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PHYSICO-CHEMICAL STUDIES ON AEROSOL SOLUTIONS FOR DRUG DELIVERY II. WATER–PROPYLENE GLYCOL–ETHANOL SYSTEMS

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SUMMARY

The output of aerosol droplets from a commercial nebulizer has been examined using water–propylene glycol–ethanol systems. In general an increased alcohol content leads to an increased total output from the nebulizer; however, much of this output is in the form of solvent vapour. The modest increase in the output of aerosol droplets below an arbitrary therapeutic limit of 5 μm is attributable to the effect of ethanol on surface tension. The use of water–propylene glycol–water systems to deliver a dose of a test steroid is examined.

INTRODUCTION

In the preceding paper Davis (1978) described the formulation and aerosol characteristics of propylene glycol–water systems. The output and particle size of droplets from the commercial nebulizer device was dependent on the propylene glycol content. A maximum delivery of particles within the therapeutically accepted range (5 μm and below) was obtained at 30% v/v propylene glycol. A further important factor was the nature of the drug substance to the delivered. For instance, with a steroidal compound the solubility of the drug in the vehicle was of great importance. Although 30% propylene glycol gave maximum aerosol output the solubility of the drug in the vehicle was not particularly good. As a consequence the optimum propylene glycol content for delivery of the test drug was 60% v/v; a compromise between aerosol characteristics and drug solubility factors. The time taken to deliver a dose of 1 mg to the lower airways was calculated to be 11 min. This was far too long for most clinical situations and the present work describes investigations into alternative delivery systems comprising propylene glycol–water–ethanol. The presence of ethanol should give the vehicle good solvent characteristics without greatly changing the important physical characteristics (e.g. viscosity).

The output and size properties of aerosol droplets produced using a commercial atomizer (Maximyst) have been examined together with the relevant physico-chemical data (viscosity, surface tension, density and vapour pressure).

METHODS

Atomizer. A Maximyst nebulizer (Mead Johnson, Evansville, Ind.) was used to generate the aerosol droplets and total output was determined by measuring weight loss. The air pressure was maintained constant at 12 psi (Maximyst generator). This gave a flow rate of 3.5 l/min through the nebulizer. The nebulizer was filled with 5 ml of solution in all experiments.

Particle size analysis. The aerosol solutions were labelled with 0.1% fluorescein sodium, and sized as in the preceding paper using a cascade impactor. The increase in concentration of the solution in the nebulizer was used to determine the proportion of useful aerosol and the proportion of solvent lost as vapor.

Physico-chemical characteristics. Solution densities were measured using the standard density bottle method. Viscosities were measured by U-tube viscometer (type B) as described in British Standards (1957). The viscometer was calibrated using double distilled water. Surface tension data were obtained using a du Nouy ring method (Cambridge surface tension apparatus). Calibration was performed using liquids of known surface tension. Vapour pressure was measured by the Smith and Menzies isoteniscope (Levitt, 1973). All physico-chemical determinations were made at 25 ± 0.5°C.

Materials. Ethanol, USP grade. Propylene glycol, Union Carbide. Fluorescein sodium, Aldrich Chemical Co.

RESULTS

Table 1 summarizes the relevant aerosol output and physico-chemical data for the various propylene glycol–water–ethanol systems.

Ethanol–water systems. Further data to those given in Table 1 have been obtained for the ethanol–water system. These are summarized in Fig. 1. The *total* output from the nebulizer increases rapidly with increase in the proportion of ethanol. However, when we resolve these values into their two constituent contributions of useful solution and vapour we see that the output of solution increases little and the greater proportion of material output from the nebulizer is alcohol–water vapour. The increased output of aerosol solution as droplets can be attributed to the surface tension-lowering effect of ethanol. Previous authors (Walkenhorst and Dautrebande, 1964; Glukov, 1969) have shown that surface tension can have a profound effect on aerosol output and mean droplet size. An increased ethanol content will give rise to an increased solution viscosity up to an ethanol content of about 40%, after which the viscosity will fall (Weast, 1975). This maximum in viscosity apparently does not play an important role in determining aerosol output.

