Review Article

Intestinal Patch Systems: A Unique Approach

Dr. Pradnya Palekar – Shanbhag*, Priyanka Deshmukh, Prerna Patil, Tejal Gawade, Supriya Lande, Riya Chandra, Drushti Rane
Department of Pharmaceutics, Oriental College of Pharmacy, Sanpada, University of Mumbai, Maharashtra, India.
***Corresponding author's E-mail:** drpradnyaps@gmail.com

Received: 20-04-2019; **Revised:** 23-05-2019; **Accepted:** 01-06-2019.

ABSTRACT

Current trend in drug development is towards peptide/ protein-based therapeutics with approximately 50% of drugs in the pharmaceutical industry comprising peptide/protein drugs. Efforts have been made to develop novel oral delivery technologies for effective administration and better bioavailability of therapeutic proteins/peptide. Oral delivery offers a compliant mode of administering these drugs but the utility is limited by proteolytic degradation in the stomach, intestine and by low permeability of the epithelial barrier. Scientists have focused on developing mucoadhesive intestinal devices as patch systems for oral delivery of therapeutic proteins such as salmon calcitonin, exenatide, insulin etc. Intestinal patch systems are similar in design as the transdermal patches but operate in the GIT. They can be used for treatment of chronic diseases such as diabetes, osteoporosis, hepatitis and chemotherapy. The present review article covers the design and applications of intestinal patch systems.

Keywords: Intestinal patch systems, mucoadhesive, gated hydrogel patch.

INTRODUCTION

Oral drug delivery is one of the most preferred routes of drug administration being noninvasive, easy and can be self-administered. According to a report by the WHO, the adherence to medication for chronic diseases such as hypertension and diabetes in developed countries is only 50% or less. This level of non-compliance leads to increased complications, co-morbidities, deaths with approximately $100 billion incurred costs.[2] Amongst the patients with Type 2 diabetes mellitus, reluctance to start insulin therapy is commonly observed and needle phobia cited as the second most common reason (13%) for failure to start insulin treatment. Further, adherence to injectable regimen was found to be notably lower than oral medications amongst diabetes patients.[1-4] Due to better patient compliance, oral systems are designed in various different forms and cost of production is comparatively lower than injectable formulations. Globally, the oral delivery market in 2013 was $64.3 billion and is predicted to be about $100.8 billion by 2018.[5-6] Oral drug delivery is dependent upon drug release from the formulation in the gastrointestinal tract (GIT), solubilization in the GI fluids, and transport across the gastric/intestinal membrane and then absorption into the systemic circulation in its active form.[7]

Intestinal patch systems are 2–4 layered unique oral mucoadhesive delivery devices designed to deliver small and large molecule therapeutics in a controlled fashion. They have similar conceptual design as that of the transdermal patch but work in different physiological environment. Intestinal patch is of around a millimeter size comprising of a pH sensitive layer, a drug reservoir mucoadhesive layer and a backing layer. Drug release from the intestinal patch is desired to occur over a time frame of hours.[8-12]

Oral delivery of proteins faces several problems due to their instability in the gastrointestinal tract (GIT) and poor permeability across biological membranes, which necessitate their parenteral administration.[13,14] Intestinal mucoadhesive devices help not only to evade the acidic environment of the stomach but also prevent access of proteolytic enzymes present in the GIT to the drug load, therefore avoiding enzymatic degradation of therapeutic proteins. In addition, these devices create high concentration gradient for drug transport, which facilitates uptake of loaded proteins through the intestinal membrane.[15-17]

Advantages of Intestinal Patch Systems

- Prolonged residence time at a single position in the small intestine.
- Sustained unidirectional drug release towards the intestinal mucosa.
- Protection from enzymatic degradation by the impermeable layer.
- Increased bioavailability.

