MucoJet: a novel noninvasive buccal mucosa immunization strategy

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Immunization by injection is by far the most widely used vaccine delivery route for the prevention of infectious diseases. Despite its wide application, its ability to induce pain, sterility of needles and syringes used for vaccination as well as several other safety concerns often lead to poor patient compliance (1). These concerns have led to the search of noninvasive routes such as oral, nasal, ophthalmic and buccal cavity delivery (2-4). The advantages for noninvasive delivery routes are that they increase patient compliance, induce local and systemic immune responses and reduce patient handling by clinicians. Although the oral and nasal routes have been widely explored, the buccal route has not been equally explored due lack of appropriate vaccine delivery strategies (3). Despite so, the buccal mucosa offers several advantages as a vaccine delivery site given that it is well supplied by vascular and lymphatic drainage systems. It has a first liver by-pass metabolism and avoids enzymatic drug decomposition in the gastrointestinal tract (GIT). As pointed out by Shojaei (5), it is highly suitable for a retentive device and with the right dosage and formulation, the permeability and local environment can be controlled in order to allow for high antigen retention and slow release.

To overcome the aforementioned shortcomings of vaccine delivery via the buccal cavity route, the power of innovation has brought a new non-invasive needle-free delivery tool to the pharmaceutical industry known as the "MucoJet" (6). The device is mechanically designed to penetrate the buccal mucosal layer. It is made of two compartments of which the outer component is made of a water chamber while the interior is made of two reservoirs separated by a porous plastic membrane and movable piston. In the interior compartment, the lower reservoir contains a dry chemical propellant made of citric acid and carbon dioxide (CO_2) and is separated from the upper reservoir by an in-built porous membrane and movable piston. On the other end, the upper reservoir is sealed from the exterior compartment by a pH-responsive polymeric membrane having a dissolution threshold of pH 6.0. The upper reservoir is designed to carry the vaccine solution and is linked to the piston from the lower chamber on one end and a sealed delivery nozzle on the other. For vaccine delivery, the devise is put in the buccal cavity where the interior and exterior compartments are clicked together resulting in dissolution of the polymeric valve membrane sealing the propellant reservoir. As water gets in contact with the chemical propellant in the reservoir, this triggers a chemical reaction that produces CO_2 gas. Increase in CO_2 production raises the pressure in the propellant chamber causing the piston to break the nozzle of the drug chamber thereby dispensing the vaccine into the mucosal layer of the buccal cavity.

Although the buccal epithelium does not have tight

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junctions between cells similar to tight junctions found in the skin epithelium, the presence of gap junctions such as desmosomes and hemidesmosomes located on the surface epithelial can reduce drug permeation. To test the permeability of drugs delivered via the buccal cavity several permeability experiments using animal buccal mucosa models have been developed (7). Squier (8) showed that horse radish peroxidase (HRP) administered through the buccal mucosa only reached the first cell layers while sub-epithelial administered HRP reached as deep as the connective tissue. In order to test the ability of the MucoJet to penetrate the buccal mucosal layer, Aran *et al.* (6) performed a series of simulations using freshly prepared porcine buccal epithelium mounted in Transwell chambers exposed to a solution of fluorescein-labelled ovalbumin. They used the porcine buccal epithelium as an animal model because of its resemblance to the human buccal mucosa both in ultra-structure and enzyme activity (9-11). One vital essential element in testing diffusant permeation is the thickness of the mucosa. Kulkarni *et al.* (12) estimated a mucosal thickness of 500 µm as ideal for the simulation of natural mucosal barriers for diffusant permeation. However, Aran *et al.* (6) set the thickness at 800 µm in their simulation studies and showed that the MucoJet had eight-fold higher capacity to deliver ovalbumin across the porcine buccal mucosa compared to the topical dropwise application. They observed that increasing the output pressure from 10 to 40 kPa significantly increased ovalbumin permeation through the buccal mucosa clearly demonstrating that delivery efficiency was a function of the exerted pressure. These findings show that the MucoJet output pressure can be optimized to penetrate different buccal mucosal layers to precisely deliver vaccines at targeted locations.

