



## Research Article

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Guest Editors: Heather Boyce, Steve R. Byrn, and Stephen W. Hoag

# Effect of Formulation Variables on the Nasal Permeability and Stability of Naloxone Intranasal Formulations

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**Abstract.** Naloxone is an opioid antagonist with high affinity for  $\mu$ -opioid receptor, and for this reason it is used for the emergency treatment of opioid overdose. Originally, it was available only as an injectable product. However, for the ease of administration, intranasal (IN) formulations have also become available. These IN formulations contain preservatives and stabilizers such as benzalkonium chloride (BKC), benzyl alcohol (BA), and ethylenediaminetetraacetic acid (EDTA). Some of these ingredients are known to affect permeability of drugs. This study focuses on investigating the effect of formulation variables including choice of preservatives, stabilizer, and pH on the permeability and stability of naloxone IN formulations. The *in vitro* permeability of naloxone was evaluated employing EpiAirway™ tissue-mounted Ussing chambers. BKC was found to enhance the apparent permeability ( $P_{app}$ ) of naloxone significantly ( $p < 0.05$ ) at very low concentration, while BA caused similar enhancement at a much higher concentration. EDTA was found to decrease  $P_{app}$  of naloxone by lowering the pH, and the  $P_{app}$  of naloxone was found to decrease approximately 51-fold with the decrease in formulation pH from 6.0 to 4.0. The product stability was, however, found optimal only below pH 5.0. Thus, selection of formulation ingredients, buffering agent, and pH of IN formulation is a balancing act for achieving desired permeability and optimal stability to achieve reasonable shelf life of naloxone IN formulation.

**KEY WORDS:** naloxone; nasal spray formulation; *in vitro* nasal permeation; absorption; stability.

## INTRODUCTION

The widespread abuse of prescription opioids has led to ever increasing episodes of opioid overdose and deaths. The opioid overdose and deaths have gained epidemic

proportions during the last few years (1). To address this issue, medical practitioners, pharmaceutical industry, and the regulatory agencies have made numerous efforts, including but not limited to changes in prescribing patterns of opioid drugs and development of abuse-deterrent formulations to discourage substance abuse of prescription opioids (2,3). Additionally, more effective policies were put in place in many states to reduce the mortality rate of opioid overdose. For example, pharmacists are allowed to dispense naloxone, a drug of choice for reversing respiratory depression caused by opioid overdose, without prescription. Good Samaritan laws were passed to facilitate bystander administration of naloxone to rescue opioid-overdosed victims and distribution of naloxone nasal sprays by public health authorities in some jurisdictions (4).

In the USA, naloxone injection has been commercially available for more than 40 years. It has been observed that for quick administration of this opioid antidote, for saving lives and reducing hypoxia due to opioid overdose, first responders and medically untrained personnel have been administering naloxone *via* intranasal (IN) instead of parenteral route (5). The off-label use by employing improvised

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atomizers has substantially increased the accessibility to this opioid antidote (4,6,7). So far one naloxone IN product (Narcan® nasal spray) has obtained the FDA approval, while at least two other applications have received complete response letters (CRL) from the agency (8,9). One of the products that received a CRL was reported to exhibit insufficient early-stage drug uptake, suggesting that optimal IN absorption at an early time point could be challenging in developing IN formulations of naloxone (8,10).

To ensure a sufficient uptake of naloxone through IN route, a more concentrated naloxone solution may be needed to enhance drug absorption and overcome the volume limitation of IN route (4,11). In addition, IN formulations of naloxone usually have more additives compared with parenteral formulations, which could potentially enhance the nasal absorption of naloxone. According to the package label of Narcan® nasal spray and the formulation example described in its corresponding patent (owned by Adapt Pharma Ltd., Table I), ethylenediaminetetraacetic acid (EDTA) and benzalkonium chloride (BKC) are employed in the formulation as a stabilizer and preservative, respectively (13–15). Both of these additives are known to enhance the drug permeation across epithelia and thus could function as permeation enhancers (16). Interestingly, another patented IN formulation of naloxone reported in the literature (owned by AntiOp Inc., Table I) also contains EDTA but uses benzyl alcohol (BA) instead of BKC as a preservative due to a stability issue (17). The latter patented formulation reported substantially lower relative bioavailability compared with intramuscular (IM) naloxone injection, implying that the composition of IN formulations may play a critical role in determining the rate and extent of nasal absorption of naloxone (4,12).