DESIGN OF INTESTINAL PATCH SYSTEMS

Intestinal Patch Systems can be designed in following three patterns:

- Two layered patch systems
- Three layered patch systems
- Four layered patch systems

Two layered patch systems

It comprises of a drug loaded mucoadhesive layer and a water impermeable backing layer. The mucoadhesive layer helps in forming a strong adhesion with the intestinal mucosa. Commonly used mucoadhesive polymers are chitosan and its thiolated derivatives, pectin, polyacrylic acids, alginates, polyvinyl alcohol and cellulose derivatives such as sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose and hydroxypropyl cellulose. Adhesion to the intestinal mucosa occurs due to charge interaction between cationic polymers and negative sialic acid on mucous layer or through formation of hydrogen bond and polymer chain entanglement.[18,19] The backing layer is made of water impermeable polymers such as ethyl cellulose or cellulose acetate and prevents the drug discharge in the lumen resulting in unidirectional drug release at the mucosal surface thus precluding access of proteolytic enzyme towards the loaded proteins preventing the degradation. The patch serves as a drug depot that creates a high concentration gradient further assisting drug transport across the intestinal mucosa. Upon contact with intestinal fluids, the patch adheres to the mucus layer and releases the drug at the site of the attachment.

Three layered & Four layered patch systems

Three layered patch system consists of a pH sensitive layer, a drug loaded mucoadhesive layer and a backing layer whereas four layered patch system consists of separate layer of mucoadhesive polymer and drug layer apart from pH sensitive layer and backing layer. The pH sensitive layer is mostly made of Eudragit polymers to prevent drug release in acidic environment of stomach. Fig. 1 depicts the design patterns of intestinal patches.

Eudragit L & S used for drug release in the intestine & colon respectively. Eudragit L and S contain ionisable carboxylic groups. In low pH environment of the stomach, the carboxylic groups remain unionized and polymer coating remains insoluble. In the intestine, the pH is above 5 and allows these carboxylic groups to ionize and prevents drug release in acidic environment of stomach (protecting them against acidic degradation), while enabling drug release at the intestine for localized site-specific delivery.

To enhance drug absorption, permeation enhancers can be used that can reversibly alter the intestinal absorption barrier and enable higher drug uptake. It is demonstrated that a permeation enhancer dimethyl palmitoyl ammonio propane sulfonate enhanced macromolecule absorption. It is a zwitterionic surfactant that functions through membrane solubilization and temporarily modulates the intercellular tight junctions thereby promoting paracellular uptake.[10]

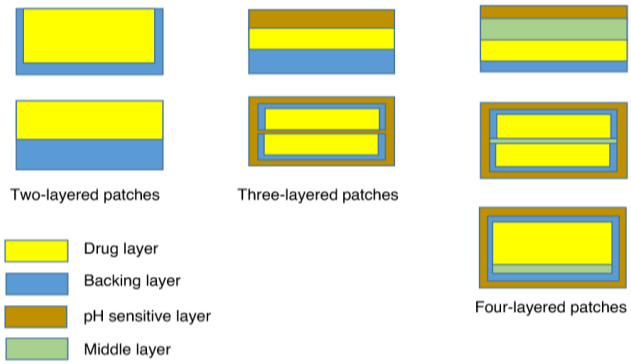

Figure 1: Designs of Intestinal Patch Systems

CLASSIFICATION OF INTESTINAL PATCHES

Intestinal patches can be fabricated in different sizes ranging from few micrometer to millimetre to obtain desired drug release rate and surface area for attachment.[17]

Following are the types of intestinal patch system as per the dimensions:

- *Microsphere patch*
- *Micropatch*
- *Gated hydrogel patch*
- *Drug in adhesive patch*

Microsphere Patch

It consists of three layers:

(i) a mucoadhesive layer;

(ii) a layer of drug-loaded microspheres partially immersed in the mucoadhesive layer;

(iii) an impermeable membrane encompassing the microspheres.

