

Intestinal Patch A Versatile Oral Delivery System Preparation and Evaluation

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History:

- Received: March 19, 2020
- Accepted: June 25, 2020
- Published: Sept 1, 2020

DOI: <https://doi.org/10.31838/ejmcm.07.02.03>

INTRODUCTION

Oral drug delivery considers as most convenient for drug administration compared with another routes but still there is big challenges in the absorption of some types of drugs like protein, peptide, nucleic acid, large hydrophilic and poor soluble molecules (1). Barriers present in the GIT will affect stability of them like low pH of stomach, enzymatic degradation, hydrolysis and limited intestinal permeation (2), to overcome these problems many strategy and modification used like nanoparticle, microparticle, liposome and most attractive mucoadhesive micro/nanoparticles with good property of better attachment to the intestinal wall so increase the residence time of the dosage form will increase drugs permeation. However also some problems present with mucoadhesive particles like the following

1-Multidirectional release so that mean specific fraction of drug will be lost into luminal fluid

2- Intestinal fluid will be in contact with particle surface of encapsulated drugs so the protection will be insufficient and proteolytic degradation (3).

Versatile Intestinal mucoadhesive devices offer an important solution to prevent acidic effect of stomach and enzymatic degradation also increase residence time and offer high concentration gradient at the absorption site (4,7).

Intestinal patch

Is multi layered oral delivery device intended to deliver small and large therapeutic particles in an organized fashion (in general composed from two to four layers) (5-7).

These layers divided into the following

ABSTRACT

Development of the dosage form aimed for safe, effective and easy administration according to that ideal way is the oral route, but great challenges stop against that like poor absorption, enzymatic degradation, low solubility and gastric effect all these barriers present in the GIT. Intestinal patch with it is a unique design, consist of protective and mucoadhesive parts resemble transdermal patch that provide good chance for developing an oral dosage form to the proteins, peptides, aminoglycoside and low permeable drugs near look about this oral intestinal device in this review.

Keywords: intestinal patch, mucoadhesion, protein, pH sensitive

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1-Mucoadhesive layer (drug loading layer)

With two important functions strong adhesion to the site of action (intestinal wall) and as a carrier to the drug. In general, the mechanism behind the biohesion still not clear but in general three steps are happened as follow the polymer swelling then interaction with mucosal membrane(interpretation) finally a chemical bond formed between them (8). Polymers mostly used are chitosan, chitosan thiolate, polyacrylic acids, pectin, polyvinyl alcohol, alginates, cellulose products like, HPMC, HPC and SCMC (9,10).

2- The backing layer

The main function is a covering the patch with water impermeable polymer that prevent intestinal juice accesses inside and degrade the drug, at the same time provide unidirectional release. Generally made from ethyl cellulose or cellulose acetate polymer.

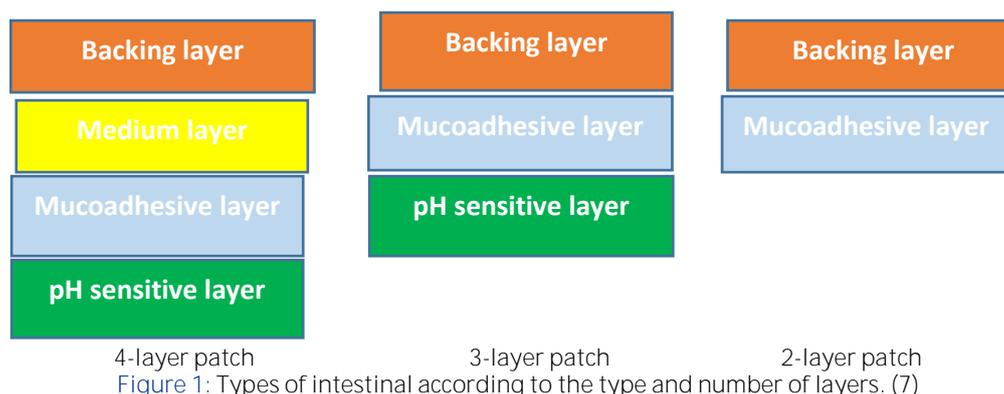
3- pH sensitive layer

Eudragit polymer L or S mostly used to promote drug release in basic medium (intestine) by this modification protect pH labile molecule from gastric media.

