Enhancing drug product portfolios for nasal aerosols and buccal spray delivery systems

A changing market environment and ways nasal aerosols and buccal sprays can provide opportunities

Geralit Williams
Aptar Pharma

The past few years have seen the leveling off of new molecular entities (NMEs) reaching the pharmaceutical market,[1-3] partly as a result of increasing drug development costs and higher regulatory standards for drug approval. Yet many opportunities still exist in this changing market for both innovator and generic pharmaceutical companies who are willing to seek new ways to innovate. One key approach is by finding novel ways of working with current drug assets.

The scientific and medical advantages of drug delivery using nasal aerosols and buccal sprays are well documented.[4] Local therapies for the mouth[5] or nose work well at the site of delivery. A good example is the use of antihistamines and corticosteroids in nasal sprays for the treatment of allergic rhinitis. The highly-vascularized, large mucosal surface of the nose and the mouth make them attractive targets for systemic drug delivery and a rapid onset of action is observed for low-molecular-weight drugs delivered to these sites. Another advantage to avoiding the oral route of delivery is that some drug's active compounds may be broken down in the gastrointestinal tract or the liver. Nasal (IN) and buccal drug delivery can offer rapid onset of action due to their pharmacokinetic profiles (Figure 1), which lie somewhere between intravenous (IV) and intramuscular (IM) delivery and are much more rapid than oral drug delivery.

Oral and sublingual sprays are easy to use with either third-party or self-administration, a feature attractive notably for geriatric and pediatric patients, and can enhance out-patient treatment and self-medication, thus reducing the burden on healthcare systems.

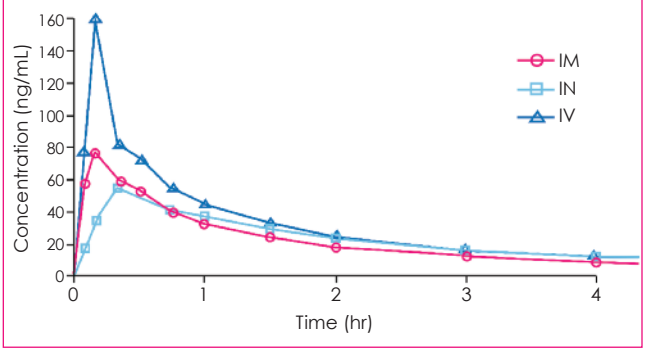
Repurposing an existing marketed product can bring added value to pharmaceutical companies by completing existing ranges of products and increasing market coverage. Due to the reduced development costs and shorter regulatory pathways, this can be done at a fraction of the cost of bringing an NME to market, now estimated to be approximately $1.8 billion.[6]

Examples of current drugs used intranasally or oromucosally

Currently, a number of drugs are successfully delivered to patients through the nasal tissues and via the buccal membranes. These include drugs for pain control such as lidocaine; for smoking cessation such as nicotine; nitroglycerine in a nasal spray for angina; drugs for epileptic seizures such

Figure 1

Concentration versus time following drug administration. Adapted with permission from Wermeling, D. P., Miller, J., Rudy, A. C. (2002) Systemic intranasal drug delivery: Concepts and applications. Drug Development & Delivery. 2 (1).



as benzodiazepines (diazepam); drugs for overdoses with opioids, such as naloxone; treatments for hypoglycemia such as glucagon; post-operative/chemotherapy emesis drugs such as ondansetron and metoclopramide; and the hormones testosterone, progesterone and estradiol.

Clear examples of drugs that have successfully made the leap to nasal or buccal drug delivery include the delivery of hormones, i.e., desmopressin for bedwetting; vitamins such as B12 for hypocobalaminemia; triptans (i.e., sumatriptan) for migraines; opioids such as nasal and buccal fentanyl; and non-narcotic analgesics ketorolac and THC (tetrahydrocannabinol) for pain management associated to multiple sclerosis therapy.

Opioids such as nasal and buccal fentanyl have been marketed for several years. Their advantages come from proven efficacy relative to other dosage forms and they compare very favorably with intravenous injections. As Table 1 shows, fentanyl reaches Tmax in approximately 6.0 minutes following intravenous injection and 12.8 minutes after intranasal administration. In comparison, fentanyl in lollipop format takes 15 minutes to administer plus an additional 15 minutes to provide effective pain relief.[8]

Table 1

Fentanyl intranasal versus intravenous dosing

Fentanyl[7]	Intranasal (IN)	Intravenous (IV)
Bioavailability	>89%	>98%
Tmax	~12.8 minutes	~6.0 minutes
AUC	Equivalent	Equivalent

The opioid morphine has also been well studied[9] with regard to nasal aerosol delivery for the treatment of breakthrough cancer pain. Morphine, like many opioids, is subject to low oral bioavailability due to extensive first pass metabolism. Human pharmacokinetic data for intranasal, oral and injection dosing of morphine is detailed in Figure 2. The data illustrates that similar onset of action (Tmax ~15 minutes) is achieved via intranasal delivery versus injections and is much faster than oral delivery (Tmax ~50 minutes). For pain management therapies of this type, providing rapid onset of action is critical.

