Expert Opinion

PecSys: *in situ* gelling system for optimised nasal drug delivery

Peter Watts† & Alan Smith
Archimedes Development Limited, Albert Einstein Centre, Nottingham Science and Technology Park, University Boulevard, Nottingham, NG7 2TN, UK

PecSys™ (PS) is a proprietary pectin-based drug delivery system designed to gel when applied to mucosal surfaces and with potential areas of application for drugs used in local and systemic disease therapy. The current area of focus is intranasal drug delivery where PS is being used to optimise absorption of lipophilic drugs into the systemic circulation. Pectin is described as GRAS (generally regarded as safe) with an excellent regulatory position through its long history of pharmaceutical and food usage. Tests to measure the functional gelling properties of pectin raw material and PS have been devised and validated. The PS-based products at the most advanced stages of development are intranasal formulations containing opioid analgesics intended to provide rapid pain relief with simple and convenient dosing and minimal side effects. The profile of such drugs may not be optimal through current routes of delivery and the ability of PS to modulate their pharmacokinetic profiles, such as attenuation of the peak plasma concentration (C_{max}), has been demonstrated in clinical testing. The lead product using PS is a fentanyl nasal spray formulation (NasalFent®), which has successfully met the primary objective in a pivotal Phase III clinical study and is scheduled for regulatory filings in the first half of 2009.

Keywords: buprenorphine, fentanyl, gel, modified release, mucosal, nasal, pain, pectin

Expert Opin. Drug Deliv. (2009) 6(5):543-552

1. Overview of the market

Intranasal drug delivery has been used successfully for many years for the administration of drugs for local action, such as decongestants, antihistamines and corticosteroids. More recently, innovative pharmaceutical products formulated as nasal sprays have been introduced that exploit the advantages of the nose as a route for systemic drug administration. As a mode for delivering systemically acting drugs, the nasal route has many attractive features, which are described in detail elsewhere. In brief, the nasal tissues are highly vascularised, they have good permeability, are easily accessible, first-pass metabolism is avoided and nasal administration is simple, rapid, convenient and hence proven to be well accepted by patients [1,2].

Systemically acting marketed drugs given intranasally generally fall into one of two categories, namely to provide rapid onset of action or to provide an alternative and more convenient route of delivery for a drug that is otherwise injected. Examples of marketed products in the first category include butorphanol (analgesic), sumatriptan, zolmitripan, dihydroergotamine (anti-migraine) and cyanocobalamin (vitamin B12) [1-4]. Marketed formulations in the second category include desmopressin, nafarelin, buserelin and calcitonin [1]. There are numerous intranasal products in clinical development, including morphine [5], apomorphine [6], midazolam [7], fentanyl [8], buprenorphine [9] and insulin [10], most of which are exploiting the rapid onset of action afforded by nasal administration.

Currently approved systemic nasal products are primarily simple aqueous solutions delivered as sprays, but this may not always be the most appropriate formulation

10.1517/17425240902939135 © 2009 Informa UK Ltd ISSN 1742-5247

approach because the absorption of the drug cannot be controlled, that is, there is no control on plasma concentrations, duration of absorption or time to reach therapeutic concentrations. Also, simple aqueous solutions can drip from the nose or drain rapidly and be swallowed, which may ultimately decrease the magnitude or increase the variability of therapeutic response. For example, the time for 50% of a simple liquid formulation to be cleared from the nasal cavity is ~ 15 – 20 min [11]. Consequently, the introduction of non-optimal products has not enhanced the reputation or status of the intranasal route for drug administration. Proprietary nasal drug delivery systems are in preclinical or clinical development by several companies and are intended to be applied to drugs for which simple formulation strategies do not provide an ideal product. Many of these technologies are designed to improve drug bioavailability through mechanisms such as bioadhesion or through effects on the drug transport mechanism, as described in Section 4. As an example, chitosan-based solution formulations have been shown to be bioadhesive, resulting in reduced nasal clearance [12] and enhanced drug bioavailability [13].

The intranasal route has also been exploited for delivery of vaccine antigens, with the most notable example being FluMist® (MedImmune), which has been licensed for influenza immunisation [14]. Positive clinical data have been reported for other intranasal vaccines, including diphtheria [15]. Other intranasal vaccine products known to be in development include anthrax [16] and avian influenza [17]. A nasally administered formulation to reduce the duration and severity of the common cold has been described [18].

A therapeutic area for which nasal delivery is especially advantageous is the treatment of acute pain, including migraine, trauma pain, post-surgical pain and cancer pain, particularly breakthrough cancer pain [1]. For many of these situations there is a need to provide rapid relief of pain using a simple, convenient, patient-acceptable means of administration. In such conditions oral or injectable drug delivery may not be acceptable or optimal, in terms of time to relieve pain, to the patient, caregiver, or physician [5]. The opioid analgesic fentanyl is increasingly being recognised as the drug of choice for treating breakthrough cancer pain, a common type of pain in cancer sufferers characterised by being rapid in onset, severe in intensity and of short duration and occurring against a background of maintenance opioid analgesia [19]. A variety of rapidly acting fentanyl dosage forms are marketed or are in various stages of development for this condition, including intranasal [8], pulmonary [20,21], oral transmucosal (buccal and sublingual) [22-24] and transdermal [25] products.

An intranasal fentanyl formulation (NasalFent®) that uses PecSys™ (PS), an *in situ* gelling pectin technology, has successfully completed phase III clinical studies and is scheduled for regulatory filings in the first half of 2009 [8]. This product has been developed by Archimedes Development Limited and will be described in further detail later in this article.