4- Medium layer

Separate mucoadhesive layer from drug layer.

The patch formulated are of different sizes (micrometer and millimeter) and in different number of layers two layers, three layers and four layers as in the figure (1). Intestinal patch act as a depot stick to the mucus membrane and discharge the drug directly to the absorption place (7).



Advantage of intestinal patch

1. Offer accepted residence time at the intestinal wall
2. Unidirectional release toward the intestinal mucosa
3. Protect the loaded drug in the formula from intestinal proteolytic enzymes and secretions
4. Increase the intestinal absorption that will increase bioavailability

Preparation

1-Conventional methods

By direct compression a Mucoadhesive layer prepared as homogenous mixture of polymers powder (pectin, carbapol, SCMC) in the following ratio 1:1:2. The mixture blended by milling (mortar and pestle) then candidate drug added until reach the required concentration. This mixture tipped into the 13 mm (pellet press) then compressed by force of 3 tons (hydraulic press) for 5 min. The product will be 400 μ m thick and patch with 13 mm diameter.

By disposable biopsy punch this patch will be divided into smaller disks with (1-5 mm) radius. These patches put on the support and coated with 5% (ethyl cellulose in acetone) from all faces of patch excepting one, after vaporization of acetone these patches placed in the enteric coated capsule with (Eudragit L 100 in isopropanol).

This capsule will dissolve in the high pH media of intestine then release these patches, which is stick to the intestinal mucus layer and release the drug (11).

Another method used to prepare three-layer patch done as following steps.

Ethyl cellulose layer (backing layer) formulated by (solvent evaporation method). 20 % ethyl cellulose prepare by dissolve EC in the (4:1) methyl chloride and methanol, backer applicator used to spread EC solution over the Teflon plate 30 \times 30 cm², wait 5 min then the EC film will be ready with thickness of 23.69 \pm 1.5 μ m.

The enteric polymer formulated with (12%w/v) HP-55 solution using the same method of the backing layer, 16.99 \pm 1.1 μ m is the thickness of the film obtained.

The drug loading layer consist of Carbapol, 160 mg of CA and 100 mg of HCO-60, 30 mg of (model drug fluorescein) mixed together. after that weigh the composition and spread over the backing layer (5 \times 5 cm²), next the pH-sensitive layer will cover drug layer. these three layer sealed and cut by (heat-sealing punching equipment) into 3mm diameter patch, these patches filled in the gelatin capsule with 400 mg effervescent powder (12).

Microsphere intestinal patch proposed as another modification for intestinal patch design simply the previously prepared microsphere loaded with drug spread over the (carbapol and pectin) mucoadhesive layer with partial pressing, then covered with backing layer. left for drying then cut into small cycles or squares as in figure (2) (13) another conventional method by thermal bonding of previously prepared three layers together (14). Sometimes the mucoadhesive layer also help in the adhesion of another patch layers (15).



Figure 2: Microsphere intestinal patch (16)

Microfabrication technology

One of microfabrication applications in the pharmaceutical dosage form is the preparation of intestinal patch (17) micropatch size generally 50-200 μm diameter and 2-5 μm thickness this size help the patch to travel freely between intestinal villi that will offer larger absorptive area. less than that size provides better adhesion but also may lead to local inflammation and phagocytosis by macrophage this may happen with the less than 5 μm particles (18).