While there may be many naloxone IN formulations under development, there is little scientific literature available on the effect of formulation variables including preservatives and stabilizers on the absorption of naloxone from these IN formulations (18–20). The objective of the present study is to evaluate the effects of various formulation variables on the permeability of naloxone from IN formulations employing an *in vitro* nasal permeation model, EpiAirway™ tissue-mounted Ussing chamber (21,22). EpiAirway™ is a mucociliary tissue model consisting of normal, human-derived upper respiratory tract epithelial cells. This primary cell culture model exhibits relevant human tissue structure and cellular morphology and thus has been extensively used for *in vitro* testing of nasal bioavailability (23,24). In addition, since some of the formulation additives mentioned above were reported to affect the stability of naloxone (17), stability studies were conducted per ICH Q1A guidance to evaluate the impact of formulation on the

stability of naloxone. The methodology developed and knowledge gained from this study could be helpful in the selection of suitable ingredients for optimal permeation and early evaluation of naloxone IN formulations.

## MATERIALS AND METHODS

### Materials

Naloxone HCl USP was purchased from RIA International LLC (East Hanover, NJ). The reference standard of naloxone was purchased from the United States Pharmacopeia (Lot No. R007WO, USP, Rockville, MD). The reference standards of noroxymorphone (Lot No. FE10141502), naloxone-N-oxide (Lot No. FE1203150), and 2,2-bisnaloxone (Lot No. NQS1405) were purchased from Cerilliant Corp (Round Rock, TX) and Noramco Inc. (Wilmington, DE). Ethylenediaminetetraacetic acid (EDTA) (USP grade), benzyl alcohol (BA) (reagent grade), benzalkonium chloride (BKC) (NF grade), and sodium chloride (USP grade) were purchased from Spectrum Chemical MFG Corp (New Brunswick, NJ). Citric acid (reagent grade) was purchased from Ricca Chemical Company (Arlington, TX); Krebs-Ringer bicarbonate buffer was purchased from Sigma-Aldrich (St. Louis, MO). Other reagents and solvents were purchased from Fisher Scientific (Norcross, GA). All materials were of analytical grade unless otherwise specified.

### Preparation of Formulations for Nasal Permeability and Stability Studies

A full factorial design of experiment (DoE) was used to investigate the effect of various formulation variables on drug nasal permeation. The DoE included one continuous factor (drug concentration) and two nominal factors (stabilizers and preservatives) which resulted in eighteen naloxone IN formulations. The composition of each formulation is described in Table II. Formulation variables for this study were selected based on the published literature on naloxone IN formulations (Table I). These factors included concentration of naloxone in the solution, pH, type of preservative (BKC or BA), and EDTA as stabilizer (14,15,17). Based on the results of a preliminary study, a concentration of 0.01% w/v of BKC was found to significantly affect the integrity of EpiAirway™ tissue in Ussing chambers (Fig. 1). Therefore, a lower concentration of 0.003% w/v was used in the DoE for permeability experiments while a concentration of 0.01% w/v of BKC was used for stability studies. In addition, because

**Table I.** Formulation Examples of IN Naloxone Described in the Literature (12)

US patent number	US 9,211,253 and US 9,775,838 (14,15)	US 9,192,570 (17)
Assignee	Adapt Pharma Ltd.	AntiOp, Inc.
Concentration of naloxone	20 or 40 mg/mL	10 mg/mL
Stabilizing agent	EDTA 0.2% w/v	EDTA 0.372% w/v
Preservative	BKC 0.01% w/v	BA 0.5% w/v
Buffering agent	–	Citric acid 0.48% w/v
Osmolality agent	Sodium chloride 0.74% w/v	Sodium chloride (q.s.)
Solution pH	4.5	4.25

