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Review Article

Development of the RapidMist™ drug delivery system for the treatment of diabetes, cardiovascular diseases and breakthrough cancer pain

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Abstract

The current advocacy of intensive diabetes therapy regimens involving multiple daily injections places a heavy burden of compliance on patients and has prompted interest in developing alternative, less invasive routes of delivery. Among alternative methods for administering insulin, Generex Biotechnology has developed the RapidMist™ Diabetes Management System. The technology allows a liquid aerosolized formulation of insulin (Oral-lyn™, formerly Oralin™) to be delivered accurately into the mouth of the patient via a spray. This novel pain-free delivery system has several important attributes: rapid absorption, a user-friendly administration technique, precise dosing control (comparable to injection within 1 U) and bolus delivery of drug. Several studies conducted in subjects with type 1 and type 2 diabetes demonstrated clearly that Oral-lyn™ provides metabolic control comparable to s.c. injections of insulin. The simplified means of pain-free prandial insulin delivery offered by this technique will significantly reduce the incidence of major complications by increasing patient compliance, resulting in the consistent drug administration necessary to regulate blood glucose levels.

Introduction

The medical and pharmaceutical industry has been working to overcome the challenges of delivering large-molecule therapeutics orally (1-8). Oral delivery of drugs is regarded as the safest, most convenient and most economical method. Patient compliance with a dosing regimen is typically higher for orally delivered medicines compared to other invasive methods of administration, such as injections. However, many drugs cannot be delivered in oral form, either because they are too large (molecular weight > 2000) or because they are electrically charged molecules unable to pass through the mucosal membrane to reach the bloodstream. These molecules are easily degraded by acids and enzymes in the digestive tract, and as such, can be delivered only by injection or other nonoral means. It is a well-known fact that many subjects refuse to accept daily injection therapy and this may affect compliance in the effective treatment of diseases such as diabetes. Noncompliance and reluctance to take multiple painful daily injections prompted the search for noninvasive methods of administration of large-molecule therapeutics, *e.g.*, insulin to treat diabetes.

This review describes the development of the RapidMist™ Delivery System and the recent results of clinical studies in type 1 and type 2 diabetic patients comparing the efficacy of the Oral-lyn™ oral insulin spray to s.c. insulin (9-13). The article also describes the applicability of the RapidMist™ technology to the treatment and management of conditions such as cardiovascular disorders and breakthrough cancer pain (14).

Rationale for Oral-lyn™ development

The search for an oral form of insulin has been under way since Banting and Best discovered insulin. Oral insulin would not only free diabetic patients from some of the painful and inconvenient daily injections, but would also provide a more physiological route of administration.

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Fig. 1. RapidMist™ delivery device.

The oral mucosa provides a nearly ideal noninvasive portal of entry into the systemic circulation for the following reasons: 1) the oral cavity is relatively permeable; 2) it is readily accessible; 3) it has a very rich blood supply, with many superficial blood vessels; and 4) it is a very robust area, with short recovery times after stress or damage. The combination of these excellent drug delivery features makes the buccal cavity the ideal route for the administration of insulin and other protein therapeutics, such as low-molecular-weight heparins, vaccines, hormones, etc.

Development of the RapidMist™ Diabetes Management System

There have been a number of efforts to develop alternative methods for administering insulin. We have developed the RapidMist™ delivery device (Fig. 1), which is characterized by fast access to the circulation, precise dosing control, a simple, self-administration procedure and bolus delivery of drug. This system is based on a proprietary formulation technology, which allows a liquid pharmaceutical formulation to be delivered accurately into the mouth via an aerosolized spray. The system introduces a high-velocity, fine-particle aerosol into the mouth, resulting in markedly increased deposition of the preparation over the regional mucosa. The oral mucosa presents a barrier for the absorption of peptides, but when the barrier is overcome using a high-velocity aerosol spray and absorption enhancers, insulin can be delivered to the bloodstream. It is a well-known fact that thin oral membranes comprised of many superficial blood vessels guard the ample surface area in direct contact with the circulation. A fast-moving, fine-particle aerosol is able to cross this thin membrane (droplets impact at speeds of 80-100 mph). Once they have penetrated these superficial thin layers, the insulin molecules are rapidly absorbed into the bloodstream with the aid of absorption enhancers, and appear in the peripheral circulation within 10 min of application. The RapidMist™ technology has demonstrated the ability to significantly enhance the absorption of both large and small molecules that are otherwise unable to cross the oral mucosal membranes. The proposed mechanism of absorption of Oral-lyn™ is shown in Figure 2.