One of the major drawbacks for buccal cavity vaccine delivery has been the lack of antigen retention at delivery sites. Moreover, the presence of saliva in the buccal cavity makes vaccine retention a challenge given that it can lead to vaccine removal from delivery sites unless the antigen is administered with a bioadhesive formulation such as polyacrylic acid, hyaluronic acid, poly methacrylate derivatives, hydrogel and chitosan to prolong vaccine release (5,13-17). To demonstrate depot formation and slow antigen release, Aran *et al.* (6) administered ovalbumin in the buccal mucosa of rabbits using the MucoJet and collected tissue samples from 2–3 hrs post immunization (hpi) up to 6 weeks post immunization (wpi) and showed large ovalbumin deposits at delivery sites for samples collected 2–3 hpi reducing to small patches after 6 wpi. They used Western blot to confirm that the patches observed by histopathology were deposits of ovalbumin earlier administered using the MucoJet. Hence, the MucoJets forms depots at delivery sites enabling slow antigen release thereby avoiding the need of bioadhesive polymers for antigen retention.

It is noteworthy that the buccal mucosa is part of an extensive and highly specialized compartmentalized mucosal associated lymphoid tissue (MALT) endowed with different immune cells that include antigen presenting cells (APCs) such as macrophages and dendritic cells (18,19). These cells play an important role in antigen uptake at vaccine delivery sites, followed by migrating to draining lymph nodes to present the processed antigen derived peptides to CD4 and CD8 T-cells via the major histocompatibility (MHC) molecules I and II. Given its high antigen retention capacity based on its ability to form depots, the MucoJet makes it possible to design systematic studies aimed at elucidating the mechanisms leading to APCs migration to vaccine delivery sites for antigen uptake followed by presentation of processed antigen derived peptides to B- and T-cells. Therefore, its application in vaccine delivery is bound to create a basis for in-depth understanding of innate immune responses induced by vaccination in the buccal cavity. Moreover, the highly adjustable size of its vaccine carrier chamber coupled with its highly flexible trajectory makes it suitable to deliver different vaccine formulations such as nanoparticles, microparticles and various adjuvant emulsions designed to enhance APCs migration to antigen delivery sites. Further, studies on the buccal mucosa MALT have not been exhaustive as the intestine mucosa MALT where several studies have been carried out (20,21). Therefore, the findings by Aran *et al.* (6) that showed threefold higher IgG and IgA levels in rabbits immunized by the MucoJet compared to rabbits immunized by topical drop application create a basis for further research on immune mechanism leading to induction of mucosal and systemic antibody secretion induced by buccal cavity vaccination. They further observed that a boost vaccination after 5 weeks significantly increased blood IgG levels indicating that prime-boost vaccination regimes efficiently increased systemic antibody levels in a similar pattern as observed in injection prime-boost vaccination regimes. Hence, the MucoJet could serve as a gateway to a better understanding of the interplay between optimizing local buccal mucosal vaccine delivery and local MALT immune responses being an area previously less studied due to lack of appropriate vaccine delivery methods.

