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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Compounding Nasal Preparations

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PHYSIOLOGY AND FUNCTION

The nose is a portion of the respiratory tract where air enters and leaves the respiratory system. It consists of bone and cartilage and is covered with skin. It contains hairs and mucosa (ciliated epithelium with goblet cells that produce mucus) which help to block the entry of dust and particulate matter. As the air passes through the nasal cavities, it is warmed by the blood supply immediately below the epithelium and humidified by the moisture content of the mucous. Another function of the nose is the sense of smell; olfactory receptors are located in the nasal mucosa.

A number of materials from various sources travel from the nose to the gastrointestinal tract. The mucous aids in entrapping dust, particulates, bacteria, etc.; these entrapped materials are continuously swept by the cilia toward the pharynx where they are eventually swallowed; any bacteria present is destroyed by the hydrochloric acid in the gastric juices. There are four paranasal sinuses that drain into the nasal cavities and, ultimately, into the gastrointestinal tract. Also draining into the nasal cavities are the lacrimal fluids that enter the nose by way of the nasolacrimal duct. Consequently, nasally administered drug products can result in systemic effects by either (1) local absorption through the nasal epithelium, or (2) as a result of being swallowed and absorbed via the gastrointestinal tract.

NASAL ADMINISTRATION

Nasal drug administration has been routinely used for administration of drugs for the upper respiratory tract, especially adrenergic agents, and is now also being used as a viable alternative for the delivery of many systemic therapeutic agents. A number of dosage forms are common and include solutions, suspensions and gels. Nasal solutions are solutions prepared for nasal administration either as drops or sprays. Nasal suspensions are liquid preparations containing insoluble materials for nasal administration, primarily as drops.

Nasal gels are semisolid preparations prepared for nasal application and can be for either local or systemic use, in a water soluble or water miscible vehicle. Nasal ointments are generally prepared from either water miscible/soluble or oleaginous bases.

APPLICATIONS/USES

The advantages of nasal delivery include (1) lower doses, (2) rapid local therapeutic effect, (3) rapid systemic therapeutic blood levels, (4) rapid onset of pharmacological activity, and (5) relatively few side effects. In addition to the nasal decongestants, saline and other routine locally acting drugs, nasal administration is being investigated for the delivery of insulin, progesterone, metoclopramide, propranolol (for migraine headaches), dihydroergotamine, desmopressin, atropine, vitamin B_{12}, antihistamines, anti-obesity agents, narcotic analgesics and a host of other agents.

An example drug that shows effectiveness upon administration as a nasal gel, as compared to an oral tablet, is vitamin B_{12}, where clinical studies showed a six fold increase in maximum blood levels, a doubling of speed in entering the bloodstream, and a 2.5 fold increase in measurable vitamin B_{12} in the blood 48 hours after administration.[1] Similar results have been reported in other studies.[2-5]

Numerous drug substances can be prepared as nasal solutions or suspensions to be administered either as drops (solutions or suspensions) or sprays (solutions); other dosage forms may include nasal

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The risk of patient-to-patient contamination is very high with nasally administered products, patients should be advised that a nasal product is for ONE PATIENT ONLY.

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gels, jellies or ointments. Some drugs are sufficiently volatile they can be carried into the nose through an inhaler.

COMPOSITION(S)

In addition to the active drugs, nasal preparations contain a number of excipients, including vehicles, buffers, preservatives, tonicity adjusting agents, gelling agents and possibly antioxidants. Important in the formulation process is the use of ingredients that are nonirritating and compatible with the nose as discussed within each category. In general, the same excipients used in ophthalmic formulations can also be used in nasal formulations.