Fig. 2 shows a microsphere patch prepared using cross-linked bovine serum albumin (BSA) microspheres 10–30 µm in diameter loaded with one of three model drugs [sulforhodamine B, phenol red or fluorescein isothiocyanate (FITC)-dextran].[17]

The drug microspheres were spread uniformly and partially pressed into a 5 µm thick mucoadhesive layer of carbopol and pectin. This layer was covered with ethyl cellulose layer. After drying, the three-layered film was cut into small squares and circles. *In vitro* release of sulforhodamine B from patches (4 mm in diameter) into phosphate buffered saline (PBS) was measured in a diffusion cell. It was found that 95% of the drug was released from the mucoadhesive layer, which is significantly higher than that from the backing layer. Drug transport across the intestine from patches (~3 mm in diameter) is tested *in vitro* on rat intestine sections. The intestinal sections were immersed and infused with PBS at a flow rate of 0.05 ml/min. The amount of drug transported across the intestinal wall is determined by

measuring the concentration of model drugs in the receiver fluid. Control experiments are performed by injecting the same total amount of model drug in solution into the intestinal lumen. A significant enhancement in transport across the intestinal wall is observed for all three model drugs: 30% of sulforhodamine B loaded in the patches is delivered across the intestine in 60 min compared with only 10% from solution; 45% of phenol red is delivered across the intestine from the patch system in 60 min compared with 10% from solution; and ~20% of dextran is delivered across the intestine from the patch system in 120 min compared with < 10% from solution. The enhancement is attributed to the localization of the drug at the intestinal wall, thereby providing a high concentration gradient for delivery and the maintenance of unidirectional diffusion towards the wall.[20]

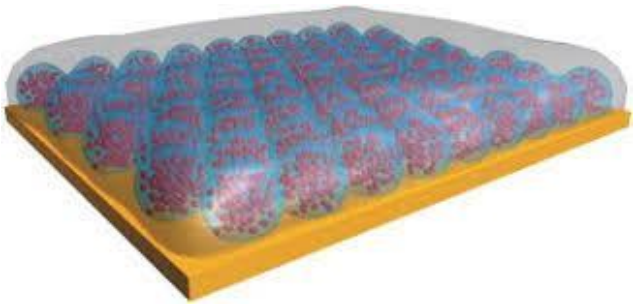

Figure 2: Microsphere Intestinal Patch

Micropatch

The size of the particles can greatly affect drug response generated in the body.[21] Although small particles of <5µm have an increased adherence to the whole gut, it is more likely to induce a localized inflammatory response followed by phagocytosis by macrophages. This leads to an increased risk of the carrier system being degraded after internalization, resulting in a loss of activity.[22] Fig. 3 depicts micropatches as intestinal patch systems. Particles of larger size are taken up less effectively by macrophages, therefore micropatch is fabricated large enough in diameter of 50-200µm and thickness of 2-5µm to prevent endocytosis. However micropatch is designed to be small to travel between intestinal villi, thereby maximizing the large absorptive surface area the intestinal folds provide.

The process for fabricating micropatch involves use of either of three different substrates viz., silicon oxide, porous silicon and poly(methyl methacrylate) (PMMA) have been developed based on standard microelectromechanical system (MEMS) techniques, including photolithography, etching and thin film deposition.

Figure 3: Micropatches as Intestinal patch

Using silicon oxide substrate

Scientists fabricated microdevices from a low temperature oxide (LTO) deposited by low-pressure chemical vapor deposition onto silicon p-type wafers of crystal orientation. The device geometry was defined by a series of photolithography and reactive ion etch (RIE) steps. Photolithography, the process by which a photosensitive polymer (photoresist) is exposed to ultraviolet light through a photomask was used to pattern the device features.[23,24]

Using porous silicon substrate

Porous silicon microdevices were fabricated on a single-side polished silicon p+ type wafer coated with silicon nitride. Photolithography was initially performed to define the area of intended porosity while protecting all other areas of the wafer. The back of the wafer was then etched with SF6 to strip the layer of silicon nitride. Exposed silicon nitride on the front of the wafer was etched with SF6 and the remaining photoresist stripped. The patterned wafers were then anodized and electropolished in an ethanol–hydrofluoric acid solution [1:1 (v/v) for anodization; 4:1 (v/v) for electropolishing in a custom built anodization tank. Porosification took place exclusively along the anodic side of the silicon wafers. Pore size and shape depend on the type of silicon used, the resistivity of the silicon, the current density and the concentration of hydrofluoric acid solution.[25,26]

Using poly(methyl methacrylate) substrate

PMMA microdevices were fabricated on Radio Corporation of America-cleaned silicon p-type wafers, which were first spin-coated with multilayers of PMMA, followed by a layer of positive photoresist.[49] A series of photolithography and RIE steps was used to define the device geometry. After exposure and development of the photoresist, the unmasked area of PMMA was reactive ion etched using O_2 plasma.[25]

