Synthesis and Formulation of Several Epinephrine Salts as an Aerosol Dosage Form

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Abstract □ A satisfactory method for the preparation of various salts of epinephrine such as the maleate, malate, and fumarate was developed. Following the synthesis of these salts, a study of the partition coefficient of these salts in higher molecular weight alcohols such as octyl and hexadecyl alcohol and water was carried out, and the results were compared to the partition coefficient of epinephrine bitartrate in these same vehicles. The solubility of these new salts in chloroform, carbon tetrachloride, and fluorinated hydrocarbons was then determined. Several systems incorporating these new salts were prepared and subjected to a preliminary stability study. The partition coefficient of epinephrine maleate determined between octyl alcohol–water and hexadecyl alcohol–water was found to be higher than the value for epinephrine bitartrate, malate, and fumarate. The solubility of epinephrine maleate and fumarate in four propellants (dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorodifluoroethane, and difluoroethane) was found to be slightly higher than the epinephrine bitartrate and malate. As expected, difluoroethane dissolved the highest amount of epinephrine salts as compared to the other propellants studied. Epinephrine maleate and bitartrate were found to have greater stability than the epinephrine malate and fumarate compounds on the basis of the preliminary stability study.

Keyphrases □ Epinephrine salts (maleate, malate, fumarate, bitartrate)—synthesis, partition coefficients, formulation of aerosol dosage forms □ Aerosols—formulation of epinephrine maleate, malate, fumarate, and bitartrate □ Partition coefficients—comparison between epinephrine maleate, malate, fumarate, and bitartrate in octyl or hexadecyl alcohol–water systems □ Inhalation therapy—synthesis and formulation of aerosol epinephrine salts

Before the introduction of the pressurized package as a pharmaceutical dosage form, many studies had been conducted on the use of medicaments for local therapy of the respiratory tract and for rapid systemic effects through absorption from the inner surface of the lungs. As newer chemotherapeutic agents of interest in inhalation therapy became available, they were investigated for a variety of pulmonary conditions (1). These substances have included sympathomimetic amines, antibiotics, antitubercular drugs, antispasmodics, surfactants, certain vitamins, hormones, and corticosteroids (2, 3). For the most part, these compounds were aerosolized through use of nebulizers, atomizers, and oxygen.

With the introduction of aerosol systems using liquefied gas propellants, the solubility of the therapeutically active ingredients in these propellants became an important consideration if the product was to be used for either local action in the lungs or for systemic therapy. In addition, the solubility of the drug in extracellular fluids plays an important role in the selection of the compounds to be used for this purpose.

Drugs directly soluble in the propellant can be dispensed as a fine mist of proper particle-size distribution through proper formulation and the use of suitable valves and applicators. For drugs that are not directly soluble in the propellant, a cosolvent such as ethanol can be used to render the drug, which has previously been dissolved in water, soluble in the propellant. Another method includes the suspension or dispersion of the selected salt in the propellant. In any event, the product must be dispensed in such a manner that the particles of active ingredient will reach the pulmonary alveoli and be dissolved in the extracellular fluids.

Epinephrine salts as well as isoproterenol salts have been generally used for the symptomatic treatment of asthma. The hydrochloride and bitartrate salts of epinephrine have been the salts of choice since they are chemically stable and have suitable solubility in the solvents and extracellular fluids. Epinephrine base is practically insoluble in any commonly used propellant. The bitartrate and hydrochloride salts do not possess sufficient solubility in the propellant to deliver a therapeutic dose from the commonly used metered valves. A review of the literature showed little investigation concerning the use of other epinephrine salts which may show a greater solubility in some nonpolar solvents. No reference was found as to the use of the maleate, malate, and fumarate salts of epinephrine for this purpose.

