Parenteral Formulation of the Kappa Agonist Analgesic, DuP 747, via Micellar Solubilization

Munir A. Hussain,[1,2] Lei-Shu Wu,[1] Christopher Koval,[1] and Arthur R. Hurwitz[1]

Received June 7, 1991; accepted November 1, 1991

The nonopioid kappa agonist analgesic amine, DuP 747, as a hydrochloride salt exhibited an aqueous solubility of 3 mg/ml. This solubility was insufficient to provide the desired dose in a solution formulation for intramuscular administration. Aqueous solutions of the hydrochloride salt exerted surface activity behavior; however, the critical micellar concentration (CMC) was not reached at the saturation solubility. Enhanced aqueous solubility required to reach the CMC could lead to micellization of the compound and a possible i.m. solution formula. The methanesulfonate salt was more water soluble than the hydrochloride salt and yielded a micellar solution with a concentration of 60 mg/ml.

KEY WORDS: micellar solution; parenteral formulation; kappa agonist analgesic; salt formation; critical micellar concentration; salt selection; solubility improvement.

INTRODUCTION

Salt formation alters the physicochemical and resultant biological characteristics of a drug without modifying its basic chemical structure. The importance of choosing the correct salt form of a drug is well documented (1,2). Organic salts were examined to enhance the aqueous solubility of an otherwise insoluble hydrochloride salt (3). These salts increase aqueous solubility through decreasing crystal lattice energy, lowering melting point, hydrogen bonding of the salt anions with water, etc. Further, the surface tension of different phenothiazines solutions changed in the presence of different buffer species (4). Different anions in solution were shown to affect the equilibrium solubility of an amine compound that can form micelles (5). Salts of tetracycline also show different surface tension behavior (6), and chlorohexidine diacetate forms micelles and displays a higher CMC than that of the digluconate salt (7).

DuP 747 (Fig. 1) is a selective kappa agonist analgesic which produces potent antinociceptive responses in mice, rats, and dogs. Chronic treatment with analgesic doses of DuP 747 produces less tolerance than achieved with equianalgesic doses of morphine; DuP 747 is not cross-tolerant to morphine in morphine-tolerant mice, and morphine is not cross-tolerant to DuP 747 in DuP 747-tolerant mice. Mice treated with a 3-day continuous infusion of DuP 747 showed no withdrawal signs following abrupt discontinuation of treatment (8). Thus, DuP 747 produces moderate to strong analgesic activity without morphine-like signs in a variety of experimental pain models in animals (8).

DuP 747 was first prepared as a hydrochloride salt which exhibited an aqueous solubility of 3 mg/ml. Although it was intended primarily for oral use, it was desired to compare it clinically to i.m. morphine. The clinical i.m. dose of ~40 mg was not feasible with a solution of the hydrochloride salt since the required volume would be too large. It was observed that DuP 747 hydrochloride exhibited surface activity behavior; however, its saturation solubility did not reach the critical micellar concentration (CMC). In this report, salt formation as a method of exceeding the CMC and increasing DuP 747 solubility through micellar solubilization is discussed.

EXPERIMENTAL

Materials and Methods

DuP 747 [racemic *trans*-3,4-dichloro-*N*-methyl-*N*-[1,2,3,4-tetrahydro-5-methoxy-2-(pyrrolidin-1-yl)] napth-1-ylbenzeneacetamide] was from The Du Pont Merck Pharmaceutical Company. Methanesulfonic acid was obtained from Sigma Chemical Company. DuP 747 base was prepared from the hydrochloride salt by dissolving the hydrochloride salt (1 g, 2 mmol) in aqueous methanol (5 ml methanol:1 ml water) and methylene chloride (100 ml) was added to the above solution in a separatory funnel. An aqueous solution containing sodium carbonate (7 g) and sodium hydroxide (1.5 g) was then added. After vigorous shaking, the methylene chloride layer was separated, dried over anhydrous sodium sulfate, and evaporated. The viscous residue was dissolved in 25 ml of absolute ethanol, and methanesulfonic acid (0.22 g, 2.2 mmol) was added. The solution was stirred for 0.5 hr and flushed with nitrogen gas until precipitation occurred. The precipitate was isolated, air-dried, and characterized by elemental analysis and HPLC.

Surface tension measurements were run at 22°C on a DuNouy tensiometer. Solubility studies were carried out by placing excess DuP 747 salt into a suitable container with distilled water and rotating end-to-end for 24 hr at room temperature (22°C). Sodium hydroxide and sulfuric acid were used to adjust the pH to a desired point. Preliminary experiments indicated that 24 hr provided sufficient time to reach equilibrium. The suspension was passed through a 0.22-μm filter, with the first portion discarded to ensure saturation of the filter. The pH of the filterate was measured and an aliquot was diluted and analyzed chromatographically.

