

Effects of physicochemical properties and other factors on systemic nasal drug delivery

C.R. Behl*, H.K. Pimplaskar, A.P. Sileno, J. deMeireles, V.D. Romeo

Nastech Pharmaceutical Company, Inc., 45 Davids Drive, Hauppauge, NY 11788, USA

Received 5 April 1996; accepted 4 March 1997

Keywords: Nasal delivery; Physical chemical properties; Absorption factors; Intranasal drug delivery; Nasal solutions; Nasal gels; Nasal powders

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*Corresponding author. Tel.: +1 516 2730101; fax: +1 516 2730252.

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1. Introduction

The most desirable and convenient method of drug administration is the oral route and the most favored dosage forms include tablets, capsules and solutions because of their ease of manufacture and administration. Failure to systemically deliver select compounds through the oral route led to research on alternate routes of drug delivery. Lack of adequate absorption through the gastrointestinal tract was the single most predominant reason for such efforts. Researchers resorted to the parenteral route as an easy solution to the problem. Absorption through the intravenous route is not an issue and other parenteral routes, e.g. intramuscular and subcutaneous, provide satisfactory delivery of most drugs. For the past few decades, the transdermal route has been explored for a number of drugs. Much has been learned about this route, but its use is limited due to understandably low permeability of the skin to many drugs.

Recently, focus has been on the nasal mucosa as an alternate route to achieve faster and higher drug absorption. Knowledge of the nasal mucosa's high permeability and use of the nasal route for drug administration can be traced to ancient times. Realization of the nasal mucosa as a therapeutically viable alternate route came in the last two decades. The nasal route was considered more seriously for systemic drug delivery with the early work of Hussain et al. [1] where the nasal absorption of propranolol was found to be comparable to the intravenous route in the Rat Perfusion Model. Convenient and practical experimental models were later developed to further

study nasal absorption of drugs. This area of drug delivery received additional attention with a timely seminar organized by Dr. Y.E. Chien in 1984 [2]. The seminar entitled 'Intranasal Drug Administration for Systemic Medications' was instrumental in placing nasally administered medications at the forefront of drug delivery. Two books, one written by Chien [3] in 1985 and another by Chien et al. [4] in 1989 provided a comprehensive review of the subject matter and a direction for other researchers to follow.

The development of nasal drug products is still faced with many challenges. A better understanding of how the properties of drug molecules, formulation matrices, the nasal mucosa itself and the drug delivery systems affect drug absorption through the nasal route, is invaluable. The whole process of determining the feasibility of a drug candidate for nasal delivery begins with appropriate and adequate preformulation studies leading to the development of potential nasal products which are stable, safe and effective. This chapter will discuss some pertinent and important issues to be considered in this regard.

2. List of nasal products

2.1. Prescription nasal drug products

Table 1 contains a list of marketed nasal prescription drug products. As can be seen, a total of 14 brand products covering 12 drugs are on the market, of which half are for seasonal or perennial allergic rhinitis. The latest product, Miacalcin, was intro-

Table 1
List of prescription nasal products currently on the market

No.	Product	Drug	Indication	Manufacturer
1	Beconase® AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal and perennial allergic rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc.
2	Vancenase® AQ Nasal Spray	Beclomethasone dipropionate monohydrate	Symptomatic treatment of seasonal or perennial allergic rhinitis	Schering Plough Corp.
3	Rhinocort® Nasal Inhaler	Budesonide	Management of symptoms of seasonal and perennial allergic rhinitis and non-allergic perennial rhinitis	Astra USA, Inc.
4	Stadol NS® Nasal Spray	Butorphanol tartrate	Management of pain including migraine headache pain	Bristol Myers Squibb
5	Miacalcin® Nasal Spray	Calcitonin — salmon	Post-menopausal osteoporosis	Sandoz Pharmaceutical Corp.
6	Nasalcrom® Nasal Solution	Cromolyn sodium	Symptomatic prevention and treatment of seasonal or perennial rhinitis	Fisons Corp. Prescription Products
7	DDAVP® Nasal Spray	Desmopressin acetate	Prevention and control of polydipsia, polyurea, and dehydration in patients with diabetes insipidus	Rhone Poulenc Rorer
8	Stimate® Nasal Spray	Desmopressin acetate	Hemophilia A, von Willebrand's disease (type 1)	Rhone Poulenc Rorer
9	Decadron® Phosphate Turbinaire®	Dexamethasone	Treatment of inflammatory nasal conditions or nasal polyps	Merck and Co., Inc.
10	Nasalide® Nasal Solution	Flunisolide	Symptomatic treatment of seasonal or perennial rhinitis	Roche Laboratories
11	Flonase® Nasal Spray	Fluticasone propionate	Management of seasonal and perennial rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc.
12	Synarel® Nasal Solution	Nafarelin acetate	Central precocious puberty; endometriosis	Roche Laboratories
13	Syntocinon® Nasal Spray	Oxytocin	Promote milk ejection in breast feeding mothers	Sandoz Pharmaceutical Corp.
14	Nasacort® Nasal Inhaler	Triamcinolone acetonide	Treatment of seasonal and perennial allergic rhinitis	Rhone Poulenc Rorer

Sources: Physicians' Desk Reference for Nonprescription Drugs, 1994, 15th ed., published by Medical Data Production Company, Montvale, NJ, and Handbook of Nonprescription Drugs, 1993, 10th ed., published by The American Pharmaceutical Association, Washington, DC.

duced in 1995. Although the number of marketed nasal products for systemic effect is small, it is expanding. As advances are made in formulation science and technology, more drugs will become viable candidates for nasal delivery. From a market standpoint, current prescription nasal drug products approach sales in excess of one billion dollars per year. This amount is expected to increase dramatically over the next several years.