One main difficulty in the formulation of epinephrine and its salts for aerosol-inhalation therapy is the lack of solubility of these compounds in nonpolar organic solvents and propellants. Since they are practically insoluble in these materials, either a cosolvent must be used or the salt must be suspended in the propellant system. Both of these methods are satisfactory and have been used commercially for aerosol dosage forms. Ethyl alcohol has been used for this purpose. Other solvents have been of limited value due to their toxicity. Dispersion or suspension aerosols may present problems of sedimentation, caking, *etc.*, which can result in valve clogging or inaccurate dosage. The choice of active ingredients as well as liquid additives can reduce this occurrence. Epinephrine hydrochloride has been used

Table I—Analytical Data for Epinephrine Salts

Epinephrine Salt	Yield, %	Melting Point	Analysis, % Calc.	Found
Bitartrate	81.94	149–150°	C 46.85	46.56
			H 5.75	5.32
			N 4.20	4.21
Maleate	71.90	182–183°	C 52.17	51.81
			H 5.68	5.78
			N 4.68	4.61
Malate	85.28	170–171°	C 50.21	53.44
			H 5.99	7.14
			N 4.41	4.30
Fumarate	74.86	103–105°	C 52.17	52.23
			H 5.68	5.60
			N 4.68	4.76

Table II—Solubility of Epinephrine Salts at 25°

Epinephrine Salt	Propellant	Solubility of Salt[a], % Weight
Bitartrate	12	0.007
	114	0.008
	142b	0.100
	152a	0.177
Maleate	12	0.009
	114	0.013
	142b	0.152
	152a	0.272
Malate	12	0.008
	114	0.006
	142b	0.069
	152a	0.131
Fumarate	12	0.008
	114	0.011
	142b	0.166
	152a	0.257

[a] Agreement was noted between results obtained by weight by difference method and spectrophotometric method of analysis. Results reported represent averages of results obtained by these two methods.

Table III—Formulation of Epinephrine Salts in Aerosol Form

Formulation	Ingredients	Quantity, % Weight
A	Epinephrine salt	0.71
	Ascorbic acid	0.10
	Sorbitan sesquioleate[a]	0.10
	Ethyl alcohol (absolute)	10.00
	Propellant 12	89.09
B	Epinephrine salt	0.71
	Sodium bisulfite	0.10
	Sorbitan sesquioleate[a]	0.10
	Ethyl alcohol (absolute)	10.00
	Propellant 12	89.09
C	Epinephrine salt	0.71
	Ascorbic acid	0.10
	Sorbitan sesquioleate[a]	0.10
	Propellant 12	99.09
D	Epinephrine salt	0.71
	Propellant 12	99.28

[a] Atlas Chemical Industries, Wilmington, Del.

for solution aerosols while epinephrine bitartrate has been utilized for suspensions. It is desirable to investigate other salts of epinephrine such as the maleate, fumarate, and malate which may possess sufficient solubility in propellant systems to warrant further investigation of their use in aerosols. No reference has been found in the literature as to the synthesis of the maleate, fumarate, and malate salts of epinephrine. Therefore, the purposes of this study were to synthesize these salts of epinephrine and to determine their partition coefficient and solubility in a variety of propellants and organic solvents. Finally, the relative chemical stability of these salts will be studied.

EXPERIMENTAL

General Method for Preparation of Epinephrine Salts—*l*-Epinephrine, 1.82 g. (0.01 mole), which was previously dried over phosphorus pentoxide for 15 hr., was dissolved in 10 ml. of anhydrous methyl alcohol; 1.16 g. of maleic acid (0.01 mole) was also dissolved separately in 10 ml. of anhydrous methyl alcohol. The acid solution was then slowly added, with constant shaking, to the *l*-epinephrine solution. After 1 hr., epinephrine maleate was precipitated from the solution by slowly adding a small quantity of anhydrous ether. To allow for complete precipitation, the solution was kept at 0° for 24 hr. The precipitate was filtered and washed with a small quantity of anhydrous ether. Repeated washings with the same quantity of ether were made to ensure the purity of the salt. The precipitated salt was then stored in a dark place in a vacuum desiccator. Epinephrine bitartrate, malate, and fumarate were prepared in a similar manner. The total yield of each salt was calculated and the melting point of each compound was determined. An elemental analysis for each salt was made, and the results are shown in Table I. The structure of each salt was confirmed by means of an IR spectrum determined for each compound. The expected absorbance was noted in each case.