Gated hydrogel patch

It provides controlled release of drug using a bilayered self-folding pH-sensitive hydrogel gate. As seen in Fig. 4, the main device consists of two parts – a poly(hydroxyl

methacrylate) [p(HEMA)]-based drug reservoir with targeting function and a hydrogel gate. A hydrogel drug entrapping matrix was prepared by free-radical photo polymerization at room temperature. Hydrogel disks 5 mm in diameter were cut, soaked in a solution containing model candidate acid orange 8 (AO8) or BSA and then dried. Pluronic F127 (BASF), a triblock polymer of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) was used to enhance the permeability. The gate (5 mm in diameter and 60 µm thick) was made from separate layers of p(HEMA) and poly(methacrylic acid-g-ethylene glycol) [p(MAA-g-EG)]. The drug reservoir, loaded hydrogel matrix and bilayered gate were then bonded together by photo-polymerization of the residual monomer from the partially cured bilayered gate. Drug release from the device was controlled by pH-dependent swelling properties of the bilayered gate. In pH 3.0 medium, p(MAA-g-EG) and p(HEMA) hydrogels showed similar swelling response and the gate remained closed and stable. No drug release was seen during a 2 h period. When the pH of the medium was increased to pH 7.3, swelling of the p(MAA-g-EG) increased significantly, whereas the swelling of the p(HEMA) layer remained constant. The increased swelling ratio caused the gate to fold outward until the bonding between the gate and reservoir broke resulting in the release of drug. It took approximately 40 min to open the device gate, after which 90% of the drug was released rapidly. Furthermore, pulsatile release can be achieved by altering the pH. When pH of the medium is returned to pH 3.0, the bilayered gate reverts to its closed state, resulting in a decreased release rate. Although the gate design has a limiting response time of minutes, the chemical structure of the hydrogel, gate thickness and the bilayer ratio can be altered to produce a response time of seconds.[26,27]

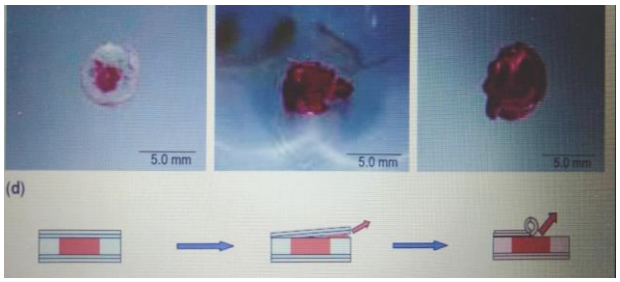

Figure 4: Gated Hydrogel Intestinal patch

Drug in adhesive patch

This device system was designed to increase loading space and hence drug loading dose can be increased. This patch system consists of three layers: (i) a backing layer of ethyl cellulose; (ii) an enteric polymer membrane of HP-55; and (iii) a new drug-carrying layer, based on carbopol, loaded with 30 mg of fluorescein or fluorescein-dextran as a model candidate. The three-layered patch was then heat sealed and cut into 3 mm diameter size. As a reference, the patch was compared with a compressed tablet of 30 mg of fluorescein or fluorescein-dextran mixed with microcrystalline cellulose.[28,29]

Polymeric mucoadhesive devices within a capsule

Polymeric mucoadhesive devices are prepared by direct compression of a homogenous mixture of carbopol/pectin/SCMC in a dry weight ratio of 1:1:2. All weighed polymers are mixed by grinding using a mortar and a pestle. Drug is added to the ground mixture so as to produce a final drug concentration. Homogeneously powdered mixture is then poured into a 13mm pellet press and it is compressed under a pressure of 3 tons using a hydraulic press for 5 min. This procedure produces 400 µm thick disk with a typical diameter of 13mm. Disposable biopsy punches are used to cut this disk into smaller disks with radii of 1-5mm. The disks are placed on a support and coated on all sides using solution of 5% w/v ethyl cellulose in acetone. Acetone is then evaporated at room temperature. These devices are then placed in capsules that are enteric coated with 12.5% w/v Eudragit L 100 in isopropanol. When taken orally, the capsule dissolves in the intestine and releases the device, which subsequently adheres to the mucus layer of the intestine, swells and releases the drug over the time.[30]