2. PecSys technology

2.1 Pectin

Pectin is a well-defined plant-derived polysaccharide and the molecular structure varies with the source and the conditions used for extraction and purification. In simple terms, pectins are polymers of galacturonic acid linked by $\alpha(1 \rightarrow 4)$ bonds and where the carboxyl groups are methylated to varying degrees. However, pectins also contain neutral sugars such as galactose, rhamnose or arabinose, either as part of the polymer backbone (e.g., rhamnose) or as side chains (e.g., arabinose). Neutral sugar side chains tend to be concentrated into particular areas of the pectin molecule described as 'hairy regions', with the sugar-free areas termed 'smooth regions' [26]. For food and pharmaceutical use, the galacturonic acid content of pectin is at least 65% [27,28]. The typical molecular mass for a commercial pectin is ~ 100,000 daltons [29].

There are two basic types of pectin, depending on the degree of esterification (DE): high methoxyl (HM) or high DE pectins have a degree of esterification > 50% and low methoxyl (LM) or low DE pectins have a degree of esterification up to 50% [29]. LM pectin is the basis of PS.

Common commercial sources of pectin are apple pomace and citrus peel [29,30], although other plant materials have been described, such as aloe [31]. Typically, pectin with high methoxyl content is extracted from these raw materials by adding acid, followed by precipitation with alcohol. The degree of esterification of the pectin may be modified by acid or base treatment. The treated material is recovered, dried, milled and, especially for food applications, can be standardised by blending with sucrose. De-esterification in the presence of ammonia will generate amidated low methoxyl pectin [29,30].

2.2 How the technology works

PecSys is a patented gelling drug delivery system designed to be applied to mucosal surfaces such as the nasal cavity, eye and vagina [32]. Comprising an aqueous solution based on LM pectin, PS forms a gel on contact with the mucosal surface. Gel formation occurs as a result of the interaction of the LM pectin with calcium ions present in the mucosal fluid: This will allow locally acting drugs to reside for longer at the site of application. For well-absorbed (lipophilic) drug compounds, gel formation provides the ability to modulate systemic uptake and thus control the pharmacokinetic profile, such as extending duration of action and modifying peak plasma concentrations (C_{max}) while retaining the ability to offer a rapid T_{max}. Developed over the last 6 years, PS is a well-characterised enabling technology with a highly innovative profile, designed to maximise the clinical potential of systemically absorbed drugs by enhancing drug performance and patient acceptance.

The composition of a specific PS formulation is developed and optimised by Archimedes according to factors including

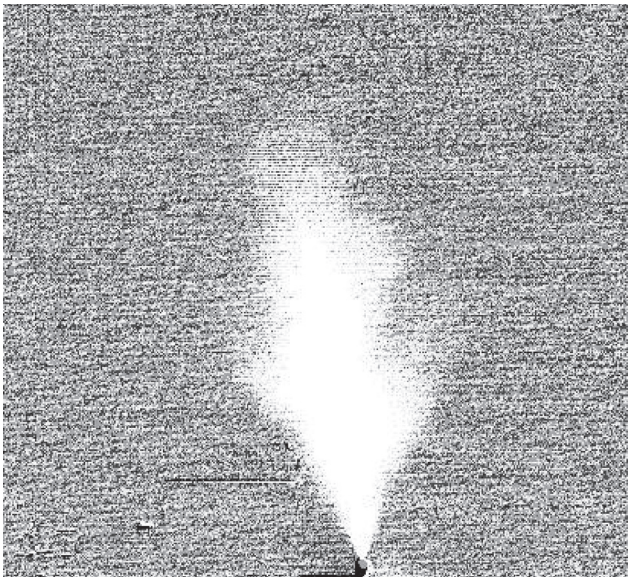

Figure 1. Image of spray plume produced by PecSys™ formulation delivered from a nasal spray device (Unit Dose, Pfeiffer GmbH, Radolfzell, Germany).

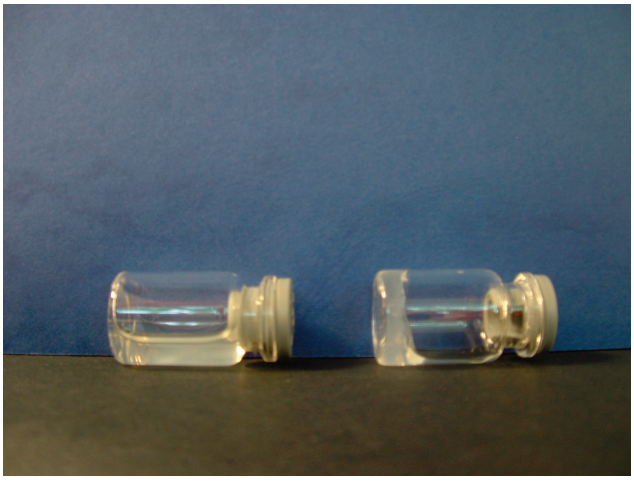

Figure 2. Photograph to show appearance of PecSys™ before (left-hand vial) and after (right-hand vial) exposure to simulated nasal electrolyte solution.

the physicochemical properties of the drug compound, the target delivery site and the desired *in vivo* performance (the drug concentration and duration of action required). Drug is typically present in PS as an aqueous solution, although other physical forms such as a suspension are possible.

PecSys solutions have a low viscosity and, for nasal delivery, can be given in a low volume (e.g., 0.1 ml or less). The solutions efficiently disperse into a plume of droplets using conventional off-the-shelf approved nasal spray devices (see **Figure 1**). An important feature of a PS formulation is the proven reproducibility of both dose delivery and spray characteristics, such as droplet size, spray pattern and plume geometry. The nasal spray droplets are deposited as a thin layer on the nasal mucosa where they come into contact with calcium ions present in the mucosal fluid at a sufficient concentration to gel the pectin. A photograph of a drug-free PS solution is provided in **Figure 2**. Also shown is the same solution when mixed with an electrolyte solution designed to simulate nasal mucosal fluid, illustrating the formation of the gel.