Determination of Partition Coefficient—One hundred milliliters of water and 100 ml. of octyl alcohol were placed in a 250-ml. conical flask. To this mixture was added 100 mg. of epinephrine salt, accurately weighed. The flask was sealed and placed in a constant-temperature water bath at 25 ± 0.1° and shaken constantly. After 6, 9, 12, and 15 hr., 1-ml. aliquots of the water layer were withdrawn from the flask. An aliquot of the aqueous layer was then assayed spectrophotometrically (4)[1]. The amount of salt present in the alcohol layer was determined by subtracting the amount found in the aqueous layer from 100 mg. It was noted that equilibrium had been obtained after 12 hr. of constant agitation; therefore, all future determinations were made following a 12-hr. period of agitation. Using this method, the partition coefficient of epinephrine maleate, fumarate, malate, and bitartrate between octyl alcohol–water and hexadecyl alcohol–water was determined. The partition coefficients for all of the salts were approximately 0.03 and 0.02 when determined in octyl alcohol–water and hexadecyl alcohol–water, respectively. These values represented the averages of three determinations.

Solubility Determinations—Saturated solutions of the salts of epinephrine were prepared by placing an excess of the salts in a plastic-coated glass aerosol container which had previously been washed with water, air dried, rinsed with acetone, and finally rinsed with the solvents and propellants to be used in the container. The salts were dried to constant weight in a vacuum desiccator over phosphorus pentoxide. The amount of salts added to the container was approximately 0.5% by weight. The aerosol container, together with the salts, was placed into a dry ice–acetone bath and cooled. The propellant or solvent was then added by the cold-fill method.

An aerosol transfer valve, fitted with male adapter and having a dip tube which extended to within 5.08 cm. (2 in.) of the bottom of the container, was crimped to the container. This valve was fitted with a special filter device[2]. The bottle containing the propellant and salt was placed into a constant-temperature shaker water bath at 25 ± 0.1° for 72 hr. It was previously demonstrated that equilibrium was attained during this period.

A female transfer valve, without a dip tube, was attached to the 80-ml. sampling container. The sampling container was then evacuated to 0.1 mm. of mercury, cooled to 0°, inverted, and placed on top of the aerosol bottle containing the saturated solution of propellant and drug. The saturated solution was then transferred to the tared 80-ml. bottle by means of the transfer valve. The sampling container was then dried over phosphorus pentoxide to constant weight. The propellant was carefully evaporated from the aerosol container by attaching an actuator to the valve and depressing the actuator. The sampling container with the residue was weighed, dried, and reweighed until constant weight was established. The amount of salt was then calculated by the weight by difference method. The valve of the sampling container was removed and the residue was assayed by spectrophotometric analysis (4).

The solubility of each of the epinephrine salts was determined in chloroform, carbon tetrachloride, and Propellants 12, 114, 142b, and 152a[3]. The results shown in Table II represent the average of three determinations.

[1] A Bausch & Lomb Spectronic 20 spectrophotometer was used in this study.

[2] Labpor filter disk cut to fit snugly inside of a piece of dip tubing of 2.54-cm. (1-in.) length. Glass wool was then placed below the filter disk in the polyethylene tubing. The entire filter assembly was then affixed to the bottom of the dip tube of the aerosol transfer valve.

[3] Propellant 12 is dichlorodifluoromethane, Propellant 114 is dichlorotetrafluoroethane, Propellant 142b is monochlorodifluoroethane, and Propellant 152a is difluoroethane.

Table IV—Relative Stability of Several Epinephrine Salts

Epinephrine Salt	Days	Concentration, % Weight A 25°	A 37°	A 47°	B 25°	B 37°	B 47°	C 25°	C 37°	C 47°	D 25°	D 37°	D 47°
Bitartrate	0	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715
	15	0.688	0.688	0.684	0.690	0.686	0.681	0.690	0.690	0.688	0.692	0.691	0.682
	30	0.666	0.665	0.642	0.669	0.663	0.620	0.660	0.667	0.665	0.678	0.671	0.652
	60	0.626	0.620	0.620	0.629	0.615	0.612	0.630	0.630	0.623	0.648	0.639	0.600
Maleate	0	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715
	15	0.684	0.656	0.651	0.694	0.690	0.687	0.689	0.687	0.648	0.699	0.684	0.682
	30	0.656	0.652	0.644	0.676	0.667	0.664	0.664	0.663	0.602	0.663	0.658	0.655
	60	0.637	0.616	0.611	0.641	0.624	0.618	0.615	0.589	0.601	0.615	0.609	0.604
Malate	0	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.175
	15	0.678	0.673	0.669	0.679	0.674	0.673	0.680	0.673	0.670	0.682	0.672	0.670
	30	0.642	0.632	0.627	0.645	0.637	0.636	0.641	0.635	0.632	0.644	0.636	0.631
	60	0.578	0.561	0.550	0.583	0.567	0.561	0.569	0.566	0.562	0.574	0.566	0.560
Fumarate	0	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715	0.715
	15	0.673	0.672	0.672	0.672	0.671	0.670	0.678	0.676	0.663	0.678	0.675	0.673
	30	0.636	0.635	0.633	0.634	0.632	0.630	0.646	0.637	0.619	0.644	0.639	0.635
	60	0.566	0.565	0.563	0.567	0.562	0.560	0.584	0.570	0.538	0.582	0.570	0.568

