THE EFFECT OF SURFACE ACTIVE AGENTS ON THE RATE OF DISINTEGRATION OF VARIOUS ANTIBIOTIC TABLETS

A Thesis

Presented to

The Faculty of the College of Pharmacy

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

Ronald Wayne Carey

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ABSTRACT

The effect of surface active agents on the disintegration time of various antibiotic tablets has been studied. Disintegration tests were conducted on five different antibiotic tablets, Pen Vee K, Potassium Penicillin G., Neomycin Sulfate, Griseofulvin, and Erythromycin Stearate, using four different types of surface active agents, polysorbate 80, sorbitan monolaurate, benzalkonium chloride, and triethanolamine oleate. It appears that the disintegration time of neomycin sulfate (a salt of a strong acid and a weak base) tablets can be decreased by nonionic surface active agents of low HLB value (sorbitan monolaurate) and by anionic surface active agents (triethanolamine oleate) while the disintegration times of Pen Vee K and potassium penicillin G. (both salts of a weak acid and a strong base) tablets can be decreased by nonionic surface active agents of high HLB value (polysorbate 80) and by cationic surface active agents (benzalkonium chloride). The disintegration time of griseofulvin (not a salt) tablets may be slightly reduced by polysorbate 80. None of the surface active agents studied appears to have a noticeable effect on the disintegration of erythromycin stearate (a salt of a weak acid and a weak base) tablets.

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CHAPTER I

HISTORY

Surface-active agents are capable of enhancing the rate of solubility of drugs through the reduction of interfacial tension (1). It is of interest to study their action on the dissolution rate to gain some understanding of the mechanisms involved. The dissolution rate could be the rate-limiting step in the absorption of a drug (2). The possibility of increasing the absorption of a drug by the use of surfactants may be useful in product development.

Recently, a great deal of attention has been focused on the problem of drug availability (3). The availability of a drug is often determined by the rate of release of the active component from the dosage form. The release of the drug is usually governed by such factors as the diffusion of the drug in the physical system, the dissolution rate of the drug, the adsorption of the drug by other components of the system, and others (3).

Many factors may influence the dissolution rate of a drug; (a) they may deal with influences applied directly to the total physical system, such as temperature and agitation; (b) they may also deal with changes in the characteristics of the solute particle and influences brought about by changes in the dissolution medium.

One way of increasing the rate of solubility of a drug is to decrease the particle size of the drug. Levy (4) has developed various methods for obtaining smaller particle size. Smaller particles may be obtained by: (a) using the microcrystalline form of the drug or micronizing the particles, (b) producing

an aqueous solution of freely water-soluble salts, (c) dissolving the drug in a water-miscible organic solvent, or (d) making a eutectic mixture composed of the active drug and a substance that dissolves readily in water. Noyes and Whitney (5) were the first to show that dissolution rate is directly proportional to surface area. By decreasing the particle size, the surface area will be increased. Therefore, one may increase the dissolution rate by decreasing the particle size of the drug.

The ideal definition of true disintegration rate would be the time required for the tablet to break up into the granules from which it was compressed (6). Each pharmaceutical manufacturer has its own manufacturing processes so that it would be difficult to establish a common granule size for all tablets.

The method of preparation of the granulation mixture can also affect the disintegration rate of the tablets. Marlowe and Shangraw (7) reported that sodium salicylate tablets made by direct compression disintegrated faster than those made by the wet granulation procedures. Bergman and Bandelin (8) stated that tablets manufactured by wet granulation methods may have different disintegration rates depending on their age. Increases in the disintegration rates were correlated with the increase in the age of the tablets.

Hamlin, Nelson, Ballard, and Wagners (9) reported the affects of agitation upon the dissolution rate of methylprednisone tablets.

Allawata, et al (10) reported that the surface-active agents increase the rate of solubility of the drug from its dosage form. Bergman and Bandelin (8) reported that the disintegration of tablets takes place in two steps due to the fact that the majority of granules compressed into a tablet retain their individual integrity. The tablet first breaks down to the granules and then the granules break down to smaller particles.

Nair and Bhatia (11) reported the use of Veegum* as a disintegrating agent in the preparation of sulfathiazole tablets. Using the U. S. P. (12) disintegration test they reported a faster rate of disintegration when most of the Veegum was added after the granulation and only a small proportion before granulation.

Jacob and Plein (13) discussed the importance of the proper selection of binder, binder concentration, and the hardness of the tablets in relation to the disintegration rate of the tablets. These should be properly controlled so that the medication will be completely released for quick physiological availability. These workers reported that an increase in the concentration of the binding agents and hardness of the tablets increased the disintegration time of phenobarbital tablets.

Commons, Bergen, and Walker (14) reported no decrease in the disintegration time of tolbutamide tablets as the percentage of the corn starch incorporated in the granulation was increased. In most

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* R. T. Vanderbilt Company

cases, tolbutamide tablets failed to disintegrate at a particular percentage of starch but disintegrated when the starch concentration was increased by about 1 per cent. For example, tablets prepared from 16/20-mesh granules containing 6 per cent corn starch failed to disintegrate within 30 minutes, whereas tablets containing 7 per cent corn starch disintegrated in an average time of 2.3 minutes.

