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Design and Evaluation of Gastrointestinal Mucoadhesive Patches Containing 6-Mercaptopurine for Enhanced Colon Cancer Therapy

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KEYWORDS

mucoadhesive patches, 6-mercaptopurine, controlled drug delivery, gastrointestinal administration, solvent casting, pH-dependent release

ABSTRACT:

This study focused on developing gastrointestinal mucoadhesive patches for controlled delivery of 6-mercaptopurine, an anticancer drug, to enhance drug release duration and improve absorption. The research team successfully formulated patches using solvent casting technology, resulting in smooth, translucent, and flexible pharmaceutical preparations suitable for gastrointestinal application.

Quality control testing demonstrated uniform weight and thickness distribution across all formulated patches. Comprehensive characterization included evaluation of pH levels, folding endurance, swelling percentage, and in vitro disintegration time to assess patch performance and stability.

In vitro drug release studies revealed enhanced release profiles with pH-dependent release patterns, indicating improved bioavailability and targeted drug delivery potential. The pH-responsive behavior suggests the patches can provide optimized drug release in different gastrointestinal environments, leading to better therapeutic outcomes.

The findings demonstrate that solvent casting represents an effective manufacturing approach for producing gastrointestinal mucoadhesive patches containing 6-mercaptopurine. This delivery system offers promising advantages for cancer treatment by providing sustained drug release and improved patient compliance through targeted gastrointestinal administration.

Introduction

Gastrointestinal cancer represents one of the most prevalent malignancies worldwide [1,2], with invasive surgical resection serving as the primary treatment modality [3,4,5]. However, the invasive nature of surgical procedures and associated sequelae significantly burden patients due to extended recovery periods and complications in the affected regions [6,7,8]. To address these limitations, extensive research has focused on developing wireless delivery structures as non-invasive alternatives for gastrointestinal treatment. These innovative approaches offer considerable advantages over conventional resections, including enhanced patient comfort and simplified operational procedures [9,10,11].

Recent advances have demonstrated the feasibility of capsule-based drug delivery systems, such as insulin-loaded microneedle capsules designed for small intestine delivery. These capsules utilize natural peristalsis for gastrointestinal tract navigation, with drug release occurring within specific pH ranges upon reaching target locations [12]. While this approach proves less invasive than subcutaneous injections and demonstrates superior absorption efficiency, limitations exist in rapid drug delivery to lesion sites due to the relatively slow peristaltic movement and pH-dependent release mechanisms.

To overcome these challenges, our research group has developed a novel mucoadhesive patch delivery system utilizing capsules as drug-loaded multilayer platforms. This innovative approach enables rapid and precise drug delivery to multiple lesion sites through strategically positioned multilayer mucoadhesive patches within the capsule system[13]. The mussel-inspired adhesive technology employed in these patches has been extensively validated as an effective tissue adhesion

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material in wet environments across various biomedical applications [14,15,16].

The proposed mucoadhesive patch system offers several key advantages:

(1) Active drug delivery capability to multiple target lesion sites,

(2) Enhanced biocompatibility, biodegradability, and superior adhesion to wet gastrointestinal surfaces due to mussel-inspired hydrogel composition, and

(3) Specific applicability for colon cancer treatment.

The etiology of colon cancer remains incompletely understood, though both environmental factors and genetic predisposition contribute to disease development. Despite significant therapeutic advances through immune-modulators and monoclonal antibodies, curative treatments remain elusive. Current standard therapies for colon cancer induction and remission maintenance primarily involve mesalazine or sulfasalazine formulations, with glucocorticoids added based on disease severity [17]. In cases of severe acute ulcerative colitis where intravenous steroid therapy fails, cyclosporine may serve as an alternative treatment option [18]. Although evidence supporting the efficacy of Azathioprine (AZA) and 6-mercaptopurine (6-MP) for remission maintenance exists, the clinical data remains limited. Among various pharmaceutical administration routes, oral delivery represents the most convenient and widely accepted method due to patient compliance and ease of administration [13]. Oral gastrointestinal mucoadhesive patches are specifically designed to retard drug release in the stomach and small intestine, making them particularly suitable for colorectal cancer treatment [18,19,20].