Benefits of Oral-lyn™

Intensive diabetes therapy requires at least 3-4 injections per day. Oral-lyn™ provides a pain- and needle-free method of administering meal-time insulin for the treatment of diabetes, which is expected to increase compliance. Oral-lyn™ is absorbed into the bloodstream faster than injected insulin, is stable at room temperature and requires no refrigeration. The small size of the device makes it convenient to carry anywhere and to use comfortably in public. The greatly reduced dosing time before a meal translates into a more flexible lifestyle and improved compliance improves the condition, leading to better quality of life. The device and the formulation are also suitable for delivering other large- and small-molecule injectable therapeutics through the oral mucosal membranes.

Preparation and pharmaceutical properties of Oral-lyn™

Oral-lyn™ is prepared by dissolving regular recombinant human insulin crystals (supplied by Eli Lilly) in water at neutral pH (7.3-7.6). The other ingredients, *e.g.*, glycerin, phenols, stabilizers (to improve stability and facilitate storage at room temperature) and absorption enhancers (to aid absorption through the oral mucosa) are added to this solution. The solution is mixed thoroughly and the pH adjusted again if necessary. All components of the formulation are FDA-approved chemicals for human consumption and pharmaceutical use. This solution is then placed in an anodized canister fitted with a proprietary metered-dose valve and charged with the non-CFC propellant HFA-134a using especially designed aerosol equipment. The end product is an aerosolized aqueous insulin solution (Oral-lyn™) delivered via the RapidMist™ device

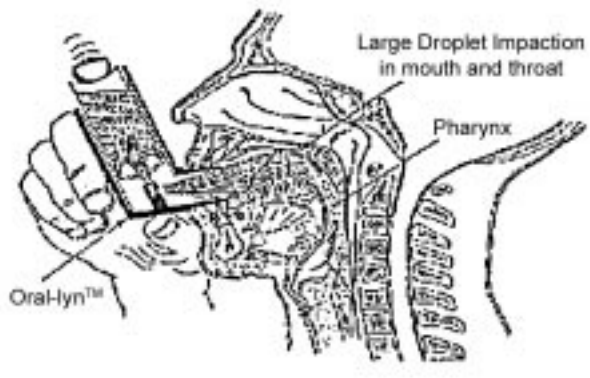

Fig. 2. Proposed mechanism of absorption of Oral-lyn™.

(a modified metered-dose inhaler, or MDI).

Oral-lyn™ is a tasteless, colorless liquid aerosol mist that causes no irritation, burning or discomfort in the mouth after repeated administration, as confirmed by the results of short- and long-term clinical studies. The formulation is rapidly absorbed in the mouth within 5-10 min and shows a faster onset of action than s.c. insulin (Humulin-R). The insulin dose per puff (spray) can be controlled by adjusting the insulin concentration in the formulation or by the metered-dose valve chamber.

Accuracy of dose delivery with the RapidMist™ device

The treatment of diabetes requires precise dosing of insulin in order to avoid the large fluctuations in glucose levels after meals and throughout the day. The RapidMist™ device is capable of delivering the precise dose (comparable to injection within 1 U) required by diabetic patients. The accuracy of dose delivery with the RapidMist™ device was examined by analyzing individual puffs and measuring the amount of insulin in each puff using the insulin HPLC assay technique (Eli Lilly). The solution from the device was sprayed into a fixed volume of buffer solution at low pH. The insulin was allowed to dissolve properly by mixing and stirring the contents of the flask, and a fixed volume of this solution was then injected into an HPLC column. The vial was weighed before and after each puff to make sure that each puff was delivered consistently, and insulin analysis was performed using the HPLC assay. The HPLC analysis of each collected puff (dose) showed quantitatively that the device is capable of delivering the required dose in a very precise manner throughout the life of the vial, as shown in Figure 3.