EVALUATION

In vitro Release Study

a. Protein release study

For protein release study, BSA and lysozyme were used as model proteins. They were loaded in 5 mm devices (17 mg weight) at 10% device w/w concentration (1.7 mg) and placed in tubes containing 10 ml PBS (pH 7.4). The tubes were subsequently placed on a shaker at 37˚C during the entire study period of 5 hr to mimic intestinal conditions including peristaltic motion. At various time intervals, predetermined volumes of solutions from the tubes were removed and replaced with equal volumes of PBS at every point. Protein concentration of BSA and lysozyme, at each time points were evaluated using micro BCA assay and the absorbance of the samples were determined at 562 nm. Drug release was analyzed as zero order kinetics and the percentage cumulative release of protein over the time was calculated and plotted as concentration-time curve profile.[31]

b. Mucoadhesion study

The strength of mucoadhesion between devices and intestinal mucosa is evaluated using porcine intestine. Porcine intestine of 5 cm pieces are put in a petri dish containing pH 7.4 PBS. 5-mm-sized devices are gently placed on the inner mucosa of the intestine such that the backing layer faced away from the intestinal surface and the whole unit is rocked gently at 37˚C for 30 min. Thereafter, the petri dish is placed inside a microbalance containing a cylindrical tube (2 cm length and 1 cm diameter), hung inside the balance with a string that passed over a pulley. To the free end of the tube, a drop of acrylate glue is added. The tube is allowed to stick gently to the device and the initial weight of the system with the device attached to the intestine is noted. The tube is then

slowly pulled away from the intestine and the weight at the point when the device detached from the mucosa is noted. The difference in these readings is used to evaluate force of mucoadhesion between the device and intestinal mucosa.[31]

***In vivo* Study**

Efficacy studies in rats

After induction of diabetes, animals fasted overnight but given free access to water. The animals are divided into six groups containing six animals each and a seventh group containing three animals. The first six groups were orally administered with insulin devices, insulin devices containing 10% device w/w dimethyl palmitoyl ammonio propane sulfonate (0.6 mg dimethyl palmitoyl ammonio propane sulfonate/animal), insulin devices with externally present 5 mg dimethyl palmitoyl ammonio propane sulfonate in capsule, empty devices, and insulin-dimethyl palmitoyl ammonio propane sulfonate (5 mg) solution. The seventh group was administered with insulin subcutaneously. Insulin dose used for the study was 100 and 1 U/kg for oral and parenteral administration, respectively. All animals were injected with 5 mg/kg metoclopramide hydrochloride prior to the start of treatment, to induce gastric emptying and enable the orally administered capsules to transit from stomach to the intestine. Blood glucose levels from the tail vein were evaluated at different time points ranging from 0 to 8 hr after administration using a commercial blood glucose meter.[32,33]

CONCLUSION

Adhesive patch drug delivery systems have been studied and established for long time due to the efficacy in drug delivery via transdermal and transmucosal routes.[34] Intestinal mucosa can be another important and favourable platform to explore such adhesive patch devices for efficacious drug delivery but has not been well investigated. Use of oral mucoadhesive patches for drug delivery has been reported indicating the benefits and scope[34–37]. This article has a brief report on the design and use of intestinal patch systems for delivering certain therapeutics for chronic diseases. A unique blend of mucoadhesive polymers with desired adhesive properties for continuous and prolonged release of encapsulated therapeutic protein/peptide in a time dependent manner is an effective approach in the intestinal patch systems. These systems present the protein in a localized manner near the intestinal epithelium in an oral drug delivery. This device helps in preventing protein/ peptide dilution or loss in luminal fluids and thus promotes their absorption by offering increased concentration gradient for the transport. Oral administration of intestinal mucoadhesive devices avoids the need for routine injection. Intestinal patch systems provide an effective alternative to injections for management of chronic diseases and can significantly improve quality of life of patients suffering from such diseases.