6-Mercaptopurine (6-MP) functions as both an effective immunosuppressant and anticancer agent, with increasing clinical applications in human and veterinary medicine for treating inflammatory conditions including Crohn's disease, ulcerative colitis, and rheumatological disorders, as well as various leukemias such as acute lymphoblastic and acute myelosuppressive leukemias [21,22]. However, prolonged therapeutic use leads to cellular accumulation of 6-MP metabolites, specifically 6-thioguanine (6-TGN) and 6-methylmercaptopurine (6-MM), resulting in myeloid, renal, and hepatic toxicities without corresponding survival benefits [23,24]. While the precise mechanism of 6-MP action remains incompletely characterized, current evidence suggests that its cytotoxic and immunosuppressive properties result from the incorporation of metabolites (6-TGN/6-MM) into cellular DNA, leading to impaired DNA synthesis and subsequent cell death.

Mucoadhesive drug delivery systems represent preferred dosage forms for colon cancer treatment due to their ability to localize drugs in specific regions for extended periods. These patches offer significant advantages through effective drug localization and targeted therapeutic effects [26,27]. The formulations must demonstrate sufficient mechanical strength to withstand bowel movement while maintaining drug delivery integrity, yet retain adequate flexibility to avoid interference with normal bowel function [28,29].

Previous studies have demonstrated excellent mucoadhesion and adhesive strength when mucoadhesive patches interact with porcine intestinal tissue. However, research on colon cancer drug release using gastrointestinal tract-delivered patches has not been previously reported. The proposed mucoadhesive patch system incorporates pectin and Eudragit S100 layers to optimize drug delivery performance.

Materials and Methods

Materials

6-mercaptopurine monohydrate (Assay purity = 98.0%), Pectin (Mw = 194.14 g/mol), Eudragit S 100 (Mw = 172.18 g/mol), and Monobasic sodium phosphate (NaH_2PO_4) and Dibasic sodium phosphate (Na_2HPO_4) and Sodium Hydroxide (NaOH) were purchased from Emplura®, Merck Specialities Private Limited [25].

Preparation of 6-mercaptopurine Gastrointestinal Mucoadhesive Patches (GIMAPS)

An appropriate quantity of pectin was dissolved in 100 ml of distilled water. The pectin solution was mixed with a sufficient amount of glycerin, and the mixture was subjected to sonication for a duration of 1 hour. Following the sonication process, the resulting polymeric solution was carefully poured into pre-lubricated petri plates. These plates were then set aside at room temperature until complete drying occurred. Once dried, small circular sections with a diameter of 0.5 cm were meticulously excised from the material [26].

For the drug layer, the second stratum was formulated by dissolving 20 mg of 6-mercaptopurine in 1 ml of methanol. This solution was vigorously mixed using a vortex for a duration of 5 minutes. Subsequently, 10 µl of the drug solution was delicately applied onto the miniature circular patches (0.5 cm in diameter) and left to undergo the drying process [27].

Moving on to the pH-sensitive layer, the third layer within the GIMAPS construct was fashioned by dissolving an appropriate quantity of Eudragit S 100 in methanol, thus creating a coating solution. The circular patches containing the drug were immersed in the

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Eudragit solution approximately 4 to 5 times and were then dried using a hair dryer. The resultant patches were earmarked for subsequent physico-chemical analyses [28].

Surface pH

Using a combination of pH electrodes, the surface pH of the Gastrointestinal Mucoadhesive Patches containing 6-mercaptopurine was evaluated. A segment of the film patch was dampened with milli-Q water, and the pH measurement was taken at the interface where the film and water made contact [30].

Thickness

The measurement of the transdermal patch thickness was conducted using a micrometer screw gauge. The rectangular patch (2×2 cm) was measured at three distinct points, and the average thickness was subsequently computed. The absence of notable variations in thickness is crucial for the efficacy of the patches [31]. This identical procedure was also implemented for the evaluation of other patches.

Folding Endurance

To ascertain the folding endurance, the film was repetitively folded at a single point until it reached a point of fracture. The folding endurance value represents the count of successful folds the film can endure at that specific point before breaking. This process was repeated in four separate tests, and the mean value was subsequently derived from these four tests [32].

Swelling Percentage (S %)

The patch's swelling index was computed under simulated conditions mirroring the pH of mucous membranes. This investigation involved weighing a patch (with a surface area of 4 cm^2) and placing it onto a designated petri-plate containing buffer media. At specific time intervals (15 seconds), the films were taken out, rapidly blotted using absorbent paper, and then re-weighed [33].