Midazolam is used on a daily basis in hospitals to sedate and relax patients undergoing therapeutic, diagnostic or endoscopic treatment as well as to treat epileptic seizures. The traditional method of delivery, intravenous administration, is painful and stressful for patients and can be time consuming and costly. However, when midazolam is given intranasally, it is painless, non-invasive, works almost instantly and lasts for the same amount of time as the drug given intravenously. It can also be used outside of hospitals, for example, in dental clinics, doctors' surgeries and private clinics.

Several clinical studies report desirable pharmacokinetic and pharmacodynamic intranasal dosing of midazolam compared to other routes of administration, such as oral and rectal dosing. Intranasal midazolam exhibits 50-80% bioavailability and has a very rapid onset (e.g., 5 minutes) comparable to injection onset of 2-5 minutes.[10]

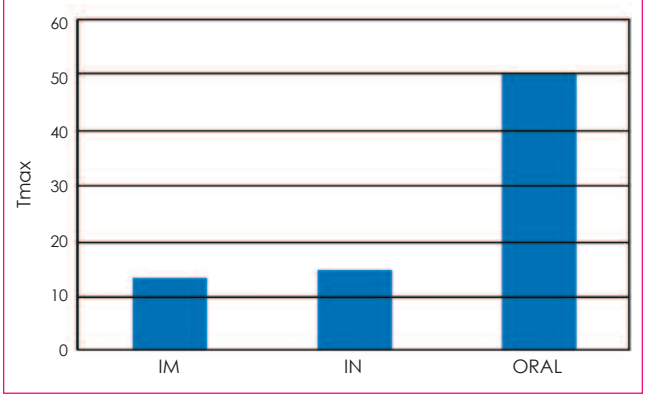
Enhancing product portfolios through effective lifecycle management

Current treatments for allergic rhinitis (including nasal decongestant sprays) cover approximately 80% of all nasal drug use. The large number of generic drugs on the allergic rhinitis market and the reduction in the number of NMEs reaching the market in the US and the EU, however, are having significant effects on market dynamics. This may result in many undifferentiated drugs crowding the market and the heavy reliance on strategies such as aggressive competition in prices, distribution networks and the quality of services.

The effective life cycle management of existing drugs can help to differentiate between companies and optimize a product portfolio without involving the cost, time and risk associated with the development of new drugs. A good example of this is the

Figure 2

Tmax PK for morphine in humans, intramuscular (IM), intranasal (IN) and oral. Adapted with permission from Costantino, H. R., Illum, L., Brandt, G., Johnson, P. H., Quay, S. C. (2007) Intranasal delivery: Physicochemical and therapeutic aspects. International Journal of Pharmaceutics. 337 (1-2): 1-24.



development of side actuation devices (Figure 3), which have been used for products such as Veramyst (fluticasone furoate, GlaxoSmithKline) to treat seasonal allergies. These devices are particularly useful for patients with weak or impaired hand function and have made the product more accessible to pediatric and geriatric patients.

Figure 3

Example of a side actuation device.

Changes to existing formulations and label use

Changes to existing formulations provides companies with added value for products that have already seen considerable financial investment and can represent a much better return on investment than new molecular entities. The strategy is not new; up to 2009, 30-40% of the drugs or biologicals approved or launched in the US were either drugs repositioned for new indications, reformulations or new combinations of existing drugs.[11]

Improvements to the formulations used in nasal sprays include the use of different esters, which when combined with the same compound can have different treatment efficacies. For intranasal drugs used to treat allergic rhinitis and asthma, examples include glucocorticoid fluticasone furoate (FF) (Veramyst and Avamys, GlaxoSmithKline) and fluticasone propionate (FP) (Flonase and Flixonase, GlaxoSmithKline). Because the ester group contributes to the physicochemical characteristics of the molecule, the type of ester can determine the dissolution rate and tissue affinity. For example, the ester in fluticasone furoate confers higher affinity for both nasal and lung tissue compared with fluticasone propionate,[12] with evidence suggesting that fluticasone furoate may be better at improving symptoms compared with fluticasone propionate,[13] giving a more effective treatment with less medication.[14]

The use of different solutions to deliver the drug, such as saline or sucrose, and the use of non-preserved formulations can also be effective strategies to improve a product portfolio. In particular, the omission of preservatives such as benzalkonium chloride and parabens can help patients avoid long-term harm that can be associated with chronic use. In addition, combinations of existing drugs can provide new and improved treatment solutions, such as the combination of an anti-inflammatory and a steroid in the Dymista (Meda Pharmaceuticals) nasal spray for allergic rhinitis.

