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A NEW APPROACH FOR TARGETING COLON: DELIVERING THE DRUG THROUGH MUCOADHESIVE PATCHES

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Abstract

An oral delivery system of anti-cancer drugs using gastrointestinal mucoadhesive patches was developed. A layered film system is enclosed in an enteric capsule. An adhesive layer was applied to the surface layer, which is composed of an enteric pH-sensitive polymer such as pectin, Eudragit L100 or S100. Our current work aims to develop a gastrointestinal mucoadhesive patch that can be used for alternative drug delivery. Pectin and Eudragit L100 or S100 were used as mucoadhesive polymers to prepare mucoadhesive gastrointestinal patches of 5-fluorouracil. We studied physical characteristics of the patches, drug content, mucoadhesive strength, diffusion in vitro, and dissolution in vitro. The percentage drug content of the formulations (F1- F8) was found to be in the range of 81.6% ±0.086 to 98.4% ±0.027. The release of drug from all the formulations (F1-F8) in phosphate buffer solution pH 6.8 was found to be in a sustained manner during the 8 hour study. The ex vivo permeations of 5-Fluorouracil from selected formulation (F7) of gastrointestinal mucoadhesive patches showed that the drug permeated well across colon mucosa (91.49%) achieved within 8 hours. It may be concluded that gastrointestinal mucoadhesive patch of 5- Fluorouracil is an alternate way to bypass hepatic first pass metabolism therefore it is expected to improve the bioavailability of 5- Fluorouracil.

Introduction

A targeted drug delivery approach involves delivering the drug at therapeutic concentrations to the target while limiting the possibility of accessing non-target tissues[1]. Targeted drug delivery systems are preferred for drugs with high stability, low solubility, short half-lives, large volume distribution, poor absorption, and low specificity[2, 3, 4].).

For the treatment of inflammatory bowel disease (IBD)[5] irritable bowel syndrome and colonic cancer as well as for the prolonged release of medication, the colon targeted or specific drug delivery system is a useful tool [6, 7, 8, 9, 10,11].

Oral drug delivery is one of the most preferred routes of drug administration being noninvasive, easy and can be self-administered. The oral administration of drugs is dependent on their release from formulation in the gastrointestinal tract (GIT), their solubilization in GI fluids, their transport across the gastric/ intestinal membrane and their absorption into the systemic circulation [12]. An intestinal patch system consists of two to four layers of unique oral mucoadhesive delivery devices designed for more controlled delivery of small and large molecules. The transdermal patch and these devices have similar conceptual designs, but work in completely different physiological environments. Generally, intestinal patches are millimeter-sized and consist of a pH-sensitive core, a mucoadhesive reservoir layer and a backing. During the first few hours after the patch is placed, the drug should be released into the intestinal system [13, 14, 15, 16, 17].A number of problems are associated with the oral delivery of proteins, due to their inability to survive in the gastrointestinal tract (GIT) and poor permeability across biological membranes, which requires their parenteral administration.[18-19] Mucoadhesive devices keep drug loads from being

enzymatically degraded by proteolytic enzymes contained in the digestive tract, not only to avoid stomach acid, but also to prevent enzymatic degradation in the GIT of therapeutic proteins. As a result of these devices, a high concentration gradient is created for drug transport, which facilitates ingesting the loaded proteins via the intestinal membrane [20, 21, 22].

It has recently been discovered that very low oral bioavailability of peptide and protein drugs can be overcome by a new oral delivery system, the gastrointestinal mucoadhesive patch system (GI-MAPS). Research in the past showed that GI-MAPS preparations enhanced the oral bioavailability of granulocyte colony-stimulating factor (G-CSF), a model protein drug. Several recent studies have demonstrated that the brush border membrane and cytosol still contain significant amounts of hydrolytic activity [23, 24, 25].There is, however, a vast difference between the hydrolytic enzyme activity of brush border membrane enzymatic activity and the activity of cytosolic enzymes in the GI luminal. There is a need for a new technology to be able to protect GCSF administered orally from the intestinal luminal hydrolytic enzymes.

A growing number of clinical conditions can be treated with patch preparations, including nitroglycerin and nicotine TTS preparations. The backing layer of this system prevents drugs from being removed. In our study, we assumed in GI lumen-localized proteolytic enzymes may attack mucoadhesive patches. Consequently, we designed the GI mucoadhesive patch system (GIMAPS), which delivers drug to the targeted intestinal site, adheres to the small intestine wall and blocks the attack by luminal proteolytic enzymes using a polymer-based backing layer.

