DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(5), 617-629 (1982)

EFFECT OF VARIOUS OPHTHALMIC OINTMENT BASES ON CARBENICILLIN AND GENTAMICIN RELEASE

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ABSTRACT

A microbiological agar plate method has been used for comparatively measuring the release of each carbenicillin and gentamicin from eighteen ointment bases for possible ophthalmic use. A significant difference in the antibiotic releasing ability of the various bases was observed. No one base was found to be consistently superior with each antibiotic tested. All the eight best bases, except one base, were composed of castor oil gelled by hydrogenated castor oil, Aerosil or white wax and may contain cetyl alcohol, Span 80, Span 40, wool alcohols, glyceryl monostearate and cetostearyl alcohol as wetting and spreading agents.

INTRODUCTION

Besides the influence of the physical state of the medicament, the ointment bases contributed significantly to efficacy[1]. Konning and Mital[2] reported that, from the standpoint of therapeutics, the most important attribute of an ointment base must be its readiness to release the active medicament it incorporates.

Plaxco and Husa[3] determined the relative availability of bacitracin in various ointment bases. Florestano et al.[4] compared the antibacterial properties of bacitracin, polymyxin B sulfate and neomycin sulfate when incorporated in a water-miscible-type base and in grease-type bases.

Rhyne et al.[5] found that the release of erythromycin, chlortetracycline HCl, neomycin sulfate, bacitracin and hexachlorophene from ointment bases varied considerably with a change in the HLB value of the base. Patel et al.[6] studied the effect of anionic and cationic surfactants on medicament release from five hydrophilic ointment bases.

Cosgrove and Poe[7] found that polyethylene glycol-type ointments containing dihydrostreptomycin exhibited more diffusion of the antibiotic than the petrolatum-type ointment. Billups and Sager[8] evaluated the drug release characteristics of six ointment bases. They found that the emulsion-type ointment bases promoted a greater release than the anhydrous hydrocarbon bases.

Thoma et al.[9] reported that by adding antiseptics to ointment bases their efficacy is influenced in any case. The factors affecting the release of the active substance are of a complex nature; they may be physico-chemical or due to chemical reactions between active and subsidiary substances.

Billups[10] concluded that the extent of drug release can be predicted for most drugs in a particular ointment base once drug diffusion data are established with a series of different drugs in that particular ointment base. Higuchi[11] devised a modified mathematical statement of Fick's law to predict the amount of drug diffusing from certain types of ointment bases.

Nakano and Patel[12] investigated the effect of dimethyl sulfoxide and two amides on the release of the drug from the ointment and permeation through the ointment base. Whitworth and Stephenson[13] studied the effect of three liquid additives on diffusion of atropine from ointment bases. They reported that the incorporation of even small concentrations of certain liquids into certain types of ointment bases may increase the diffusion of some drugs from these bases.

Following a preliminary review of pertinent literature situations, a total of 84 semisolid, water-soluble, anhydrous bases for possible ophthalmic use was formulated[14]. Of these 84 exploratory bases, five were designated evaluatory bases for further study on the basis of apparent pH and/or desirable physical spreadability characteristics over the temperature range of 0-50°. Four of the five bases were further characterized by rotational viscometer studies, and an organogel was selected on the basis of several of its listed attributes as the best attempt to formulate the type of semisolid base desired for possible ophthalmic use.

Selected formulations were studied[15] as possible oleaginous, semisolid bases for use as ophthalmic ointments over 0 to 50° and compared to two commonly used ointment bases for physical characteristics and drug release.

Schoenwald et al.[16] prepared gel formulations containing 2% pilocarpine HCl. The influence of the high viscosity vehicles on miotic effect of pilocarpine was investigated. It was reasoned that the increased duration was a consequence of the gel's increased yield value such that appreciable *in vivo* thinning of the gel does not take place with eyelid and/or eyeball movement. As a result, the residence time of the drug in the eye would be expected to increase, thus promoting an increased duration.