The gel droplets that form on the mucosal surface will contain drug that must then diffuse out in order to be available for absorption. The need for diffusion modulates the rate of systemic drug absorption and hence the pharmacokinetic profile, allowing rapid absorption and a short time to the peak plasma concentration (C_{max}) but controlling C_{max} to be within desired therapeutic levels. The modified profile will typically be manifested by an attenuated C_{max} when compared with a simple aqueous solution administered as a nasal spray and an increase in the duration of absorption. It is expected that the gel droplets will be cleared with a half-life of ~ 30 – 40 min by the action of the cilia on the nasal mucosa, swallowed and excreted by means of normal routes.

Although measurements of nasal calcium have been made, it is not a straightforward process and the reported values vary [33,34]. However, physiological concentrations of calcium are controlled very precisely in healthy humans because of its key role in physiological processes [35]; this will be reflected in the concentrations found in nasal secretions. The effect of disease state on intranasal calcium concentrations is not known, although conditions such as allergic rhinitis and viral infections will affect the local nasal environment. Studies have demonstrated that such conditions and their treatments generally have little impact on drug absorption [36-38]. Furthermore, although calcium concentrations will affect the consistency of LM pectin gels, the diffusion characteristics of gelled PS formulations have been shown by Archimedes to be tolerant to calcium concentration-related changes in gel properties. Consequently, it is expected that the *in vivo* performance of PS formulations will remain relatively unaffected in the event of local changes in nasal calcium concentrations.

Other delivery systems have been described that gel when administered into the nasal cavity. Examples of thermoresponsive formulations that undergo a sol-to-gel transformation when exposed to the temperature found in the nasal cavity include systems based on chitosan and polyethylene glycol [39] and Pluronic® (poloxamer) and Carbopol [40]. A gelling formulation based on the sensitivity of gellan gum to cations has been reported [41].

2.3 Gelling properties of pectin

Pectin can form gels by two different mechanisms and the gel structure of a particular pectin will be strongly influenced by its DE value. High methoxyl pectins will form gels at

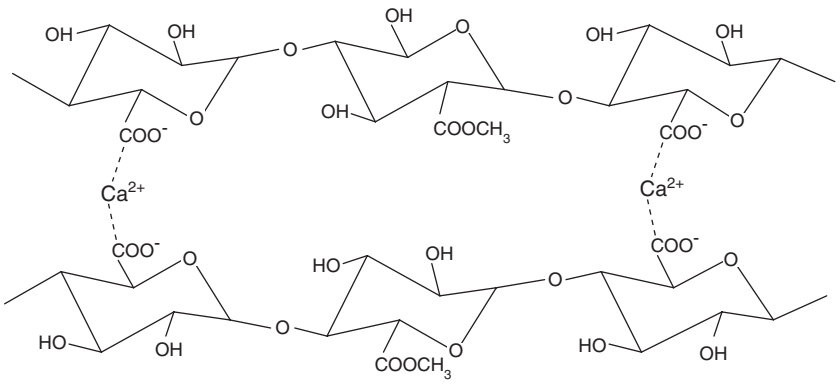

Figure 3. Gel formation by low methoxyl pectin in the presence of calcium ions.

low pH values and at high solid contents, for example, with addition of sucrose. The gels are thermoreversible, being in the liquid state at elevated temperature and setting on cooling. Mechanistically, at low pH the carboxyl groups on the polymer chain will be in an unionised state, allowing the pectin molecules to interact by hydrogen bonding [26].

Low methoxyl pectins form gels through a susceptibility to divalent metal ions, in particular calcium. As stated earlier, it is the calcium ions present in mucosal fluids that cause PS to form a gel *in vivo*. The calcium ions bind to the carboxylic acid groups of two separate pectin chains to form an ordered three-dimensional network. The structure of the gel has been described as an 'egg box' [26,42] and is represented in **Figure 3**. As calcium ions interact only with pectin at the carboxylic acid groups, the reactivity to calcium increases as the DE value is reduced.

2.4 Non-pharmaceutical uses of pectin

The most extensive use of pectin is in the food industry as a thickening and gelling agent, although it is also used in cosmetic products, paper substitutes, foams and plasticisers [43].

2.5 Pharmaceutical and medical uses of pectin

Pectin has adsorbent and bulk-forming properties and has a long-established medical use in the management of diarrhoea and constipation and may also be found in obesity treatments [44-46]. In these products pectin is often used in combination with other ingredients such as kaolin [46].

A monograph for pectin is included in the United States Pharmacopeia National Formulary and describes HM material [28]. As an excipient, pectin is listed in the FDA Inactive Ingredients Guide and in the Canadian List of Acceptable Non-medicinal Ingredients [47]. Commercial products containing pectin include Orabase® paste, which is used for treating oromucosal lesions, and ostomy adhesives, such as Stomahesive® [46]. At present all approved pharmaceutical products on the market use HM pectin.

There are numerous publications describing the experimental use of pectin in drug delivery systems, often in combination with other polymers. Pectin has been described primarily in orally administered formulations, for example those intending to provide gastroretention, sustained release and colon targeting [48-50]. The use of pectin in vaginal formulations has also been described [51]. The evaluation of LM pectin-containing solutions for delivery of drugs to the olfactory region of the nasal cavity is reported: it is concluded that the formulations provided an increase in nasal residence compared with pectin-free controls [52,53].

Two drug delivery systems based specifically on LM aloe pectin are under development: GelSite® is an *in situ* gelling liquid formulation that is being evaluated as a depot injection and GelVac™ is a powder that is being explored for intranasal vaccine delivery [54,55]. By contrast, PS is the only liquid formulation of pectin designed to gel when applied to mucosal surfaces.

2.6 Pectin safety

High methoxyl, LM and LM amidated pectins are permitted as food additives across the world and neither JECFA (Joint FAO/WHO expert committee on food additives) nor the European Union has set any limits on acceptable daily intake. In the US, pectin has GRAS (generally regarded as safe) status. In Europe, pectin is food additive E440 [47,56].