REFERENCES

1. Garcia-Perez L, Alvarez M, Dilla T. García-Pérez LE[1], Alvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to Therapies In Patients With Type 2 Diabetes. Diabetes Ther., 4, 2013, 175-194. doi: 10.1007/s13300-013-0034-y.

2. Marie TB, Jennifer KB. Medication Adherence: WHO Cares? Mayo Clinic Proceedings, 86, 2011, 304-314. doi: 10.4065/mcp.2010.0575.

3. Jimmy B, Jose J. Patient Medication Adherence: Measures In Daily Practice. Oman Med J, 26, 2011,155-159, doi: 10.5001/omj.2011.38.

4. World Health Organization: Adherence to Long-Term Therapies. 2003. Available at http://www.who.int/chp/knowledge/publications/adherencefullreport.pdf.

5. World Health Organization: Comparison of Pharmacokinetics and Efficacy of Oral and Injectable Medicine. 2017. Available at http://www.who.int/occupational_health/activities/5injvsora.pdf.

6. Global Oral Drug Delivery Market Research Report. 2017. Available at http://www.micromarketmonitor.com/market-report/oral-drug-delivery-reports.

7. M. Sherry Ku. Use Of The Biopharmaceutical Classification System In Early Drug Development. AAPS J, 10, 2008, 208-212. doi: 10.1208/s12248-008-9020-0.

8. Banerjee A, Onyuksel H. Peptide Delivery Using Phospholipid Micelles. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 4, 2012, 562–574. doi: 10.1002/wnan.1185..

9. Gao X, Cao Y, Song X, Zhang Z, Zhuang X, He C, Chen X. Biodegradable, pH-Responsive Carboxymethyl Cellulose/Poly(Acrylic Acid) Hydrogels For Oral Insulin Delivery. Macromol. Biosci. 14, 2014, 565–575. doi: 10.1002/mabi.201300384.

10. Gupta V, Hwang BH, Doshi N, Mitragotri S. A Permeation Enhancer For Increasing Transport Of Therapeutic Macromolecules Across The Intestine. J Control Release. 172, 2013, 541–549. doi: 10.1016/j.jconrel.2013.05.002..

11. Tao S, Desai T. Gastrointestinal Patch Systems For Oral Drug Delivery. Drug Discovery Today. 10, 2005, 909-915.

12.Teutonico D, Ponchel G. Patches For Improving Gastrointestinal Absorption: An Overview. Drug Discovery Today. 16, 2011, 991- 997.

13. Goldberg M, Gomez-Orellana I. Challenges For The Oral Delivery Of Macromolecules. Nat Rev Drug Discov., 2, 2003, 289–295.

14. Hamman JH, Enslin GM, Kotzé AF. Oral Delivery of Peptide Drugs: Barriers and Developments. Bio. Drugs., 19, 2005, 165–177.

15. Fu AZ, Qiu Y, Radican L. Impact of Fear of Insulin or Fear of Injection on Treatment Outcomes of Patients with Diabetes. Curr Med Res Opin., 25, 2009, 1413–1420. doi: 10.1185/03007990902905724.

16. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to Insulin Treatment, Glycaemic Control, And Ketoacidosis in Insulin-Dependent Diabetes Mellitus. Lancet., 350, 1997, 1505–1510.

17. Kirsch K, Hanke U, Weitschies W. An Overview of Intestinal Wafers for Oral Drug Delivery. Eur J Pharm Biopharm., 114, 2017, 135-144. doi: 10.1016/j.ejpb.2017.01.003.

18. Rossi S, Ferrari F, Bonferoni MC, Caramella C. Characterization of Chitosan Hydrochloride–Mucin Interaction by Means of Viscosimetric And Turbidimetric Measurements. Eur J Pharm Sci, 10, 2000, 251-257.

19. Banerjee A, Lee J, Mitragotri S. Intestinal Mucoadhesive Devices for Oral Delivery of Insulin. Bioeng Transl Med, 1, 2016, 338-346. doi: 10.1002/btm2.10015.

20. Shen Z, Mitragotri S. Intestinal Patches for Oral Drug Delivery. Pharm. Res., 19, 2002, 391–395.

21. Tomazic-Jezic VJ, Merritt K, Umbreit TH. Significance of The Type and The Size of Biomaterial Particles on Phagocytosis and Tissue Distribution. J. Biomed. Mater. Res., 55, 2001, 523–529.