PREPARATION METHODS/TECHNIQUES

Solutions:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Add sufficient Sterile Water for Injection to volume and mix well.
4. Determine the pH, clarity and other quality control factors from a sample of the solution.
5. Filter through a sterile 0.2 µ filter into a sterile nasal container.
6. Package and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Suspensions:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve/mix the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Add sufficient Sterile Water for Injection to volume and mix well.
4. Determine the pH, and other quality control factors from a sample of the suspension.
5. Package in a suitable container for autoclaving.
6. Autoclave, cool and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Suspensions (alternate method):

1. Accurately weigh/measure each of the ingredients.
2. Sterilize each of the ingredients by a suitable method.
3. Dissolve/mix the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
4. Add sufficient Sterile Water for Injection to volume and mix well.
5. Determine the pH, and other quality control factors from a sample of the suspension.
6. Package and label.
7. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Ointments:

1. Accurately weigh/measure each of the ingredients.
2. Sterilize each of the ingredients by a suitable method.
3. Mix each of the ingredients with the sterile vehicle.
4. Determine the quality control factors from a sample of the product.
5. Package and label.
6. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

Gels:

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the ingredients in about 3/4 of the quantity of Sterile Water for Injection and mix well.
3. Filter through a sterile 0.2 µ filter into a sterile container.
4. Add the gelling agent (previously sterilized) and mix well.

5. Add sufficient Sterile Water for Injection to volume/weight and mix well.
6. Determine the pH, clarity and other quality control factors from a sample of the gel.
7. Package and label. (Sterile 1 mL syringes preloaded with individual doses work well).
8. If a large number are to be prepared, select a random sample to be checked for sterility and to be assayed.

PHYSICOCHEMICAL UNIQUENESS OF COMMON INGREDIENTS

The attributes of a vehicle for a nasal solution include:
(1) pH generally in the range of 5.5-7.5,
(2) mild buffer capacity,
(3) isotonic,
(4) not modify the normal mucus viscosity,
(5) compatible with normal ciliary motion and ionic constituents of nasal secretions,
(6) compatible with active ingredient,
(7) stable,
(8) sterile,
(9) and preserved.

pH- Nasal preparations are ordinarily prepared at the pH of maximum stability for the drug(s) they contain; generally in the range of 4-8 is considered optimum. Sometimes it may be necessary to adjust outside this range.

Buffers-The buffers are included to minimize any change in pH during the storage life of the drug. Any changes in pH can affect the solubility and the stability of drugs, consequently, it is important to minimize fluctuations in pH. The buffer system should be designed sufficient to maintain the pH throughout the expected shelf-life of the product but with a low buffer capacity. Phosphate buffer systems are widely used and are generally compatible with most nasal medications.

Tonicity Adjustment-The preferred agents for adjusting the tonicity of nasal solutions include sodium chloride, boric acid and dextrose. Severely hypertonic solutions should be avoided. Nasal fluid is isotonic with 0.9% sodium chloride solution. A value of 300 mOsm/L is ideal with a range of 200-600 mOsm/L being acceptable. If a product is applied that is outside of the proper range, the nasal ciliary movement may slow or even stop. Tonicity values in the range of 0.6% to as high as 1.8% sodium chloride equivalency are generally acceptable. If the solution of the active drug is hypotonic, it may be necessary to add a substance to attain the proper tonicity range. Sodium chloride, boric acid and dextrose are commonly used.

Normal mucous viscosity-Most nasal preparations are aqueous based and generally will not significantly alter the viscosity of the mucous. A strongly hypertonic product, however, may result in a slight "drying" effect and thickening of the mucous. The opposite may occur for a strongly hypotonic product. This can have an adverse effect on the efficiency of the cilia in mucous and particulate removal.

Compatibility-Strict attention must be paid to the compatibility of all the various ingredients, including all the excipients, of the product to ensure a safe, effective and esthetic product.

Stability-Stability is largely influenced by pH, temperature, light, oxidation and other factors. In addition to proper formulation, proper packaging is essential. Occasionally, antioxidants may be required for selected active drug ingredients. The same antioxidants used in ophthalmic products can usually be used in nasal products.