Given the high molecular mass of LM pectin and the fact it forms a gel in the nose, the material will not be absorbed intranasally and will be cleared by the normal action cilia and swallowed. The use of LM pectin in nasal PS formulations represents a new route of administration for the material, and regulatory authorities will consequently require an appropriate package of local toxicology data for any pharmaceutical product in which it is used. With products such as NasalFent nearing filing for registration, it is evident that satisfactory local tolerability of PS has been demonstrated.

2.7 *In vitro* characterisation

The functional properties of PS relate to its ability to form gels in the presence of calcium ions. *In vitro* tests have been devised and validated by Archimedes to measure this functionality

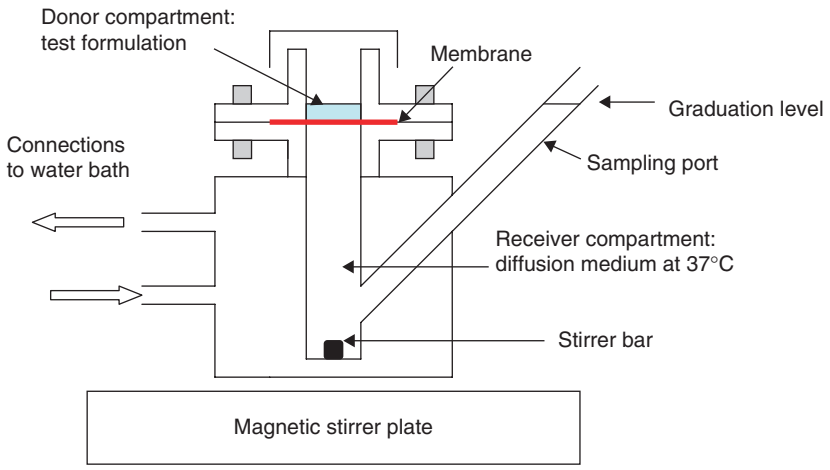

Figure 4. Schematic diagram of Franz diffusion cell apparatus.

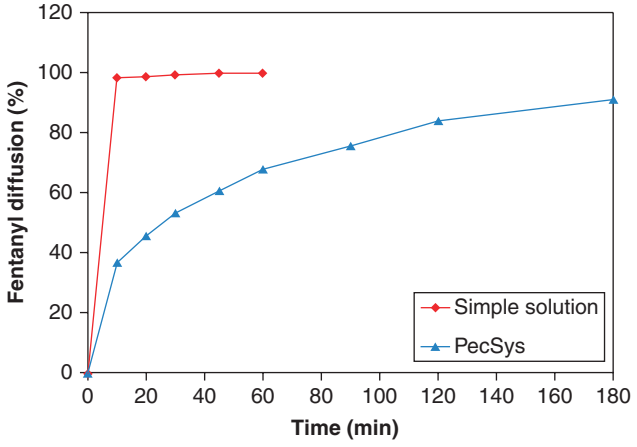

Figure 5. Diffusion characteristics of fentanyl from a simple aqueous solution and a PecSys™ formulation, measured using a Franz diffusion cell.

and have been used successfully to support product development and quality control activities.

Quantitative measurements may be performed by mixing the PS formulation with calcium solution provided the consistency of the gel is suitable for measurement, for example using a force probe such as a Stable Microsystems Texture Analyser [57]. A qualitative assessment of the gel can also be performed by mixing the PS formulation, for example, with physiological electrolyte solutions.

Ultimately, the role of the pectin gel is to modulate drug diffusion and hence absorption. The *in vitro* drug release characteristics of intranasal formulations can be conveniently measured using Franz diffusion cell models [40,58]. Archimedes has implemented a diffusion cell model for evaluating the *in vitro* performance of PS formulations (see **Figure 4**). The receiver compartment of the test cell is filled with simulated nasal electrolyte solution maintained at 37°C and the test formulation is applied onto the membrane in the donor compartment. The electrolyte solution will permeate through the membrane and a thin layer will sit on the surface. The PS test formulation will form a gel on the membrane surface through interaction with the electrolyte solution. Drug will diffuse from the gel, through the membrane and into the receiver compartment where samples are collected through the sampling port and analysed for drug content. This enables drug diffusion kinetics to be measured.

Figure 5 shows diffusion profiles for fentanyl from a simple aqueous solution and from a typical PS formulation. It can be seen that in simple solution form fentanyl diffuses rapidly through the membrane in an uncontrolled manner into the diffusion cell. By contrast, when fentanyl is incorporated into PS a gel forms on the membrane and drug diffusion into the cell is modulated. This change in diffusion characteristics would be expected to have an impact on drug absorption characteristics *in vivo* and is demonstrated by the comparative pharmacokinetics of PS and simple solution formulations of fentanyl, which are described below.

Depending on the outcome of *in vitro* characterisation, the composition of the PS formulation can be altered until the desired characteristics are achieved, for example by changing the concentration of pectin or its DE value. Individual PS systems are designed for each molecule.

3. Clinical experience

3.1 Intranasal fentanyl

A specific PS-based nasal spray formulation of fentanyl citrate (NasalFent, Archimedes) has successfully completed Phase III clinical studies and regulatory filings are scheduled in the first half of 2009.

In a study conducted for Archimedes, the pharmacokinetic performance of NasalFent was compared with a non-gelling

Table 1. Pharmacokinetic parameters following administration of three fentanyl-containing formulations to healthy volunteers (n = 18): PecSys and non-PecSys nasal formulations and Actiq (oral transmucosal lozenge).

Parameter	Nasal non-PecSys 100 µg fentanyl	Nasal PecSys 100 µg fentanyl	Oral Actiq 200 µg fentanyl
C_{max} (pg/ml)	647	337	264
T_{max} (min)	10	20	90
AUC (pg.h/ml)	1279	1130	1544
F_{rel}* (%)	168	146	N/A

*Bioavailability relative to Actiq.
All values are mean, apart from T_{max}, which is median.