some researcher uses this technology as drug delivery approach like. Leoni et al designed a (nanoporous biocapsule) for passive transmittion of insulin through fine controlled holes as a prolonged drug release (19). While Santini et al established a reservoir having micrpach which liberate drugs across an electrochemical reaction of a gold layer (20). But these two delivery systems are invasive because they need implantation inside the body while orally micro device apply good way for protein and peptide oral formulation with several advantage like precise shape and size of device also thin, flat and disc shape offer maximum contact area with the intestinal wall and minimum contact sides with flow of liquids in the intestine. The selectivity could be added by some modifications like use the lectin which is plant derivative show high affinity to the sugar molecule that is present in the oligosaccharide the main component of the mucin that is lining intestinal wall this lead to good mucoadhesion(21). Ahmed et.al prepare an enteric coated capsule dissolve in the upper intestine then release the microdevices content so the mucoadhesion occur from one side coated with lectin or mucoadhesive polymer.

A multiple drug reservoir could be done according to this study that's mean more than one peptide or protein can be delivered in one dosage. photolithography, deposition and etching are three steps of micropatch formulation (22).

Another modification applied is porous silicon micro device which is prepared on the one -side refined silicon <100> p \pm type patch shielded with silicon nitride (23) to define only the intended porosity sites on the microchip photolithography performed then etching of the backside with SF₆ to peel of the silicon nitride layer. after that the front side of the patch etched by SF₆ so the present photoresist cleans out. After that the microchip anodized and electro polished in the mixture of 1:1 hydrofluoric acid and ethanol solution for anodization and 1:4 (v/v) for electro polishing in a custom-built anodization chamber. Porosification done only to the anodic edge of the silicon microchip. Shape and pore size of the device depend on the kind, resistivity of silicon, hydrofluoric concentration and the current mass. (figure 3).

The micropatches offer a (cyto-adhesive cell targeting) in addition to the simple mucoadhesion by the following three steps

1. Formation of amine group on the device
2. Avidin and carbodiimide coupling reagent coupled together to form avidin-carboxylate which is interact with amine sorts of substrate forming avidin conjugate
3. Strong affinity between avidin and biotin lead to the surface attachment of the biotinylated lectin (22,23).