Sieg and Robinson[17] studied the *in vitro* and *in vivo* pilocarpine release from water-in-oil emulsion ointments. They found that pilocarpine release from the vehicle to the ocular fluid was dependent on shear, i.e., blinking, and the dosing system emulsifying efficiency. Also, increasing the vehicle emulsifying efficiency by surfactant addition decreased shear-facilitated drug release and *in vivo* performance. Finally, increasing the internal aqueous phase volume fraction decreased *in vivo* performance and was linked to the influence of effective drug concentration in the vehicle.

In vitro assessment of release of medicaments from ointment bases has been carried out by various techniques. Agar diffusion using chemical or bacteriological methods, membrane diffusion, chromatographic and radioactive tracer methods have been used to evaluate release from ointments[18,19]. Although many of the *in vitro* methods enjoy only limited application, they nevertheless have shown to measure the rate and extent of medicament release from an ointment base under the condition of the test[6,8]. It should be emphasized, however, that "drug release" is not "drug absorption" but is rather the process by which the drug is released from the dosage form immediately prior to entering into absorption[10].

The inhibition zone, produced by the diffusion of an antibacterial drug through an innoculated agar medium, has been used to measure the ability of an ointment base to release its drug content[1-10, 19-28].

The author[28] previously investigated the release of tetracycline HCl, oxytetracycline HCl, chloramphenicol and penicillin G sodium from four ophthlamic ointment bases by a microbiological agar plate method. The purpose of this study was to compare the release of carbenicillin and gentamicin from eighteen ointment bases suggested for ophthalmic use and to select the most satisfactory ointment bases. Carbenicillin

and gentamicin has been chosen in this study because of their wide spectrum of antimicrobial activity especially against Pseudomonas aeruginosa[29-43], a potential cause of keratitis and corneal ulceration[36].

EXPERIMENTAL

Materials

Carbenicillin disodium (Pfizer) and gentamicin (Schering) were supplied as dry sterile powders and were used as received. All other chemicals were USP, USNF or analytical grade and were used without further purificaiton.

Ophthalmic Ointment Bases

The compositions of the eighteen ointment bases investigated are given in Table 1. Bases 1 and 2 are the official eye ointment bases specified in BP 1953[44] and BP 1980[45] respectively while Base 3 is the official eye ointment base specified for sulphacetamide eye ointment[45], and were used as standards for comparison with the other investigated ointment bases. Bases 4 and 5 are recommended by Stenbeck-Gjertz and Ostholm[46]. Materials used in the formulation of the other bases were selected with consideration of low incidence of eye irritation, ability to form semisolid oleaginous or absorption bases with satisfactory consistency and texture and ability to permit diffusion of the drug throughout the secretions bathing the eye.

The ingredients of each base were melted together on a water bath with stirring at medium speed. The hot mixture was then filtered through coarse filter paper placed in a heated funnel, except Bases 12 and 18 where Aerosil was added after filteration of the other ingredients, and sterilized by dry heat[45].

Preparation of Antibiotic Ointments

Thirty six different ointments were compounded from carbenicillin,

TABLE 1

The Composition of Ophthalmic Ointment Bases

	Constituent, % for Bases																	
Constituents	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Aerosil 200	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	5
Castor Oil	-	-	-	-	-	-	75	85	84.6	80.8	-	90	-	-	85	-	-	93
Cetyl Alcohol	-	-	-	-	5	-	-	-	-	5	-	-	-	-	-	-	-	-
Cetostearyl Alcohol	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	5	5	-
Glyceryl Monostearate	-	-	-	-	-	0.5	-	-	0.5	-	0.5	-	-	-	-	-	-	-
Hard Paraffin	-	-	-	-	-	-	-	-	-	-	19.5	-	4	5	-	-	-	-
Hydrogenated Castor Oil	-	-	-	-	-	-	15	15	14.9	14.2	-	5	-	-	-	-	-	-
Liquid Paraffin	-	10	10	20	19	19.9	-	-	-	-	60	-	10	20	-	5	10	-
Span 40	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-
Span 80	-	-	-	-	-	-	10	-	-	-	-	-	-	-	-	-	10	2
White Wax	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	-	-
Wool Alcohols	-	-	-	-	-	-	-	-	-	-	-	-	-	5	5	-	-	-
Wool Fat	10	10	-	-	-	-	-	-	-	-	20	-	4	-	-	5	-	-
Yellow Soft Paraffin	90	80	90	80	76	79.6	-	-	-	-	-	-	82	70	-	85	75	-