Material and Mathod

Preparation of GI-MAPS*-**The backing layer and the pH-sensitive surface layer were prepared by casting/solvent evaporation technique. Backing Membrane /Mucoadhesive Polymer Layer was prepared by solvent evaporation technique Optimization trials were performed using different concentration of polymers and different solvent system. Suitable amount of pectin was dissolve in 100ml of distilled water. Adequate quantity of glycerine dissolved in pectin solution and sonicated for 1hr. After sonication polymeric solution was poured in pre-lubricated petriplate. Kept a side at room temperature for complete dry. After drying tiny patches of (0.5cm) diameter were cut down. Drug Layer: Second layer was prepared by 20 mg of 5 Fluorouracil was dissolve in 1ml of methanol and vortex for 5 min. 10µl of drug solution was then poured on tiny patches of (0.5cm) diameter and allow to dry. ***pH Sensitive Layer: The third layer in GIMAPS was prepared by taking suitable amount of eudragit L 100 dissolved in methanol to prepare coating solution. The drug containing patches were 4-5 times dipped in eudragit solution and dried by hair drier.

Evaluation of Drug Loaded Patches

Physicochemical Evaluation:

Physical Appearance: Developed patches were evaluated physically, uniformly, for air bubble entrapment, and for precipitation of drug on a patch, which dictates patient acceptance and therapeutic success to a great extent [26].

Thickness:A micrometre screw gauge was used to measure the thickness of the transdermal patch. There were three points where the thickness of a rectangular patch (2x2cms) was determined, and the average thickness was calculated. Same was performed for other patches also. There should not be any significant variances in the thickness of individual patches [26].

Weight Variation: In order to study weight variation, 10 randomly selected patches were individually weighed and the average weight was calculated. There should be no significant deviation between the average weight and the individual weight[26, 27].

Folding Endurance: In order to assess folding endurance, patches must be tested for their folding capacity. When a patch is repeatedly folded at the same place until it breaks, it is considered to have great folding endurance [27]. As a measure of folding endurance, the patch can be folded at the same place several times without breaking.

Tensile Strength: Measurements of tensile strength were convenient tools for determining the mechanical properties of the patches [28, 29]. The tensile strength of the patches was measured using an assembly designed for measuring tensile strength. An assembly was created by hanging the pan with strong thread and attaching the patch to the other end of the thread. Weights were kept on the pan and the whole assembly was held like a beam balance. Based on this formula, the tensile strength was calculated: The following formula was used to calculate the tensile strength:

Tensile Strength= Break Force/ a. b (1+ ΔL/L)

Where: a = width of the patch,

b = thickness of the patch,

L = length of the patch,

ΔL = elongation of patch at break point,

Break Force= weight required to break the patch (Kg).

Moisture Uptake: The patch was stored at room temperature in a desiccator. After that, the patch was taken out and exposed to 84% relative humidity using a desiccator containing a saturated solution of potassium chloride until a constant weight was achieved. The % moisture uptake was calculated by using following formula.

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Content: After weighing the patches individually, they were placed in a desiccator containing calcium chloride and kept at room temperature for 24 hours. After a specified interval, the patches were weighed again until they showed a constant weight. Using the following formula, we calculated the percent moisture content.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Drug Content Uniformity: In 100ml phosphate buffer solution (pH 7.4), a patch with a size of 2x2cm^2 was completely dissolved and the amount of drug entrapped was determined. The patch was placed on a shaker for about 24 hours to achieve complete dissolution. Spectrophotometric evaluation of the solution at 244nm was performed after suitable dilution of the drug solution.

In-vitro drug release

At a temperature of 37°C and 75 rpm, an in vitro dissolution test was conducted in a USP 2 apparatus. By using a UV-VIS spectrophotometer with double beam, samples were collected at predetermined intervals and the drug content was estimated after suitable dilution. For the initial drug release studies, 900 ml of 0.1N HCI was used followed by 900 ml of 7.4 potassium phosphate buffer solution for the following 3 hours. Following that, 900 ml of buffer solution of potassium phosphate 6.8 used for the rest of the procedure [30, 31].

