Drug Absorption Analysis from Pharmacological Data III: Influence of Polymers and pH on Transcorneal Biophasic Availability and Mydriatic Response of Tropicamide

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Abstract □ Pharmacological data were employed to determine the time course of transcorneal absorption of the mydriatic drug tropicamide directly to its vicinal site(s) of action (biophase) and peripheral dissipation by other routes following ophthalmic dosing. The method is described and applied to the elucidation of the influence of vehicle composition. Semilogarithmic plots of the time variation of unabsorbed drug were linear; this finding allowed the evaluation of apparent first-order rate constants to characterize the biophasic availability of the drug in each dose studied. The effects of including an anionogenic, cationogenic, and nonionic polymer in the ophthalmic vehicles, buffered at pH 5.0 and 7.4, on the transcorneal absorption and pharmacological response behavior of tropicamide are presented. The concentration of each polymer in the vehicles was adjusted to obtain the same vehicle viscosities in the range of 4.4–16.5 cps. No general patterns of strongly significant effects were found to be attributable to viscosity and the inclusion of the polymers in the vehicles.

Keyphrases □ Ophthalmic drugs—polymer and pH effects on transcorneal biophasic availability and mydriatic response of tropicamide □ Tropicamide—effects of anionogenic, cationogenic, and nonionic polymers and pH on bioavailability and mydriatic response □ Mydriatic drugs—influence of vehicle composition □ Drug absorption—influence of polymers and pH on tropicamide bioavailability □ Bioavailability—tropicamide, polymer and pH effects on transcorneal biophasic availability and mydriatic response

The importance of controlling the pharmacological response characteristics of ophthalmic drugs, particularly mydriatic agents, becomes apparent from considering the wide range of uses of these drugs and the potential hazards that can result from systemic toxicities and unduly prolonged effects (1–3).

Previous studies (4–7) on control of the characteristics of ophthalmic drug response have been concerned with the addition of nonionic polymers, *e.g.*, methylcellulose, to the ophthalmic vehicle. Such effects of polymeric adjuvants have been commonly attributed to an enhanced viscosity of the vehicle causing an increased contact time of the drug with the corneal surface; this influences the amount and rate at which the drug is absorbed to its local sites of action. Adjuvants can also induce effects, independent of viscosity, specific to their chemical nature. This is exemplified by the reported (8) effect of the replacement of magnesium sulfate by sodium sulfate in an atropine preparation; the duration of the mydriatic response dramatically decreased from 26 to 1 hr. It appears that the composition of the ophthalmic vehicle can provide a means by which the solute permeability properties of tissue barriers and, therefore, characteristics of the pharmacological response to ophthalmic drugs may be controlled and ultimately optimized.

A means by which the transference of a drug from its site of administration to its site of action can be studied is a useful tool in approaching this objective. Methods of computing drug absorption have been described (9) and developed (10). However, these methods of drug absorption analysis require the detection of the drug in the blood, urine, or tissues and are not generally applicable for the study of drug absorption from an ophthalmic site of administration. However, the use of pharmacological data for the determination of the cumulative amounts of drug absorbed from a site of administration to the site(s) of action at any time following dosing by any route, as previously described (11–17), can be used. This technique was applied in the present study to determine if vehicle viscosity, pH, and the addition of polymeric materials can influence the pharmacological response and bioavailability characteristics of the mydriatic drug tropicamide following ophthalmic dosing.

Table I—Physical Properties of Polymers

Property	Polymer A[a]	Polymer B[b]	Polymer C[c]
Functionality	Neutral	Anionic	Cationic
Concentrations, expressed as cps (37°)	4.4	5.0	4.4
	8.2	8.1	8.2
	12.0	12.5	11.7
	16.4	16.5	16.7
Viscosity[d] of aqueous solutions at 25°			
0.5%	80	—	—
1.0%	325	1000	1400
2.0%	50,000	—	—

[a] Methylcellulose HG, supplied by Dow Chemical Co., Midland, Mich. [b] Reten A-1, supplied by Hercules, Inc., Wilmington, Del. [c] Reten 205, supplied by Hercules, Inc., Wilmington, Del. [d] Brookfield viscometer.