2.2. Over the counter nasal drug products

Table 2 contains a list of marketed non-prescription nasal drug products. There are currently more than 30 such over-the-counter (OTC) nasal products for the symptomatic treatment of a variety of con-

ditions. Several of these products were introduced in recent years. This number may increase as some nasal drug products are switched from prescription to OTC status.

2.3. Non-drug nasal products

A total of 12 non-drug nasal products are currently marketed which do not require FDA approval (Table 3). These products are sodium chloride solutions.

2.4. Drugs currently under investigation

A review of the literature [5–15] [16–25] [26–36] [37–46] [47–52] indicates that at least 45 drugs have

Table 2
List of over the counter (OTC) nasal drug products currently on the market

No.	Product	Drug	Indication	Manufacturer
1	Pretz-D® Nasal Drops	Ephedrine	Nasal decongestant	Parnell
2	Adrenalin® Chloride	Epinephrine hydrochloride	Nasal decongestant	Parke Davis
3	Privine® Nasal Spray, Nasal Solution and Nasal Drops	Naphazoline hydrochloride	Prompt and prolonged relief of nasal congestion due to common colds, sinusitis, hay fever etc.	Ciba Consumer Pharmaceuticals
4	Afrin® Cherry Scented Nasal Spray (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
5	Afrin® Nasal Spray Pump (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
6	Afrin® Extra Moisturizing Nasal Spray (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
7	Afrin® Menthol Nasal Spray (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
8	Afrin® Nose Drops (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
9	Afrin® Children Strength Nose Drops (0.025%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
10	Cheracol® Nasal Spray Pump Cherry Scented	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Roberts Pharmaceutical Corporation
11	Duration® 12 hour Nasal Spray (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare
12	Duration® 12 hour Nasal Spray Pump	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Schering Plough Healthcare Products
13	4-Way® Long Lasting Nasal Spray	Oxymetazoline hydrochloride	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Bristol Myers Squibb
14	NTZ® Long Acting Nasal Spray and Drops (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Sterling Health
15	Neo-Synephrine® Maximum Strength 12 hour Nasal Spray and Nasal Spray Pump (0.05%)	Oxymetazoline hydrochloride	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Sterling Health
16	Nostrill® Long Acting Nasal Decongestant	Oxymetazoline hydrochloride	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Ciba Consumer Pharmaceuticals
17	Vicks® Sinex® Long Acting Decongestant Nasal Spray and Ultra Fine Mist	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Proctor and Gamble
18	Allerest®	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Ciba Consumer Pharmaceuticals

Table 2. Continued

No.	Product	Drug	Indication	Manufacturer
19	Benzedrex 12 hour Nasal Spray	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Menley and James
20	Dristan® 12 hour Nasal Spray	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Whitehall Labs.
21	Sinarest® Nasal Spray	Oxymetazoline hydrochloride	Temporary relief of nasal congestion associated with colds, hay fever and sinusitis	Ciba Consumer Pharmaceuticals
22	Neo-Synephrine® Nasal Sprays, Pediatric, Mild, Regular and Extra Strength	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Sterling Health
23	Nostril® Nasal Decongestant, Mild and Regular Strength	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Ciba Consumer Pharmaceuticals
24	Vicks® Sinex® Regular Decongestant Nasal Spray and Ultra Fine Mist	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to colds, hay fever, upper respiratory allergies or sinusitis	Proctor and Gamble
25	Alconefrin® Nasal Drops and Spray	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to colds, hay fever, upper respiratory allergies or sinusitis	Polymedica
26	Benzedrex® Nasal Spray	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to colds, hay fever, upper respiratory allergies or sinusitis	Menley and James
27	Dristan® Nasal Spray	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to colds, hay fever, upper respiratory allergies or sinusitis	Whitehall Labs, Inc.
28	Dristan® Menthol	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to colds, hay fever, upper respiratory allergies or sinusitis	Whitehall Labs, Inc.
29	Rhinall® Nasal Spray and drops	Phenylephrine hydrochloride	Temporary relief of nasal congestion due to colds, fever, upper respiratory allergies or sinusitis	R P Scherer
30	4-Way® Fast Acting Nasal Spray (regular/mentholated)	Phenylephrine hydrochloride, naphazoline hydrochloride, pyrilamine maleate	Temporary relief of nasal congestion due to the common cold, sinusitis, hay fever or other upper respiratory allergies	Bristol Myers Squibb
31	Benzedrex® Nasal Inhaler	Propyl hexedrine	Temporary relief of nasal congestion due to colds, hay fever, upper respiratory allergies or sinusitis	Menley and James
32	Otrivin® Nasal Spray and Drops	Xylometazoline hydrochloride	Nasal decongestant	Ciba Consumer Pharmaceuticals
33	Otrivin® Pediatric Nasal Drops	Xylometazoline hydrochloride	Nasal decongestant	Ciba Consumer Pharmaceuticals

Sources: Physicians' Desk Reference for Nonprescription Drugs, 1994, 15th ed., published by Medical Data Production Co., Montvale, NJ and Handbook of Nonprescription Drugs, 1993, 10th ed., published by The American Pharmaceutical Association, Washington, DC.

been or are being evaluated in humans for nasal delivery (Table 4). The list is not comprehensive because of ongoing investigational studies that are not always reported. Although most of these drugs

may not reach the market place, it demonstrates the level of interest in the area of nasal drug delivery. A major focus of present research efforts is on the nasal delivery of injectable only peptide/protein drugs.

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