**Table II.** Composition of Naloxone IN Formulations (DoE)

Formulation no.	Naloxone HCl		EDTA		BA		BKC*	
	mg/mL		mg/mL	% w/v	mg/mL	% w/v	mg/mL	% w/v
F-1	4		3.5	0.35	–	–	–	–
F-2	4		–	–	–	–	–	–
F-3	4		3.5	0.35	5.0	0.5	–	–
F-4	4		–	–	5.0	0.5	–	–
F-5	4		3.5	0.35	–	–	0.03	0.003
F-6	4		–	–	–	–	0.03	0.003
F-7	22		3.5	0.35	–	–	–	–
F-8	22		–	–	–	–	–	–
F-9	22		3.5	0.35	5.0	0.5	–	–
F-10	22		–	–	5.0	0.5	–	–
F-11	22		3.5	0.35	–	–	0.03	0.003
F-12	22		–	–	–	–	0.03	0.003
F-13	40		3.5	0.35	–	–	–	–
F-14	40		–	–	–	–	–	–
F-15	40		3.5	0.35	5.0	0.5	–	–
F-16	40		–	–	5.0	0.5	–	–
F-17	40		3.5	0.35	–	–	0.03	0.003
F-18	40		–	–	–	–	0.03	0.003

These ingredients were dissolved in Krebs-Ringer buffer (pH 5.0) for the permeability study. The formulations were prepared in purified water for the stability study

\*A concentration of 0.01% w/v of BCK was used for the stability study instead of 0.003% w/v

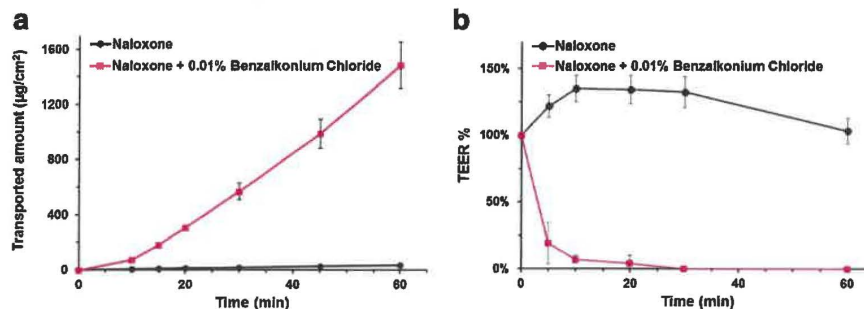
naloxone does not completely dissolve in Krebs-Ringer buffer (pH 7.4) at the concentrations of 22 mg/mL and 40 mg/mL, the formulations for the permeability study were prepared using Krebs-Ringer buffer (pH 5.0) without adjusting the final pH. The lower solution pH improves the solubility of naloxone, while it does not affect the transepithelial electrical resistance (TEER) values of EpiAirway™ tissue, significantly. The Krebs-Ringer buffer was used to provide glucose and salts for the optimal function of EpiAirway™ tissue. For the stability study, the pH of the solutions was adjusted to 4.5 using 1 N sodium hydroxide. Stability formulations were prepared in an isolation glovebox filled with nitrogen.

#### Nasal Permeability Study Employing Ussing Chambers and EpiAirway™ Tissues

Ussing chambers (Physiologic Instruments, Inc., San Diego, CA) mounted with human upper airway epithelia

inserts (EpiAirway™ AIR-100, MatTek, Inc., Ashland, MA) were employed for studying the *in vitro* nasal permeability of naloxone formulations. The TEER of individual tissue inserts was measured throughout the experiment to assess the integrity and viability of each tissue insert. The readings were first set to zero in blank Krebs-Ringer buffer without mounted EpiAirway™ tissues to compensate for the solution electrical resistance, and EpiAirway™ tissue inserts with TEER greater than 300  $\Omega \cdot \text{cm}^2$  TEER were used in the permeability study.