Propylene glycol–ethanol–water systems. Three different combinations have been studied. In each case the total water content has been held constant and the remaining solvent content has been varied from totally ethanol to totally propylene glycol. Water contents of 30, 50 and 70% were chosen. Data for the total output from the nebulizer,

TABLE 1

PHYSICO-CHEMICAL DATA FOR WATER–PROPYLENE GLYCOL–ETHANOL SYSTEMS

Water	Solution		Density (g/ml)	Viscosity (mP)	Surface tension (dynes/cm)	Vapour pressure (mm Hg)	Output (μl/l)		
	Propylene glycol %	Ethanol %					Total	Solu-tion	Vapour
30	0	70	0.895	21.87	25.0	55	149	51	98
30	10	60	0.914	26.17	25.4	50	120	58	62
30	20	50	0.933	31.56	27.4	43	89	44	45
30	30	40	0.946	36.01	29.4	35	69	40	29
30	40	30	0.964	48.35	31.6	26	53	35	18
30	50	20	0.981	56.21	34.6	23	41	30	11
30	60	10	0.996	68.93	38.4	19	31	19	12
30	70	0	1.152	82.49	42.3	10	22.5	20	2.5
50	0	50	0.9304	23.6	27.5	50	123	50	73
50	5	45	0.9408	25.4	26.3	43	112	–	–
50	10	40	0.9495	27.5	25.2	38	106	59	47
50	15	35	0.9626	29.8	26.2	36	95	–	–
50	20	30	0.9734	31.5	28.5	34	85	55	30
50	25	25	0.9847	33.8	30.6	31	72	–	–
50	30	20	0.9957	36.7	31.9	27	65	42	23
50	35	15	1.0074	39.0	34.1	25.5	57	–	–
50	40	10	1.0182	42.8	35.4	24	53	40	13
50	45	5	1.0291	46.2	39.4	20	43	–	–
50	50	0	1.0401	51.2	45.0	17	37	32	5
70	0	30	0.965	19.26	33.0	43	131	67	64
70	5	25	0.975	20.56	35.4	36	121	–	–
70	10	20	0.986	21.61	38.1	31	115	71	44
70	15	15	0.992	22.39	39.4	27	101	–	–
70	20	10	1.0691	24.77	42.1	23	92	63	29
70	25	5	1.1479	27.00	47.5	19	78	–	–
70	30	0	1.2602	30.62	52.0	17	66	45	21

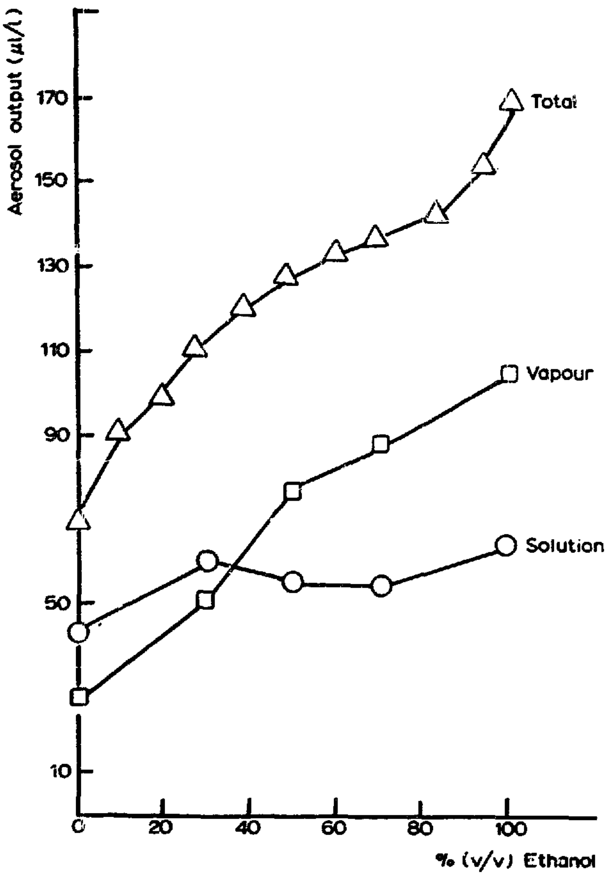

Fig. 1. Nebulization of ethanol solutions. △, total output; ○, solution and □, vapour outputs.