THEORETICAL

Determination of Transcorneal Biophasic Availability—The details of the manner in which the results of monitoring the time variation of mydriatic response intensity can be employed to determine biophasic drug availability behavior following ophthalmic dosing have been well described and confirmed for tropicamide (11–13). Briefly, however, the time course of the relative cumulative amounts, A_t, of tropicamide that become transcorneally absorbed and traverse the biophase can be computed using Eq. 1:

$$A_t = \frac{Q_B + K_{BO'} \int_0^t Q_B \, dt}{K_{BO'} \int_0^t Q_B \, dt} \qquad \text{(Eq. 1)}$$

where $K_{BO'}$ is an overall elimination constant from the biophase. The value of $K_{BO'}$ was previously reported (11, 13) as 0.051 min^{-1}. The biophasic drug levels, Q_B, are obtained by transforming observed mydriatic response intensities through a dose–effect curve (11–17).

When the clearance of the drug from its site of administration can be described to occur by apparent first-order processes, as is the present case (13), the slope of a linear plot constructed in ac-

Table II—Mydriatic Response Characteristics of Tropicamide following Ophthalmic Dosing[a]

pH of Vehicle	Tropicamide Concentration, % w/v	Onset	t_{max}[b]	Maximum Intensity	Duration	t_m[c]	t_B[d]
7.4	0.010	10.5	17.0	0.603	58.5	13.3	17.7
7.4	0.015	8.8	20.5	0.722	61.0	21.3	15.7
7.4	0.020	9.2	22.5	0.788	73.3	16.0	19.8
7.4	0.030	10.2	27.0	0.936	86.0	24.6	13.3
5.0	0.015	6.1	14.5	0.695	79.9	47.3	21.8

[a] The solutions were approximately isotonic; 0.02 ml of each was instilled into the cul-de-sac of rabbits. Each parameter listed is the average of four determinations on different rabbits. [b] The t_{max} is the time corresponding to the maximum intensity. [c] The t_m is the apparent mydriatic response dissipation half-life and represents least-squares regression values. [d] The t_B is the apparent biophasic drug elimination half-life and represents least-squares regression values.

cordance with Eq. 2 provides a means of evaluating the dissipation rate constant, K_D:

$$\log (1 - A_t) = -K_D t \qquad \text{(Eq. 2)}$$

The dissipation of the drug from its site of administration can be described to occur by the parallel processes of transcorneal absorption and peripheral loss. The latter process can be attributed to volume loss of drug through the lacrimal nasal duct, scleral absorption, and flow of aqueous humor. The dissipation rate constant can be resolved into two contributing constants, K_{AB} and K_{AP}, which describe the dissipation of the drug by transcorneal and peripheral loss routes, respectively; *i.e.*, $K_D = K_{AB} + K_{AP}$. The separate evaluation of each constant is accomplished using Eqs. 2 and 3:

$$\frac{K_{AB}}{K_{AB} + K_{AP}} = \frac{\int_0^\infty Q_B \, dt}{D_e} \qquad \text{(Eq. 3)}$$

where D_e represents an intravenously equivalent ophthalmic dose obtained by extrapolating a plot of log Q_B *versus* time, obtained from the results of ophthalmic dosing, to an ordinate value corresponding to a time of 1.88 min. The basis for this procedure and the rationale for this treatment were fully described previously (13).

