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Note

The impact of co-solvents and the composition of experimental formulations on the pump rate of the ALZET® osmotic pump

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Abstract

The water-miscible co-solvents polyethylene glycol 400 (PEG400), *N*-methyl-2-pyrrolidone (NMP), and *N*, *N*-dimethylacetamide (DMA) exhibit the potential to increase the solubility of poorly water-soluble compounds and therefore they represent promising vehicles for compound delivery using osmotic pumps in early discovery experiments. Thus, the selected co-solvents were investigated for their compatibility with the interior of ALZET® osmotic pumps. Moreover, 1-week pumps were filled with mixtures of either the co-solvents with water (60:40, v/v), with neat PEG400, or with PEG400/water mixtures of different concentrations. It was determined whether the composition of an experimental formulation could have an impact on the overall pump rate with ^{14}C-mannitol being used as the model compound. It was found that neat PEG400 was compatible with the reservoir material, whereas NMP and DMA were tolerable only in aqueous solutions up to 60%. PEG400, NMP, and DMA mixtures with water (60:40) resulted in release rates comparable to those of water and PEG400/water mixtures of lower co-solvent concentration. Moreover, as demonstrated using the various PEG400/water mixtures, the amount of co-solvent in the formulation had no significant impact on the overall release profile. By contrast, the use of neat PEG400 resulted in a significant decrease in the pump rate.

Keywords: Osmotic pump; Solubility; Polyethylene glycol 400; *N*-methyl-2-pyrrolidone; *N*, *N*-dimethylacetamide; Controled release

ALZET® osmotic pumps offer the possibility to administer compounds to experimental animals without the need of repeated dosing due to continuous controlled delivery, often at the target tissue site. For example, various drugs such as Interleucin-1ra (Pellicane et al., 1993), thyroid hormones (Barter and Klaassen, 1992), insulin like growth factor (Nachemson et al., 1990), and thymidine (Clowes et al., 1989) have been infused using an ALZET® osmotic pump.

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In contrast to these hydrophilic molecules, compounds to be delivered with osmotic pumps can often be very lipophilic and the formulation of a suitable dosing solution is rather time consuming. Therefore, the development of a suitable experimental formulation in a reasonable period of time represents an important issue in early drug discovery. Fortunately, water-miscible co-solvents often provide the potential to increase the solubility of various drugs (Sweetana and Akers, 1996), and commonly used co-solvents such as polyethylene glycol 300 (PEG300), propylene glycol (PG), and ethanol have been reported by ALZA (ALZET, 1992, product information) to be compatible with the pump interior. Thus, according to the product information, PEG300 and PG are compatible with the reservoir material neat or in water, while ethanol is tolerable in concentrations up to 10% in water.

However, the above mentioned co-solvents are not always suitable for dissolving lipophilic compounds. Consequently, the aim of the current study was to test PEG400 (Fluka), NMP (Fluka), and DMA (Fluka) for their compatibility with the pump material and for their potential to be released from the osmotic pump at constant rates, since these co-solvents are capable of increasing the solubility of certain lipophilic drug candidates. Additionally, different compositions of PEG400/water mixtures were investigated in osmotic pumps to determine the effect of the composition of a formulation on the pump rate. The different formulations tested are reported in Table 1.

Compatibility with the pump material was performed using the alzaid™ test kit for ALZET® osmotic pumps. The alzaid™ test kit consists of polymer spheres identical to the polymer used in the reservoir of ALZET® osmotic pumps. To determine the compatibility of the different formulations with the pump material, approximately 25 polymeric spheres were weighed in a 10-ml screw-cap test tube and 5 ml of the formulation under investigation were added. The samples were stored at 37°C for 1 week after which time the spheres were removed from the test tubes, dried with an absorbent tissue, and accurately weighed. Compatibility with the pump material was determined using the equation recommended by the manufacturer:

$$\text{Final Weight} - \text{Initial Weight}/\text{Initial Weight} * 100 = A\%$$

According to the manufacturer:
when $A = 0–7\%$ the formulation is suitable for pump delivery; and
when $A \geq 7\%$ or the spheres are deformed in shape, the formulation is not suitable for pump delivery.

The results of the pump material compatibility study of neat co-solvents and co-solvent/water mixtures are given in Table 2. It was found that neat PEG400 was compatible with the reservoir material. By contrast, neat NMP and DMA could not be used in the pump material, since the calculated A [%] value for the neat co-solvents was significantly higher than 7%, indicating an incompatibility with the pump interior. Moreover, in

Table 1
Formulation details and average volume of formulation released per hour

Formulation	Solvents	Co-solvent (%)	Tube length (cm)	Density (g/ml)	Release/h from day 2 (μl)	St. dev. (μl)
1	Water	0	17	1.020	11.11	1.16
2	Water	0	34	1.020	10.58	1.25
3	PEG400:water	5	17	1.027	10.54	1.23
4	PEG400:water	30	17	1.070	11.62	1.78
5	PEG400:water	60	17	1.115	10.66	2.47
6	PEG400	100	17	1.139	6.54	1.95
7	DMA:water	60	17	1.014	10.89	1.39
8	NMP:water	60	17	1.061	10.81	1.41