Bates, Lin, and Gibaldi (15) reported an increase in the dissolution rate of water-insoluble drugs in the presence of lysolecithin. If physiological surfactants such as lysolecithin, which is found in the fluids of the upper regions of the small intestine, can increase the rate of dissolution of poorly soluble drugs then the usefulness of surfactants in pharmaceutical dosage forms is obvious. Thakkar and Hall (16) reported the behavior of an anhydrous form of testosterone in various concentrations of polysorbate 20. In low concentration solutions of polysorbate 20 (0.01%, 0.50%, 1.00%) in distilled water the time required to attain the solubility peak of testosterone was less than in pure distilled water. Further increase in the surfactant concentration decreased the rate of solubility. Finholt and Solvang (17) ran in vitro experiments showing the rate of dissolution of phenacetin in 0.1N hydrochloric acid with different amounts of polysorbate 80. An increase in the concentration of the polysorbate 80 caused a significant increase in the dissolution rate. Wurster and Seitz (18) made a comparison of the dissolution rate of benzoic acid

tablets in solutions of sodium lauryl sulfate and distilled water. The dissolution rate of the benzoic acid tablets in a solution of 0.2% sodium lauryl sulfate was found to be faster than in distilled water. They concluded that by lowering the surface tension with sodium lauryl sulfate, the rate of dissolution was increased. Gantt, Gochman, and Dyniewicz (19) discussed the effects of polysorbate 80 on the absorption of aldactone from the gastrointestinal tract. A plasma level of 21 mcg./100 ml. of aldactone was recorded (after 4 hours) when 400 mg. of aldactone in distilled water was administered orally. After the addition of 40 mg. of polysorbate 80 per 400 mg. of aldactone the plasma level (after 4 hours) was 42 mcg./100 ml. Parrott and Sharma (20) studied the dissolution kinetics of benzoic acid in the presence of certain surface-active agents. These workers found that when surfactants such as polysorbate 80, tyloxapol,* and sodium lauryl sulfate were added to the dissolving fluid, the rate of solubility of benzoic acid was increased. The dissolution rate of benzoic acid attained its maximum value at five percent concentration of tyloxapol and then decreased as the concentration of the surface-active agent was increased.

Wurster and Taylor (21) recorded the disintegration rates of various crystalline forms of prednisolone using different rates of agitation. They reported an increase in the dissolution

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* Alevaire, Breon Laboratories, Inc., New York, New York

rate for both hydrous and anhydrous crystalline forms of prednisolone as the stirring speeds were increased. These results correlate very well to those reported by Hamlin et al (9).

Bates, Gibaldi, and Kanig (22) have stated that surface-active agents may increase the dissolution rate of relatively water-insoluble drugs by one of two mechanisms. They may increase the dissolution rate by micellar solubilization or decrease the interfacial tension between the drug and the dissolution medium. The latter will allow the dissolution medium to wet the drug more completely. Elworthy and Lipscomb (23) have reported the possibility of using surfactants to increase the rate of absorption of griseofulvin.

In 1961, Sekigucki and Obi (24) first proposed the utilization of solid dispersions (ie. eutectics) to increase the dissolution and oral absorption rate of drugs which have a low water solubility. They felt that these eutectic mixtures could possibly be one of the means of increasing the rate of absorption of drugs. A eutectic mixture is composed of microscopically fine crystals of each component, mixed very intimately. If a eutectic mixture is composed of a slightly soluble drug and a very soluble inactive ingredient it may result in a faster disintegration in water or intestinal fluid, into the original finely divided particles of the drug. Goldberg, Gibaldi, and Kanig (25) produced a eutectic mixture of griseofulvin and succinic acid. A six and one-half to seven times increase in the rate of solubility of griseofulvin over that

of the pure material of the same particle size was reported.

Strickland, Nelson, Busse, and Higuchi (26) studied the effect of lubricants on the disintegration time of tablets. They reported that the addition of lubricants in usual concentrations significantly prolonged the disintegration rate and at the same time tended to produce slightly softer tablets.

Levy and Gumtow (27) found that while magnesium stearate retarded the dissolution rate of salicylic acid tablets; sodium lauryl sulfate markedly enhanced it. The increase in dissolution rate by sodium lauryl sulfate was due to better penetration of the solvent into the tablets and their component granules due to a reduction in the surface tension. The decrease in dissolution rate by the lubricants was attributed to the formation of a coat around the individual granules which remained more or less intact during the process of tablet compression. The survey of literature indicates that surface active agents can be used to enhance the rate of dissolution of drugs contained in compressed tablets. Nevertheless, one has to be careful about the incompatabilities of surfactants with the active ingredients of the tablets and their affect on the stability of drugs. One example of this type of incompatability was reported by Pirila, Salo, and Pirila (28). It was found that neomycin was incompatable with sodium lauryl sulfate and this incompatability was reflected in the weak antibacterial and allergenic activities of the neomycin-sodium lauryl sulfate complex.

CHAPTER II

INTRODUCTION

Numerous reports have appeared in the literature (1-28) concerning the disintegration time of tablets and the factors that may affect their time of disintegration. It is important to investigate these factors since they affect the rate of absorption of drugs. One of these factors which is under investigation by many scientists (10, 15-20) is the correlation of the concentration of the surface active agents with the disintegration time. Surface-active agents can cause a reduction in the surface tension and an increase in the rate of absorption of drugs from their dosage forms. The objective of this research was to determine the effect of surface active agents on the rate of disintegration of various antibiotic tablets. Because of their current extensive therapeutic use, the following antibiotics were studied: Potassium Penicillin G[a], Pen Vee K[b], Griseofulvin[c], Erythromycin[d], and Neomycin[e]. Four surface active agents were investigated: a cationic surface active agent (benzalkonium chloride); two non-ionic surface-active agents (sorbitan monolaurate, polysorbate 80); and an anionic surface active agent (triethanolamine oleate).

(a) Wyeth Laboratories, Inc., Philadelphia, Penn., Lot No. 1683029

(b) Potassium phenoxymethyl penicillin, Wyeth Laboratories, Inc., Philadelphia, Penn., Lot No. 1693339

(c) McNeil Laboratories, Inc., Fort Washington, Penn., Lot No. JE3338

(d) Abbott Laboratories, North Chicago, Ill., Lot No. 832-1873-21

(e) E. R. Squibb and Sons, New York, New York., Lot No. 9C521

CHAPTER III

EXPERIMENTAL

SURFACE ACTIVE AGENTS AND TABLETS

The following surface active agents Polysorbate 80[a], Benzalkonium Chloride[b], Sorbitan Monolaurate[c], and Triethanolamine Oleate[d], were used without further purification. The antibiotic tablets, Pen Vee K, Potassium Penicillin G., Neomycin Sulfate, Griseofulvin, and Erythromycin Stearate were generously supplied by the manufacturers. The name of these manufacturers with the lot numbers of the antibiotics tablets are listed in the Introduction.