together with the solution and vapour contributions are shown in Figs. 2, 3 and 4. Each particular system gives a similar pattern. At zero ethanol content (water–propylene glycol systems) the output is mainly solution droplets and there is little attendant vapour. As the proportion of ethanol increases and the proportion of propylene glycol decreases the output of droplets increases, but so does the quantity of vapour. For the 50 and 30% water systems containing only alcohol, more vapour than solution is generated during the atomization process. Thus by the use of mixed solvents it is possible to increase total output from the nebulizer; however, much of this increased output will be in the form of vapour and the solution in the nebulizer will become more concentrated. The increase in the output of aerosol solution droplets can be attributed directly to the effect of ethanol in reducing the surface tension and viscosity of the delivery solutions (Table 1). In the previous paper it was found that an increased viscosity led to a reduced output whereas a reduced surface tension led to an increased output. In this case viscosity and surface tension are both changing in the same direction.

The quantity of material lost as vapour (µl/l) is obviously related to the vapour pressure of the solution in the nebulizer (Fig. 4).

Particule size analysis. The particle size analysis of aerosol systems containing volatile

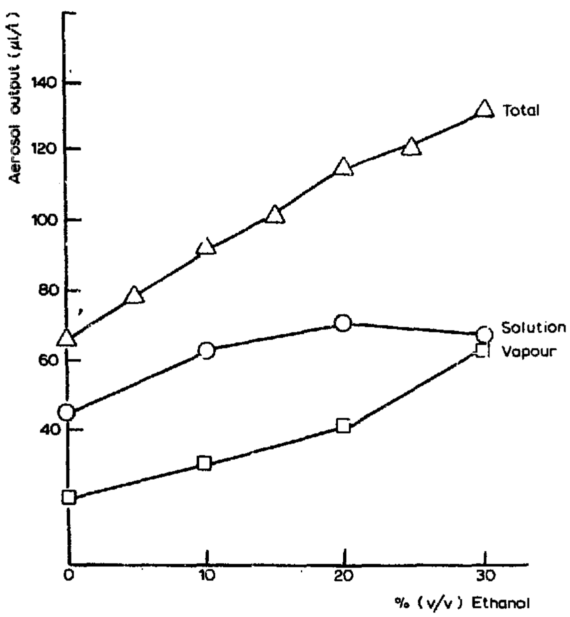

Fig. 2. Nebulization of ethanol–propylene glycol–water system, solvent content 30%–water 70%. △, total output; ○, solution and □, vapour outputs.

solvents such as ethanol is very difficult since the droplets can change in size rapidly once they have left the nebulizer. Some representative data for the 50% v/v water systems containing upwards of 25% v/v ethanol are given in Fig. 5. The mass median diameter increases as the percentage of ethanol is increased (and accordingly as the percentage of propylene glycol is decreased). These results are in accord with our general observation

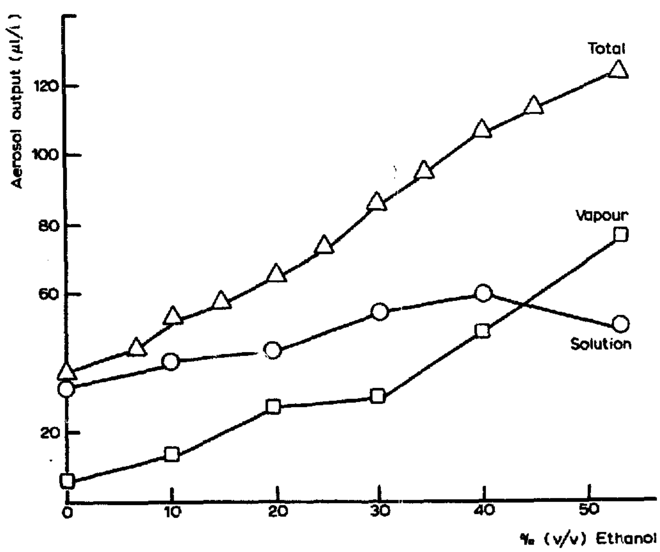

Fig. 3. Nebulization of ethanol–propylene glycol–water system, solvent content 50%–water 50%. △, total output; ○, solution and □, vapour outputs.

