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RESEARCH ARTICLE

Trends and Advancements in Drug Delivery: What is the "perfect" method of drug delivery?

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ABSTRACT

In this imperfect world, given that humans often need to treat or prevent disease by delivering medicine to the target cells earlier and for longer than previously possible, certain optimum requirements should be met. Treatment, or prevention, by a therapeutic molecule should be delivered at the right time, at the right dose, to the right target cell, by the safest, most convenient, inexpensive and effective method of delivery.

Most new drugs go through a phase, usually in early development, when they are administered by intravenous delivery, but many of these products end up being delivered by a different modality later, and locally acting drugs for local disease may benefit from topical administration to the epithelium, or adjacent tissue, of interest. With many of the newer medicines being proteins or peptides, oral delivery is not an option due to their degradation in the gut, so non-oral formulations are becoming even more important.

This editorial highlights some of the challenges facing developers when considering how to deliver their products. It focuses on a new route of administration that recently received approval that may represent an opportunity for non-invasive delivery of acutely needed medications.

Introduction:

Drug delivery can be sub divided into several different stages:

1) Delivery - formulation
   Getting the drug(s) into the right formulation so that the right concentration/amount is delivered to the body. This part of Drug Delivery Systems (DDS) development can involve pharmaceutical carriers such as liposomes[1], nanoparticles [2,3], or others[4,5], attachment to specific ligands, or antibody-drug conjugates (ADCs, directed to specific tumor-associated antigens).
2) Delivery - mechanical
   Getting the drugs actually into the body, delivering the above formulation directly into the body or to the epithelium across which it is absorbed.
3) Targeting - tissue.
   Once in the body, getting the drug to the tissue of interest, which may involve immune cells, with inbuilt targeting ability, taking up the drug initially and conveying it to the required tissue, as with immuno-oncologics[6] and may require specific formulations (covered above)
4) Targeting - release
   Once at the target tissue, releasing the drug payload to the cell, which may require a feature of the product being susceptible to local conditions at the target tissue, such as pH, temperature, enzyme activity, oxygen concentration etc., or mediated by other techniques, such as High Intensity Focused Ultrasound (HIFU)[7]. This also requires DDS work.

Delivery:

I will here focus on Step 2, the Delivery – mechanical aspects of drug delivery to the systemic circulation, which sometimes gets overlooked amongst all the impressive advances in the other areas of DDS. Some of the main pros and cons of various mechanical routes of administration are covered in Table 1.

Table 1. Some of the Advantages and Disadvantages of various different routes of systemic administration

Route	Advantages	Disadvantages
Intravenous (IV)	Quick access to the systemic circulation and rapid distribution	Requires Healthcare Practitioner (HCP) to administer
	May require less pharmaceutical development in early stages of a program	Requires clean location, equipment, and access to a (usually peripheral) vein
	100% bioavailability	Can cause pain, infection, bruising, and bleeding
	Can be used in conscious or unconscious patient	Requires cooperation or restraint in the conscious patient
	Avoids first pass metabolism in gastrointestinal (GI) tract and liver	Trauma from repeat (or prolonged) IV dosing can lead to thrombophlebitis
		Extravasation can lead to necrosis of surrounding tissues
Intrathecal	Direct access to brain tissue via cerebrospinal fluid (CSF)	Requires HCP to administer
	Good for drugs otherwise unable to cross Blood Brain Barrier	Requires clean location, equipment, access, and lumbar puncture-experienced HCP
	Avoids GI tract/liver	
Intramuscular	Autoinjectors allow self-administration	Can cause pain, infection, bruising, bleeding, and nerve injury
	Avoids GI tract/liver	
	Volume restricted	Absorption can vary by muscle/activity level
	~ 100% bioavailability	Slower time to maximal serum concentration (T_{max}) than IV
Subcutaneous	Self-administration possible	Can cause pain, irritation, bruising, and bleeding
	Good for "depot" preparations	Variable rate of absorption
	Available for delivery of large molecules	Site needs to be changed frequently to avoid local tissue damage
	~ 100% bioavailability	Slower time to T_{max} (than IV)