SOLUTIONS

One, two, three, and five per cent V/V aqueous solutions of polysorbate 80, benzalkonium chloride (W/V), sorbitan monolaurate, and triethanolamine oleate were prepared using the simple solution method. The compositions of the various solutions are reported in Table I.

(a) Tween 80, Atlas Chemical Industries, Wilmington, Delaware.

(b) Magnolia Chemical Company, Dallas, Texas.

(c) Span 20, Atlas Chemical Industries, Wilmington, Delaware.

(d) Emkay Chemical Company, Elizabeth, New Jersey.

Table I. Composition of Various Surfactant Solutions

A. POLYSORBATE 80		
1%	Polysorbate 80	70 ml.
	Distilled Water Q. S.	7000 ml.
2%	Polysorbate 80	140 ml.
	Distilled Water Q. S.	7000 ml.
3%	Polysorbate 80	210 ml.
	Distilled Water Q. S.	7000 ml.
5%	Polysorbate 80	350 ml.
	Distilled Water Q. S.	7000 ml.
B. BENZALKONIUM CHLORIDE		
1%	Benzalkonium Chloride (12.8%)	547 ml.
	Distilled Water Q. S.	7000 ml.
2%	Benzalkonium Chloride (12.8%)	1093 ml.
	Distilled Water Q. S.	7000 ml.
3%	Benzalkonium Chloride (12.8%)	1638 ml.
	Distilled Water Q. S.	7000 ml.
5%	Benzalkonium Chloride (12.8%)	2730 ml.
	Distilled Water Q. S.	7000 ml.
C. SORBITAN MONOLAURATE		
1%	Sorbitan Monolaurate	70 ml.
	Distilled Water Q. S.	7000 ml.
2%	Sorbitan Monolaurate	140 ml.
	Distilled Water Q. S.	7000 ml.
3%	Sorbitan Monolaurate	210 ml.
	Distilled Water Q. S.	7000 ml.
5%	Sorbitan Monolaurate	350 ml.
	Distilled Water Q. S.	7000 ml.

Table I. continued

D. TRIETHANOLAMINE OLEATE

1%	Triethanolamine Oleate	70 ml.
	Distilled Water Q. S.	7000 ml.
2%	Triethanolamine Oleate	140 ml.
	Distilled Water Q. S.	7000 ml.
3%	Triethanolamine Oleate	210 ml.
	Distilled Water Q. S.	7000 ml.
5%	Triethanolamine Oleate	350 ml.
	Distilled Water Q. S.	7000 ml.

PROCEDURE

Using the U. S. P. method (12), all the antibiotic tablets were tested for their disintegration time in distilled water and various solutions of surface active agents. The results are presented in Tables II through VI and Figures 1 through 4.

CHAPTER IV

RESULTS

Table II. Disintegration Times of Pen Vee K Tablets in Distilled Water and Various Surface Active Agents[a]

Surface Active Agent	Disintegration Time When the Concentration of Surface Active Agent is				
	0%[b]	1%	2%	3%	5%
Polysorbate 80					
First Tablet	7'49.0"	7'39.8"	7'47.0"	7'15.0"	7'16.1"
Last Tablet	8'15.3"	8'37.3"	8'31.6"	7'39.1"	7'42.9"
Average	7'57.1"	8'08.6"	8'09.7"	7'27.0"	7'29.5"
Sorbitan Monolaurate					
First Tablet	7'49.0"	8'00.6"	8'44.0"	9'08.1"	8'39.1"
Last Tablet	8'15.3"	9'27.8"	10'02.7"	10'09.8"	10'58.3"
Average	7'57.1"	8'44.2"	9'23.3"	9'38.8"	9'48.7"
Benzalkonium Chloride					
First Tablet	7'49.0"	7'35.8"	7'07.2"	7'44.2"	9'36.1"
Last Tablet	8'15.3"	8'13.8"	7'59.6"	8'19.9"	10'30.9"
Average	7'57.1"	7'54.8"	7'33.4"	8'02.1"	10'03.5"
Triethanolamine Oleate					
First Tablet	7'49.0"	10'41.2"	8'40.8"	8'11.6"	7'58.1"
Last Tablet	8'15.3"	13'55.0"	9'52.5"	8'53.1"	8'48.6"
Average	7'57.1"	12'18.1"	9'16.6"	8'32.3"	8'23.3"

(a) All results are an average of two experiments. The variation between individual readings was not more than ± three seconds.

(b) This is in distilled water.

Table III. Disintegration Times of Potassium Penicillin G. Tablets in Distilled Water and in Various Surface Active Agents[a]

Surface Active Agent	Disintegration Time When The Concentration of Surface Active Agent is 0%[b]	1%	2%	3%	5%
Polysorbate 80					
First Tablet	5'57.4"	5'55.1"	5'29.3"	5'00.5"	5'07.5"
Last Tablet	6'30.1"	7'06.6"	6'49.1"	5'21.9"	5'34.8"
Average	6'13.8"	6'30.8"	6'09.2"	5'11.2"	5'21.1"
Sorbitan Monolaurate					
First Tablet	5'57.4"	8'04.6"	9'59.3"	8'14.4"	11'28.6"
Last Tablet	6'30.1"	10'08.7"	12'16.1"	11'29.8"	14'27.9"
Average	6'13.8"	9'06.5"	11'07.7"	9'52.1"	12'53.3"
Benzalkonium Chloride					
First Tablet	5'57.4"	5'32.5"	5'46.2"	4'55.4"	4'58.8"
Last Tablet	6'30.1"	7'03.0"	6'05.1"	5'22.5"	5'21.3"
Average	6'13.8"	6'17.9"	5'55.6"	5'08.9"	5'10.1"
Triethanolamine Oleate					
First Tablet	5'57.4"	10'33.3"	7'31.1"	8'05.6"	8'40.2"
Last Tablet	6'30.1"	15'26.2"	11'37.0"	9'20.3"	9'50.2"
Average	6'13.8"	12'59.7"	9'34.0"	8'42.1"	9'15.2"

(a) All results are an average of two experiments. The variation between individual readings was not more than ± three seconds.