Finally, suffice to point out that apart from vaccine

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delivery, the MucoJet can be used for drug delivery. Local drug delivery has several applications that include treatment of toothaches, periodontal diseases, microbial infections and dental stomatitis while in dentistry it can facilitate tooth removal. Advantages for using the MucoJet as a local drug delivery device are that it can bypass physical mucosal barriers and avoid local drug degradation by mucosal surface enzymes. Further, it avoids the need for mucoadhesive formulations by inducing drug retention at delivery sites and it has the potential to induce maximum drug absorption through the highly permeable vascular drainage system underlying the mucosa, which could lead to rapid onset of drug action. On the other hand, systemic applications using the MucoJet have the potential to deliver drugs through the highly permeable vascular system underlying the buccal mucosa to other body sites without passing through the gut acidic environment, GIT that contains adverse enzymes that can degrade peptide and protein drugs, and bypass the hepatic first-pass metabolism known to reduce drug bioavailability. Therefore, it is highly anticipated that the MucoJet will find wide applications among clinicians and patients for the treatment of local buccal cavity diseases as well as systemic diseases that require drug delivery aimed at avoiding the gut acid environment and enzymatic degradation in the GIT.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Benet LZ. Effect of route of administration and distribution on drug action. J Pharmacokinet Biopharm 1978;6:559-85.
2. Cleland JL, Langer R. Formulation and delivery of proteins and peptides: design and development strategies. ACS Publications, 1994.
3. Jitendra, Sharma PK, Bansal S, et al. Noninvasive routes of proteins and peptides drug delivery. Indian J Pharm Sci 2011;73:367-75.
4. Pettit DK, Gombotz WR. The development of site-specific drug-delivery systems for protein and peptide biopharmaceuticals. Trends Biotechnol 1998;16:343-9.
5. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci 1998;1:15-30.
6. Aran K, Chooljian M, Paredes J, et al. An oral microjet vaccination system elicits antibody production in rabbits. Sci Transl Med 2017;9. pii: eaaf6413.
7. Morales JO, McConville JT. Novel strategies for the buccal delivery of macromolecules. Drug Dev Ind Pharm 2014;40:579-90.
8. Squier CA. The permeability of keratinized and nonkeratinized oral epithelium to horseradish peroxidase. J Ultrastruct Res 1973;43:160-77.
9. Lesch CA, Squier CA, Cruchley A, et al. The permeability of human oral mucosa and skin to water. J Dent Res 1989;68:1345-9.
10. de Vries ME, Boddé HE, Verhoef JC, et al. Developments in buccal drug delivery. Crit Rev Ther Drug Carrier Syst 1991;8:271-303.
11. Wertz PW, Squier CA. Cellular and molecular basis of barrier function in oral epithelium. Crit Rev Ther Drug Carrier Syst 1991;8:237-69.
12. Kulkarni U, Mahalingam R, Pather SI, et al. Porcine buccal mucosa as an in vitro model: relative contribution of epithelium and connective tissue as permeability barriers. J Pharm Sci 2009;98:471-83.
13. Ch'ng HS, Park H, Kelly P, et al. Bioadhesive polymers as platforms for oral controlled drug delivery II: synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J Pharm Sci 1985;74:399-405.
14. Leung SH, Robinson JR. Polymer structure features contributing to mucoadhesion. II. J Control Release 1990;12:187-94.
15. Guo JH. Investigating the surface properties and bioadhesion of buccal patches. J Pharm Pharmacol 1994;46:647-50.
16. Sanzgiri YD, Topp EM, Benedetti L, et al. Evaluation of mucoadhesive properties of hyaluronic acid benzyl esters. Int J Pharm 1994;107:91-7.
17. Watanabe K, Yakou S, Takayama K, et al. Drug release behaviors from hydrogel prepared with water soluble dietary fibers. J Pharm Sci Technol 1991;51:29-35.
18. Nudel I, Elnekave M, Furmanov K, et al. Dendritic cells in distinct oral mucosal tissues engage different mechanisms to prime CD8+ T cells. J Immunol 2011;186:891-900.
19. Czerkinsky C, Anjueie F, McGhee JR, et al. Mucosal immunity and tolerance: relevance to vaccine development.

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Immunol Rev 1999;170:197-222.
20. Gibbons DL, Spencer J. Mouse and human intestinal immunity: same ballpark, different players; different rules, same score. Mucosal Immunol 2011;4:148-57.
21. Brandtzaeg P, Kiyono H, Pabst R, et al. Terminology: nomenclature of mucosa-associated lymphoid tissue. Mucosal Immunol 2008;1:31-7.

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