Result and Discussion

Explorative Study. It was found that all batches of Gastro-Intestinal Mucoadhesive Patch **(**GIMAP) had thickness variations between 0.07- 0.15 mm as shown in Table 1. There was a substantial thickness difference between batches, which may be due to coating of Eudragit L100, which results in uneven polymer layer distribution. All the batches of GIMAP showed tensile strength and % elongation in uniform range from 2.3 to 4.4 respectively (Table 1). The cumulative drug release of drug from the Gastro-Intestinal Mucoadhesive Patch **(**GIMAP) was in the batch no. F7 is very good (91.49±0.15) in 8 hours.

Conclusion –

Using a solvent evaporation technique, 5 – Fluorouracil drug in patches formulation were successfully prepared for use in gastrointestinal mucoadhesion. Based on the physical appearance, weight, thickness, flatness, tensile strength, moisture absorption, moisture uptake, and uniformity of drug content, it was concluded that the formulation method used to make gastrointestinal mucoadhesive patches was reproducible and assured outstanding quality and uniformity in patch characteristics. In vitro tests, F7

revealed efficacious drug release in all formulations, with nearly complete drug release (91.49%) achieved within 8 hours. Considering these findings, it is possible that 5 Fluorouracil mucoadhesive patches may have applications in therapeutic areas, increasing patient compliance, decreasing dosing frequency, and improving bioavailability while reducing the time between dosing.

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Table 1: Evaluation of drug loaded patch Evaluation of drug loaded patch [Thickness, Folding Endurance, Water-vapour transmission rate, Tensile strength]

FC	Thickness	Folding Endurance	Weight variation (mg)	Water vapour transmission rate (gms/cm^2)	Tensile strength (dynes/cm2)	% Drug release
F1	0.07mm	437	58.3	0.134	3.3	72.41±1.99%
F2	0.11mm	479	45.6	0.141	4.4	87.45±1.44%
F3	0.11mm	389	47.8	0.113	2.3	78.48±0.56%
F4	0.11mm	486	47.3	0.196	3.3	95.25±2.10%
F5	0.15mm	387	49.2	0.202	3.7	93.05±0.38%
F6	0.15mm	469	48.2	0.131	3.3	86.35±0.46%

F7	0.07mm	369	72.5	1.13	3.8	69.28±0.84%
F8	0.12mm	387	64.4	0.113	4.4	94.02±0.55%
F9	0.11mm	388	66.3	0.124	4.3	93.01±0.54%

Factorial Design

Table 2: Experimental Design Employed with two Independent Variable at three level:

Formulation	**Variable**	
	X1	**X2**
F1	+1	+1
F2	+1	0
F3	+1	-1
F4	0	+1
F5	0	0
F6	0	-1
F7	-1	+1
F8	-1	0
F9	-1	-1

Coded Variables:
***X1 (Pectin Concentration):- +1 = (2%), 0 = (4%), -1 = (6%)**
***X2 (Eudragit L Concentration):- +1 = (2%), 0 = (1.5%), -1 = (1%)**

Table 3: Cumulative drug release

Time (Min)	**Cumulative drug release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
15	10.00± 0.36	11.7 ± 0.34	7.88 ± 0.37	7.88 ± 0.38	6.36 ± 0.17	6.08 ± 0.05	9.21±0.07	5.39 ± 0.15	6.72±0.36
30	20.8 ± 0.76	18.27±0.10	18.20 ±0.28	15.06 ±0.12	13.31±0.11	11.59±0.23	19.6 ± 0.34	11.31 ± 0.14	10.08±0.30
60	32.0 ± 0.07	24.7 ± 0.31	27.30±0.12	22.32±0.15	25.45±0.16	16.59±0.28	34.41±0.15	19.93±0.38	21.01±0.55
120	42.0 ± 0.08	35.96±0.46	36.4±0.72	31.80±0.40	34.41±0.08	32.63±0.24	48.6±0.31	32.86±0.47	39.91±0.33
180	55.77±0.32	43.04±0.18	46.11±0.07	45.20±0.10	41.66±0.28	42.58±0.31	58.4±0.10	49.03±0.20	52.02±0.12
240	65.8±0.42	52.47±0.16	57.03±0.24	56.36±0.14	50.90±0.51	55.30±0.14	78.80±0.40	58.18±0.46	67.20±0.25
360	79.90±0.55	74.29±0.13	69.78±0.32	63.16±010	78.12±0.08	72.45±0.20	87.91±0.27	66.27±0.13	79.30±0.25
480	81.80±0.38	74.80±0.37	70.99±0.38	63.16±0.14	79.28±0.13	81.85±0.35	91.49±0.15	87.82±0.37	88.20±0.53

Fig. 1 - Cumulative Drug Release Profile of Formulations