The percentage of water uptake was determined using the following formula:

S% = [(Wf - Wi) / Wi] × 100

Where Wf represents the weight of the wet grafted patch, and Wi signifies the weight of the dry grafted patch. These parameters are essential for determining the percentage of water uptake in the patch [34].

Drug Content

A 3 cm^2 sample was dissolved in 10 ml of a 0.1N sodium hydroxide solution using vortex mixing for a duration of 5 minutes, in order to extract the drug from the film. The resulting solution was then filtered through a Whatman filter paper. Subsequently, the solution was subjected to spectrophotometric analysis at a wavelength of 325 nm, with methanol being used as the reference blank [35].

Tensile Strength

Tensile strength measurements served as practical means to assess the mechanical characteristics of the patches [35, 36]. The process involved using a specially designed apparatus for measuring tensile strength. This assembly was constructed by suspending a pan using a robust thread, with the patch affixed to the opposite end of the thread. Weights were then placed on the pan, and the entire assembly was handled similar to a beam balance. The calculation of tensile strength was derived from the following formula [37]:

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)

This method allowed for the determination of the patches' tensile strength, a crucial aspect of their mechanical behavior [38].

Moisture Content

Following the individual weighing of the patches, they were introduced into a desiccator containing calcium chloride and left at room temperature for a duration of 24 hours. At predetermined time intervals, the patches were re-weighed until their weight remained consistent. Utilizing the subsequent formula, the percentage of moisture content was computed[39]:

Moisture Content (%) = [(Initial Weight - Final Weight) / Initial Weight] × 100

In Vitro Drug Release

A kinetic study was undertaken employing USP Apparatus-I, operating at 50 rpm, utilizing 600 ml of PBS (Phosphate Buffered Saline) sustained at 37°C and maintained at pH levels of 3.4, 6.4, and 7.4. In this study, separate dialysis tubes were employed, each containing 10 mg (with a concentration of 2 mg/ml) of both pure drug and Pectin-Eudragit S100 mucoadhesive patches. These tubes were immersed in PBS at a pH of 7.2 [40].

At predetermined intervals (0, 15, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours), a 4 ml

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aliquot of the release medium was withdrawn. The concentration of the withdrawn sample was subsequently determined using UV spectroscopy at a wavelength of 325 nm. Importantly, to maintain a constant volume, fresh buffer (4 ml) was added without replacing the entire dissolution medium. This methodology allowed for the examination of the release kinetics of the substances under various pH conditions, shedding light on their dissolution behavior over specific time intervals [38].

Stability study: Effect of temperature – This study utilized accelerated thermal aging conditions to assess the long-term stability of gastrointestinal mucoadhesive patches containing two active drugs: 5-Fluorouracil (5-FU) and 6- Mercaptopurine (6MP). Patches were subjected to elevated temperatures of 40°C, 50°C, and 60°C for a period of three months, emulating potential long-term storage scenarios under stress.

To monitor potential drug degradation, samples were extracted from the patches at regular intervals of 14 days. The concentrations of both 5-FU and 6MP were meticulously quantified through UV absorbance measurements at their respective characteristic wavelengths: 244 nm for 5-FU and 325 nm for 6MP. This analysis utilized a Shimadzu 1800-U.V. Spectrophotometer in a phosphate buffer solution with a pH of 7.4, mimicking physiological conditions.

This accelerated aging study is designed to assess the stability and degradation kinetics of the drugs within the patches when exposed to elevated temperatures for an extended period. It helps in understanding how the drug content changes over time under these conditions, providing insights into their shelf life and storage recommendations [41].

Results

This study developed colon-targeted gastrointestinal mucoadhesive patches containing 6-mercaptopurine using solvent casting technique with pectin and Eudragit S 100 as targeting polymers. Various drug-to-polymer ratio formulations were comprehensively evaluated for physical characteristics including surface pH, thickness, folding endurance, swelling percentage, drug content, tensile strength, moisture content, and in vitro drug release profiles.