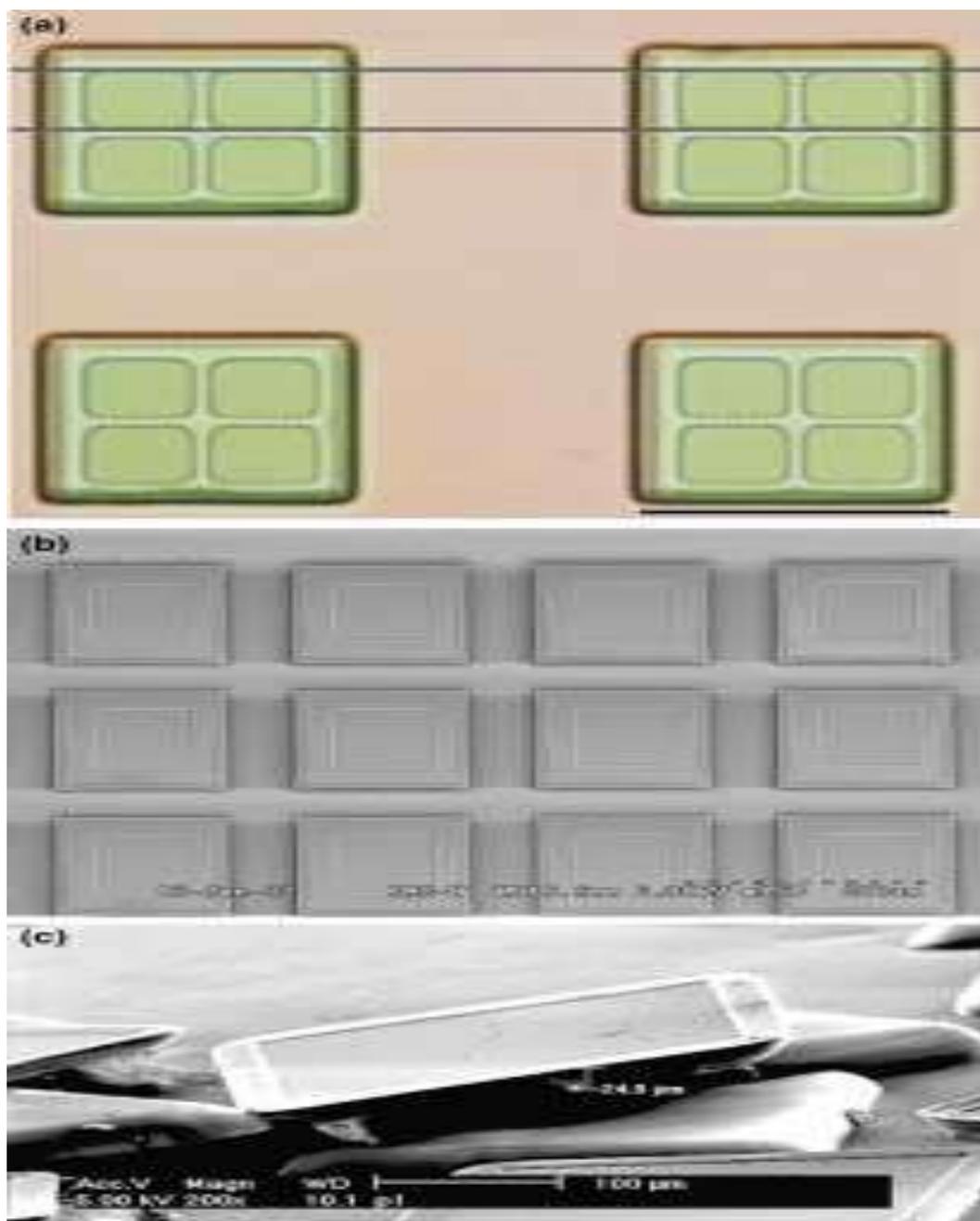


Figure 3: Polymer- and silicon-based microdevice (a) Silicon dioxide microchips with diverse **35 µm diameter reservoirs within a 100 µm diameter body 2 µm dense**. Bar denotes **100 µm**. (b) Scanning electron micrograph of PMMA microchips **with 80 µm diameter reservoirs in a 150 µm diameter body 5 µm thick**. (c) Scanning electron micrograph of a porous silicon microchips **with a 200 µm diameter reservoir in a 250 µm diameter body 25 µm dense (5)**.

pH hydrogel intestinal patch

The transdermal gel preparations have been widely used (24). although, the pH hydrogel intestinal patch consists of drug reservoir, pH sensitive polymer and may add a mucoadhesive layer a self fold cover of pH sensitive hydrogel based oral delivery intestinal patch prepared by He et al. as a (controlled delivery system) (25).

The patch formulated as a drug tank created of poly (hydroxyl methacrylate) [p(HEMA)] covered by a surfactant, Pluronic F127 Prill for bioadhesion and a poly (meth acrylic

acid-g-ethylene glycol) [p (MAA-g- EG)] hydrogel as pH sensitive gated drug delivery.

For up to 2 hours at pH 3.0 both p (MAA-g-EG) and p(HEMA) swell and the gated technique did not amenable to discharge inserted drug. At high pH The swelling ratio of the gel change leading to open the gate and drug release from the formula. by using p(MAA) conjugated with PEG for pH sensitive layer Peppas et al. established a gel supply system of insulin as oral route (26) (fig 4)