A total of 5 mL of naloxone test formulation was added to the donor side of each Ussing chamber (apical side of the epithelium), and 5 mL of Krebs-Ringer buffer (pH 7.4) was added to the receiver side (basolateral side of the epithelium) of the chambers. The solutions on both sides of Ussing chambers were treated with carbogen (95% oxygen and 5% carbon dioxide) and maintained at a temperature of 37°C. Samples of 1 mL were collected at 10, 15, 20, 30, 45, and



**Fig. 1.** Effect of concentrated benzalkonium chloride (BKC) on nasal permeation of naloxone. **a** Naloxone transport in the presence or absence of BKC. **b** TEER of EpiAirway™ tissues in the presence or absence of BKC ( $n = 4$ )

60 min time points from the receiver side of the chambers, and the lost fluid volume was immediately replaced by fresh Krebs-Ringer buffer. The samples were analyzed for naloxone content using a Waters ACQUITY H-class UPLC system. The apparent permeability ( $P_{app}$ ) of naloxone across the EpiAirway™ tissues was calculated using the following equation (25).

$$P_{app} = V_r \times \frac{dC}{dt} \times \frac{1}{AC_0} \quad (1)$$

Whereas  $V_r$  is the volume of the solution in the receiver chamber,  $dC/dt$  is the slope of the cumulative concentration of naloxone in the receiver chamber at the steady state (10 to 45 min),  $A$  is the surface area of the insert (1.2 cm<sup>2</sup>), and  $C_0$  is the initial concentration of naloxone in the donor chamber.

To evaluate the effects of pH on the permeability of naloxone, the naloxone solutions (4 mg/mL) were prepared in Krebs-Ringer buffer with final pH adjusted to 4.0, 4.5, 5.0, 5.5, and 6.0. The permeability of above naloxone solutions was measured using the method described above.

#### Evaluation of the Buffering Ability of In-House Prepared Patented Naloxone IN Formulations

For assessing the buffering ability, the formulation examples described in the patents were prepared along with a buffer-free naloxone aqueous solution in-house. Briefly, in-house formulation A was prepared to represent the formulation example described in Adapt's patent, which contains naloxone HCl, EDTA, and BKC (Table I) (14,15). The pH of the solution was adjusted to 4.5 using 1 N sodium hydroxide. In-house formulation B was prepared to represent the formulation example described in AntiOp's patent, which contains naloxone HCl, EDTA, BA, and citric acid (Table I) (17). The pH of the solution was adjusted to 4.25 using 1 N sodium hydroxide. The buffer-free naloxone solution (0.4 mg/mL) was prepared in purified water, and the pH was adjusted to 4.0 using 1 N hydrochloric acid, representing naloxone injections used with the improvised IN device (26,27). To determine the buffering ability, 15 mL of each naloxone IN formulation was titrated with 0.1 N sodium hydroxide to raise the pH to 6.0. The buffering ability is equivalent to the amount (nmol) of sodium hydroxide required to raise the pH of 100 µL of IN solution to pH 6.0.

#### Stability Studies on Naloxone IN Formulations

The stability of all formulations listed in Table II was evaluated. The stability samples were prepared by filling 1 mL of the formulation solution in a 2-mL USP type I amber vial under nitrogen purge and sealed with PTFE faced 14B rubber lined caps (Wheaton, Millville NJ). The samples were placed in upright position with the cap down in stability chambers (ES2000 Series, Bahnsen ES, Clemmons, NC) under accelerated (40°C/75% RH), intermediate (30°C/75% RH), and long-term (25°C/60% RH) conditions. The samples were analyzed at 0, 3, 6, and 12 months using a chromatographic method described below. In addition, the stability of naloxone solution with pH adjusted to 4.0 and 6.0 was also

evaluated. These naloxone solutions were prepared by dissolving naloxone (10 mg/mL) in purified water with or without EDTA (0.35% w/v). The pH was adjusted by 1 N sodium hydroxide or 1 N hydrochloric acid. The formulations were filled in 2-mL vials as described earlier and placed on stability at 60°C for 7 days. The samples were analyzed using a chromatographic method.

