.

EXPERIMENTAL

Chemicals

Pilocarpine hydrochloride (Mallinckrodt, St. Louis, MO) and pilocarpine nitrate (Merck & Co., Rahway, NJ) were U.S.P. grade. Pilocarpine pamoate was prepared according to the procedure described by Cohen, et al (16). Prior to use, each pilocarpine salt was pulverized via a mortar and pestle. Only the fraction of powder passing through a number 60 mesh sieve (250 μm opening) was used).

Three different viscosity grades of food grade hydroxypropyl cellulose (Klucel, Hercules, Inc. Wilmington, DE) were employed. Each viscosity grade of hydroxypropyl cellulose reflects differences in the average polymer chain length. The typical average molecular weights for each grade is: 1,000,000 for 'Klucel HF' type; 300,000 for 'Klucel GF' type; and, 125,000 for 'Klucel JF' type.

Compression Molding Equipment

A laboratory hydraulic press (Carver, Model C, Fred S. Carver, Inc., Menomonee Falls, WI) equipped with heating and cooling platens was used to compression mold each film. Two 15.24 cm x 15.24 cm (6 in x 6 in) aluminum sheets and a 15.24 cm x 15.24 cm (6 in x 6 in)

stainless steel shim measuring 0.6 mm in thickness with an open square center portion which measured 10.16 cm (4 in x 4 in) was used. The shim had an outer border measuring 2.54 cm (1 in).

Preparation of Pilocarpine Hydrochloride/Hydroxypropyl Cellulose Films

Films containing pilocarpine hydrochloride (19.5% w/w) and hydroxypropyl cellulose ('Klucel HF' grade) were prepared by placing an eight gram (8 g) sample of the powder mixture in the middle of the shim and in between the lubricated 15.24 cm x 15.24 cm (6 in x 6 in) aluminum sheets. The lubricant utilized was a food grade aerosolized lecithin (PAM, Boyle - Midway, New York, NY). The "sandwich" was transferred onto the preheated (150°C) bottom platen of the press. The preheated (150°C) top platen and bottom platen were brought together as much as possible to heat the sample under pressure (10,000 to 12,000 pounds (4,545 kg - 5,455 kg) gauge) for one minute. Then, cold water was circulated through the platens for 3.5 minutes to cool the sample down while under pressure. The pressure was released and the "sandwich" was removed from the press. The film was removed from the aluminum sheets and cut into 4 cm by 1 cm strips with scalpel and metal ruler.

Preparation of Pilocarpine Nitrate/Hydroxypropyl Cellulose Films

Films containing pilocarpine nitrate (21.6% w/w) and hydroxypropyl cellulose ('Klucel HF' grade) were prepared by compression molding as follows. An eight gram (8 g) sample of the powder mixture was placed

on one lubricated 15.24 cm x 15.24 cm (6 in x 6 in) aluminum sheet. The lubricant utilized was a food grade aerosolized lecithin. The shim was placed around the powder. The second 15.24 cm x 15.24 cm (6 in x 6 in) lubricated aluminum sheet was placed over the powder. This "sandwich" was transferred onto the preheated (110°C) bottom platen of the press. This temperature was required for the nitrate salt to prevent browning during the molding step. The preheated (110°C) top platen and the bottom platen were brought together as much as possible to heat the sample under pressure (10,000 to 12,000 pounds (4,545 kg-5,455 kg) gauge) for one minute. Then, cold water was circulated through the platens to cool down the sample while it was still under pressure. After cooling (3.5 minutes), the pressure was released and the "sandwich" was removed from the press. The film was removed from the aluminum sheets and cut into 4 cm x 1 cm strips with a scalpel and metal ruler.

Preparation of Pilocarpine Pamoate/Hydroxypropyl Cellulose Films

Compression molded films containing pilocarpine pamoate (8.3% w/w, 16.6% w/w, or 33.3% w/w) and hydroxypropyl cellulose ('Klucel JF', Klucel GF', or 'Klucel HF') were prepared in the same manner as described for the preparation of the pilocarpine hydrochloride/hydroxypropyl cellulose films.