Formulation of Epinephrine Salts in Aerosol Form—To determine the relative stability of these salts, several aerosol formulations were prepared utilizing the different epinephrine salts. Various formulations are shown in Table III. These were prepared in the following manner. The epinephrine salt, previously dried over phosphorus pentoxide and micronized through use of a jet mill[4], was dispersed into absolute ethyl alcohol in which the antioxidant and surfactant had been dissolved (Formulations A and B). Formulation C was similar to Formulation A, except that absolute ethyl alcohol was excluded. In Formulation D, the antioxidant, alcohol, and surfactant were excluded. The formulations were thoroughly shaken and transferred to a clean, dry, plastic-coated aerosol container. An aerosol transfer valve, fitted with a male adapter and having a dip tube which extended to within 1.27 cm. of the bottom of the container, was crimped to the container. Propellant 12 was added to the aerosol container by the pressure filling process. The air was removed from each container through use of a vacuum pump. Three containers of each variable were then stored at 25, 37, and 47 ± 1°. These formulations were then examined after 15, 30, and 60 days.

An assay was conducted to determine the amount of epinephrine initially present. After the elapsed time, a sample of each formulation was withdrawn through use of dip tubing fitted onto the male valve. The tubing was long enough so that it could be directed into a glass cylinder. The aerosol container of each formulation was accurately weighed. A 50-ml. portion of distilled water was transferred into a clean and dried glass cylinder. The transfer tube from the aerosol container was placed under the surface of the water so that the sample could be bubbled through the water. The formulation was dispensed slowly into a glass cylinder and the propellant was allowed to escape.

After dispensing a sufficient amount of sample, the aerosol container with the transfer tube was reweighed. The aqueous mixture was then transferred to a 100-ml. volumetric flask. The glass cylinder was washed with a small portion of water and the rinsing was transferred to the 100-ml. flask. Sufficient water was added to give a volume of 100 ml. An aliquot portion of this mixture was then analyzed by the spectrophotometric assay, and the concentration of epinephrine salt was calculated. These results are shown in Table IV and represent the average of three determinations made upon each sample. These data were then plotted as shown in Figs. 1–4 which illustrate a plot of log concentration *versus* time for each epinephrine salt. The rate of decomposition, k, for each epinephrine salt in the respective formulations was calculated using the equation for first-order kinetics:

$$\log C = \frac{kt}{2.303} \qquad \text{(Eq. 1)}$$

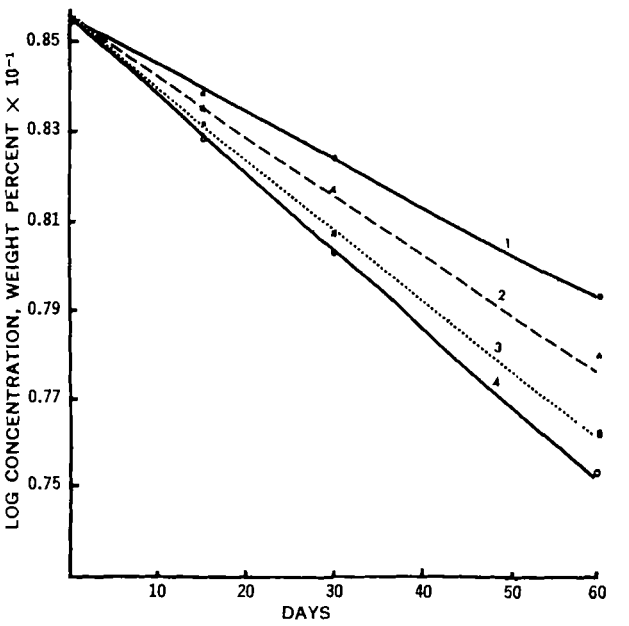

Figure 1—*Decomposition of epinephrine salts at 25°, Formulation A. Key: 1, bitartrate; 2, maleate; 3, malate; and 4, fumarate.*