Changes and/or improvements in the methods of delivery of nasal aerosols and buccal sprays can include switching from aqueous formulations with nasal spray pumps to hydrofluoroalkane (HFA) propellant formulations delivered with pressurized metered-dose inhalers (pMDIs). This can provide new dosage forms that may be easier and more comfortable to administer. The delivery of beclomethasone dipropionate (BDP, Teva) to treat allergic rhinitis and ciclesonide (Sunovion) to treat allergic rhinitis and asthma are two recent market launches that attest to this. In these cases, the use of a "dry" pMDI is sometimes preferable to patients because it avoids dripping of the product which leaves an aftertaste, and allows small doses (i.e., 25 µl) to be more easily administered.

Extending a product leaflet to reach diverse groups of patients, such as geriatrics or pediatrics, can also ensure the broadening of the market and the optimization of the product portfolio. The priority at all times, however, is to ensure that any changes to the product must bring value to patients and/or drug payers or healthcare insurance companies; with an emphasis on improved efficacy, lower side effects, improved compliance and the convenience of an improved ability to self-administer the medication.

Unit-dose and multi-dose drug delivery solutions

Sprix (Roxro) is a first-in-class reformulation of the first non-narcotic analgesic into nasal spray form and has recently been introduced in the market for delivery with a multi-dose device. Instanyl (fentanyl, Takeda) and Subsys (fentanyl, Insys Therapeutics) are also recent examples of pain treatment that use a unit-dose device approach (Figure 4).

Other interesting nasal aerosol projects in development include a unit-dose nasal powder system con-

taining dihydroergotamine for the treatment of migraine (Shin Nippon Biomedical Labs) as well as a novel, breath-powered nasal delivery device currently undergoing clinical studies for the treatment of ailments such as nasal polyps, migraine and chronic rhinosinusitis (Optinose).

eDose counter technology and eLockout technology platforms

Product portfolios can be enhanced by investing in nasal and oral drug delivery mechanical devices equipped with electronic modules or 'e' devices that permit self-dosing of treatments (Figure 5). Self-administration of drugs helps to move towards increased out-patient treatment without direct professional supervision, by providing protection to the patient with built-in "lockout" and "dose counter" systems. These devices provide manufacturers with new market potential, new product applications and advances in technology, as well as ensuring user needs are fulfilled.

Electronic counters can indicate the number of doses remaining in a nasal spray to aid in reissuing a prescription and ensuring the product does not run out. In addition, they can provide clear visual information for patients with impaired vision, such as the elderly. For the physician, eDose counter technology platforms can potentially provide information on how and when doses have been taken. In turn, that information can support a telemedicine approach to patient care, allowing doctors to download data stored in e-devices then make adjustments to dosage regimens to improve efficacy of therapy on a patient-by-patient basis. Such eDevice technology platforms can also help make regulatory approvals easier for controlled substances and potent molecules and reduce liability issues that may result from drug diversion. Electronic devices can reassure government regulators there will be no overdosing or abuse of drugs and that more safe and efficacious medicines can be provided to patients.

Figure 4

Examples of unit-dose devices.

Figure 5

Examples of nasal eDevice technology platforms.

Innovation, growth and improved patient treatment: The future of nasal aerosols and buccal sprays

The consideration of novel methods of drug delivery can be an important contributor to pipeline growth and help companies address some of the pressures changing the face of the pharmaceutical industry. Existing drugs, with their proven safety, can be more effective if investments are made to couple them with new delivery opportunities.

Product portfolios can be managed for longer life cycles through a viable portfolio strategy, which allows companies to consolidate their products. Through the use of nasal aerosols and buccal sprays, the products in a company's portfolio can reach a diverse and broader patient range, which can grow a company's market, enhance its image and add value for money.

The examples in this article have shown how existing drugs can be used in nasal aerosols and oral sprays to improve patient treatment, in particular patient safety, convenience and compliance. Emerging technology in this area can foster the future direction of medicine (i.e., telemedicine) and the move from in-patient to out-patient treatment.

Switching from an existing drug delivery form (oral, injectable) to the use of more patient-friendly delivery systems, such as nasal aerosols and buccal sprays, can provide a real benefit to various stakeholders, such as patients and caregivers.

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Gerallt Williams is Director of Scientific Affairs at Aptar Pharma, Prescription Division, Route des Falaises 27100 Le Vaudreuil Cedex, France, Tel: +33 2 32 63 73 73, gerallt.williams@aptar.com. Website: www.aptar.com/pharma.