Determination of Pilocarpine Release from the Films

The sample preparation as described by Borodkin and Tucker (17) was

modified slightly. The film was mounted onto a glass microscope slide using a coating of silicone lubricant (Dow Corning Corp., Midland, MI). The slide holding the film was placed on the bottom of a 1000 ml dissolution flask which contained 900 ml of water at the desired temperature (22°C or 37°C). A propellor stirrer which was placed 2 cm above the sample was used to agitate the system. The aqueous solution was automatically assayed using a Gilford spectrophotometer (Gilford Instrument Co., Oberlin, OH) set a 215 nm and equipped with a flow through cell. Absorbance at 215 nm was found to be a maximum for pilocapine and no absorbance at 215 nm was noted for hydroxypropyl cellulose solutions made at concentrations equivalent to that which would be obtained if the entire film dissolved. The percent of pilocarpine released from the matrix was calculated as a function of the absorbance value plotted on an automatic strip chart recorder (Heath Co.).

RESULTS AND DISCUSSION

It was found that the incorporation of pilocarpine into a hydrophilic thermoplastic matrix such as hydroxypropyl cellulose by the compression molding technique allowed the facile preparation of various pilocarpine salt/hydroxypropyl cellulose compositions. The use of a thermoplastic polymer allowed precise films of drug and polymer to be fabricated *via* compression molding without using any other additives. Using this technique many of the problems associated with large scale

tablet compression, and the long time periods required to prepare solvent cast films or matrix films by the freeze-drying technique were avoided.

The pilocarpine release characteristics were evaluated for each film. Knowing that the results of a release study could be dependent upon the experimental conditions chosen, it was first necessary to investigate the effect of the degree of agitation and the effect of temperature on the pilocarpine release from the hydroxypropyl cellulose matrix. If the agitation is not great enough, too large a diffusion layer would be created causing the system to become convection controlled rather than diffusion controlled. Figure 1 shows that the release of pilocarpine hydrochloride from the 'Klucel HF' matrix seems to be independent of stirring rate. This would indicate that the system is diffusion controlled. It should be noted that the data suggest that there might be some slight diffusion layer built up at 50 rpm and 100 rpm, but for practical purposes it seems negligible.

It has been noted that as the temperature of an hydroxypropyl cellulose solution is raised, the less soluble the polymer becomes (15). Hydroxypropyl cellulose will precipitate from aqueous solution at temperatures higher than 45°C. In addition, as various solutes (such as sucrose and sodium chloride) are added to aqueous hydroxypropyl cellulose solutions the temperature at which precipitation occurs becomes lower. To determine if the release of pilocarpine hydrochloride

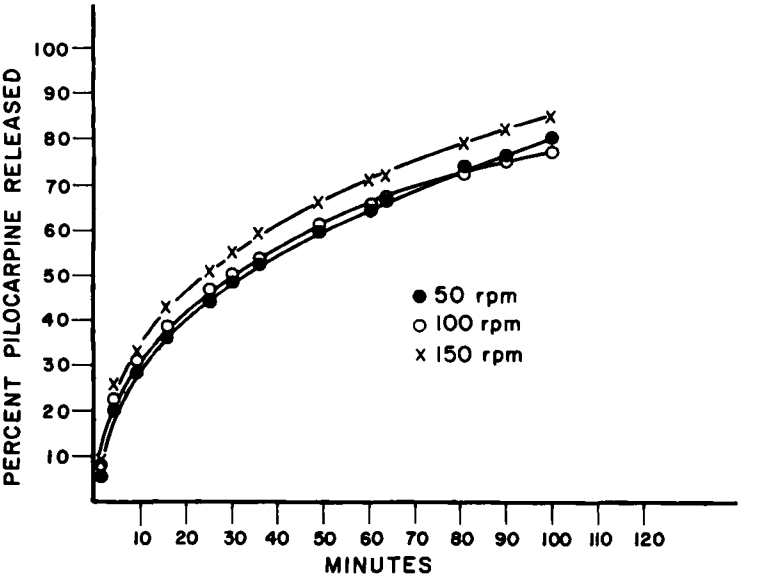

Fig. 1: Percent pilocarpine released vs. time from films containing pilocarpine hydrochloride and hydroxypropyl cellulose ('Klucel HF') at 37°C.

from 'Klucel HF' changes as the temperature approaches the precipitation temperature, a study was conducted at both 22°C and 37°C. The results are shown in Figure 2. Overall, there seems to be a very slight decrease in release at 37°C when compared to the release at 22°C but again this was considered negligible. This was not as dramatic a change as that observed with methylcellulose systems studied at 37°C (18) - the temperature at which aqueous methylcellulose solutions gel and change drug dissolution behavior of film coated tablet formulations.