Evidence for buccal absorption of insulin

To definitively measure the amount of insulin absorbed into the mouth, and not in the lungs, a γ-scintigraphy study was conducted. This open-label, nonrandomized study was conducted in Nottingham, U.K. by Pharmaceutical Profile, Ltd. using a Tc^{99m}-labeled Oral-lyn™ formulation in 7 healthy volunteers. A simple procedure was followed to administer the dose of Tc^{99m}-labeled Oral-lyn™; the subjects were asked to position the device in the mouth and spray the Oral-lyn™ formulation by simply depressing the device once. The subjects were asked not to exhale or breathe for 5 s to keep the dose in the mouth, without expelling the mist out of the mouth during the exhaling process. The subjects repeated the same procedure again to take the next dose. Five minutes after the spray, subjects were photographed with the γ-camera to quantify the distribution of the formulation in the mouth, oropharynx, esophagus, stomach and lungs. As expected, no lung deposition was observed and most of the insulin was detected in the mouth, oropharynx and gastroinestinal tract, as seen in Figure 4.

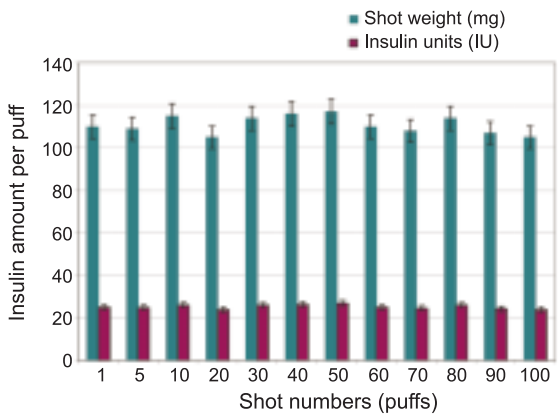

Fig. 3. Accuracy of dose delivery with the RapidMist™ device.

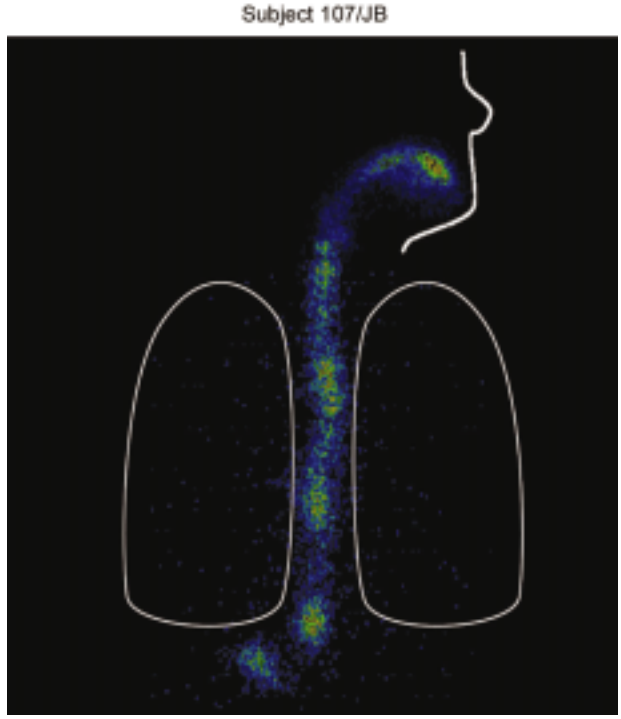

Fig. 4. γ-Scintigraphy study of the deposition of Tc^{99m}-labeled Oral-lyn™.

Clinical studies in diabetes

A study was designed to compare the efficacy of Oral-lyn™ spray in subjects with type 1 diabetes being treated with a Minimed CSII (continuous s.c. insulin infusion) pump to control postprandial glucose levels. The trial was an open-label, randomized, comparative study in 11 patients with type 1 diabetes. Each subject was provided with a placebo device to practice the administration

technique as taught by a video demonstration. All subjects received the following treatments in a completely randomized fashion 3-14 days apart: their regular bolus dose of insulin via CSII pump (bolus dose of 7-10 U administered within 10-15 s); Oral-lyn™ spray (10 puffs administered in less than 15 s); CSII pump running at basal rate (0.7-1.0 U/h) with 10 placebo puffs. Ten minutes after the dose of Oral-lyn™, the bolus CSII or placebo, subjects were asked to consume 360 Kcal of a Boost Plus® liquid meal, as suggested by the FDA. Blood samples for glucose and insulin (free and total) were taken just prior to the meal (–30, 0 min) and for 4 h after the meal. The postprandial glucose levels were significantly reduced by Oral-lyn™ compared to the CSII pump injection treatment (142 ± 6 mg/dl *vs.* 186 ± 9 mg/dl at 60 min; $p < 0.003$). The rise in serum insulin levels was significantly higher with Oral-lyn™ compared with s.c. injections (C_{max} = 98 ± 6 μU/ml for Oral-lyn™ at 30 min *vs.* 65 ± 3 μU/ml for CSII bolus at 62 min; $p < 0.001$). The absorption and onset of action of Oral-lyn™ were faster than the CSII bolus (20 ± 2 min *vs.* 60 ± 7 min). There was no statistically significant difference in the variability of absorption of Oral-lyn™ *vs.* CSII bolus injections, and both treatments were comparable in their absorption characteristics. The absolute bioavailability of Oral-lyn™ was estimated to be 7-8% compared to the CSII bolus injection (Figs. 5 and 6).