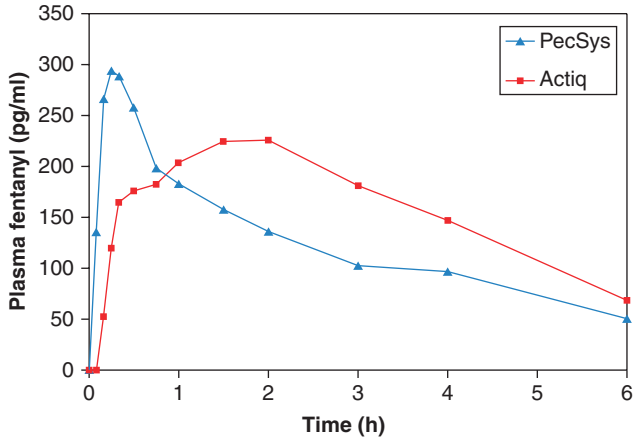

Figure 6. Mean fentanyl plasma concentration–time profiles following administration of PecSys™ (100 µg fentanyl) and Actiq® (200 µg fentanyl) formulations to healthy volunteers (n = 18).

intranasal formulation and an oral transmucosal fentanyl citrate lozenge (Actiq®, Cephalon). The study was a crossover design performed in 18 healthy volunteers. The dose of fentanyl was 100 µg for the nasal formulations (one × 0.1 ml spray) and 200 µg for Actiq (the lowest commercially available dose). Key pharmacokinetic parameters are provided in **Table 1** and show that a higher C_{max} was seen with the non-PS nasal formulation (647 ng/ml versus 337 ng/ml for PS): this difference in C_{max} values was statistically significant ($p < 0.0001$). The rate of fentanyl systemic absorption should have an impact on the speed of pain relief. Based on T_{max} values, fentanyl absorption from NasalFent is very rapid compared with Actiq, with values of 20 and 90 min, respectively. The AUC and relative bioavailability data indicate a higher proportion of fentanyl was absorbed from the two nasal formulations compared with Actiq. A review of published data suggests that T_{max} values of more recently developed oral transmucosal formulations are still substantially longer than with NasalFent. For example, T_{max} values of ~ 40 – 60 min have been reported for fast-dissolving buccal fentanyl tablets [24]. **Figure 6** displays the plasma concentration time profiles for the PS formulation and Actiq from the volunteer study and illustrates clearly the faster absorption achieved for the nasal formulation.

The pharmacokinetics of 50 µg of fentanyl administered intranasally as a buffered aqueous solution has been reported [59]. The mean C_{max} was 470 pg/ml (0.47 ng/ml), that is, adjusted for dose, the simple solution produced a C_{max} apparently uncontrolled and approximately threefold higher than PS.

In a clinical setting there may be concerns that reaching very high plasma concentrations too rapidly may be associated with greater side effects for fentanyl. The primary effect of the PS formulation is to reduce significantly the C_{max} while retaining therapeutically effective concentrations for the necessary period to confer advantages over simple solution formulations.

Phase II and III data on NasalFent have also been reported. In a pilot Phase II study, cancer patients receiving opioid treatment for background pain were titrated to an effective dose of NasalFent and then treated for up to four episodes of breakthrough pain. There were improvements in pain relief and in pain intensity from 5 min after dosing, and these reached clinically meaningful levels in most treated episodes as early as 10 min after administration. NasalFent was tolerated well [60-62]. Data have recently been reported for a Phase III placebo-controlled study. The study achieved its primary efficacy end point with patients treated with NasalFent showing a highly statistically significant improvement in pain at 30 min (Summary of Pain Intensity Difference at 30 min [SPID30]) compared with placebo ($p < 0.0001$). Also, patients reported statistically significant differences in pain score compared with placebo at 5 min, demonstrating onset of pain relief as early as 5 min [8].

3.2 Intranasal buprenorphine

PS-based formulations for intranasal delivery of buprenorphine are under development [9]. Buprenorphine is an opioid analgesic with partial agonist and antagonist properties and is used both as an analgesic for treating moderate-to-severe pain and in the treatment of drug addiction.

Table 2. Other proprietary nasal delivery technologies, areas of application and development status.

Technology	Company	Description and applications	Current development status of product(s) using technology	Refs.
ChiSys®	Archimedes	Chitosan-based solution or powder for enhanced transmucosal drug absorption and for nasal vaccine delivery	Phase III	[2,63-65]
CPE-215	CPEX	Absorption enhancer technology using macrocyclic permeation enhancers	Phase II	[10,66,67]
GelVac™	DelSite	Pectin-based powder for nasal drug and vaccine administration	Phase I	[55]
Intravail®	Aegis	Surfactant-based delivery systems for enhanced mucosal drug absorption	Phase I	[68,69]
Lyonase	Britannia (Stada)	Dry powder technology	Phase III	[70,71]
Thiolated polymers	Thiomatrix	Thiolated polymers (e.g., chitosan and polyacrylates) with properties such as mucoadhesion, absorption enhancement and *in situ* gelling	Phase I	[72,73]
Tight junction modification	Nastech*	Cell-based screening used to identify combinations of ingredients that can improve epithelial drug transport (e.g., cyclodextrins, phospholipids, surfactants)	Phase II	[74,75]

*Became MDRNA, Inc. during 2008 and plans were announced to divest intranasal programmes.

An intranasal PS-buprenorphine formulation has completed Phase I and Phase II clinical trials. In two Phase I clinical trials, rapid attainment of analgesic plasma levels was achieved with the intranasal PS formulation [9].