gentamicin and eighteen ointment bases, so that each base contained one of the antibiotics in 0.3% concentraiton. Using aseptic precautions, the appropriate amount of antibiotic was triturated with the sterile base by means of a sterile mortar and pestle. The finished ointment was packed in previously sterilized collapsible tubes and stored at 4-5^{o} until required.

Release of Antibiotics from Ointments

A microbiological agar plate method as described by Yousef[25] was employed using Staph aureus 209 P as the test organism for the two antibiotics. The medium was adjusted to pH 6 for carbenicillin, and to pH 8 for gentamicin[47]. The extent of growth inhibition was measured from the edge of the hole to the periphery of the zone (radius segment) to the nearest 0.1 mm. The results of zones of inhibition produced by the ointments represent the average of four separate experiments, with a standard deviation of not more that $\pm$ 0.5 mm in each instance, are illustrated in Figure 1.

A ranking of the investigated ointment bases was computed from Figure 1 by adding the number of first, second, third, etc., place positions for each of the eighteen ointment bases with each of the two antibiotics. The eighteen ointment bases and the total points for each base are presented in Table 2 in decreasing order of antibiotic release effectiveness.

RESULTS AND DISCUSSION

In this study the general order of effectiveness of carbenicillin and gentamicin is taken as the amount of inhibition of growth produced by Staph. aureus, this indeed dependent upon the release of antibiotic from the ointment into the agar medium.

Figure 1 and Table 2 indicate a significant difference in the antibiotic releasing ability of the investigated ophthalmic ointment

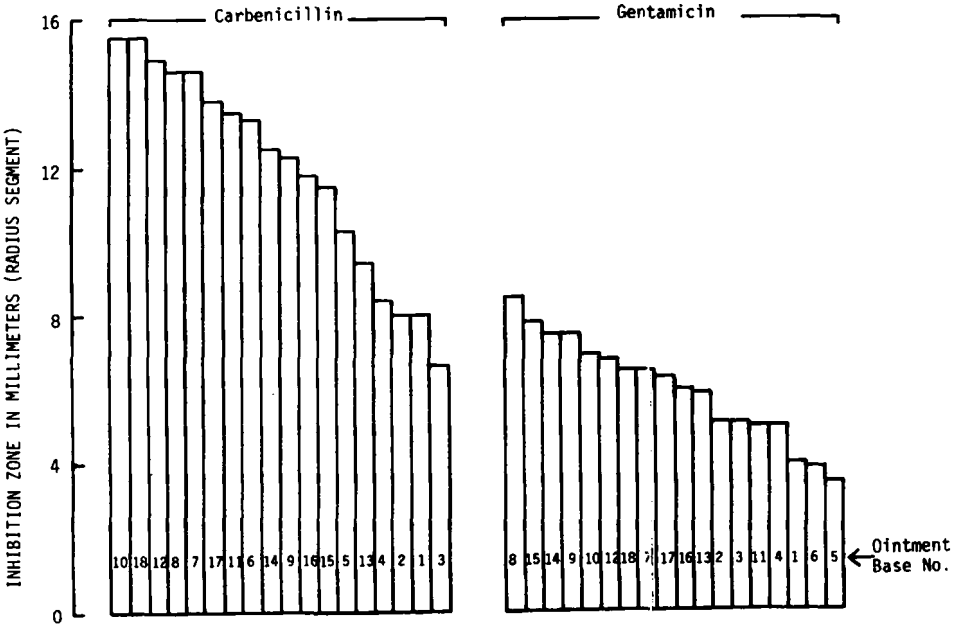

FIGURE 1

Effect of Various Ophthalmic Ointment Bases on Carbenicillin and Gentamicin Release Effectiveness

bases. No one base was found to be consistently superior with each antibiotic tested. This is evident from the change in the rank order of effectiveness of antibiotic release from the ointment bases with the tested antibiotics.