(b) This is in distilled water.

Table IV. Disintegration Times of Neomycin Sulfate Tablets in Distilled Water and Various Surface Active Agents[a]

Surface Active Agent	Disintegration Time When The Concentration of Surface Active Agent is				
	0%[b]	1%	2%	3%	5%
Polysorbate 80					
First Tablet	5'38.8"	5'48.6"	6'08.6"	6'00.7"	7'06.4"
Last Tablet	6'16.0"	6'21.3"	7'10.7"	6'41.4"	7'31.5"
Average	5'57.4"	6'04.9"	6'39.6"	6'21.0"	7'18.9"
Sorbitan Monolaurate					
First Tablet	5'38.8"	4'43.7"	5'23.6"	5'36.1"	6'14.0"
Last Tablet	6'16.0"	6'03.1"	5'52.2"	6'15.3"	6'49.6"
Average	5'57.4"	5'23.4"	5'37.9"	5'55.7"	6'31.8"
Benzalkonium Chloride					
First Tablet	5'38.8"	5'40.1"	6'09.8"	6'38.7"	6'05.1"
Last Tablet	6'16.0"	6'26.9"	6'52.1"	7'26.5"	7'19.5"
Average	5'57.4"	6'03.5"	6'30.9"	7'02.6"	6'42.3"
Triethanolamine Oleate					
First Tablet	5'38.8"	7'08.1"	5'33.0"	4'40.5"	5'08.6"
Last Tablet	6'16.0"	8'25.8"	6'04.5"	5'42.4"	5'38.5"
Average	5'57.4"	7'47.0"	5'48.7"	5'11.4"	5'23.5"

(a) All results are an average of two experiments. The variation between individual readings was not more than ± three seconds.

(b) This is in distilled water.

Table V. Disintegration Times of Griseofulvin Tablets in Distilled Water and Various Surface Active Agents[a]

Surface Active Agent	Disintegration Time When the Concentration of Surface Active Agent is				
	0%[b]	1%	2%	3%	5%
Polysorbate 80					
First Tablet	11'13.7"	10'49.0"	10'31.1"	10'26.6"	8'06.6"
Last Tablet	11'40.0"	11'35.2"	11'54.5"	11'11.4"	10'53.9"
Average	11'26.8"	11'12.2"	11'12.8"	10'49.0"	9'30.2"
Sorbitan Monolaurate					
First Tablet	11'13.7"	13'44.7"	12'34.4"	13'53.1"	14'19.3"
Last Tablet	11'40.0"	15'20.6"	14'49.1"	15'33.8"	16'25.8"
Average	11'26.8"	14'32.6"	13'41.7"	14'43.7"	15'22.5"
Benzalkonium Chloride					
First Tablet	11'13.7"	11'59.9"	11'18.7"	12'12.7"	10'18.1"
Last Tablet	11'40.0"	13'12.8"	13'43.8"	13'49.3"	12'40.8"
Average	11'26.8"	12'36.3"	12'31.2"	13'01.0"	11'29.5"
Triethanolamine Oleate					
First Tablet	11'13.7"	12'58.0"	13'44.1"	13'51.9"	14'40.1"
Last Tablet	11'40.0"	15'13.1"	14'58.3"	15'10.3"	16'32.7"
Average	11'26.8"	14'05.6"	14'21.2"	14'31.0"	15'36.3"

(a) All results are an average of two experiments. The variation between individual readings was not more than ± three seconds.

(b) This is in distilled water.

Table VI. Disintegration Times of Erythromycin Tablets in Distilled Water and Various Surface Active Agents[a]

Surface Active Agent	Disintegration Time When the Concentration of Surface Active Agent is				
	0%[b]	1%	2%	3%	5%
Polysorbate 80					
First Tablet	16'13.8"	16'39.4"	17'52.5"	18'21.7"	18'53.4"
Last Tablet	17'28.0"	18'12.0"	19'31.6"	19'35.2"	20'59.6"
Average	16'50.9"	17'25.7"	18'42.1"	18'58.4"	19'26.5"
Sorbitan Monolaurate					
First Tablet	16'13.8"	17'29.9"	19'08.7"	18'22.3"	19'36.7"
Last Tablet	17'28.0"	19'03.3"	21'02.4"	20'39.2"	21'34.5"
Average	16'50.9"	18'16.5"	20'05.5"	19'30.7"	20'35.6"
Benzalkonium Chloride					
First Tablet	16'13.8"	21'44.0"	22'12.4"	22'26.4"	24'22.7"
Last Tablet	17'28.0"	25'10.0"	24'46.1"	24'50.4"	26'36.4"
Average	16'50.9"	23'27.0"	23'29.2"	23'38.4"	25'29.5"
Triethanolamine Oleate					
First Tablet	16'13.8"	17'38.3"	16'04.0"	15'48.5"	17'06.2"
Last Tablet	17'28.0"	20'29.4"	17'52.5"	17'31.9"	18'29.6"
Average	16'50.9"	19'03.8"	16'58.2"	16'40.2"	17'47.9"

(a) All results are an average of two experiments. The variation between individual readings was not more than ± three seconds.

(b) This is in distilled water.