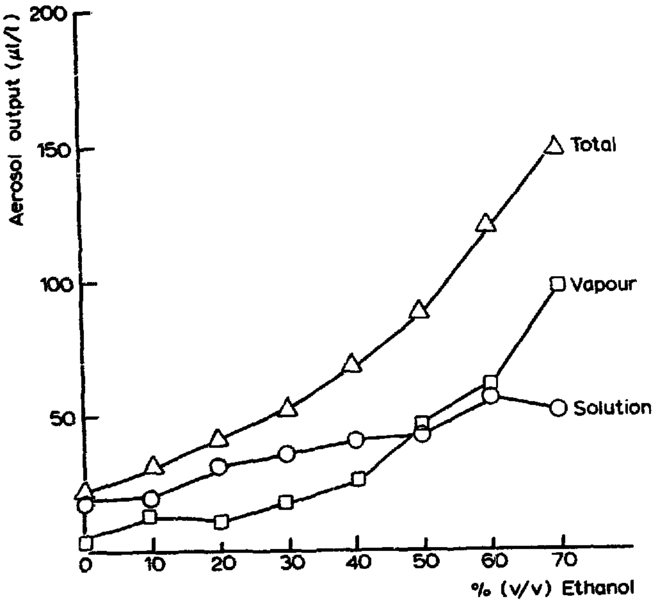

Fig. 4. Nebulization of ethanol–propylene glycol–water system, solvent content 70%–water 30%. △, total output; ○, solution and □, vapour outputs.

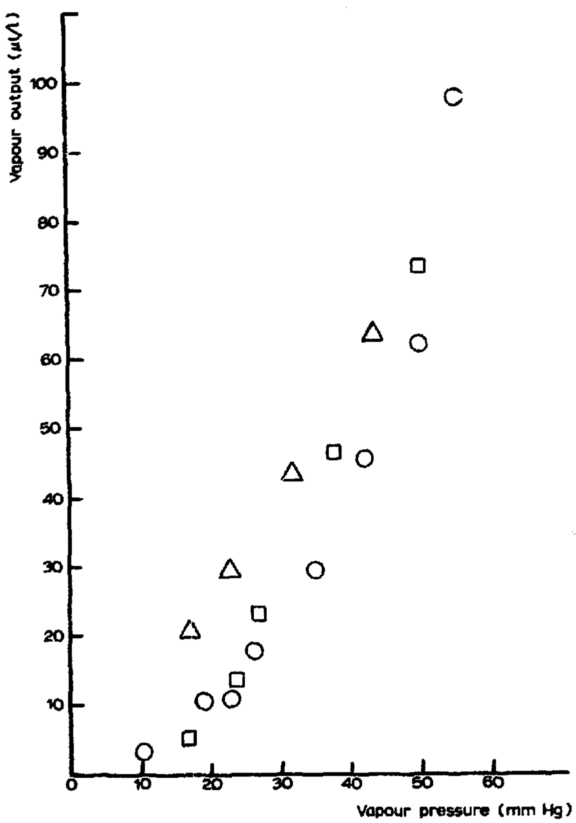

Fig. 5. Relation between solution vapour pressure and vapour output. ○, □ and △ are: for solvent 30, 50 and 70%, respectively, and for water 70, 50 and 30%.

that an increased aerosol output is at the expense of an increased mean particle size (Davis, 1978). However, at 10% v/v ethanol and 40% v/v propylene glycol the mean size begins to fall. This fall in size probably reflects shrinkage of the droplets after they have left the nebulizer due to solvent loss. Thus the sizes recorded using the cascade impactor may not truly reflect the sizes of the particles leaving the nebulizer. Particle shrinkage (and growth) under different ambient conditions of temperature and humidity will be considered in a subsequent publication.