Chromatographic Method

DuP 747 was analyzed by high-performance liquid chromatography (HPLC). The components of the HPLC system were a solvent delivery pump (Waters 590 programmable HPLC pump); an autosampler (Waters, WISP 710B); a reverse-phase, 25-cm × 4.6-mm-i.d. stainless-steel column prepacked with 6-μm C-8 particles (Zorbox, Du Pont); a variable-wavelength spectrophotometric detector (Lambda-Max Model 481; Waters Instruments) set at 272 nm; and a

[1] The Du Pont Merck Pharmaceutical Co., Experimental Station, P.O. Box 80400, Wilmington, Delaware 19880-0400.
[2] To whom correspondence should be addressed.

0724-8741/92/0600-0750$06.50/0

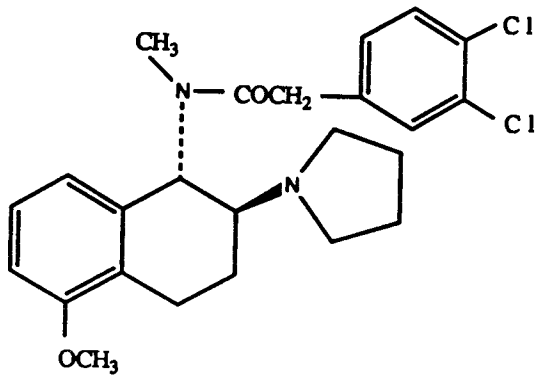

Fig. 1. Chemical structure of DuP 747 base.

recording integrator (Hewlett-Packard, Model 3392A). The mobile phase consisted of 0.3% acetic acid:acetonitrile:triethylamine:sodium heptane sulfonate (470 ml:530 ml:1 ml:0.7 g) and was delivered at a flow rate of 2 ml/min. Retention time for DuP 747 was 6 min.

RESULTS AND DISCUSSION

The aqueous solubility of DuP 747 HCl was 3 mg/ml. Since it was desired to administer this compound intramuscularly in a solution formulation at a dose of ~40 mg, a higher solubility was needed.

The pH–solubility profiles of DuP 747 hydrochloride and methanesulfonate are shown in Fig. 2. Solubility as a function of pH can be described as follows:

$$S_T = S_0\left(1 + \frac{[H^+]}{K_a}\right)$$

$$\log\left(\frac{S_T}{S_0} - 1\right) = \log [H^+] - \log K_a$$

where S_T represents the total drug solubility at any pH, S_O is the solubility of the free base (10 ng/ml), and $[H^+]$ is the hydrogen ion concentration. The pK_a determined by plotting $\log [(S_T/S_O) - 1]$ vs $\log [H^+]$ was 9.2.

The surface tension behavior of the hydrochloride salt is shown in Fig. 3, which shows that the compound is surface active; however, at the saturation solubility, the critical micelle concentration (CMC) was not reached. To enhance solubility, the methanesulfonate salt was prepared. The surface tension behavior of the methanesulfonate is shown in Fig. 4. As can be seen, the compound exhibited a CMC of ~4 mg/ml and provided a micellar solution with an aqueous solubility of 60 mg/ml. Solubility between pH 10 and pH 5.8 was similar for both salts, however, at pH <5.8 an enhancement in the aqueous solubility of the methanesulfonate was observed as compared to the hydrochloride salt. This breaking point in the solubility of the two salts corresponded to the CMC of the compound as shown in Figs. 2 and 4. Similar solubility and surface tension behavior were observed with a phosphate salt.

It is worth mentioning that the hydrochloride salts of both enantiomers of DuP 747 exhibited melting points lower than that of the hydrochloride salt of DuP 747 and a micellar solubility similar to that of DuP 747 methanesulfonate. This result is due to the higher intrinsic solubility of both hydrochloride salts of the pure enantiomers, exceeding the CMC, as compared to that of DuP 747 hydrochloride.

Formulation of the methanesulfonate salt in saline led to depression in solubility and precipitation, probably because of conversion to the hydrochloride salt. Therefore, a solution formulation of 20 mg/ml at pH 4.7 containing mannitol (to adjust tonicity) was developed.

In conclusion, DuP 747 hydrochloride is surface active, however, its aqueous solubility is below its CMC. Changing

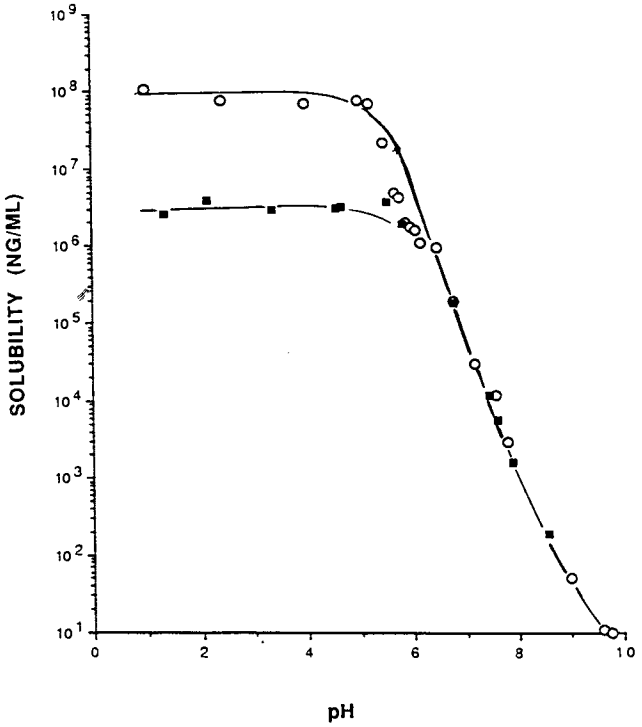

Fig. 2. pH–solubility profile of DuP 747 hydrochloride (■) and DuP 747 methanesulfonate (○).