EXPERIMENTAL

Materials—Isotonic, phosphate-buffered, tropicamide[1] solutions were prepared in concentrations of 0.010, 0.015, 0.020, and 0.030% (w/v) at pH 7.4; a concentration of 0.015% was prepared at pH 5.0. These solutions were employed for ophthalmic drug administration. Additional ophthalmic solutions were prepared containing tropicamide at pH 7.4 and 5.0 in combination with an anionic, cationic, or nonionic polymer. The polymers selected are listed in Table I along with viscosities of the vehicles. The charged anionic and cationic polymers are linear, water-soluble, polyelectrolytes with molecular weights exceeding 10^6; they retain their ionic functionality over a pH range of 2–12. The concentration of tropicamide in all polymer solutions was 0.015%; the viscosities of the vehicles were determined[2] at 37°. Although these ionogenic polymers are not cleared or recommended for other than experimental use, their presence in the vehicles caused no observable eye irritation or lacrimation.

Four, 3–4-month old, male New Zealand white rabbits were chosen on the basis of: *(a)* their similar pupillary response to varying light intensities, *(b)* the similitude of their mydriatic response to ophthalmic and intravenous doses of tropicamide, and *(c)* the clarity of their pupil definition. This screening procedure served to minimize intersubject variation.

Measurement of Pupillary Response—The experimental arrangement and methodology utilized for the measurement of the rabbit's pupillary diameter have been described previously (11).

The mydriatic response intensity, I, was related to the experimentally determined pupil diameters by Eq. 4:

$$I = \frac{d_t - d_0}{d_0} \qquad \text{(Eq. 4)}$$

where d_t represents the pupil diameter at time t following administration of the drug, and d_0 represents the pupil diameter at time zero.

RESULTS

Mydriatic Response Behavior of Tropicamide—Following ophthalmic dosing, the pupillary diameter was monitored with time and the observed measurements were transformed into mydriatic response intensities, I, using Eq. 4. Values for pharmacological response characteristics, *i.e.*, onset, maximum intensity, time of maximum intensity (t_{max}), and duration of response for each ophthalmic solution employed, are listed in Tables II and III. Onset is defined as the period of time following dosing that is necessary for one-half the maximal mydriatic response to be attained; duration is defined as the period of time between the onset and the time of reappearance of one-half the maximum intensity. Each value listed in the table represents the average of four determinations on different rabbits.

A Student t-test was performed to determine the level of significance for differences appearing in the tables relative to the pH 7.4, 0.015% tropicamide solution without polymer which was used as a standard. When employing a 95% statistical confidence level, only the values of 6.1 and 14.5 min obtained for onset and t_{max}, respectively, with a polymer-free vehicle of pH 5.0 were significantly different from the standard, which provided values of 8.8 and 20.5 min. Although some trends can be found in the results, none of the remaining treatments was significantly different from the standard.

Transformation of experimentally acquired I values into biophasic drug levels, Q_B, was accomplished through the use of the dose–response curve reported earlier (Ref. 11, Fig. 4). Biophasic half-lives, computed from the slopes of the latter, linear segments of plots of log Q_B *versus* time, for each dose and pH are included in Table II. The mydriatic half-life, similarly obtained from log I *versus* time plots, and the drug biophasic elimination half-life, although related, need not necessarily be the same. For any given drug, the precise nature of the relationship between the decay of I and biophasic drug levels depends upon the form of the dose–response relationship (13).

Transcorneal Biophasic Availability—If following ophthalmic administration the dissipation of tropicamide from the surface of the eye can be described by Eq. 3, then a semilogarithmic plot of the fractional amount of drug unabsorbed, $1 - A_t$, *versus* time should be linear. Values of $1 - A_t$ were computed[3] and plotted semilogarithmically (as shown in Figs. 1 and 2 of Ref. 13) for the polymer-free pH 7.4 and 5.0 vehicles. The slope of the regression lines in such plots represents the total proportional rate of loss, K_D, of drug from the site of administration. These values are listed in Table IV along with the linear correlation coefficients of the plots from which they were derived. The transcorneal biophasic availability and peripheral loss constants, obtained with the use of Eq. 3, are also listed in Table IV.