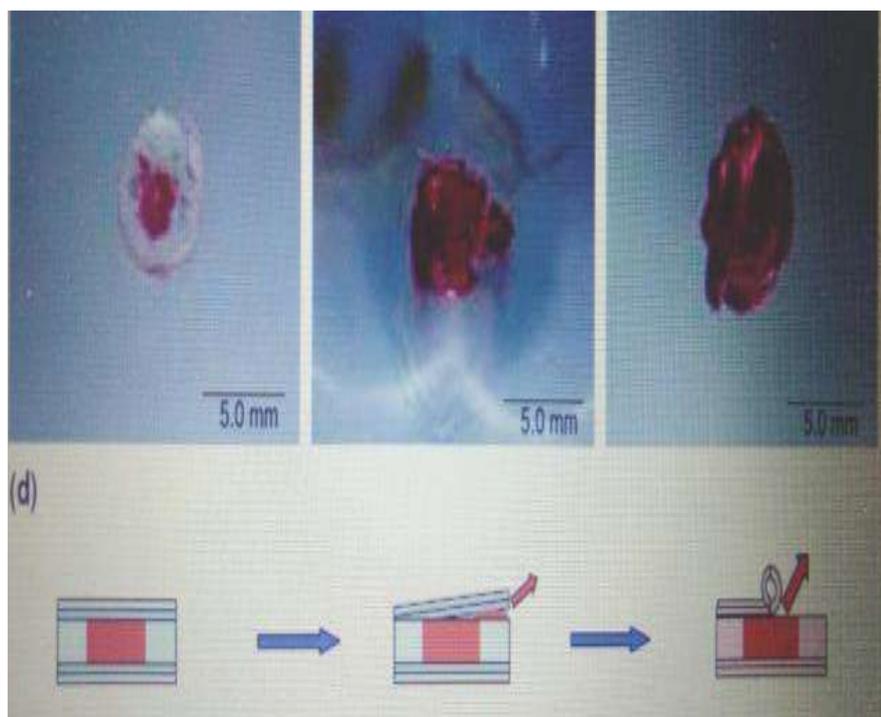


Figure 4: Gated Hydrogel Intestinal patch (27)

Evaluation

1- invitro release studies

More than one method used in this evaluation test according to the design of the patch we will explore some examples of them

1- This technique used for sandwich pH sensitive patch design

The pre-evaluation test is to determine stability of the patch against the acidic medium of the stomach to be sure from protection efficiency of the formula in low pH media this done by put the patch in the simultaneous gastric media consist of (1.2 ml, 80ml, 0.2% NaCl, pH 1.2 HCl) and wait for 2 hours the whole media put in the orbital shaker at magnetic stirrer at 200 rpm under 37° C.

After that put the same tested patch in anther media composed of (1.2 ml phosphate buffer composed of 9mM Na₂HPO₄, 5mM EDTA, 1.6 mM KH₂PO₄, 0.14M NaCl, 10% DMSO and 5mM TRIS adjusted to pH 7.4 this media mimics the intestinal ambient where we need our formula to be release. DMSO role in this media to increase the solubility of insulin released. Sampling at predetermined time for 6 hours these samples tested by HPLC. Sink condition should be maintained (28).

2- study with 2-layer insulin intestinal patch the unidirectional release study

The diabetic patients experienced many of inflammatory conditions enforcing the development of current strategies

(29). Moreover, enhancing the activity and reducing the toxicity are other objectives that researchers seeking for (30). A modified design of two chambered put side to side in between them an opening to the tested patch, the solution used is PBS the samples drawn from 2 sides then read at HPLC. Samples taken from the mucoadhesive chamber side to see the release profile while from coating side to evaluate coating efficiency (11). Vivek Gupta et al used the following method for invitro release study of calcitonin intestinal patch incubate one patch in the 10 ml of PBS with pH 7.4 gentle shaking to mimic the intestinal mucocilliary movement the samples routinely drawn from the media in predetermined times and quantify it by ELISA kit (31).

Mucoadhesion study

1- Invitro bioadhesion force

Frozen sheep fundus piece rinse with saline fluid at room temperature as soon as used in the experiment this piece (E) connect with glass vial (C) the mucosal side should be to the outside. The membrane diameter will be 1.1 cm this glass vial with intestinal patch will keep at 37 °c for 10 min. after that connect the vial with the balance (A) the other glass vial tie with the (F). Mucoadhesive dosage form (D) connect with (F) fixed by adhesive tape this state will promote adhesion between tested dosage form and mucosal piece in one side of the balance (A) on the other side 10 gm weight put on the pan (B) and continue adding until the dosage side separated. This result will be calculated mathematically to represent the detachment force invivo bioadhesion evaluation (32).