Figure 1. Polysorbate 80 versus Disintegration Time of Various Antibiotic Tablets

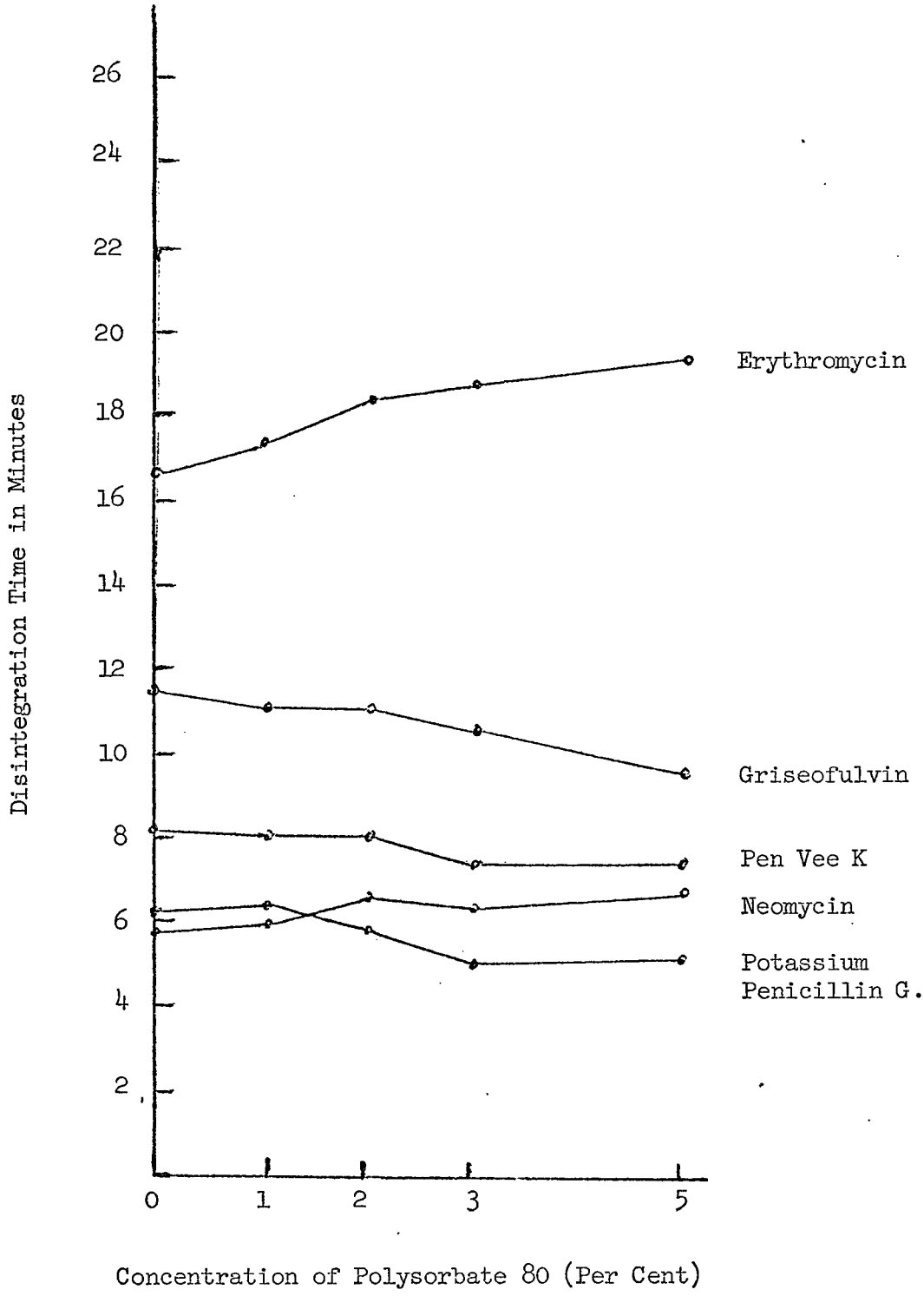


Figure 2. Sorbitan Monolaurate versus Disintegration Time of Various Antibiotic Tablets