Transdermal	Convenient (patch) application	Limited range of drugs (due to physicochemical properties of drug and dose required)
	Avoids GI tract/liver	Often complex chemistry, manufacturing, and controls (CMC) issues
	Possible to control rate of delivery (daily or less frequent dosing)	Skin irritation and local/general allergic reactions possible
+/- options: iontophoresis, microneedles	Broader range of molecules can be delivered	Even more complex CMC
Pulmonary	Rapid administration (Metered Dose Inhaler [MDI]/Dry Powder Inhaler [DPI])	Slower administration (Nebulizer)
		The delivered dose (emitted or ex-valve dose) from an inhaler is generally greater than the Fine Particle Dose (FPD, of 4 microns diameter or less) that can be drawn through the many divisions of the pulmonary tree to the alveolae. This requires sophisticated manufacturing to ensure consistency of the FPD
	Avoids GI tract/liver	Inefficient. Only ~ 10-40% (the "respirable fraction") of ex-device dose deposits in lung[8]
	Rapid T_{max}	Local side effects can include cough, bronchospasm
	Self-administered	Requires particle engineering, complex formulation, and CMC challenges
	Portable (MDI/DPI) convenient devices	Nebulizers require power source
	Good for local treatment of lung disease	Require cooperative patient for forced inhalation
	Good bioavailability (depending on fine particle fraction)	All parts of the lung are not the same. Difficult to deliver to specific lobe or airway level
Nasal	Rapid administration (mostly)	Variable bioavailability
	Self-administration possible	Local irritation and drainage (front and back) lead to drug loss
	Good for local nasal disease	Local disease (e.g. rhinitis, common cold, COVID etc) may affect absorption
	Reduced systemic side effects	Formulation and device required increasing cost and development complexity
	Avoids GI tract/liver	Particle/droplet in non-respirable range easier to manufacture than MDI/DPI, and indeed minimal output in the FPD[9] range is desired for deposition in the respiratory bronchioles and alveolae
	Portable, convenient devices may improve patient compliance	Patient unfamiliarity; Some training required and may face cultural challenges
	Sterile technique not required	–All parts of the nose are not the same

	Retention in nose can be enhanced by mucoadhesive or absorption enhanced	More complex formulation
Oral (tablets/ capsules/elixirs, etc)	Most popular and familiar	May need to be taken on an empty stomach or with food, or have other requirements
	Portable and discrete to self administer	May be slow to get to small intestine for absorption, thus slow T_{max}
	Stable (on storage)	May be affected by GI disease (sometimes unrecognized)
	(Generally) painless administration	Prone to first pass metabolism by GI mucosa and/or liver
	Extended release preparations reduce dosing frequency	Less than 100% bioavailability
Buccal	Low risk of pain	May require complex formulation
	Avoids GI tract/liver	Taste masking may be required
	Rapid absorption	Spray or patches possible but will require complex CMC
	Easy and discrete to administer	Dissolving drug may be swallowed before absorbed
	Self, caregiver or HCP administered	Unsuitable for uncooperative patients
	Product can be spat out once therapeutic effect obtained	Product can be spat out before therapeutic effect obtained
	Can be used by patients with swallowing difficulty	Slower onset (than IV)

CSF = Cerebrospinal Fluid; T_{max} – Time to maximum plasma concentration; IV = Intravenous; MDI/DPI = Metered Dose Inhaler/Dry Powder Inhaler; FPD = Fine Particle Dose (less than 4μ diameter); CMC = Chemistry, Manufacturing, and Controls; GI = Gastrointestinal; HCP = Healthcare Practitioner

All of the above modalities are worthy of full discussion, and within each route of administration the pace of change and the range of adaptations (either to formulations, physical delivery systems, or both) to enhance each option are dramatically increasing. For instance, with injectable products, new infusion pumps, autoinjectors, and even self-sheathing syringes have become available, but require the same tissues to inject into. Transdermal products have evolved from the older occlusive patch to include iontophoresis or microneedles, but they all deliver through the skin. Nebulizers with different core technologies, either jet, ultrasonic, or mesh, and even delivering dry powder[10] have proliferated, while other metered dose or dry powder inhalers have been widely accepted for treating airway disease with dose counters, utilizing breath actuation and other advances. Systemic delivery via the pulmonary route requires manufacturers to maximise the amount of drug delivered by particles in the respirable, or FPD, range with a diameter of 4 microns or less. Even after this has been achieved, commercial success is not guaranteed, as Pfizer's Exubera® insulin delivery product was withdrawn from the market[11], and neither Alexza's Staccato® delivery of loxapine, currently marketed as Adasuve®, nor Acorda's delivery of levodopa marketed as Inbrija®, have delivered outstanding commercial results. With all pulmonary delivered drugs, the inhaled drug has to first reach and cross the pulmonary epithelium into the pulmonary circulation. There are other routes that can potentially provide systemic drug levels not covered above, e.g. implanted devices (subcutaneous pumps) which may feature microchip controlled drug release from an inbuilt reservoir, drug eluting products (e.g. vascular stents), intraventricular, vaginal, intrauterine, rectal, intra-arterial, and topical eye installation. This review focuses on a novel device for administration to the systemic circulation, via the upper nasal space, which is genuinely a new route of administration not previously employed, but which holds considerable promise.