A randomized, crossover, proof-of-concept study evaluated the safety and efficacy of Oral-lyn™ in 23 patients with type 2 diabetes in place of meal-time insulin injections. All subjects were receiving multiple daily insulin injections to control their diabetes. Subjects received the following treatments in random order 3-7 days apart: s.c. injection (0.1 U/kg) of Humalog® with placebo puffs at time 0 min, or Oral-lyn™ spray (100 U, equivalent to 7-8 U s.c. insulin) at time 0 min. Ten minutes after each treatment, subjects were given a standard breakfast (360 Kcal of Ensure or Boost liquid meal), as specified by the FDA. Blood samples for glucose and insulin were taken just prior to dosing and for the duration of the study. There were significant differences in the glucose excursions at

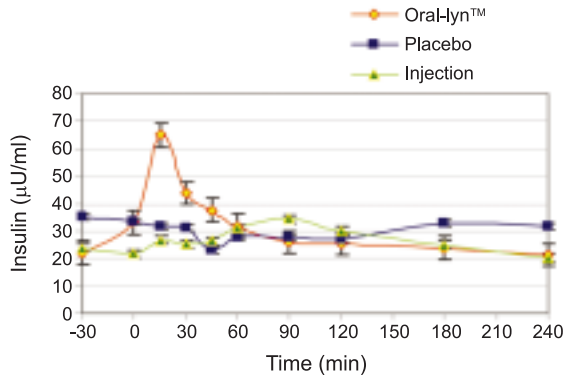

Fig. 6. Mean insulin levels after Oral-lyn™ spray or CSII bolus doses in patients with type 1 diabetes following challenge with 360 Kcal of a Boost Plus® liquid meal.

30 and 60 min after a standard meal, as derived from the lower glucose levels after Oral-lyn™ compared to injections. The 30- and 60-min postprandial glucose levels were significantly lower (19-21%) with Oral-lyn™ compared to the injections (146 ± 5 mg/dl *vs.* 184 ± 7 mg/dl at 30 min and 192 ± 6 mg/dl *vs.* 236 ± 9 mg/dl at 60 min; $p < 0.003$). The increase in serum insulin levels was significantly higher (35%; C_{max} = 98 ± 6 μU/ml for Oral-lyn™ *vs.* 65 ± 3 μU/ml for injections at 30 min; $p < 0.001$). The absorption of Oral-lyn™ through the buccal mucosa was significantly faster (t_{max} = 30 ± 5 min) compared to s.c. Humalog® (t_{max} = 60 ± 10 min). There was no statistically significant difference in the variability of absorption between the two formulations and both treatments showed comparable absorption characteristics. The absolute bioavailability of Oral-lyn™ was estimated to be 7-8% compared to s.c. bolus injections (Figs. 7 and 8).

Potential applications in other diseases

The low-molecular-weight heparin enoxaparin is a powerful anticoagulant and blood thinner that is widely

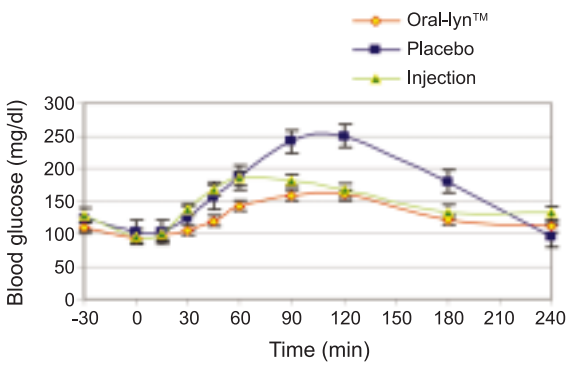

Fig. 5. Mean postprandial glucose excursions after Oral-lyn™ spray or CSII bolus doses in patients with type 1 diabetes following challenge with 360 Kcal of a Boost Plus® liquid meal.