Sterility-Nasal preparations should be sterile. Sterility is conveniently achieved through sterile filtration using a sterile membrane filter of 0.45 or 0.2 µ pore size and filtering into a sterile container. Other methods of sterilizing ingredients include dry heat, steam under pressure (autoclaving) and gas sterilization (ethylene oxide).

Preservation-Since most nasal preparations are prepared in multiple use containers, they must be preserved (unless individual doses are separately packaged). The selected preservative must be compatible with the active drug as well as all the other excipients in the product. Common preservatives that can be used for nasal products are shown in Table 1. Generally, the same preservatives used in ophthalmic formulations can be used in nasal formulations.

Specific Quality Control

Sterility checks, clarity (solutions), pH, volume/weight.

PACKAGING/STORAGE/LABELING

Most nasal preparations are packaged in glass dropper bottles or plastic spray bottles, usually containing 15 to 30 mL of product. Gels are packaged in either tubes or syringes for ease of administration.

Generally, nasal preparations should be stored at either room or refrigerated temperatures and should not be frozen.

STABILITY

Beyond-use dates for water-containing formulations are not later than 14 days, when stored at cold temperatures, for products prepared from ingredients in solid form. If nonaqueous liquids, the beyond-use recommendation is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier. For all others, the recommended beyond-use recommendation is the intended duration of therapy or 30 days, whichever is earlier. These beyond-use recommendations can be extended if there is supporting valid scientific stability information.

COUNSELING

The risk of patient-to-patient contamination is very high with nasally administered products, consequently, patients should be advised that a nasal product is for ONE PATIENT ONLY and should not be passed around.

Containers for dispensing include dropper bottles, spray bottles and syringes (for gels). For systemic therapeutic drugs, it may be necessary to calibrate a dropper or spray container to deliver a consistent and uniform dose. Therapeutic drugs, such as dihydroergotamine mesylate or morphine sulfate, among others, can be administered after the administration device is calibrated and the patient is taught to use it properly. For potent drugs, it may be advantageous to pre-load individual nebules or 1 cc syringes with each individual dose. After application or administration of the accurately measured dose, the container would be discarded.

It may be necessary to calculate the quantity of drug actually administered per drop or per spray of nasal product. This can be done as follows.

1. Calculation of medication administered per drop of product.
   Using the dropper that will be used by the patient, dropwise, drop the product into a cylindrical graduate until 2 mL of product has been measure, counting the number of drops required. Dividing this number by two, will give the number of drops per milliliter of product. From this information, the required number of drops that will deliver quantity of product can be calculated.

2. Calculation of medication administered per spray of product.

The calibration can be easily accomplished by weighing the container with the solution. keeping in mind the variables of pressure on the container sides, the time the pressure is applied, etc., hold the container in the usual upright position and deliver 10 sprays into a disposable plastic bag. Weigh the container again, subtract from the original weight and divide by 10. This would give an "approximate" volume delivered per squeeze, assuming a specific gravity of 1.0. Obviously it would be best to also have the patient do this to refine the quantity administered under actual use conditions. To accommodate for the differences in specific gravity, viscosity, etc., it may be beneficial to prepare a "blank" solution for practice containing all the ingredients except for the active drug.

EXAMPLE FORMULATIONS

Rx **General Nasal Solution Vehicle (pH 6.5 and isotonic)**

$NaH_2PO_4.H_2O$		0.65
$Na_2HPO_4.7H_2O$		0.54
NaCl		0.45
Benzalkonium chloride		0.05-0.01%
Distilled Water	qs ad	100 mL

Rx **Isotonic Sodium Chloride Solution**

Sodium Chloride		0.9 g
Benzalkonium Chloride		1:10,000
Sterile Water for Injection	qs	100 mL

Rx **Atropine sulfate 0.5% nasal solution**

Atropine sulfate		500 mg
Sodium chloride		835 mg
Sterile water for injection	qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the atropine sulfate and the sodium chloride in about 95 mL of water for injection.
4. Add sufficient water for injection to make 100 mL.
5. Filter through a 0.2 µ filter into a sterile container.
6. Package and label.