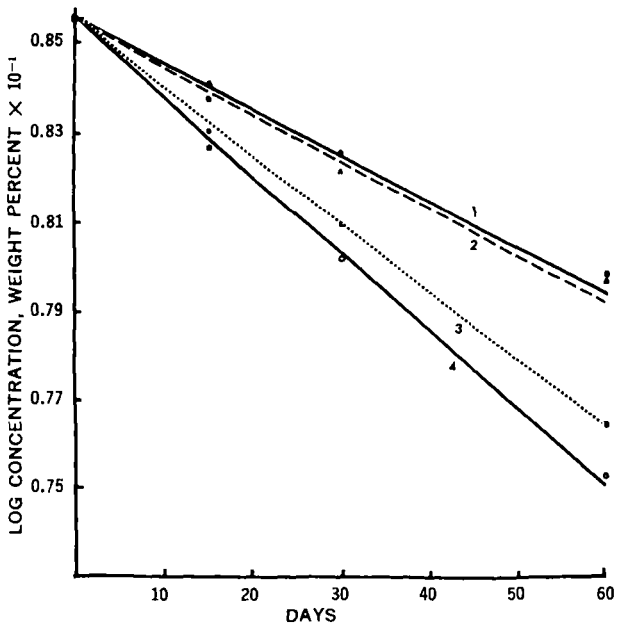

Figure 2—*Decomposition of epinephrine salts at 25°, Formulation B. Key: 1, bitartrate; 2, maleate; 3, malate; and 4, fumarate.*

[4] Gem T Research Jet Mill, Trost Equipment Corp., Newtown, Pa.

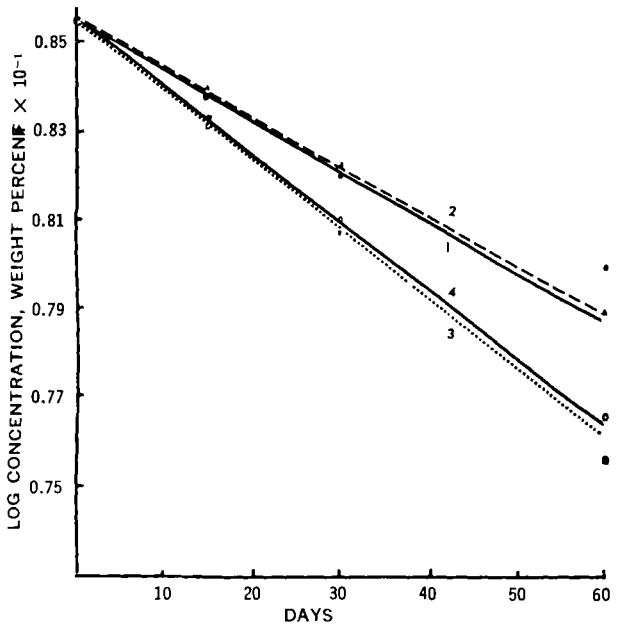

Figure 3 – *Decomposition of epinephrine salts at 25°, Formulation C. Key: 1, bitartrate; 2, maleate; 3, malate; and 4, fumarate.*

The value of k was obtained from the slope of the line which, in turn, was obtained by the least-squares method[5]. The rate of decomposition for each of the salts is shown in Table V.

DISCUSSION

Several salts of epinephrine were prepared. According to a method reported in the literature (5), salts of epinephrine could be prepared by taking epinephrine base and the appropriate acid and dissolving them in ethyl alcohol. The salt would then precipitate from the ethanol solution. This method was utilized during this investigation. However, it was noted that the salts did not precipitate following the addition of ethyl alcohol, because these salts