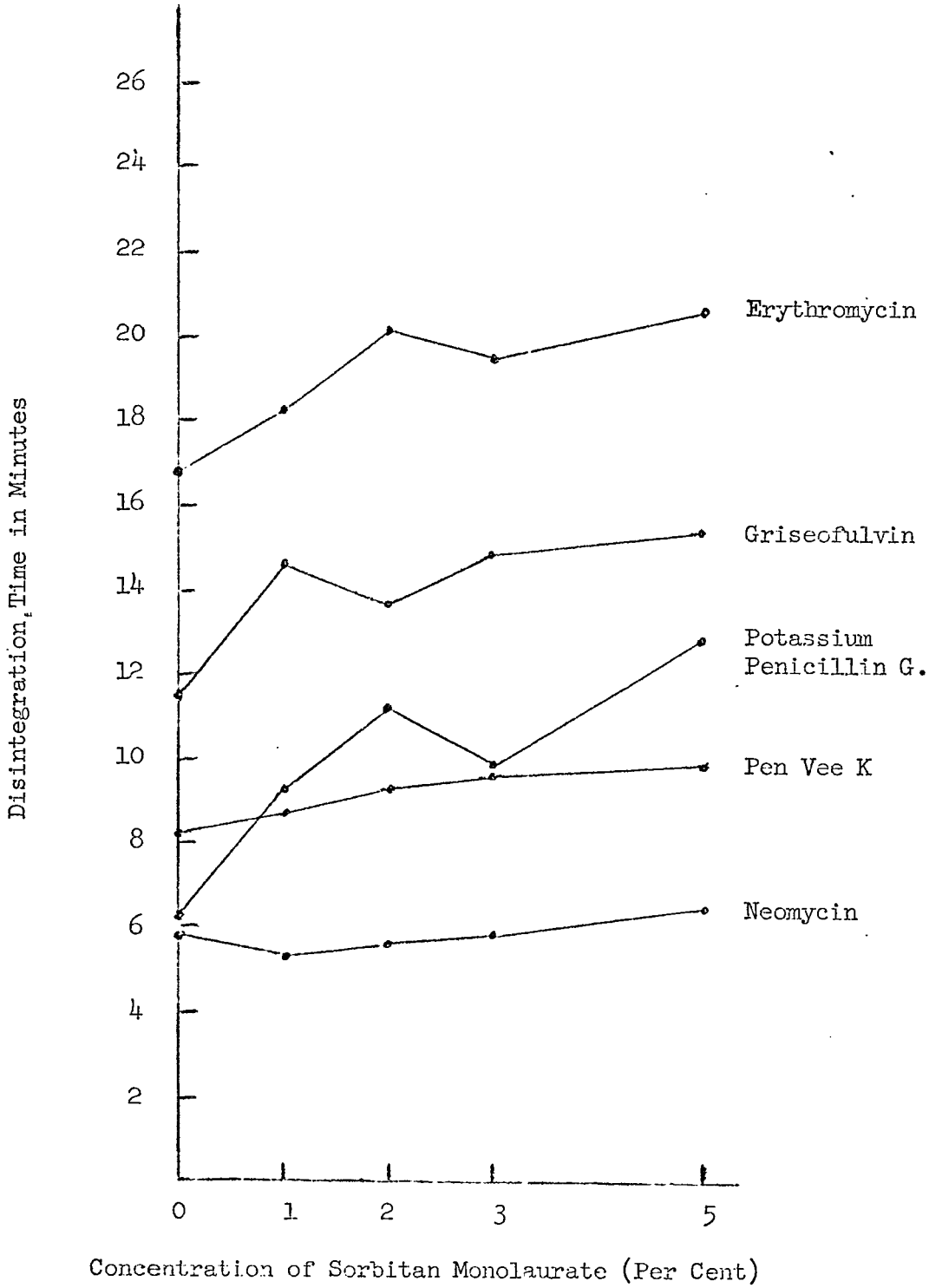


Figure 3. Benzalkonium Chloride versus Disintegration Time of Various Antibiotic Tablets

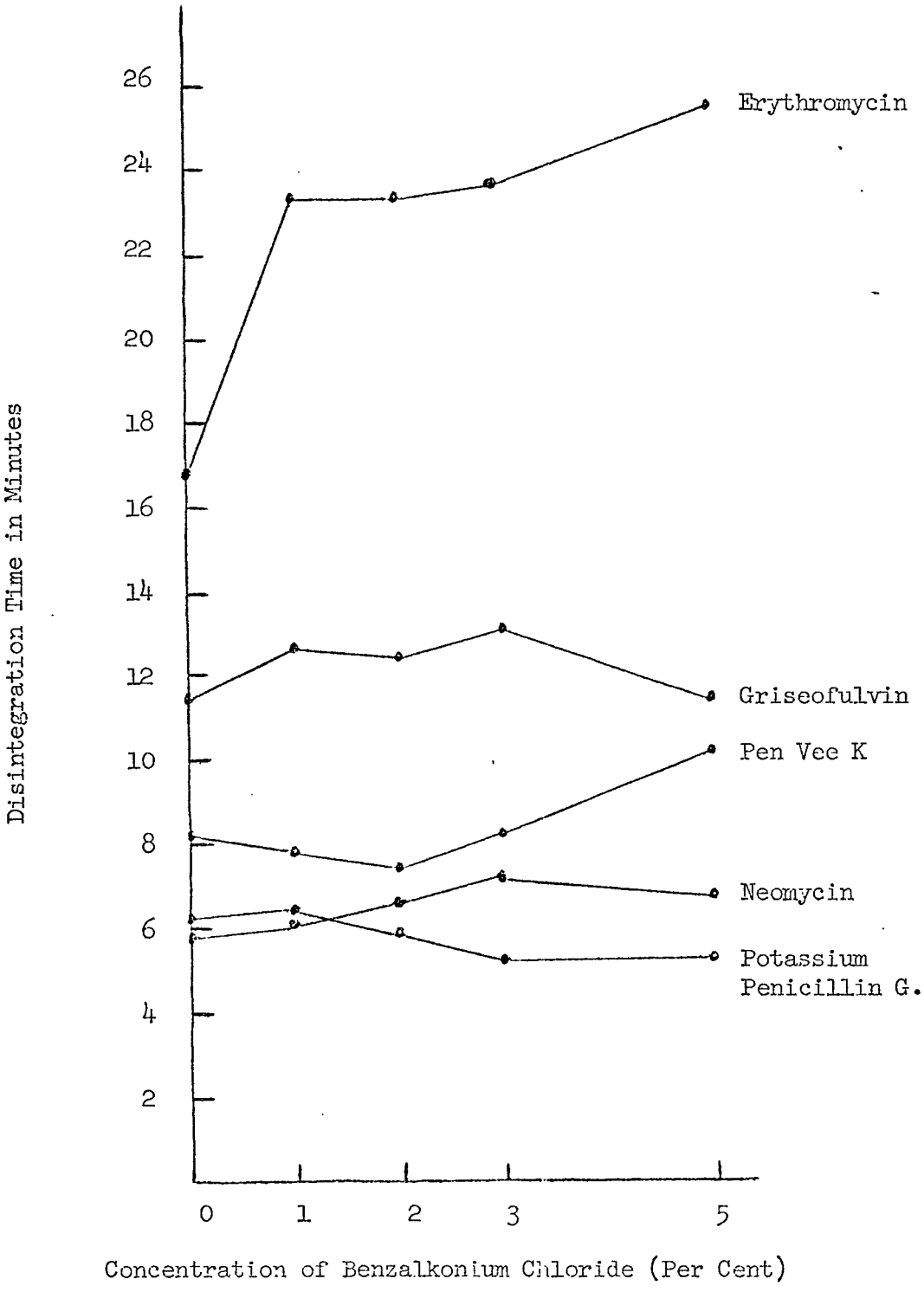
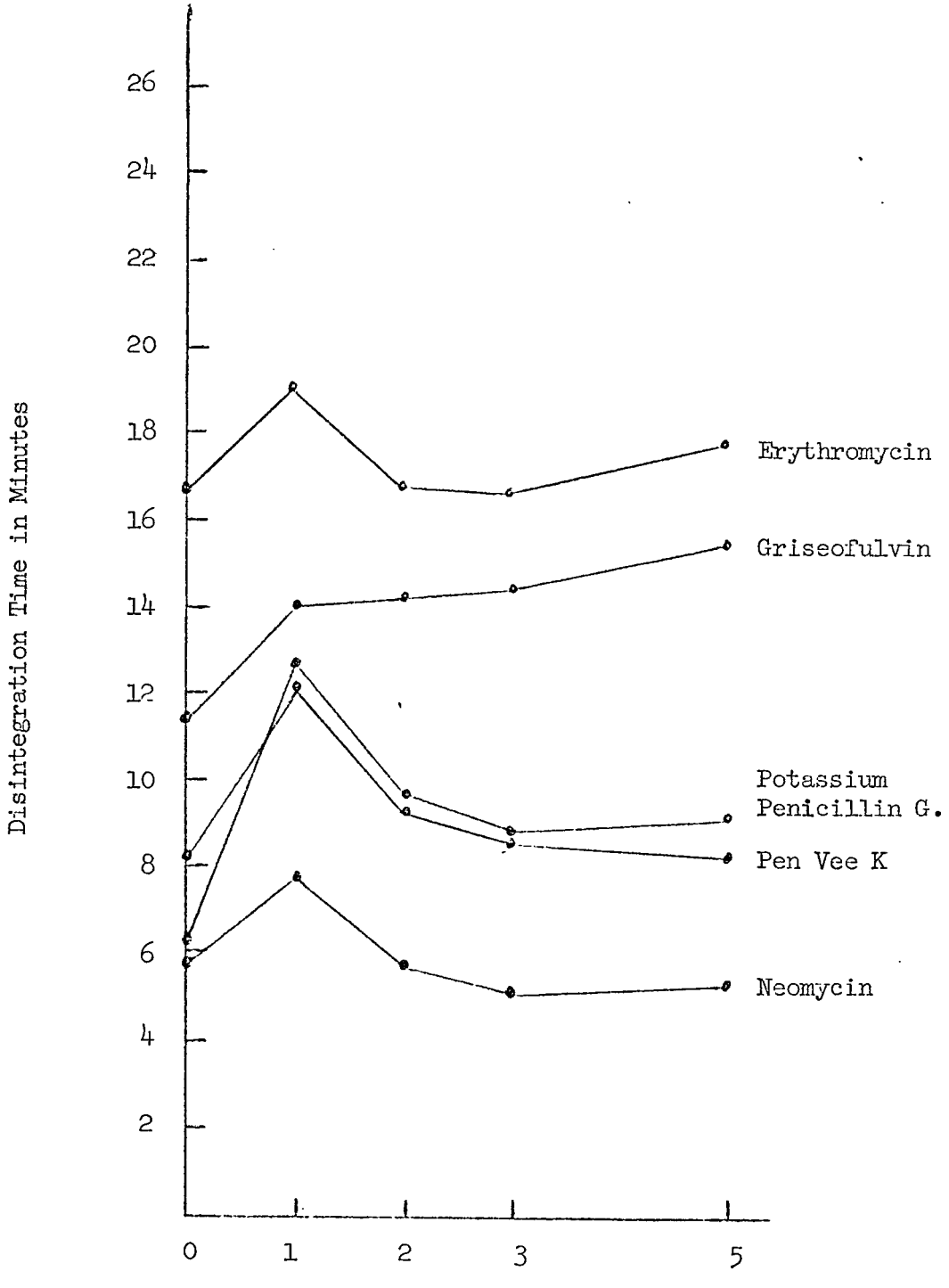