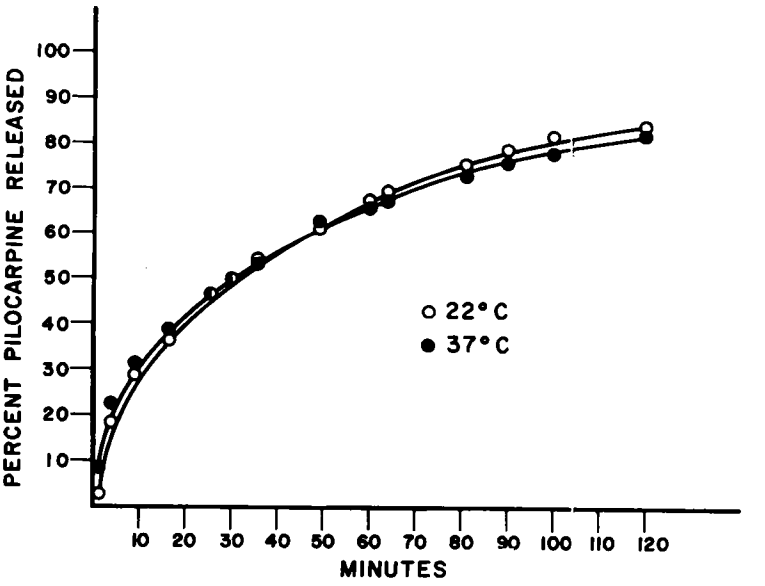

Fig. 2: Percent pilocarpine released vs. time from films containing pilocarpine hydrochloride and hydroxypropyl cellulose ('Klucel HF') at 100 rpm.

A close look at the initial rates at both of the temperatures tested indicated that there is a difference in the initial dissolution process. Initially the percent dissolved at 22°C is greater than 37°C. This difference may be attributed to the polymer dissolving and/or swelling faster at 22°C than at 37°C. Inasmuch as the overall release pattern was not changed dramatically as a function of temperature, it was concluded that the remainder of the studies should be conducted at the physiological temperature (37°C).

The data in Figure 2 were replotted as a $\sqrt{t}$ function and are

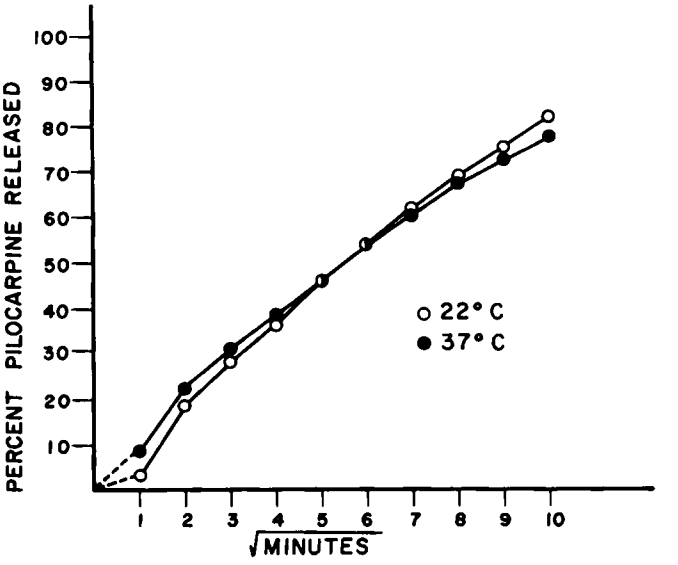

Fig. 3: Percent pilocarpine released vs. $\sqrt{\text{time}}$ from films containing pilocarpine hydrochloride and hydroxypropyl cellulose ('Klucel HF') at 100 rpm.

shown in Figure 3. It can be seen in Figure 3 that in the time period from 4 minutes to 25 minutes (20 to 50% release), there is a linear relationship between the percent pilocarpine released and $\sqrt{t}$ as in the models proposed by Higuchi (19) and Higuchi (20). The basic relationship for the release of solid drug from an insoluble, inert matrix is given as

$$Q = \left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)\, C_s t\right]^{\frac{1}{2}} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released per unit surface area at time

t, D is the diffusion coefficient of the drug in the solvent, ε and τ represent the porosity and tortuosity of the matrix, respectively, A is the concentration of drug in the matrix, and C_s is the solubility of the drug in the solvent (19).