22. Tabata Y, Inoue Y, Ikada Y. Size Effect on Systemic and Mucosal Immune Responses Induced by Oral Administration Of Biodegradable Microspheres. Vaccine., 14, 1996, 1677–168.

23. Ahmed A, Chris B, Tejal D. Bioadhesive Microdevices With Multiple Reservoirs: A New Platform for Oral Drug Delivery. J. Control. Release., 81, 2002, 291–306.

24. Ahmed A, Chris B, Tejal D. Bioadhesive Microdevices For Oral Drug Delivery: A Feasibility Study. Biomed. Microdevices., 3, 2001, 89–96. DOI: 10.1016/S0168-3659(02)00074-3 ·.

25. Foraker AB, Walczak RJ, Cohen MH, Boiarski TA, Grove CF, Swaan PW. Microfabricated Porous Silicon Particles Enhance Paracellular Delivery of Insulin Across Intestinal Caco-2 Cell Monolayers. Pharm. Res., 20, 2003, 110–116.

26. Tao S, Lubeley M, Desai T. Bio Adhesive Poly(Methyl Methacrylate) Micro Devices For Controlled Drug Delivery. J. Control. Release., 88, 2003, 215–228.

27. He H, Cao X, Lee LJ. Design of A Novel Hydrogel Based Intelligent System for Controlled Drug Release. J. Control. Release., 95, 2004, 391–402.

28. Eaimtrakarn S, Rama Prasad Y, Puthli S., Possibility of A Patch System as A New Oral Delivery System. Int. J. Pharm., 250, 2003, 111–117.

29. Eaimtrakarn S, Prasad Y, Puthli S. Evaluation of Gastrointestinal Transit Characteristics of Oral Patch Preparation Using Caffeine as A Model Drug in Human Volunteers. Drug Metab. Pharmacokinet., 17, 2002, 284–291.

30. Whitehead K, Shen Z, Mitragotri S. Oral Delivery of Macromolecules Using Intestinal Patches: Applications for Insulin Delivery. J. Control. Release., 98(1), 2004, 37-45.

31. Gupta V, Hwang BH, Lee J, Anselmo AC, Doshi N, Mitragotri S. Mucoadhesive Intestinal Devices for Oral Delivery of Salmon Calcitonin. J Control Release., 172, 2013, 753–762. doi: 10.1016/j.jconrel.2013.09.004.

32. Goldberg M, Gomez-Orellana I. Challenges for The Oral Delivery of Macromolecules. Nat Rev Drug Discov., 2, 2003, 289–295.

33. Maliś F, Fric P, Stépánková R, Kruml J.Digestive Enzymes Of The Mucosa Of The Small Intestine And Trypsin And Chymotrypsin Proteolytic Activity Of The Intestinal Contents Of Germ-Free, Mono Contaminated And Conventional Rabbits. Acta Univ Carol Med Monogr., 77(1), 1977, 119–123.

34. Shakya P, Madhav NV, Shakya AK, Singh K. Palatal Mucosa as A Route for Systemic Drug Delivery: A Review. J. Control. Release., 151, 2011, 2–9. doi: 10.1016/j.jconrel.2010.11.003.

35. Bernkop-Schnurch A, Walker G. Multifunctional Matrices for Oral Peptide Delivery. Crit. Rev. Ther. Drug Carrier Syst. 18, 2001, 459–501. doi: 10.1016/j.ddtec.2005.05.001.

36. Eiamtrakarn S, Itoh Y, Kishimoto J, Yoshikawa Y, Shibata N, Murakami M, Takada K. Gastrointestinal Mucoadhesive Patch System (GI-MAPS) For Oral Administration Of G-CSF, A Model Protein. Biomaterials., 23, 2002, 145–152.

37. Tao SL, Lubeley MW, Desai TA. Bioadhesive Poly(methylmethacrylate) Microdevices For Controlled Drug Delivery. J. Control. Release., 88, 2003, 215–228.

Source of Support: Nil, **Conflict of Interest:** None.