Figure 1 illustrates that the inhibition zones of carbenicillin in Bases 10 and 18 were more than twice the zone produced by the same antibiotic in the official eye ointment base specified for sulphacetamide eye ointment (Base 3) and about twice the zones produced in case of the official eye ointment bases specified in BP 1953 (Base 1) and BP 1980 (Base 2). While in the case of gentamicin, the inhibition zone produced by the antibiotic in Base 8 was found to

TABLE 2

Rank Order of Ophthalmic Ointment Bases in Decreasing Order of Antibiotic Release Effectiveness

Rank	Ophth. Oint. Base	Rank Order With Carbenicillin	Rank Order With Gentamicin	Total Rank Points	Rank	Ophth. Oint. Base	Rank Order With Carbenicillin	Rank Order With Gentamicin	Total Rank Points
1	8	4	1	5	10-11	11	7	14	21
2	10	1	5	6	10-11	16	11	10	21
3-4	18	2	7	9	12-13	6	8	17	25
3-4	12	3	6	9	12-13	13	14	11	25
5	14	9	3	12	14	2	16	12	28
6	7	5	8	13	15	4	15	15	30
7-8	9	10	4	14	16-17	3	18	13	31
7-8	15	12	2	14	16-17	5	13	18	31
9	17	6	9	15	18	1	17	16	33

be more than twice the zone produced in case of Base 1 and about 167% the zones produced in case of Bases 2 and 3. Also it is evident from Table 2 that the five poorest ointment bases in their ability to release each of carbenicillin and gentamicin were Bases 1, 5, 3, 4 and 2, even though the rank order of effectiveness changed with the tested antibiotics. This means that the suggested ophthalmic ointment bases are significantly superior with each antibiotic tested than the reference bases. Possible reason for this poor antibiotic release exhibited by the former bases is the stiff body and consistency of these bases.

The experimental results indicate that all the eight best ointment bases (Bases 8, 10, 18, 12, 14, 7, 9 and 15) except Base 14 were composed of castor oil gelled by hydrogenated castor oil, Aerosil or white wax and may contain cetyl alcohol, Span 80, Span 40, wool alcohols, glyceryl monostearate and cetostearyl alcohol as wetting and spreading agents. Possible reason for the superiority in carbenicillin and gentamicin release exhibited by castor oil gelled bases is the thixotropic behavior of these semisolid lipogels as upon extrusion from the collapsible tubes, they underwent shear thinning and liquefy. This is in agreement with earlier study[28], where it was found that a base containing 75% castor oil, 15% hydrogenated castor oil and 10% Tween 80 to be superior in antibiotics release than three ophthalmic ointment bases (Bases 2, 4 and 5 in this study) even after the addition of 10% Tween 80 to the latter bases.

From this study, it seems that it is not the type of the base nor the presence of specific wetting or spreading agent which produces the superiority of one base to release the antibiotic it incorporates. For carbenicillin, the best two bases (Base 10 and 18) were absorption bases containing cetyl alcohol and Span 80 respectively

while the poorest base (Base 3) was oleaginous. For gentamycin, the best base (Base 8) was oleaginous containing no wetting or spreading agent while the poorest base (Base 5) was absorption base containing cetyl alcohol. However, the factors affecting drug release from an ointment are of complex nature[9]. Generally, drug release from an ointment is attributed to partitioning and/or diffusion, depending on the drug properties and the specific vehicle selected[17].

Further work is currently being conducted on these eighteen exploratory ointment bases for possible ophthalmic use.

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