One of the assumptions upon which Eq. 1 is based is that $2A >> \varepsilon C_s$ and only drugs of low solubility will meet this requirement.

For a soluble drug where the condition that $2A >> \varepsilon$ Cs does not hold, (i.e., in the absence of a solid/liquid boundary) the release profile can be described by the equation (20).

$$Q = 2 C \varepsilon \left[\frac{Dt}{\pi \tau} \right]^{\frac{1}{2}} \qquad \text{(Eq. 2)}$$

where C is the concentration of the drug solution in the matrix (20). In this case a linear $\sqrt{t}$ plot is still expected.

The straight portion of Figure 3 occurs, presumably, after polymer hydration and only when the area and volume of the matrix are relatively constant. The deviation from linearity after 50% release is presumed to be due to free drug leaving the matrix at a faster rate than the matrix is dissolving. Because the matrix is changing (swelling and dissolving) it is not unexpected that the data would deviate from the square root of the time models. The basic assumption upon which these models were derived is that the matrix is inert and insoluble. Because the changes are slow, there does appear to be

straight line portion of the square root plot which adequately describes the data. Some adherence to the $\sqrt{t}$ function is consistent with the results of Lapidus and Lordi (10,11) and with Borodkin and Tucker (17) who had utilized hydrophilic polymers in their systems prepared by other methods.

A study was undertaken to determine if pilocarpine release would be affected by pilocapine salt from. The solvent temperature used was 37°C and the stirring rate was chosen to be 100 rpm. A comparison of release rate of pilocarpine was made using films containing either the hydrochloride salt or the nitrate salt. Figure 4 clearly shows that pilocarpine release from the matrix is faster with the more soluble hydrochloride salt (solubility is 1 g per 0.3 ml water at 25°C (21)) as compared to the nitrate salt (solubility is 1 g per 4 ml water at 25°C (21)). The ratio of the solubilities of hydrochloride salt (C_sHCl) to nitrate salt (C_sHNO_3) is 13.32 at 25°C. Since the ratio of initial release rates of the hydrochloride salt to nitrate salt is about 2.3 at 37°C, it is obvious that the differences noted in the initial release rate are not directly proportional to the relative solubilities. The ratio of the slopes of the corresponding $\sqrt{t}$ plots (1.40) was not proportional to the ratio of solubilities of the two salts as predicted by equation 2 nor to the ratio of the square root of the solubilities of the two salts (3.64) as predicted by equation 1. These observations indicate that a combination of factors is at play in this system. Opposing factors such as the "burst effect", osmotic pressure, drug

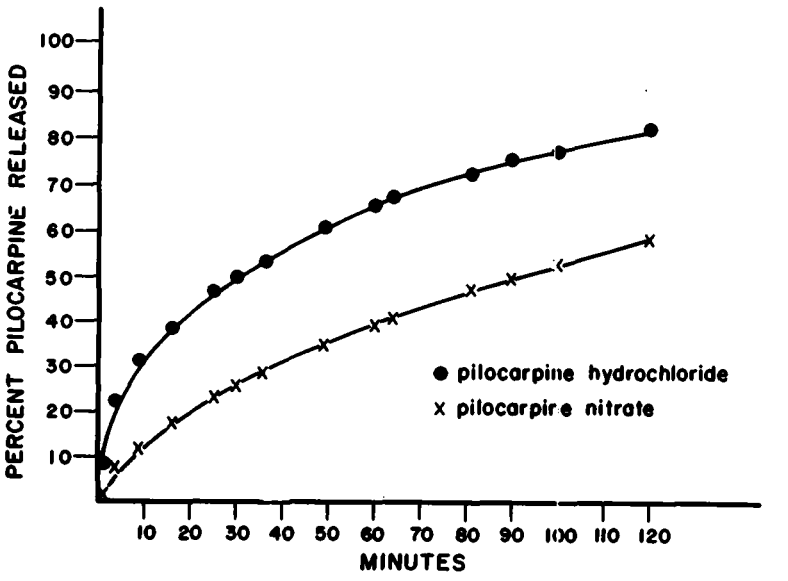

Fig. 4: Percent pilocarpine released vs. time from hydroxypropyl cellulose ('Klucel HF') films at 37°C and 100 rpm.