Upper Nasal Space – as a promising new route of administration:

Impel Pharmaceuticals developed a specific, core technology, Precision Olfactory Delivery (POD®) over the last 14 years, and in September 2021,

gained US FDA approval delivering a long-established nasal liquid formulation of dihydroergotamine (DHE) for the acute treatment of migraine. The POD system uses propellant to push drug formulation through the nasal valve and deep into the upper nasal space, where only ~5% of traditional nasal spray delivered drug may penetrate, without the need for any mucoadhesive, absorption enhancers or any other modifications to the previously approved liquid formulation.

Precision Olfactory Delivery:

The novel POD system can use multiple different propellants (e.g. hydrofluoroalkane (HFA), carbon dioxide (CO_2), compressed air or nitrogen); keeps drug and propellant separate until the point of delivery; can be self, caregiver or healthcare practitioner administered; can be used when the patient is awake, unconscious, or otherwise uncooperative; is delivered in less than 0.5 seconds; and importantly is designed to deliver large diameter droplets (300-700 microns), or particles (~ 20-100 microns), well above the size that can pass through the airways and deposit in the peripheral lung. With these attributes, the POD system is unique.

In July 2022, a further clinical phase 2 study started, dosing with a different version of the POD system (I-231) using a novel, spray-dried powder formulation of olanzapine for the acute treatment of agitation in patients with autism[12]. It is rare for a new route of mechanical delivery to the systemic circulation to be approved, so a further look at how the technology works is justified, especially as the system has potential broad utility to deliver old but previously non-optimized medications, as well as for new drugs in multiple therapeutic areas, not just for neurologic disease.

The nose is more complex than widely recognized, even in microsmotic mammals such as humans and primates. The highly developed sense of smell that other macrosmotic mammals, for instance dogs, possess is better appreciated. Yet even humans have an organ that can be divided into several different sections, with different mucosae for varying functions[13]. Another reason for great interest in the Pharmaceutical Research & Development world, as indicated by the significant focus given to it at the 2022 Respiratory Drug Development conference, is in targeting drugs to deposit on the olfactory epithelium. This epithelium is the only place in the (human) body where the Central Nervous System (CNS) is in direct contact with the environment, through the approximately 6-10 million olfactory sensory neurons and their apically projecting dendrites[14]. Being able to get drugs across the Blood Brain Barrier remains the "holy grail" for many organizations treating CNS disease, especially with non-invasive administration. But even aiming for systemic rather than "direct to brain" delivery, can drug delivered to different regions of the nose lead to improved bioavailability and pharmacokinetics? The answer is yes.

POD – Pharmacokinetic data:

In a phase 1 study in healthy volunteers (NHVs) the exact same formulation of liquid DHE was given by a traditional nasal spray to the lower nasal space and at < 75% of the dose by the POD to the upper nasal space[15], resulting in a four-fold increase in maximum plasma concentration (C_{max}), and a three-fold increase in Area Under Curve (AUC), with reduced variability and faster T_{max} when delivered by POD compared to the traditional nasal spray. In this 3-way, 3-period crossover study, the NHVs also received the approved IV DHE formulation. The C_{max} with the IV formulation was ~ 10-fold greater than the POD DHE, and despite pre-treatment with antiemetic led to nausea and vomiting in some subjects, attributed to the high C_{max}, whereas no cases of drug-related nausea or vomiting were reported with POD delivery. POD delivery of DHE reached levels seen after IV dosing by 30 minutes and then matched IV-administered drug levels out to 48 hours. This is the only clinical study that compares delivery of the same drug formulation to two different areas of the nose. Thus, the POD system demonstrated enhanced bioavailability compared to the traditional nasal spray, with less reports of unpleasant taste suggestive of the slower mucociliary clearance from the non-motile cilia found on the olfactory mucosa, compared to the brisk clearance from the ciliated, columnar respiratory epithelium that lines much of the lower nasal space.

Another study was conducted by the same group comparing a novel, spray-dried powder formulation of olanzapine (OLZ), a commonly used second generation antipsychotic, to the approved intramuscular OLZ injection[16] delivered by a research version (I-231) of the POD. That study also reported encouraging results. While the C_{max} and AUC for 5 mg doses delivered by POD and IM, again to NHVs, were essentially similar, the time to C_{max} (T_{max}) was much faster with the POD system. In fact, 4 of 10 dosed with POD-OLZ recorded the C_{max} at the first blood draw of 5 minutes, suggesting the medication could have actually peaked before that time, making the POD-OLZ product of potential interest to Emergency Room teams, anesthesiologists, and intensivists[17], compared to the IM OLZ with a median T_{max} of 20 minutes.