#### Analytical Method

A stability-indicating UPLC method was developed and validated for analyzing stability samples of naloxone IN formulations and samples from *in vitro* permeation studies. The method is also capable of separating and quantifying the two naloxone-related compounds (noroxymorphone and 2,2-bisnaloxone listed in the USP monograph of naloxone HCl) and a potential degradant (naloxone-N-oxide) in nasal spray formulations. The method employed a Waters ACQUITY H-class UPLC system with photodiode array detector (PDA). The output signal was processed using Waters Empower 3 software. An ACQUITY UPLC BEH C18 2.1 × 100 mm column with 1.7-µm particle size and with a 2.1 × 5 mm pre-column containing the same packing materials was used. The separation was achieved using a gradient method. Solvent A is an aqueous solution containing 1.4 g Sodium 1-octanesulfonate, 1.0 g sodium chloride, and 1.0 mL phosphoric acid per liter. Solvent B is a methanol/acetonitrile (4:1) mixture. The flow rate of the mobile phase was 0.5 mL/min. The gradient program (min/%B) was set as 0.50/25%, 4.0/50%, 6.0/50%, 6.05/25%, and 10.00/25%. The injection volume was 2.0 µL. The column temperature was set at 50°C and the PDA detection was at 229 nm. The method was validated per USP <1225> and deemed suitable for intended use per the results in Table III. The short run time of this method, 10 min, helps in high-throughput analysis of large sets of samples during *in vitro* permeation and stability studies.

#### Statistical Analysis

The permeation data obtained in this study was analyzed using JMP software (ver. 13) to evaluate the effect of formulation variables on the permeability ( $P_{app}$ ) and % change in TEER. The formulation variables (independent variables) included naloxone concentration, EDTA, and the type of preservative (BA, BCK, or none). The response factors were the  $P_{app}$  of naloxone from the formulations and the % change in TEER of the tissues. Data was fitted in a three-way full factorial linear model using least squares fit. Analysis of variance (ANOVA) was utilized to determine the significance of the model and the effect of each variable.

## RESULTS AND DISCUSSION

#### Effect of Formulation Variables on Nasal Permeation of Naloxone

The results in Table IV and Fig. 2a describe the transport rate and  $P_{app}$  of naloxone from IN formulations. Figure 2b describes the % change in TEER of tissues when exposed to various IN formulations for 30 min.  $P_{app}$  values of

**Table III.** Validation of the Stability-Indicating UPLC Method for the Analysis of Naloxone

Parameter	Naloxone (for assay)	Naloxone (for related substances)	Noroxymorphone	Naloxone-N-oxide	2,2-Bisnaloxone
LOQ ( $\mu\text{g/mL}$ )	–	0.40	0.25	0.30	0.20
LOD ( $\mu\text{g/mL}$ )	–	0.15	0.09	0.10	0.07
Regression equation <sup>a</sup>					
Slope	3609.9	3727.4	4806.6	3974.2	7085.2
Intercept	13,194.02	105.00	– 87.70	– 4.27	– 208.48
Y-intercept <sup>b</sup>	1.88%	< 0.01%	< 0.01%	< 0.01%	< 0.01
$r^2$ value	0.9992	0.9998	0.9996	0.9999	0.9997
Precision (% RSD) <sup>c</sup>	1.04%	3.13%	3.86%	3.38%	2.34%
Accuracy (% recovery) <sup>c</sup>	99.20%	101.83%	109.00%	104.56%	105.33%

<sup>a</sup>Linearity range is 50–600  $\mu\text{g/mL}$  for assay and LOQ to 6.4  $\mu\text{g/mL}$  for related substances

<sup>b</sup>Compared with 100% level (200  $\mu\text{g/mL}$ )