solubility, and polymer hydration could account for the differences noted. It has been noted earlier that this sytem should not follow the Higuchi models because the matrix interacts with the solvent. A further consideration in studying this system is that there may be an interaction between the pilocarpine salts with the hydroxypropyl cellulose matrix. It is known that various dissolved inorganic salts, when added to aqueous hydroxypropyl cellulose solutions, can cause hydroxypropyl cellulose to precipitate from solution (15). This incompatibility varies according to the salt. For example, a 10% (w/w) sodium chloride solution is incompatible with hydroxypropyl cellulose whereas a 10%

(w/w) sodium nitrate solution does not precipitate hydroxypropyl cellulose from solution. By extrapolation to the hydroxypropyl cellulose films containing either pilocarpine hydrochloride or pilocarpine nitrate, it would appear that in water the anion present could certainly affect the hydroxypropyl cellulose matrix and thus affect the pilocarpine release from the matrix. If one assumes that interference of the hydration of the hydroxypropyl cellulose is greater with pilocarpine hydrochloride than with pilocarpine nitrate, it can be surmised that there would be less of a gel barrier which would prevent the release of pilocarpine to the dissolution medium.

A novel pilocarpine salt, pilocarpine pamoate, was prepared in the laboratory (16). The pamoate anion can be considered to be a substituted phenolic compound and, as such, would be expected to interact with the hydroxypropyl cellulose matrix (15). It was not certain how this type of interaction would affect pilocarpine release from the matrix. Films of pilocarpine pamoate at various drug levels were made. The release rate of pilocarpine (Figure 5) is not proportional to the initial pilocarpine pamoate level. It was expected that as drug load was increased, the percent release of drug per unit of time would increase as well. Obviously this was not the case. In fact, in the case of this system, just the opposite was found: as the pilocarpine pamoate concentration was increased from 8.3% (w/w) to 16.6% (w/w) in the 'Klucel HF' matrix, the pilocarpine release slowed down. This was considered as evidence that the pamoate anion

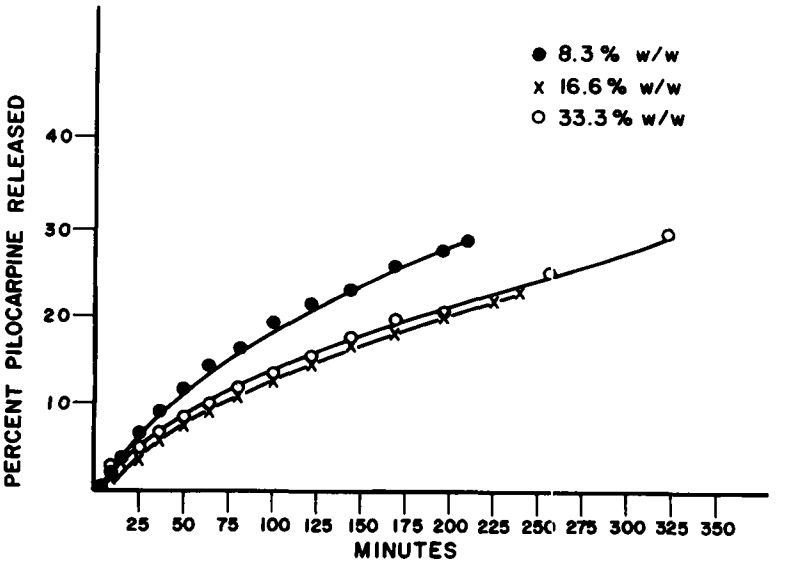

Fig. 5: Percent pilocarpine released vs. time as a function of pilocarpine pamoate load in hydroxypropyl cellulose ('Klucel HF') at 37°C and 100 rpm.

interacted with the hydroxypropyl cellulose matrix. The fact that solubility data obtained in the laboratory indicated that the disproportionation of the salt could take place (22) led one to conclude that the pilocarpine moiety could be released from the matrix at a different rate than that of the pamoate moiety. Evdence for this was the fact that a pilocarpine depleted matrix remained yellow. Another possibility for the delayed release in this case might be the precipitation of free pamoic acid which could delay the release of the pilocarpine by reducing the available porosity. This could occur with or without pamoate/matrix interaction.