A Phase II clinical trial of the intranasal PS-buprenorphine formulation achieved its primary end point of pain relief over the period of 8 h from drug administration [9]. The randomised, double-blind, placebo-controlled single dose study in 360 patients undergoing bunionectomy compared the PS formulation at buprenorphine doses of 0.1, 0.2, 0.4 and 0.6 mg with both placebo and oral hydrocodone/paracetamol (10 mg/1000 mg). A dose response was demonstrated and 0.6 mg intranasal buprenorphine was statistically superior to the oral medication for pain relief with a strong trend to superiority at lower doses. The secondary efficacy measure was time to rescue medication, and a strong trend to superiority over the oral medication was also demonstrated. The most frequent adverse events were opioid-related, and there were few reports of local irritancy from the nasal medication.

Further buprenorphine-containing PS intranasal products are in development for the treatment of chronic pain and opiate addiction [9].

4. Alternative technologies

Table 2 provides a summary of other proprietary intranasal drug delivery technologies, their potential areas of application and stage of development.

5. Conclusions

PecSys is an innovative drug delivery system that turns from a liquid into a gel when applied to mucosal tissue surfaces. This property opens up a wide range of opportunities for developing enhanced drug products.

Applications of PS so far have focused on intranasal drug delivery and crisis conditions, particularly acute pain and breakthrough cancer pain. The nasal route of administration is still relatively underexploited despite having the obvious advantages of fast absorption and simple, convenient dosing. Although simple aqueous solution formulations have been the preferred option (in the same way an immediate release tablet or capsule is the first choice for oral administration), such an approach may not always be appropriate based on the physicochemical properties of the drug, its nasal permeability or the target pharmacokinetic profile. Hence, the availability of a new delivery technology such as PS should expand the range of drugs for which nasal administration is viable.

6. Expert opinion

From a developmental and regulatory viewpoint PS is an attractive drug delivery technology because it is based on pectin, a well-characterised and long-established ingredient. The safety profile of pectin supports its routine use in medicines on an acute or chronic basis. Gel formation has been shown to modify the rate of systemic drug absorption and clearly has the proven ability to modulate the pharmacokinetic

profile and produce innovative new medicines, particularly in the area of pain control.

Applications so far have focused on intranasal delivery of potent analgesic agents. Such drugs can be associated with potentially serious side effects. The potential for PS to modulate absorption and attenuate the high C_{max} associated with well-absorbed drugs and thus improve the side effect profile is a highly attractive proposition. The utility of this technology has been applied to optimise fentanyl pharmacokinetics for intranasal use in breakthrough cancer pain. The Phase III clinical trial data from NasalFent have already demonstrated how these pharmacokinetic benefits translate into products that provide enhancements in care for patients with breakthrough cancer pain, with rapid onset of pain relief and high acceptability. NasalFent is expected to be among the first commercial products using PS and will be used for treatment of breakthrough cancer pain, where it will compete with several other delivery technologies, all of which have the aim of providing rapid and effective pain relief. The performance of NasalFent in this arena will provide a valuable insight into the patient and prescriber acceptance of a nasal formulation, and more specifically PS technology, when put alongside other non-invasive routes of delivery.

Not all drugs may be suitable for intranasal delivery, with potential limitations arising from unfavourable dose and solubility characteristics. If the therapeutic dose of a drug is high then it may not be possible to formulate a solution containing the required amount in a suitable volume for nasal administration (typically up to 0.2 ml per nostril). Similarly, the solubility of a drug may limit its ability to be given intranasally in the form of a solution.

As with any delivery system, the compatibility of the drug with the PS vehicle needs to be considered. In this regard, pectin is an anionic polymer and the potential for charge interaction with cationic drugs needs to be considered on a case-by-case basis.

Work so far has focused on the use of PS for intranasal delivery, but there are also opportunities to develop products for application to other mucosal surfaces such as the eye, oral cavity and vagina for local or systemic drug treatments.

Declaration of interest

P Watts and A Smith are both employees of Archimedes Development Limited.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Costantino HR, Illum L, Brandt G, et al. Intranasal delivery: physicochemical and therapeutic aspects. Int J Pharm 2007;337:1-24
   •• **Formulation-focused review of nasal delivery.**
2. Illum L. Nasal drug delivery - possibilities, problems and solutions. J Control Release 2003;87:187-98
   •• **Concise review of nasal delivery.**
3. Rapoport A, Winner P. Nasal delivery of antimigraine drugs: clinical rationale and evidence base. Headache 2006;46 Suppl 4:S192-201
4. Nascobal (cyanocobalamin USP) nasal spray. Available from: www.nascobal.com/product website [Last accessed 26 January 2009]
5. Christensen KS, Cohen AE, Mermelstein FH, et al. The analgesic efficacy and safety of a novel intranasal morphine formulation (morphine plus chitosan), immediate release oral morphine, intravenous morphine, and placebo in a postsurgical dental pain model. Anesth Analg 2008;107:2018-24
6. Britannia Pharmaceuticals, Apomorphine nasal. Available from: www.britannia-pharm.co.uk/partnerships.shtml#Apo-nasal%20PD [Last accessed 26 January 2009]
7. Ikano Therapeutics Inc. Midazolam. Available from: http://www.intranasal.com/midazolam.html [Last accessed 23 March 2009]
8. Archimedes Pharma Announces First Positive Phase III Clinical Trial Results for NasalFent. Available from: www.archimedespharma.com/newseventsNews-091008.html [Last accessed 30 March 2009]
9. Vernalis R&D Centre, Post operative pain: V1003. Available from: www.vernalis.com/ver/rdc2/pain/v1003/ [Last accessed 26 January 2009]
10. Leary AC, Dowling M, Cussen K, et al. Pharmacokinetics and Pharmacodynamics of Intranasal Insulin Spray (Nasulin™) Administered to Healthy Male Volunteers: Influence of the Nasal Cycle. Journal of Diabetes Science and Technology 2008;2:1054-1060
11. Washington N, Washington C, Wilson CG. Physiological Pharmaceutics: barriers to drug absorption, 2nd edition, Taylor & Francis, London, 2001; p. 211
12. Soane RJ, Frier M, Perkins AC, et al. Evaluation of the clearance characteristics of bioadhesive systems in humans. Int J Pharm 1999;178:55-65
13. Cheng YH, Dyer AM, Jabbal-Gill I, et al. Intranasal delivery of recombinant human growth hormone (somatropin) in sheep using chitosan-based powder formulations. Eur J Pharm Sci 2005;26:9-15
14. FluMist® nasal flu vaccine spray for children and adults. Available from: www.flumist.com [Last accessed 26 January 2009]
15. Mcneela EA, Jabbal-Gill I, Illum L, et al. Intranasal immunization with genetically detoxified diphtheria toxin induces T cell responses in humans: enhancement of Th2 responses and toxin-neutralizing antibodies by formulation with chitosan. Vaccine 2004;22:909-14
16. Klas SD, Petrie CR, Warwood SJ, et al. A single immunization with a dry powder anthrax vaccine protects rabbits against lethal aerosol challenge. Vaccine 2008;26:5494-502
17. DelSite Files IND for Nasal Powder H5N1 (Bird Flu) Influenza Vaccine. Available from: www.reuters.com/article/pressRelease/idUS170526+20-Aug-2008+GNW20080820 [Last accessed 26 January 2009]