Rx **Desmopressin acetate nasal solution 0.033 mg/mL**

Desmopressin solution 0.1 mg/mL	2.5 mL
0.9% Sodium chloride solution	5 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Mix the two solutions together and mix well.
4. Filter through a 0.2 µ filter into a sterile container.
5. Package and label.

Rx **Saline Nasal Mist**

Sodium chloride		650 mg
Monobasic potassium phosphate		40 mg
Dibasic potassium phosphate		90 mg
Benzalkonium chloride		10 mg
Sterile water for injection	qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the ingredients in sufficient sterile water for injection to make 100 mL of solution.
4. Filter through a 0.2 µ filter into a sterile solution.
5. Package in a nasal spray bottle.

Rx **Xylometazoline hydrochloride nasal drops**

Xylometazoline hydrochloride		100 mg
Sodium chloride		850 mg
Benzalkonium chloride		10 mg
Sterile water for injection	qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve all the ingredients in sufficient sterile water for injection to make 100 mL.
4. Filter through a sterile 0.2 µ filter into a sterile container.
5. Package and label.

Rx **Progesterone nasal suspension**

Progesterone	20 mg
Dimethyl-β-cyclodextrin	62 mg
Sterile water for injection	1 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the dimethyl-β-cyclodextrin in 0.9 mL of sterile water for injection.
4. Add the progesterone and stir until dissolved.
5. Adjust the pH to 7.4 using either dilute hydrochloric acid or dilute sodium hydroxide solution.
6. Add sufficient sterile water for injection to make 1 mL.
7. Package and label.

Rx **Scopolamine hydrobromide 0.4 mg/0.1 mL nasal solution**

Scopolamine hydrobromide	400 mg
pH 5.0 buffer	5 mL
in 0.9% Sodium chloride solution qs	100 mL

1. Calculate the quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh or measure each ingredient.
3. Dissolve the scopolamine hydrobromide in about 50 mL of the 0.9% sodium chloride solution.
4. Add the pH 5.0 buffer and mix well.
5. Add sufficient 0.9% sodium chloride solution to volume and mix.
6. Filter through a 0.2µ sterile filter into a sterile container.
7. Package in a metering nasal spray container and label.

Table 1. Common preservatives used in nasal products.

Name	Usual Concentration (%)
Chlorobutanol	0.5
Benzalkonium Chloride	0.004-0.02
Benzethonium Chloride	0.004-0.02
Phenylmercuric Acetate	0.001-0.01
Phenylmercuric Nitrate	0.001-0.01
Thimerosal	0.01
Parahydroxybenzoates	0.1

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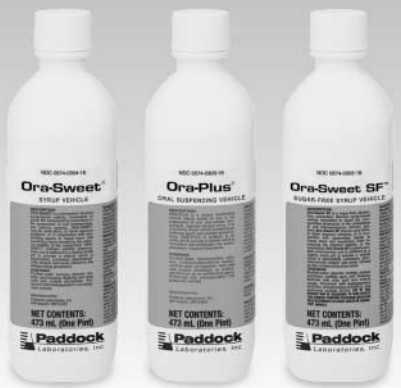

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Alprazolam	Domperidone	Metolazone	Sumatriptan Succinate
Amiodarone HCl	Enalapril Maleate	Metoprolol Tartrate	Tacrolimus
Aminophylline	Famotidine	Metronidazole	Terbinafine HCl
Atenolol	Flecainide Acetate	Mycophenolate Mofetil	Tetracycline HCl
Azathioprine	Flucytosine	Naratriptan HCl	Tiagabine
Baclofen	Gabapentin	Norfloxacin	Tramadol
Bethanechol Chloride	Ganciclovir	Ondansetron HCl	Ursodiol
Captopril	Granisetron HCl	Procainamide HCl	Valacyclovir HCl
Chloroquine Phos.	Hydralazine HCl	Propylthiouracil	Valganciclovir
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