The particle size data and the output data may be combined as previously (Davis, 1978) to give values for the output of aerosol solution droplets of 5 μm and below. Fig. 6 shows that this parameter increases more or less linearly with ethanol content. The delivery of a test steroidal compound (flunisolide) can be considered in the light of these data (Table 2). For a dose of 1 mg the time to administer a dose using the 25% ethanol, 25% propylene glycol, 50% water system is about 4 min. This may be contrasted with the 21 min required when propylene glycol is used alone (Davis, 1978). A linear relation between delivery time and ethanol content is evident. It is expected that similar relations will hold for other ethanol–propylene glycol mixtures. The addition of ethanol does improve delivery

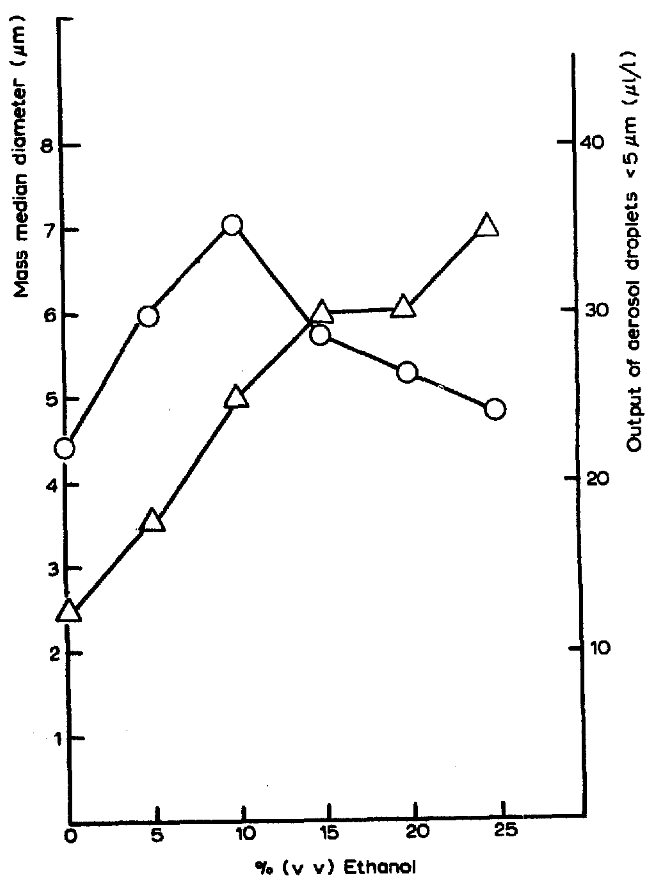

Fig. 6. Particle size and aerosol output characteristics of ethanol–propylene glycol–water system. △, output; ○, size.

TABLE 2

OUTPUT OF FLUNISOLIDE USING PROPYLENE GLYCOL–ETHANOL MIXTURES – MAXIMYST NEBULIZER – DOSE 1 mg

Propylene glycol % (v/v)	Ethanol % (v/v)	Solubility [a] flunisolide (mg/ml)	Quantity of solution for dose (ml)	Aerosol solution output (<5 μm) (μl/l)	Volume of air (l)	Time for nebulization (min)
50	0	1.00	1	13	77	21
45	5	1.15	0.87	18	55	15
40	10	1.33	0.75	25	30	8
35	15	1.50	0.67	30	22	6
30	20	1.67	0.60	30	20	5.5
25	25	1.85	0.54	35	15	4.2

[a] Values for mixed solvents estimated from binary solubility data (assuming that a linear relation holds).

but not as dramatically as would be concluded from studying total output data alone. One must also consider the output of vapour (considerable at high ethanol contents), the particle sizes of droplets produced and the solubility of the drug in the vehicle.

CONCLUSIONS

(1) The addition of ethanol to water produces an increased output from a nebulizer; however, the major proportion of this increase is solvent vapour.

(2) Propylene glycol–ethanol–water systems show a similar trend, namely that at fixed water content the output increases as the ratio of ethanol to propylene glycol increases. Much of this increased output is solvent vapour.

(3) The output of aerosol solution droplets can be correlated with the physico-chemical properties of the vehicle: surface tension, viscosity. A decrease in these two parameters leads to an increased output.

(4) The output of solvent vapour is directly related to solvent vapour pressure.

(5) For a 50% v/v water, 50% ethanol–propylene glycol system the output of aerosol solution droplets of 5 μm and below increases with ethanol content.

(6) The time required to give a dose of a steroidal drug decreases linearly with increase in the ethanol content of a mixed ethanol–propylene glycol vehicle.

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