18. Rennie P, Bowtell P, Hull D, et al. Low pH gel intranasal sprays inactivate influenza viruses in vitro and protect ferrets against influenza infection. Respir Res 2007; 8: 38
19. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain 1990;41:273-281
20. Akela Pharma, products, Fentanyl TAIFUN®. Available from: www.akelapharma.com/products.html [Last accessed 26 January 2009]
21. Alexza pharmaceuticals product pipeline. Available from: www.alexza.com/products [Last accessed 26 January 2009]
22. Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. Curr Med Res Opin 2007;23:223-33
23. Darwish M, Kirby M, Robertson P, et al. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. J Clin Pharmacol 2007;47:343-50
24. Lennernäs B, Hedner T, Holmberg M, et al. Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. Br J Clin Pharmacol 2004;59:249-53
25. Hartrick CT, Bourne MH, Gargiulo K, et al. Fentanyl iontophoretic transdermal system for acute-pain management after orthopedic surgery: a comparative study with morphine intravenous patient-controlled analgesia. Reg Anesth Pain Med 2006;31:546-54
26. Tombs M, Harding SE. An Introduction to Polysaccharide Biotechnology, Taylor & Francis, London, 1998; p. 47-94
27. Food Chemicals Codex, Fifth Edition. National Academies Press, Washington, 2003; 321-4
28. United States Pharmacopeia 30 / National Formulary 25. US Pharmacopeial Convention, Rockville, MD, 2006; 2869
29. Rolin C. Chapter 10. Pectin. In: Whistler RL and BeMiller JN, Editors, Industrial Gums. Academic Press, New York, 1993; 257-93
30. May CD. Industrial Pectins: Sources, production and applications. Carbohydrate Polymers 1990;12:79-99
31. Carrington Laboratories Inc. Aloe pectins. US5929051; 1999
32. West Pharmaceutical Services Drug Delivery & Clinical Research Centre Limited. Pectin compositions and methods of use for improved delivery of drugs to mucosal surfaces. US6432440; 2002

•• **Patent covering PecSys technology.**

33. Eichner H, Behbehani AA, Hochstrasser K. Diagnostic value of nasal secretions, current state: normal values. 1. Laryngol Rhinol Otol (Stuttg) 1983;62:561-5
34. Lorin MI, Gaerlan PF, Mandel ID. Quantitative composition of nasal secretions in normal subjects. J Lab Clin Med 1972;80:275-281
35. Guyton AC, Hall JE. Guyton & Hall, Textbook of medical physiology, tenth edition, W.B. Saunders, Philadelphia, 2000;899-915
36. Davis GA, Rudy AC, Archer S, et al. Effect of fluticasone propionate nasal spray on bioavailability of intranasal hydromorphone hydrochloride in patients with allergic rhinitis. Pharmacotherapy 2004;24:26-32
37. Davis GA, Rudy AC, Archer SM, et al. Bioavailability and pharmacokinetics of intranasal hydromorphone in patients experiencing vasomotor rhinitis. Clin Drug Investig 2004;24:633-9
38. Greiff L, Andresson M, Svensson J, et al. Absorption across the nasal airway mucosa in house dust mite perennial allergic rhinitis. Clin Physiol Funct Imaging 2002;22:55-7
39. Wu J, Wei W, Wang LY, et al. A thermosensitive hydrogel based on quarternized chitosan and poly(ethylene glycol) for nasal drug delivery system. Biomaterials 2007;28:2220-32
40. Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RSR. Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan. AAPS PharmSciTech 2006; 7: Article 67 (http://www.aapspharmscitech.org)
41. Cao SL, Ren XW, Zhang QZ, et al. In-situ gel based on gellan gum as new carrier for nasal administration of mometasone furoate. Int J Pharm 2009;365:109-115
42. Axelos MAV, Thibault J-F. Chapter 6. The chemistry of low methoxyl pectin gelation. In: The Chemistry and Technology of Pectin. Walter RH, Editor, Academic Press, San Diego, 1991; 109-18
43. Thakur BR, Singh RK, Hanada AK. Chemistry and uses of pectin – a review. Crit Rev Food Sci Nutr 1997;37:47-73
44. Pietrusko RG. Drug therapy reviews: pharmacotherapy of diarrhea. Am J Hosp Pharm 1979; 36: 757-67
45. Di Lorenzo C, Williams CM, Hajnal F, Valenzuela JE. Pectin delays gastric emptying and increases satiety in obese subjects. Gastroenterology 1998;95:1211-5
46. Martindale, Thirty-fifth edition. Sweetman SC, Editor, Pharmaceutical Press, London, 2007; 1948
47. Handbook of Pharmaceutical Excipients, Fifth Edition. Rowe RC, Sheskey PJ and Owen SC, Editors, Pharmaceutical Press, London and American Pharmacists Association, Washington, 2006; 507-8
48. Itoh K, Hirayama T, Takahashi A, et al. In situ gelling pectin formulations for oral drug delivery at high gastric pH. Int J Pharm 2007;335:90-6
49. Badve SS, Sher P, Korde A, Pawar AP. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. Eur J Pharm Biopharm 2007;65:85-93
50. Sriamornsak P, Thirawong N, Weerapol Y, et al. Swelling and erosion of pectin matrix tablets and their impact on drug release behaviour. Eur J Pharm Biopharm 2007;67:211-9
51. Valenta C. The use of mucoadhesive polymers in vaginal delivery. Adv Drug Deliv Rev 2005;57:1692-712
52. Charlton ST, Davis SS, Illum L. Evaluation of bioadhesive polymers as delivery systems for nose to brain delivery: in vitro characterisation studies. J Control Release 2007;118:225-34
53. Charlton S, Jones NS, Davis SS, Illum L. Distribution and clearance of bioadhesive formulations from the olfactory region in man: effect of polymer type and nasal delivery device. Eur J Pharm Sci 2007;30:295-302
54. DelSite Biotechnologies, Inc., Technology, GelSite® polymer. Available from: www.delsitebiotechnologies.com/newfiles/gelsite.html [Last accessed 26 January 2009]
55. DelSite Biotechnologies, Inc., Technology, GelVac™ Intranasal Powder Vaccine Delivery System. Available from: www.delsitebiotechnologies.com/newfiles/gelvac.html [Last accessed 26 January 2009]