Figure 4. Triethanolamine Oleate versus Disintegration Time of Various Antibiotic Tablets



CHAPTER V

DISCUSSION

PEN VEE K TABLETS:

In polysorbate 80 the disintegration time of Pen Vee K tablets decreased from 477.1 seconds to 447.0 seconds at 3 per cent and from 477.1 seconds to 449.5 seconds at 5 per cent concentrations of the surfactant (Table II and Figure 1). A concentration of 1-2 per cent of polysorbate 80 does not appear to have much effect on Pen Vee K tablets since disintegration times in these solutions (488.6 seconds and 489.7 seconds respectively) are very close to that in distilled water (477.1 seconds). Sorbitan monolaurate actually increased (1 per cent - 524.2 seconds, 2 per cent - 563.3 seconds, 3 per cent - 578.8 seconds, 5 per cent - 588.7 seconds versus 477.1 seconds for distilled water) the disintegration time of Pen Vee K tablets (Table II and Figure 2). This may be due to its low HLB value of 8.6. The disintegration time of Pen Vee K tablets was 453.4 seconds in a 2 per cent solution of benzalkonium chloride (Table I and Figure 3). However, at higher concentrations there was a noticeable increase in the disintegration time (3 per cent - 482.1 seconds, 5 per cent - 603.5 seconds). This behavior is not unusual and has been well explained by Parrott, E. L., and Sharma (20). Triethanolamine oleate does not appear to have any noticeable effect on the disintegration time of Pen Vee K tablets (Table II and Figure 4). Out of all the surfactants studied, the disintegration time of Pen Vee K tablets was found to be the

lowest in a 3 per cent solution of polysorbate 80. It appears, therefore; that nonionic surface active agents with a high HLB value, such as polysorbate 80 (HLB value of 15.0), may be useful to decrease the disintegration time of Pen Vee K tablets.