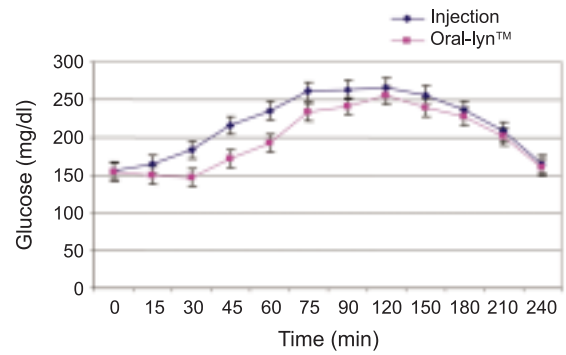

Fig. 7. Mean postprandial glucose excursions after Oral-lyn™ spray or s.c. bolus injection in patients with type 2 diabetes following challenge with 360 Kcal of a Boost Plus® liquid meal.

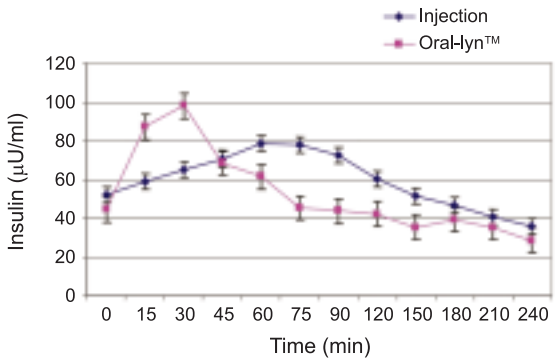

Fig. 8. Mean insulin levels after Oral-lyn™ spray or s.c. bolus injection in patients with type 2 diabetes following challenge with 360 Kcal of a Boost Plus® liquid meal.

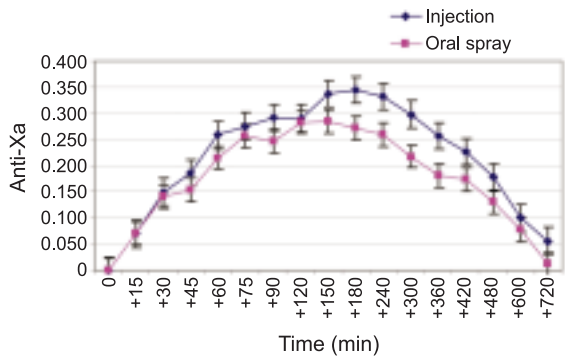

Fig. 9. Low-molecular-weight heparin delivery. Comparison of oral spray formulation of enoxaparin *vs.* s.c. injection of enoxaparin (anti-factor Xa levels).

used for the prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism. Enoxaparin is not absorbed through the mouth and the gastrointestinal tract because of its hydrophilic nature, large molecular weight (~12 kDa) and anionic structure. The preferred routes of administration are continuous i.v. infusion and s.c. injection. Continuous i.v. injection usually requires hospitalization and is painful. Typically, the absorption and antithrombotic efficacy of heparin are estimated by measuring the plasma levels of anti-factor Xa and/or prolongation of the activated partial thromboplastin time (APTT).

An open-label, randomized, crossover, proof-of-concept study was carried out in 25 healthy volunteers to compare the efficacy of oral enoxaparin spray using the RapidMist™ device *vs.* s.c. injection. The study was carried out over a period of 7 days (each visit was scheduled at least 7 days apart to provide an adequate washout period). At the first visit, subjects were given an s.c. injection of enoxaparin (40 mg) under fasting condition and blood samples were collected at 0, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min. At the second visit, subjects were given an equivalent dose of the oral spray of enoxaparin under the same conditions**.** The results are illustrated in Figure 9. There were no statistically significant differences between the oral spray and the s.c. injection, which were comparable to s.c. heparin in anti-factor Xa activity. The absolute bioavailability of the oral preparation was estimated to be 32.7%.