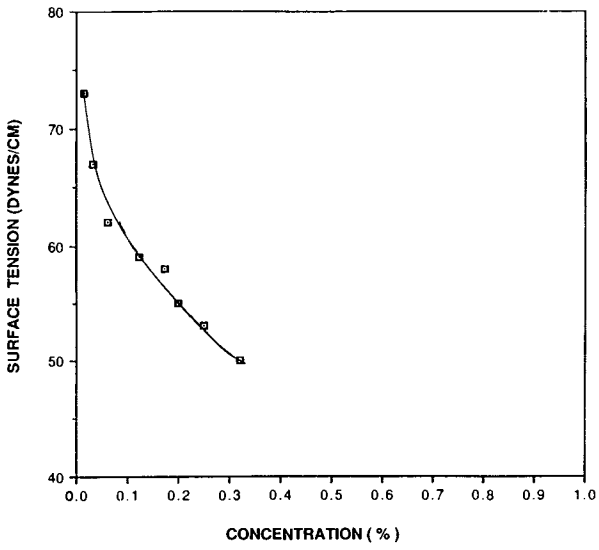

Fig. 3. Surface tension behavior of DuP 747 hydrochloride.

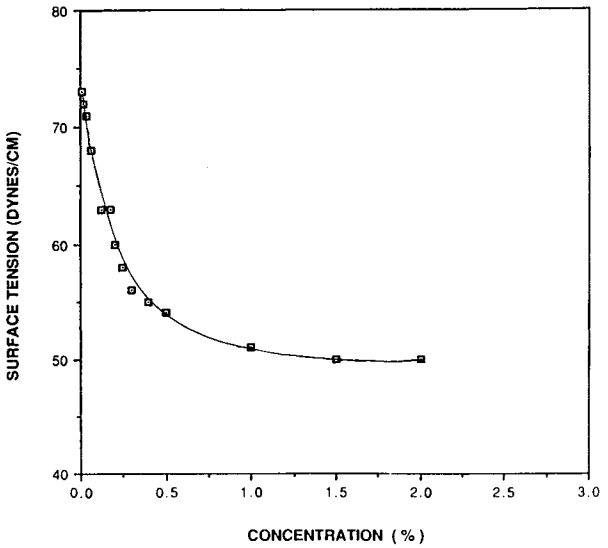

Fig. 4. Surface tension behavior of DuP 747 methanesulfonate.

the salt form was used as a means of increasing its aqueous solubility via micellar solubilization.

ACKNOWLEDGEMENTS

The technical assistance of Ms. Susan Koch and Mrs. Jenan Salman is greatly appreciated.

REFERENCES

1. S. M. Berge, L. D. Bighley, and D. C. Monkhouse. Pharmaceuticals salts. *J. Pharm. Sci.* 66:1–19 (1977).
2. P. L. Gould. Salt selection for basic drugs. *Int. J. Pharm.* 33:201–217 (1986).
3. S. Agharkar, S. Lindenbaum, and T. Higuchi. Enhancement of solubility of drug salts by hydrophilic counterions: Properties of organic salts of an antimalarial drug. *J. Pharm. Sci.* 65:747–749 (1976).
4. G. Zografi and I. Zarenda. The surface activity of phenothiazine derivatives at the air-solution interface. *Biochem. Pharmacol.* 15:591–598 (1986).
5. L. J. Ravin, E. G. Shami, and E. S. Rattie. Micelle formation and its relationship to solubility behavior of 2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride. *J. Pharm. Sci.* 64:1830–1833 (1975).
6. J. H. Perrin and J. J. Vallner. The effect of the anion on the absorption of tetracycline from the rat stomach. *J. Pharm. Pharmacol.* 22:758–762 (1970).
7. D. D. Heard and R. W. Ashworth. The colloidal properties of chlorhexidine and its interaction with some macromolecules. *J. Pharm. Pharmacol.* 20:505–512 (1968).
8. W. K. Schmidt, P. Rajagopalan, L. Cook, M. E. Marynowski, S. W. Tam, L. C. Johnson, G. F. Steinfels, R. M. Scribner, P. Pennev, P. L. Mattei, and A. L. Johnson. Preclinical pharmacology of DuP 747—a new, potent, kappa-opioid analgesic. American Chemical Society (ACS) 200th Meeting, Washington, D.C., Aug. 26, 1990. Abstracts of Papers of the American Chemical Society 200, 1990, p. 59-MEDI.