The linearity of the semilogarithmic plots of $1 - A_t$ *versus* time, as evidenced by the values of the linear correlation coefficients, indicates that the transcorneal absorption and peripheral loss of tropicamide occurs by an apparent first-order process, such as passive diffusion, and justifies the computation of the proportional rate constants. Table IV also contains percent biophasic availability, %

[1] Lot No. 2092, supplied by Alcon Laboratories, Fort Worth, Tex.
[2] Brookfield viscometer. A U-L adapter to the viscometer was employed for viscosities of 0–100 cps.
[3] CDC 6500 digital computer.

Table III—Influence of Polymers, Viscosity, and pH of the Vehicle on Mydriatic Response Characteristics of Tropicamide following Ophthalmic Dosing[a]

pH of Vehicle	Solution Administered to Eye: Tropicamide (0.015%) in Presence of Polymer[b]	Onset	t_{max}[c]	Maximum Intensity	Duration
7.4	A, 4.4 cps	9.3	18.0	0.731	71.0
7.4	A, 8.2 cps	8.8	17.5	0.700	60.5
7.4	A, 12.0 cps	10.5	21.0	0.679	67.1
7.4	A, 16.4 cps	9.75	20.0	0.634	69.5
7.4	B, 5.0 cps	12.0	19.0	0.625	63.0
7.4	B, 8.1 cps	8.5	18.5	0.668	74.8
7.4	B, 12.5 cps	10.8	22.0	0.665	58.5
7.4	B, 16.5 cps	9.5	21.5	0.697	66.5
7.4	C, 4.4 cps	9.0	22.5	0.679	67.0
7.4	C, 8.2 cps	10.3	22.5	0.727	69.0
7.4	C, 11.7 cps	11.0	22.0	0.756	80.8
7.4	C, 16.7 cps	10.3	22.0	0.667	67.3
5.0	A, 12.4 cps	8.8	20.5	0.754	76.8
5.0	B, 12.2 cps	8.8	24.5	0.729	65.0
5.0	C, 12.6 cps	12.0	21.5	0.545	61.3

[a] The solutions were approximately isotonic; 0.02 ml of each was instilled into the cul-de-sac of rabbits. Each parameter is the average of four determinations on different rabbits. [b] The polymers are nonionic methylcellulose (A), anionic Reten A-1 (B), and cationic Reten 205 (C). [c] The t_{max} is the time corresponding to the maximum intensity.

BA, values, which represent the percent of the drug dissipated from the surface of the eye which is transcorneally absorbed to reach its sites of action in the biophase. The percent biophasic availability values were computed as equal to $K_{AB}/(K_{AB} + K_{AP}) \times 100$, as discussed previously (13).

The values for percent biophasic availability for tropicamide without the addition of polymeric materials for each dose at pH 7.4 indicate that a range of 45.3–74.9% of the ophthalmic dose was transcorneally absorbed directly into the biophase and the remaining 25.1–54.7% of the dose was dissipated from the surface of the eye by peripheral routes. Also included in Table IV are values of percent biophasic availability for tropicamide at 0.015% as a function of viscosity, polymer functionality, and pH.

DISCUSSION

Influence of pH and Viscosity on Biophasic Availability and Pharmacological Response Behavior—When consideration of "active transport" is neglected, it can be said that solutes traverse tissue barriers by passive diffusion through interstitial spaces or by migration involving tissue binding sites, which can be described as facilitated diffusion (18). Tropicamide is essentially 100% unionized at pH 7.4 (pKa ~ 5). Considering the relative lack of hydrogen bonding sites on the tropicamide molecule and its relative nonpolarity, the contribution of a facilitated diffusion mechanism to the tissue transport of this drug may be expected to be nonexistent or negligible (19, 20). From these considerations and from the linearity of the log $(1 - A_t)$ *versus* time plots, tropicamide is apparently absorbed from the ophthalmic administration site into the biophase by passive diffusion at both pH 7.4 and 5.0. As previously reported (13), a comparison of the pharmacological and biokinetic parameters for the 0.015% solutions of tropicamide without polymer at pH 5.0 and 7.4 showed their differences to be statistically insignificant at the 95% level of confidence. However, the onset, percent biophasic availability, and t_{max} effects exhibited statistical differences between confidence levels of 75 and 92%. The probability level of the difference might have been greater if more than four animals had been studied.