Medical efforts to treat pain, known as pain management, address a large market. Clinical pain is a worldwide problem with serious health and economic consequences. For example, in the United States, it is estimated that the effects of pain cost approximately USD 100 billion annually. Patients experiencing acute pain require fast-acting, short-lived opioid therapy. Fentanyl is a synthetic opioid analgesic which is 50-100 times more potent than morphine. Patients with cancer whose pain is not adequately controlled by very high doses of i.v. morphine or hydromorphone, or those who are experiencing intolerable side effects from these drugs, might be candidates for therapy with fentanyl. Fentanyl can also be given by the epidural or intrathecal route. Today, fentanyl formulations are extensively used for anesthesia and analgesia. Duragesic®, for example, is a transdermal fentanyl patch used in chronic pain management, and Actiq® is a solid formulation of fentanyl citrate on a stick that dissolves slowly in the mouth for transmucosal absorption. However, the absorption profiles of these systems are not fast enough to provide relief from breakthrough pain.

An oral fentanyl spray formulation using the RapidMist™ device and s.c. fentanyl were therefore compared in an open-label, randomized study in 16 healthy subjects. Subjects were given an i.m. injection of fentanyl (25 μg, a dose that does not induce a deep anesthetic effect) under fasting conditions on day 1 and blood samples were collected at 0, 10, 20, 30, 40, 50, 60, 75, 90, 120, 180, 240, 300 and 360 min. On day 2, the subjects were given an oral spray of fentanyl (25 μg) under the same conditions. There were no statistically significant differences in the blood levels of fentanyl after s.c. injection or oral spray administration. The absorption and onset of action of the oral fentanyl spray occurred within 2-3 min after the application. The absolute bioavailability of this preparation was estimated to be 100% (Fig. 10).

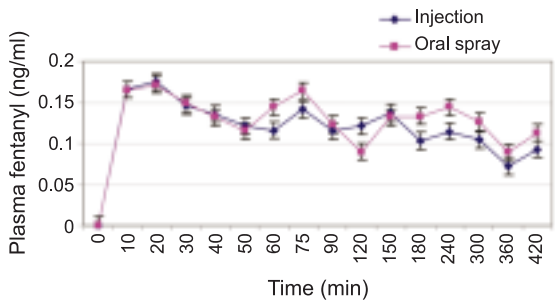

Fig. 10. Oral fentanyl spray delivery. Comparison of oral spray formulation *vs.* s.c. injection (fentanyl plasma levels).

Conclusions

HPLC analysis of each dose showed quantitatively that the RapidMist™ device is capable of delivering the required dose of insulin in a very precise manner throughout the life of the vial. In healthy subjects, Oral-lyn™ spray administered via the RapidMist™ device resulted in insulin deposition in the mouth and not in the lungs. Thus, this formulation does not pose any lung safety issues, in contrast to the pulmonary delivery of dry powder insulin formulations.

Studies conducted in subjects with type 1 diabetes receiving multiple daily insulin injections showed that Oral-lyn™ was absorbed faster than insulin given by injection and was able to control postprandial glucose levels after a standard meal in a manner similar to s.c. injection. Studies performed in subjects with type 2 diabetes receiving multiple daily insulin injections also demonstrated that Oral-lyn™ treatment resulted in significantly reduced postprandial glucose excursions and a statistically significant and potentially clinically relevant improvement in glycemic control. Furthermore, there was no statistically significant difference in the variability of absorption of Oral-lyn™ compared to s.c. injection.

The RapidMist™ device was found to be very efficient in delivering the low-molecular-weight heparin enoxaparin. The plasma anti-factor Xa concentrations were comparable to after s.c. injection of enoxaparin. Thus, the RapidMist™ device may be useful in the treatment of DVT and other thromboembolic disorders.

The RapidMist™ technology was also found to be very efficient for delivering fentanyl for the treatment of breakthrough pain. The peak plasma concentration of oral fentanyl spray was comparable to that of s.c. fentanyl, with a very rapid onset of action (within 5 min of application). This makes it an ideal candidate for breakthrough pain management.

Taken together, these data suggest that noninvasive buccal delivery via the RapidMist™ technology may offer important advantages in the treatment of diabetes, cardiovascular diseases and breakthrough cancer pain. The RapidMist™ device may increase compliance, as patients will be more willing to take their medication without the reluctance and fear associated with painful injections.

In summary, the RapidMist™ technology is able to successfully deliver a broad range of challenging therapeutic macromolecules, including large proteins, and is associated with clinically relevant bioavailability and efficacy in human subjects.

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