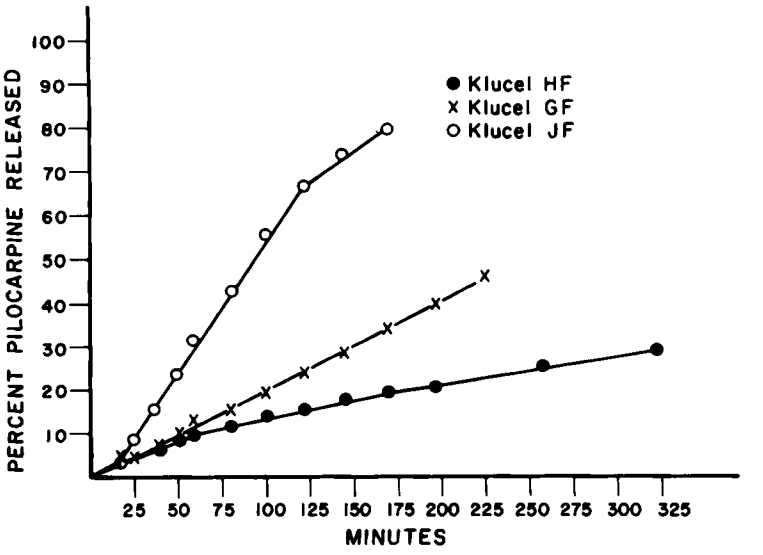

Fig. 6: Percent pilocarpine released vs. time as a function of molecular weight of hydroxypropyl cellulose ('Klucel') at 33 1/3% (w/w) drug load, 37°C, 100 rpm.

A follow-up to this part of the experiment was to determine the effect of molecular weight grade of hydroxypropyl cellulose on pilocarpine release from pilocarpine pamoate/hydroxypropyl cellulose systems. Generally speaking, it was found that pilocarpine release was faster from the lower viscosity grades of hydroxypropyl cellulose; the lower the viscosity grade, the faster the release rate (Figure 6). It can be seen from Figure 6 that the release rate of pilocarpine is apparent zero order from the 'Klucel JF' film between 25 minutes and 100 minutes. For the 'Klucel GF' films, the release rate is apparent zero order from 50 minutes to 225 minutes. For 'Klucel HF' films

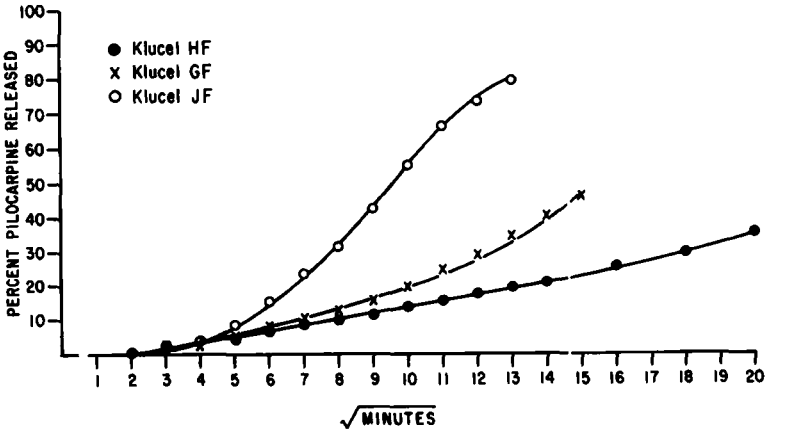

Fig. 7: Percent pilocarpine released vs. $\sqrt{\text{time}}$ as a function of molecular weight of hydroxypropyl cellulose ('Klucel'), at 33 1/3% (w/w) drug load, 37°C, 100 rpm.

the release rate is apparent zero order between 50 and 169 minutes. In all three cases it appears that initial deviation was due to the polymer hydration step. The deviation noted after 50% pilocarpine depletion of the matrix was probably due to a combination of polymer gelation and swelling along with polymer dissolution or erosion.

In Figure 7, these data were also plotted as a function of $\sqrt{t}$. The data for the Klucel HF film appears linear. The lower molecular weight containing films exhibit positive deviation supporting the above hypothesis.

CONCLUSION

The use of compression molding allowed facile preparation of

hydroxypropyl cellulose/pilocarpine films without the use of any other additives. This preliminary study showed that the choice of hydroxypropyl cellulose molecular weight and the pilocarpine salt can significantly affect pilocarpine release from the polymer matrix. Follow-up studies are being designed to further characterize and quantitate the release rate of pilocarpine as well as the drugs from water-soluble matrices such as hydroxypropyl cellulose.

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