Since the acidic pK of tropicamide is approximately 5.0, a relatively more rapid availability of the drug into the biophase may be expected to occur at pH 7.4, relative to pH 5.0, due to the relatively higher concentration of the more permeable unionized form of the drug (19, 20). However, the time of maximum response for the 0.015% tropicamide vehicle without polymer at pH 5.0 occurred at 13 min as compared to 22 min at pH 7.4. These differences were statistically significant at the 95% confidence level and are antithetical to expectations based on a pH–partition hypothesis (20). A comparison of the absorption rate constants under the same conditions indicated that overall absorption from the surface of the eye was not statistically different.

The increased percent biophasic availability observed at pH 5.0 for 0.015% tropicamide without polymers in the vehicle was equal to 73.8%, relative to 43.3% at pH 7.4. As discussed earlier (13), this difference may be speculatively attributed to the interaction of tropicamide cations with anionic binding sites affixed to the colloids composing the corneal tissue (21).

As shown in Table IV, no systematic effects of viscosity in the

Table IV—Influence of Polymers, Viscosity, and pH of the Vehicle on the Biophasic Availability Characteristics of Tropicamide from Ophthalmic Doses[a]

pH of Vehicle	Solution Administered to Eye	$K_{AB} + K_{AP}$	r^b	K_{AB}	K_{AP}	%*BA*[c]
	Tropicamide Alone					
7.4	0.010	0.0687	0.9766	0.0348	0.0340	50.3
7.4	0.015	0.0528	0.7475	0.0230	0.0300	43.3
7.4	0.020	0.0163	0.9965	0.0454	0.0159	74.9
7.4	0.030	0.0387	0.9905	0.0294	0.0093	47.5
5.0	0.015	0.0667	0.9937	0.0461	0.0206	73.8
	0.015% Tropicamide with Polymer[d]					
7.4	A, 4.4 cps	0.0691	0.9887	0.0422	0.0269	65.6
7.4	A, 8.2 cps	0.0694	0.9772	0.0314	0.0381	49.1
7.4	A, 12.0 cps	0.0426	0.9164	0.0250	0.0176	41.2
7.4	A, 16.4 cps	0.0691	0.9655	0.0245	0.0446	38.6
7.4	B, 5.0 cps	0.0569	0.9355	0.0159	0.0420	31.3
7.4	B, 8.1 cps	0.0390	0.9625	0.0193	0.0197	40.4
7.4	B, 12.5 cps	0.0677	0.9463	0.0218	0.0459	35.8
7.4	B, 16.5 cps	0.0673	0.9502	0.0300	0.0373	49.7
7.4	C, 4.4 cps	0.0403	0.9757	0.0234	0.0179	59.1
7.4	C, 8.2 cps	0.0740	0.9919	0.0483	0.0257	69.5
7.4	C, 11.7 cps	0.0516	0.9946	0.0328	0.0188	70.8
7.4	C, 16.7 cps	0.0640	0.9698	0.0260	0.0381	43.8
5.6	A, 12.4 cps	0.0520	0.9954	0.6410	0.1100	85.1
5.0	B, 12.2 cps	0.0559	0.9000	0.0389	0.0179	75.2
5.0	C, 12.6 cps	0.0400	0.9784	0.0110	0.0290	29.4