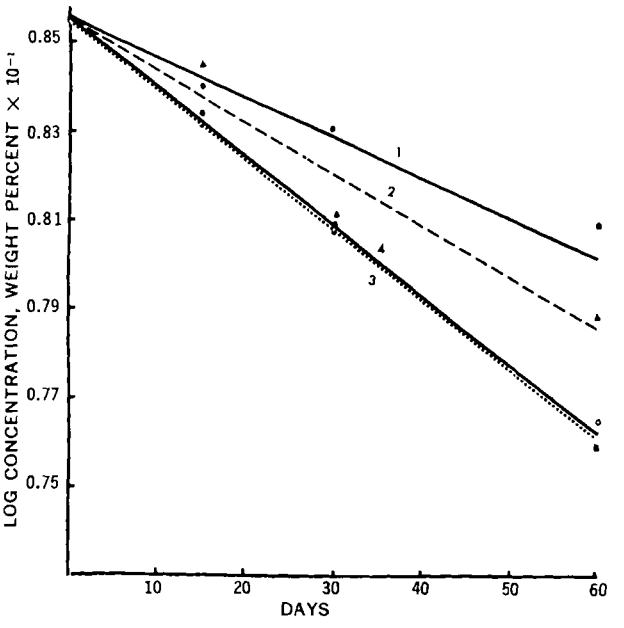

Figure 4—*Decomposition of epinephrine salts at 25°, Formulation D. Key: 1, bitartrate; 2, maleate; 3, malate; and 4, fumarate.*

[5] The program and data were fed into a Controlled Data Corporation (CDC) 6400 computer by means of a Type ASR33 teletype terminal.

Table V—Rate of Decomposition for Epinephrine Salts

Epinephrine Salt	Formulation	Rate of Decomposition, $k \times 10^{-3}$ 25°	37°	47°
Bitartrate	A	3.370	3.600	3.670
	B	3.270	3.770	4.060
	C	3.268	3.283	3.601
	D	2.536	2.906	4.369
Maleate	A	2.940	3.40	3.590
	B	2.803	3.499	3.719
	C	3.827	4.865	4.914
	D	3.997	4.013	4.226
Malate	A	5.245	5.907	6.311
	B	5.055	5.646	5.910
	C	5.663	5.680	5.807
	D	5.466	5.692	5.903
Fumarate	A	5.677	5.707	5.817
	B	5.657	5.828	5.915
	C	5.009	5.606	6.748
	D	5.074	5.515	5.622

are soluble in ethyl alcohol. Therefore, precipitation was accomplished by adding a nonpolar organic solvent in which the salts were insoluble. Ether was used for this purpose. Epinephrine maleate, fumarate, and malate were prepared by this modified method. Their melting points, yields, and IR spectra were taken. Elemental analyses of the synthesized epinephrine salts confirmed the salt formation. Epinephrine bitartrate was also prepared by this method, and the analytical data obtained from this sample were compared to a known sample of epinephrine bitartrate. The results indicated the usefulness of this method for the preparation of several salts of epinephrine.

Since the physicochemical properties of drugs play an important role in delivering the drug to the site of action and subsequent absorption, it is important to examine the extent to which any one property of these salts can be correlated with the observed biological activity. The partition coefficient of epinephrine maleate, malate, and fumarate was compared to the partition coefficient of the known epinephrine bitartrate. From the results obtained, it was noted that the malate, maleate, and fumarate had a partition coefficient similar to the bitartrate when determined in similar immiscible solvents.

The biological activity of epinephrine bitartrate, when administered by aerosol inhalation, was reported previously (6, 7). Other salts of epinephrine, such as the hydrochloride, were noted to have the same biological activity. However, when formulating an aerosol dosage form containing epinephrine, the solubility of the active ingredient becomes an important consideration because either a solution or dispersion can be formulated. Where a dispersion system is desired, a salt must be used that will show minimum solubility in the propellant-solvent system and sufficient solubility in extracellular fluids so as to be delivered to the site of action. Epinephrine bitartrate has been found to possess this desired solubility in that it shows minimal solubility in the propellant system but does possess sufficient solubility in the body fluids. It was on the basis of this discussion that the partition coefficient was determined for each salt studied. By comparing these results, it was noted that the partition coefficients of these new epinephrine salts determined between octyl alcohol–water were approximately the same for each salt. Some difference was noted when the partition coefficient was determined in octyl alcohol–water as compared to hexadecyl alcohol–water. This observation seems to indicate that as one increases the nonpolar part of the hydrocarbon chain of the alcohol, the partition coefficient of the epinephrine salts is decreased. However, by comparing the results obtained in any one system with a known salt such as the bitartrate, one can obtain an indication of the suitability of the salt for use as a replacement for existing epinephrine salts. Based upon partition coefficient, it would seem that these salts of epinephrine are suitable for use. The solubility of all four epinephrine salts studied was found to be greater in Propellant 152a than in the other propellants. Additionally, the maleate and fumarate were shown to be the most soluble of all the salts studied. The solubility of the epinephrine salts decreased as the hydrogens on the molecule were replaced with a halogen. This typical solubility behavior can be explained by observing the chemical structure of the