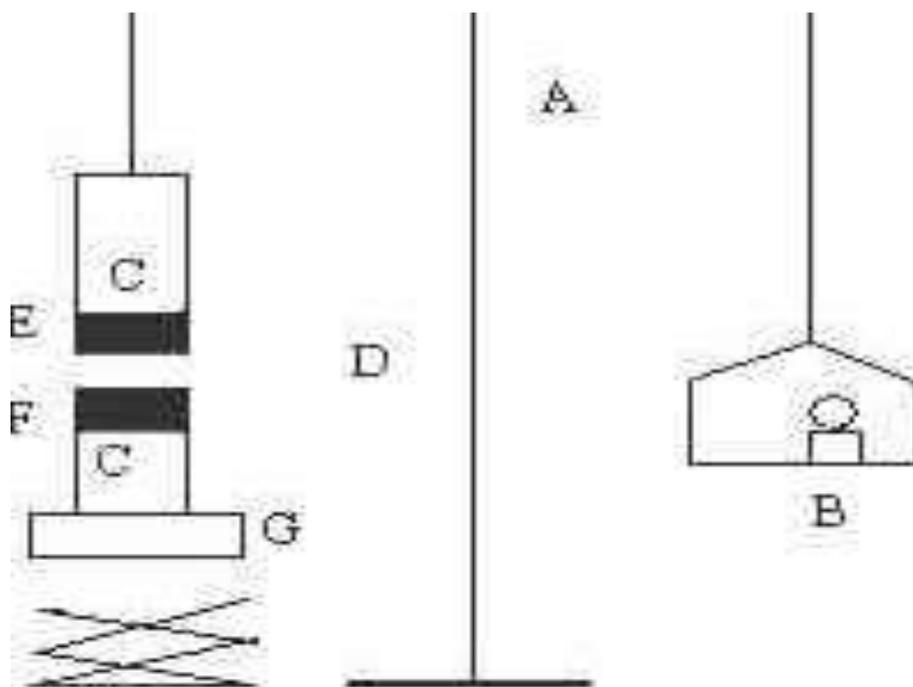


Figure 5: Modified balance for mucoadhesion force measurement

A: modified balance; D: Bioadhesive bilayer tablet; G: height adjustable pan

B: weights; E: Intestine tissue

C: glass vial; F: supportive adhesive tape (16)

2-Invivo bioadhesion study

1-Gamma scintigraphy technique

This method used to confirm invivo distribution by gamma ray camera that follow the emitted ray from the tested dosage form previously a radio tracer added to it so by this technique we can measure the bioadhesion time (33).

2-X-ray studies

X- ray can be monitor the mucoadhesive formulation gastrointestinal transit time. The tested dosage form coated with radio-opaque marker for example (barium sulphate) the different pictures at different times promote good information about the transit time (34).

Invivo study

Nondiabetic rats from 250-350 gm male used in this study. Five groups each one with six except one with three. Fastened animal over the night but with free water drinking. After that every rat injected (subcutaneously) with metoclopramide 5mg/kg to increase gastric emptying. Oral capsule with empty device/insulin device/insulin pps (dimethyl palmitoyl ammonio propanesulfonate as a permeation enhancer) device or insulin device externally present pps given to them. The fifth sort was injected subcutaneously with insulin 1 unit/kg. The dose used for oral about 0.6 mg pps for each animal and 50 unit of insulin/kg given with 5 ml saline solution. Blood samples taken from the tail vein and measured by blood glucose meter at different time for 8 hours (35,36).

CONCLUSION

Intestinal patch according to the research done in this field show high promising results in spite of its short life of course the whole idea is perfect but it need more researches to prove its efficacy and applicability in the industrial level also reliable evaluations tests still not enough and high percent of researcher directed only to protein and peptide while a lot of drugs show similar problems like aminoglycosides and this delivery system can be suitable solution.

CONFLICT OF INTEREST: Nil

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