[a] The solutions were approximately isotonic; 0.02 ml of each was instilled into the cul-de-sac of rabbits. Each parameter is the average of four determinations on different rabbits. [b] Pearson *r* linear correlation coefficients for plots of log $(1 - A_t)$ *versus* time. [c] The values of percent biophasic availability represent the percent of the dose of drug transcorneally absorbed into the biophase. [d] The concentration of tropicamide in all the polymer vehicles was 0.015%. The polymers are nonionic methylcellulose (A), anionic Reten A-1 (B), and cationic Reten 205 (C).

ranges of 4.4 and 16.5 cps on the absorption characteristics of tropicamide were apparent. Previous studies showed that an increase in viscosity of an aqueous ophthalmic solution results in an increase in contact time between the solution and the cornea, which enables a greater fraction of drug to be absorbed; the pharmacological effects are, therefore, enhanced. However, a minimum concentration of polymer that significantly increases the pharmacological effects is not obvious for any particular drug.

For example, Mueller and Deardorff (5) used rabbits in a study of 0.1 and 1% methylcellulose solutions, which were approximately 14 and 230 cps, respectively, and found that 0.1% homatropine hydrobromide produced a response comparable to that produced by an aqueous solution of the drug alone. Blaug and Canada (4), on the other hand, found that for 0.02% solutions of scopolamine hydrobromide, viscosities above 22.5 cps significantly increased the time required for the pupillary diameter to return to control levels. Mice were used in these studies. In summary, it appears that the effect of methylcellulose as an adjuvant in ophthalmics is tenuous and appears to depend on the drug as well as the test animal used.

Influence of Polymers on Biokinetic and Pharmacological Characteristics of Tropicamide—It was considered that, in addition to the nonspecific effects of vehicle viscosity, the polymers could influence the biophasic availability of the drug by effects whose magnitude would depend on their specific chemical nature. Their effects could include: *(a)* reversible polymer–drug interactions which, by virtue of the large molecular size of the polymers, could retard the diffusive peripheral loss of interacted drug while concomitantly diminishing the rate(s) of biophasic drug availability; and *(b)* the mediation of drug interactions with the tissue surfaces exposed to the drug upon its instillation into the eye. Since such interactions have been shown (21–23) to modulate pharmacological behavior, their promotion or inhibition may be expected to influence biophasic availability.

However, inspection of Tables III and IV indicates that the inclusion of polymers may have some apparently systematic effects on biophasic availability, even though these are not significant at the $p < 0.05$ level of confidence; therefore, the present results preclude any firm conclusions concerning postulated mechanisms for the observed behavior of the systems. Among the most significant effects observed were those produced by the cationic polymer at a vehicle pH of 5.0; the confidence levels for t_{max}, K_{AB}, and percent biophasic availability are between 90 and 95%. If these effects can be considered other than random, they indicate an overall diminution in apparent drug transference rates which is opposite to that expected on the basis of a nonspecific Donnan-type exclusion of the ionized drug which would arise from the presence of relatively immobile charges on the polymer (21). The alternative would be to attribute the observed changes to the specific nature of the polymer. Interestingly, the results do not substantiate the formation of any unabsorbable complexes which could be expected to be formed between the anionic polymer and the cationic drug at pH 5.0.

CONCLUSIONS

Unlike the profound influence of the addition of small quantities of polymeric adjuvants to carbachol, for example (22, 23), the results with tropicamide indicate that the addition of polymers and vehicle viscosity within the range of 4.4–16.5 cps produces no significant influence on the drug transference and pharmacological behavior of tropicamide. However, some trends in the results appear to indicate that several tested polymers (at pH 5 only) could be inducing a slight effect by interacting with tissues at the absorption site and/or with the drug itself.

In view of the uncertainty of the effects of methylcellulose and the other polymers on ophthalmic drug effectiveness and the problems associated with their presence (24), it is best to consider carefully any addition of methylcellulose and other polymeric materials to ophthalmic vehicles except where a promoted effectiveness of the drug can be clearly demonstrated.

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