Table 2
Compatibility of formulations with the pump material

Solvent	Conc. of solvent (%)	Initial weight of spheres (mg)	Final weight of spheres (mg)	Sphere appearance	*A* (%)[a]
Polyethylene glycol 400	100	635.0	650.59	Light yellow	2.45
1-Methyl-2-pyrrolidone	100	814.4	3001.1	Yellow	268.51
1-Methyl-2-pyrrolidone	80	831.8	949.9	Light yellow	14.20
1-Methyl-2-pyrrolidone	70	1212.4	1300.8	Light yellow	7.29
1-Methyl-2-pyrrolidone	60	710.7	745.2	Light yellow	4.85
1-Methyl-2-pyrrolidone	40	692.0	720.5	Light yellow	4.12
1-Methyl-2-pyrrolidone	20	717.8	735.4	Light yellow	2.45
1-Methyl-2-pyrrolidone	10	871.4	890.0	White	2.13
N, *N*-Dimethylacetamide	100	960.4	2278.5	Yellow	137.25
N, *N*-Dimethylacetamide	80	753.5	852.1	Light yellow	13.09
N, *N*-Dimethylacetamide	70	1248.0	1338.9	Light yellow	7.28
N, *N*-Dimethylacetamide	60	841.2	892.9	Light yellow	6.15
N, *N*-Dimethylacetamide	40	788.7	822.2	Light yellow	4.25
N, *N*-Dimethylacetamide	20	881.4	903.5	Light yellow	2.51
N, *N*-Dimethylacetamide	10	927.8	947.2	White	2.09
Water	100	1210.4	1226.4	White	1.32

[a] Final Weight − Initial Weight/Initial Weight*100 = *A*%

contrast to PEG 400, the spheres incubated in neat NMP and DMA were swollen and brittle at the end of the incubation period. Additionally, the color of the spheres changed from white to yellow. However, the addition of water to the co-solvents demonstrated that NMP and DMA could be used in the pump at a concentration of up to 60% in water (Table 2).

After assessing the compatibility of the formulations with the pump material, ALZET® 7-day osmotic pumps (model 2ml1, Lot. 042402, pumping rate reported as 11.38 ± 0.58 μl/h, filling volume 2213 ± 39.4 μl) were used to discriminate between the pump rates of the different formulations tested. ^{14}C-mannitol (1 μg/ml, NEN) was chosen as the model compound to monitor the amount of formulation released. Radioactivity was measured using a Beckmann LS6000TA after addition of Ultima Gold (Packard).

As described in Table 1, seven different formulations were investigated. An additional experiment was conducted in which there was a variation in tube length (17 and 34 mm), since tubes of different length can be connected to the pumps in order to target the compound directly to a certain region in the animals' body. Each formulation was assayed in triplicate and pumps were filled with the formulations by means of a syringe and incubated in 0.9% saline solution at 37°C for 8 days. The formulation released into the tubes was collected into plastic vials. Every 24 h vials were replaced and stored at +4°C until samples were analyzed for total radioactivity.

Fig. 1 illustrates the release of the various ^{14}C-mannitol solutions from a 7-day osmotic pump, and as can be seen the volume of formulation released from the pumps was similar, independent on the composition of the formulation or on the tube length. The only exception to this was the solution of ^{14}C-mannitol in neat PEG400. In this particular case lower amounts of formulation were released during the time course compared to the other vehicles. The first day of incubation in the aqueous sodium chloride solution was needed for the initiation of the pumping and was therefore lower than 10 μl. The average pump rates per hour starting from day 2 are given in Table 1 and only the solution in neat PEG400 shows lower levels than the average pump rate.

From the above results it can be concluded that PEG400, NMP and, DMA (in concentrations in water up to 60%) were found to be suitable as vehicles for osmotic pump delivery. As demonstrated using neat PEG400, a certain amount of

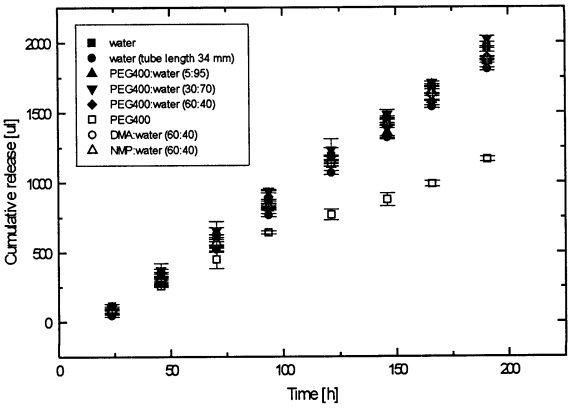

Fig. 1. Release of ^{14}C-mannitol from formulations.

aqueous phase seems to be necessary for constant pump rates and sufficiently high volume release. Moreover, the average volume released from the pump per hour matched very well with the value given by the manufacturer. Therefore, we found additional experimental formulations facilitating the screen of lipophilic, poorly water-soluble compounds in osmotic pump studies.

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