POTASSIUM PENICILLIN G. TABLETS:

In polysorbate 80 the disintegration time of potassium penicillin G. tablets decreased from 373.8 seconds to 369.2 seconds at 2 per cent, 373.8 seconds to 311.2 seconds at 3 per cent, and 373.8 seconds to 321.1 seconds at 5 per cent (Table III and Figure 1). In a 1 per cent solution of polysorbate 80 an increase from 373.8 seconds to 390.8 seconds was recorded. Sorbitan monolaurate actually increased (1 per cent - 546.5 seconds, 2 per cent - 667.7 seconds, 3 per cent 592.1 seconds, 5 per cent - 773.3 seconds versus 373.8 seconds for distilled water) the disintegration time of potassium penicillin G. tablets (Table III and Figure 2). This behavior has already been explained under Pen Vee K tablets. The disintegration time of potassium penicillin G. tablets was highest (377.9 seconds) in a 1 per cent solution of benzalkonium chloride. However, at higher concentrations there was a noticeable decrease in the disintegration time (2 per cent - 355.6 seconds, 3 per cent - 308.9 seconds, 5 per cent - 310.1 seconds versus 373.8 seconds in distilled water). Triethanolamine oleate appears to have actually increased the disintegration time of potassium penicillin G. tablets (1 per cent - 779.7 seconds, 2 per cent - 574 seconds, 3 per cent - 522.1 seconds, and 5 per cent - 555.2 seconds versus

373.8 seconds for distilled water). Obviously anionic type of surface active agents have adverse effect on the disintegration time of these tablets. Out of all the surfactants studied, the disintegration time of potassium penicillin G. tablets was found to be the lowest in a 3 per cent solution of benzalkonium chloride. It appears, therefore, that only nonionic surface active agents with a high HLB value, such as polysorbate 80, and cationic surface active agents, such as benzalkonium chloride, may be useful to decrease the disintegration time of potassium penicillin G. tablets. This behavior was also observed for Pen Vee K tablets which is obvious since both of these compounds have similar structures (salts of weak acids and strong bases).

NEOMYCIN SULFATE TABLETS:

Polysorbate 80 actually increased (1 per cent - 364.9 seconds, 2 per cent - 399.6 seconds, 3 per cent - 381.0 seconds, 5 per cent - 438.9 seconds versus 357.4 seconds for distilled water) the disintegration time of neomycin sulfate tablets (Table IV and Figure 1). In sorbitan monolaurate the disintegration time of neomycin sulfate tablets decreased from 357.4 seconds to 323.4 seconds at 1 per cent, from 357.4 seconds to 337.9 seconds at 2 per cent, and from 357.4 seconds to 355.7 seconds at 3 per cent and a concentration of 5 per cent sorbitan monolaurate actually increased the disintegration time of these tablets from 357.4 seconds to 391.8 seconds. Benzalkonium chloride does not appear to have decreased the disintegration time of neomycin sulfate tablets at any

concentration since the disintegration times in these solutions (1 per cent - 363.5 seconds, 2 per cent - 390.9 seconds, 3 per cent - 422.6 seconds, 5 per cent - 402.3 seconds versus 357.4 seconds for distilled water) were higher than in distilled water (Table IV and Figure 3). The disintegration time of neomycin sulfate tablets was highest (467.0 seconds) in a 1 per cent solution of triethanolamine oleate (Table IV and Figure 4). However, at higher concentrations there was a noticeable decrease in the disintegration time (2 per cent - 348.7 seconds, 3 per cent - 311.4 seconds, 5 per cent - 323.5 seconds versus 357.4 seconds for distilled water). Of all the surfactants studied the lowest disintegration time was recorded in a 3 per cent solution of triethanolamine oleate. It appears, therefore, that only nonionic surface active agents with a low HLB value, such as sorbitan monolaurate, and anionic surface active agents, such as triethanolamine oleate, may be useful to decrease the disintegration time of neomycin sulfate tablets. Lower concentrations of the nonionic surface active agent (less than 1 per cent) with a low HLB value may be more useful. It is interesting to note that the disintegration time of neomycin sulfate (a salt of a strong acid and a weak base) tablets was decreased by nonionic surface active agents of low HLB value (sorbitan monolaurate) and by anionic surface active agents (triethanolamine oleate) while the disintegration times of Pen Vee K and potassium penicillin G. (both salts of weak acid and strong base) tablets were decreased by nonionic surface active agents of high HLB value

(polysorbate 80) and by cationic surface active agents (benzalkonium chloride).

GRISEOFULVIN TABLETS:

In polysorbate 80 the disintegration time of griseofulvin tablets decreased from 686.8 seconds to 672.2 seconds at 1 per cent, 686.8 seconds to 672.8 seconds at 2 per cent, 686.8 seconds to 649.0 seconds at 3 per cent, and 686.8 seconds to 570.2 seconds at 5 per cent concentrations of the surfactant (Table V and Figure 1). Sorbitan monolaurate does not appear to have lowered the disintegration time of griseofulvin tablets at any concentration since the disintegration times in the solutions (1 per cent - 872.6 seconds, 2 per cent - 761.7 seconds, 3 per cent - 883.7 seconds, 5 per cent - 922.5 seconds) were higher than the disintegration time in distilled water (686.8 seconds). The disintegration times of griseofulvin tablets were higher in all concentrations of triethanolamine oleate solutions and in all the concentrations of benzalkonium chloride solutions (Table V). Out of all the surfactants studied, the disintegration time of griseofulvin tablets was found to be the lowest in a 5 per cent solution of polysorbate 80. It appears, therefore, that only nonionic surface active agents with a high HLB value may be useful to decrease the disintegration time of griseofulvin (not a salt) tablets. Higher concentrations of this nonionic surface active agent may be more useful.

ERYTHROMYCIN STEARATE TABLETS:

The disintegration times of erythromycin stearate tablets in all concentrations of polysorbate 80, sorbitan monolaurate, benzalkonium chloride, and triethanolamine oleate were higher (except in 3 per cent solution of triethanolamine oleate) as compared with distilled water (Table VI). In a 3 per cent solution of triethanolamine oleate the disintegration time decreased slightly from 1010.9 seconds in distilled water to 1000.2 seconds. It appears, therefore, that the surface active agents may not be useful to lower the disintegration time of erythromycin stearate (salt of a weak acid and a weak base) tablets.

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