56. IPPA, International Pectin Producers Association, Safety and legal status of pectins. Available from: www.ippa.info/safety.htm [Last accessed 26 January 2009]
57. Stable Microsystems, Texture analysis. Available from: www.stablemicrosystems.com [Last accessed 26 January 2009]
58. Leitner VM, Guggi D, Krauland AH, Bernkop-Schnürch A. Nasal delivery of human growth hormone: in vitro and in vivo evaluation of a thiomer/glutathione microparticulate delivery system. J Control Rel 2004; 100: 87-95
59. Moksnes K, Fredheim O, Klepstad P, et al. Early pharmacokinetics of nasal fentanyl: is there a significant arterio-venous difference? Eur J Clin Pharmacol 2008; 64: 497-502
60. Davies G, Fisher A, Knight A, Love R. Nasalfent, a novel intranasal formulation of fentanyl, is well-tolerated during treatment of breakthrough cancer pain. Proceedings of 10th Congress of the European Association for Palliative Care, Budapest, 2007; oral abstract 25
61. Davies G, Fisher A, Knight A, Love R. Nasalfent, a novel intranasal formulation of fentanyl, is rapidly effective and well-tolerated during treatment of breakthrough cancer pain, Proceedings of 10th Congress of the European Association for Palliative Care, Budapest, 2007; poster abstract 711
62. Davies G, Fisher A, Knight A, Love R. Rapid pain relief with fentanyl citrate nasal spray (Nasalfent) in cancer patients with breakthrough pain, Proceedings of 10th Congress of the European Association for Palliative Care, Budapest, 2007; poster abstract 712
63. Danbiosyst UK. Systemic drug delivery compositions comprising a cationic substance. US5554388; 1996
64. Archimedes Development. Vaccine compositions including chitosan for intranasal administration and use thereof. US7323183; 2008
65. Archimedes Pharma Limited, Nasal technology, ChiSys®. Available from: www.archimedespharma.com/productArchiDevChiSys.html [Last accessed 26 January 2009]
66. Bentley Pharmaceuticals Inc. Pharmaceutical compositions and methods for peptide treatment. US7244703; 2007
67. CPEX Pharmaceuticals Inc, CPE-215® Permeation Enhancement Technology. Available from: www.cpexpharm.com/company.htm [Last accessed 26 January 2009]
68. The UAB, Research Foundation. Absorption enhancers for drug administration. US5661130; 1997
69. Aegis Therapeutics, Inc. Intravail® Technology. Available from: http://aegisthera.com/technology.html [Last accessed 26 January 2009]
70. Britannia Pharmaceuticals Limited. Powdered compositions of sensitive active materials in at least partially amorphous state. WO2005084646; 2005
71. Britannia Pharmaceuticals, Apomorphine nasal. Available from: www.britannia-pharm.co.uk/partnerships.shtml#Lyonase%20delivery%20description [Last accessed 26 January 2009]
72. Thiomatrix, Drug delivery technologies. Available from: www.thiomatrix.com/technology/technology.html [Last accessed 26 January 2009]
73. Bernkop-schnürch A. Muco-adhesive polymers, use thereof and method for producing the same. EP1126881; 2004
74. Nastech Pharmaceutical Company, Inc. Compositions and methods for enhanced mucosal delivery of Y2 receptor-binding peptides and methods for treating and preventing obesity. US7157426; 2007
75. Nastech Pharmaceutical Company, Inc. Compositions and methods for enhanced mucosal delivery of parathyroid hormone. US7244709; 2007

Affiliation

Peter Watts[†1] PhD & Alan Smith[2] PhD
[†]Author for correspondence
[1]Director, Pharmaceutical Development,
Archimedes Development Limited,
Albert Einstein Centre,
Nottingham Science and Technology Park,
University Boulevard,
Nottingham NG7 2TN, UK
Tel: +44 0 115 9078700; Fax: +44 0 115 9078701;
E-mail: peterwatts@archimedespharma.com
[2]Vice-President,
Research and Development,
Archimedes Development Limited,
Albert Einstein Centre,
Nottingham Science and Technology Park,
University Boulevard,
Nottingham NG7 2TN, UK