fluorinated hydrocarbon and noting that the degree of halogenation increases in going from Propellant 152a to 142b to 114 or 12.

To determine the relative stability of the prepared epinephrine salts compared to epinephrine bitartrate, several formulations were prepared and studied over a 60-day period. Based upon the results of the solubility study, it was decided to formulate several aerosol preparations by suspending the salt in the propellant. Since epinephrine bitartrate is slightly soluble in alcohol, those formulations containing alcohol (Formulations A and B) would have some of the epinephrine salt in partial solution. The other formulations contain the salt in suspension. The former formulations were prepared so that some indication of the stability of the salt in solution could be obtained. The results gained from this study of the epinephrine salts in various aerosol formulations indicate that the decomposition taking place under these conditions can be treated as first order. This finding can be noted in Figs. 1–4 where a straight line resulted from a plot of log concentration *versus* time.

Of all the salts studied, epinephrine bitartrate and maleate seem to be the most stable under the conditions of this study. It was also noted that sodium bisulfite, present as an antioxidant, had a tendency to reduce the rate of decomposition as compared to ascorbic acid. No attempt was made to adjust the pH of the solutions but the effect of pH upon the stability of these formulations is currently under study. The presence of ethyl alcohol in the formulation seemed to have very little effect, if any, upon the decomposition of the epinephrine salts. In fact, a comparison of Formulation D, containing only epinephrine salt and propellant, with the other formulations shows very little difference. However, these results might be quite different if extended over a longer period of time. The presence of ethyl alcohol, however, can affect the stability of the dispersion, resulting in agglomeration and caking. The same conclusion can be stated for those formulations containing a surfactant. Additional studies are underway to study more fully the stability of these epinephrine salts, both from a physical and a chemical viewpoint. Of all of the salts studied, epinephrine maleate shows the greatest potential for use in aerosol form and is under further study.

SUMMARY

Epinephrine maleate, fumarate, and malate were prepared by modification of an existing method. The partition coefficient of these epinephrine salts was determined between octyl alcohol–water and between hexadecyl alcohol–water and found to be similar to the partition coefficient of epinephrine bitartrate. Epinephrine bitartrate and malate were found to be the least soluble in the fluorocarbon propellant while the maleate and fumarate showed a higher degree of solubility in these propellants. The results of the solubility study of these epinephrine salts in the propellants indicated that the formulation of epinephrine salts as an aerosol dosage form must be accomplished through use of a cosolvent or by formulating a dispersion system. From the stabilty study of the epinephrine salts in an aerosol formulation, it was noted that the decomposition which took place followed first-order kinetics and that epinephrine maleate and bitartrate seem to be more stable than the other salts of epinephrine. Further studies are indicated to determine the extent of this stability.

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Dissolution Rate Patterns of Log-Normally Distributed Powders

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Abstract □ Particles dissolving in a dissolution medium initially decrease in linear dimension, while the number of particles remains unaltered. At a particular point in time (t_c) the smallest particle disappears, and from that point on the number of particles decreases. These phenomena were simulated on a digital computer, and the agglomerate dissolution pattern under sink conditions was shown to follow a cube root law, but the slopes differ according to whether $t < t_c$ or $t > t_c$.

Keyphrases □ Dissolution rates—patterns of log-normally distributed powders □ Powders, dissolution under sink conditions—rate patterns, (approximate) numerical solution of log-normal distribution integrals □ Computer simulations—particle dissolution, disappearance □ Particle dissolution, sink conditions—powder, log-normal distribution, rate patterns, computer simulation

Rates of dissolution and the mechanisms involved in the dissolution process have been the subjects of large volumes of literature in the last decade. The importance of dissolution rates in biopharmaceutics is manifested by the official methods for dissolution rate testing recently adopted by the USP and the NF.