The I-231 research POD device was designed specifically for rapid clinical evaluation of powder drug formulations that can be manufactured and filled into standard capsules. Research pharmacies are able to take the capsules, carefully open them and load them on to the tip of the I-231 POD device and assemble the device so that the clinical staff have only to administer the medication nasally to the subjects, making it an ideal option for early clinical studies. The functional performance of the system is then maintained as development proceeds on the "to-be-commercialized device" for each specific drug-device combination product.

Getting the drug to the upper nasal space for a single dose study is necessary to generate the pharmacokinetic (PK) data, but that will not provide reassurance on longer term safety and tolerability.

POD – Safety data:

In the case of POD DHE, safety data were provided by a 24/52 week open label study (STOP 301) with some unique safety endpoints[18]. For regulatory approval, serial assessments of both mucosal integrity and function were required in at least 150 patients who continued to suffer from at least two migraine attacks per month, self-medicated with INP104, over 6 months. If there was concern about the safety and tolerability of INP104 over 6 months, then data from at least 50 patients continuing to experience, and treat, at least 2 attacks per month for a full 12 months were required. Early in study planning it was clear that it would be logistically more efficient to collect that data from the earlier patients completing the 24-week treatment period, and thus the study data set comprised populations completing both 24- and 52-week periods, even if ultimately the 24-week safety profile was encouraging.

The unique request for monitoring upper nasal safety resulted in the use of the University of Pennsylvania Smell Identification Test (UPSIT), developed in 1984, and widely used, but never before as a tool for pivotal olfactory function safety assessment[18]. Since the advent of COVID-19, smell, and its loss/restoration, has attracted more attention, and testing for it in phase 2 studies is now being done more commonly[19]. In addition, independent otolaryngologists were contracted to perform endoscopic assessments of both upper and lower nasal spaces, capturing video or still photographs if equipment was available, and mucosal integrity was evaluated using a specially developed Quantitative Scoring Scale – Nasal Mucosa (QSS-NM), that was modelled off the Modified Lund Kennedy Scoring system, familiar to otolaryngologists during routine nasal endoscopy[20].

To avoid bias in the interpretation of these data from an open-label trial, data were collected and blinded as to which visit they had been collected at and then reviewed by an independent panel of three highly experienced otolaryngologists who, after making their assessment, were allowed to review the data again with visit data revealed to see if their opinion changed. This Nasal Safety Review Committee concluded that patient-reported adverse events (AEs) were sufficient to monitor the nasal safety of INP104, and that nasal endoscopies and repeated UPSIT testing added no clinical value. There were no significant safety concerns, and all nasal AEs were minor. Their opinion was not modified by disclosure of the duration of exposure to the investigational product.

POD – disadvantages:

The disadvantages of the INP104 product include the need to assemble the device, which requires removing the metal crimp cap off the bottle of liquid formulation, removing the rubber stopper, screwing the bottle into the base of the POD device having removed the dip tube protector (that draws the liquid DHE formulation into the assembled device), and then priming the system by spraying 4 times. These disadvantages were recognized. The first generation INP104 device was always planned to utilize the liquid DHE formulation produced by the same manufacturer as the approved nasal spray, using identical bottles and manufacturing method in order to reduce the chance, often encountered by drug-device combination product manufacturers, of the New Drug Application being rejected by the US Food and Drug Administration due to concerns about the manufacturing process. Indeed, for this iteration, the device was specifically designed around the existing approved bottle as the primary container. These disadvantages of the current device, part of the now approved combination product, may be addressed by a "Next Generation Device" technology being intensively investigated.

Many migraine attacks are treated with oral medications, but oral treatment may be suboptimal for many patients and/or many attacks. Indeed, with increasing recognition of the direct link between the brain and the GI tract, research into Disorders of Gut-Brain Interaction (DGBI)[21], suggest that GI dysfunction may be greatly underestimated as a cause of failure of orally administered treatments to provide effective relief, thus a new non-oral route of administering a long established, effective, but never before optimized molecule is welcome[8], particularly in acute treatment of migraine.

Conclusion:

While a perfect method of drug delivery may never exist, the POD system offers promise to be one step closer to that for patients with migraine, and in another program now ongoing in acute agitation in autism[11] a novel powder formulation of the also long-established olanzapine offers potential for this other high unmet need to finally have a welcome, convenient and self- or caregiver-administered, rapidly effective, therapeutic option too.

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