<sup>c</sup>Six determinations using 100% level sample (200  $\mu\text{g/mL}$ ) for assay and LOQ for related substances

formulations that do not contain any excipient (formulations F2, F8, and F14) range from  $1.17 \times 10^{-6}$  to  $2.41 \times 10^{-6}$  cm/s. These  $P_{\text{app}}$  values for naloxone are in line with those reported in the literature (23). The data in Table IV and Fig. 2 were fitted to linear regression models using a least squares method. The  $r^2$  between experimental and model predicted values were found above 0.9 for both models ( $P_{\text{app}}$  and % change in TEER). The ANOVA on the observed means of the responses shows that the formulation factors significantly affect the  $P_{\text{app}}$  of naloxone and the % change in TEER of tissues ( $p < 0.05$ ). Figure 3 describes the main effect and significance of each formulation factor.

The results in Table IV and Fig. 3a show that an increase in naloxone concentration reduced the  $P_{\text{app}}$ , and the results in Fig. 3b show that an increase in the concentration of naloxone did not significantly affect the % change in TEER of tissues. Although the  $P_{\text{app}}$  of naloxone from more concentrated naloxone solutions were lower, the greater concentration gradient still resulted in significantly higher drug transport

rates across the tissue inserts. For instance, the  $P_{\text{app}}$  of naloxone formulation containing 40 mg/mL of naloxone is around 50% lower than that of formulation containing 4 mg/mL of naloxone (Table IV), but the transport rate of naloxone from formulation containing 40 mg/mL is nearly 5 times higher. These results confirm that a higher concentration of naloxone solution would increase the amount of naloxone absorbed (4,11). This approach may be useful in formulating IN solutions where the drug has limited residence time for absorption in the nasal cavity.

The results in Figs. 2a and 3a show that addition of BKC at a concentration of 0.003% w/v and BA at 0.5% w/v both resulted in increased  $P_{\text{app}}$  of naloxone across the EpiAirway™ tissue. As shown in Fig. 3b, BKC and BA produced significant reduction in TEER of tissues, suggesting compromised tissue integrity and a consequential increase in naloxone permeation. Among the two preservatives, BKC is clearly a more effective permeation enhancer since it produced a comparable increase in  $P_{\text{app}}$  of naloxone at a

**Table IV.** The Naloxone Transport Rate and  $P_{\text{app}}$  Across EpiAirway™ Tissues

Formulation no.	Naloxone conc. (mg/ml)	Transport rate (ng·cm <sup>2</sup> ·s)	$P_{\text{app}}$ ( $\times 10^{-6}$ cm/s)
F-1	4	1.70 ± 0.13	0.42 ± 0.03
F-2	4	9.63 ± 0.66	2.41 ± 0.16
F-3	4	3.07 ± 0.49	0.77 ± 0.12
F-4	4	11.16 ± 0.11	2.79 ± 0.03
F-5	4	5.28 ± 1.69	1.32 ± 0.42
F-6	4	14.44 ± 0.90	3.61 ± 0.23
F-7	22	8.51 ± 0.85	0.39 ± 0.04
F-8	22	33.71 ± 5.39	1.53 ± 0.25
F-9	22	26.28 ± 1.84	1.19 ± 0.08
F-10	22	47.18 ± 1.80	2.14 ± 0.08
F-11	22	20.44 ± 4.01	0.93 ± 0.18
F-12	22	46.72 ± 3.98	2.12 ± 0.18
F-13	40	10.84 ± 3.07	0.27 ± 0.08
F-14	40	46.65 ± 2.45	1.17 ± 0.06
F-15	40	76.28 ± 5.12	1.91 ± 0.13
F-16	40	73.70 ± 5.38	1.84 ± 0.13
F-17	40	48.43 ± 21.01	1.21 ± 0.53
F-18	40	59.01 ± 4.55	1.48 ± 0.11

The exposure area of EpiAirway™ tissue is 1.2 cm<sup>2</sup>

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