Film weight and thickness increased proportionally with polymer coating concentration, while surface pH values matched colonic pH across all formulations, indicating absence of mucosal irritation potential. Folding endurance and tensile strength tests revealed that higher polymer concentrations enhanced both flexibility and mechanical strength, likely due to strong covalent polymer-drug bonds. Drug content remained consistent across formulations, demonstrating uniform distribution throughout the GIMAP matrix (Table 1).

Proper swelling behavior is essential for uniform drug release and effective mucoadhesion. All formulations exhibited approximately 35% swelling within the first hour, followed by minimal changes in swelling and moisture absorption from M1 to M9, indicating stable film properties. Drug release studies (Figure 1) showed polymer concentration-dependent release patterns with no lag time upon dissolution medium exposure. Initial hour release ranged from 5-12%, attributed to the erodible, hydrophilic polymer layer that creates pores and channels facilitating drug diffusion. Formulation M8 demonstrated the highest drug release and was selected for further studies.

Bioadhesive force and mucoadhesive residence time assessments confirmed M8's excellent mucoadhesive properties, favorable for this administration route. In vitro permeation studies revealed gradual drug permeation with approximately 89.38% permeation achieved after 8 hours (Table 2).

Table 1: - The drug-loaded patch was subjected to comprehensive evaluation, encompassing [thickness measurement, folding endurance assessment, determination of water-vapor transmission rate, and evaluation of tensile strength] of 6 – Mercaptopurine

FC	Surface pH	Thickness	Folding Endurance	Weight variation (mg)	Water vapour transmission rate (gm/m^2/day)	Tensile strength (dynes/cm2)	% Drug Content*
M1	6.3	0.08mm	> 435	56.3	0.132	3.1	70.41±1.99%
M2	6.4	0.10mm	> 469	43.6	0.139	4.2	83.45±1.44%
M3	6.3	0.10mm	> 378	44.8	0.11	2.8	74.48±0.56%
M4	6.4	0.10mm	> 476	46.3	0.189	2.9	93.25±2.10%
M5	6.6	0.14mm	> 385	48.2	0.199	3.5	89.05±0.38%

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M6	6.5	0.14mm	> 472	46.2	0.129	3.3	82.35±0.46%
M7	6.8	0.08mm	>374	71.5	0.112	3.8	67.28±0.84%
M8	6.5	0.11mm	> 385	64.4	0.142	4.4	94.02±0.55%
M9	6.4	0.10mm	> 386	63.3	0.14	4.3	90.01±0.54%

*Mean ± standard deviation

Table 2: Cumulative drug release

Time (Min)	Cumulative drug release*								
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
0	0	0	0	0	0	0	0	0	0
15	8.94± 0.36	8.69± 0.34	7.73± 0.37	7.73 ± 0.38	6.28± 0.17	6.65 ± 0.05	5.31 ± 0.07	8.21± 0.15	6.76± 0.36
30	19.81± 0.76	16.43 ±0.10	17.15 ±0.28	14.01± 0.12	13.04 ±0.11	11.35 ±0.23	11.35± 0.34	17.63± 0.14	10.87 ±0.30
60	26.32± 0.07	21.50 ±0.31	26.33 ±0.12	21.26 ±0.15	22.22 ±0.16	22.22 ±0.28	19.81 ±0.15	35.27 ±0.38	21.50 ±0.55
120	35.27± 0.08	29.95 ±0.46	35.51± 0.72	30.68 ±0.40	32.61±0.08	31.64 ±0.24	31.64 ±0.31	47.58 ±0.47	39.86 ±0.33
180	48.79 ±0.32	39.86 ±0.18	45.17 ±0.07	44.20 ±0.10	40.58 ±0.28	42.51 ±0.31	50.00 ±0.10	57.48 ±0.20	52.90 ±0.12
240	54.11 ±0.42	47.34 ±0.16	56.04 ±0.24	55.31 ±0.14	48.79 ±0.51	53.14 ±0.14	57.25 ±0.40	76.81 ±0.46	64.01 ±0.25
360	69.81±0.55	66.18 ±0.13	68.60 ±0.32	62.07 ±010	68.12 ±0.08	71.50 ±0.20	66.43 ±0.27	86.81±0.13	78.26 ±0.25
480	72.71± 0.38	78.26 ±0.37	71.98 ±0.38	64.98 ±0.14	77.03 ±0.13	80.68 ±0.35	86.71 ±0.15	89.37 ±0.37	87.92 ±0.53

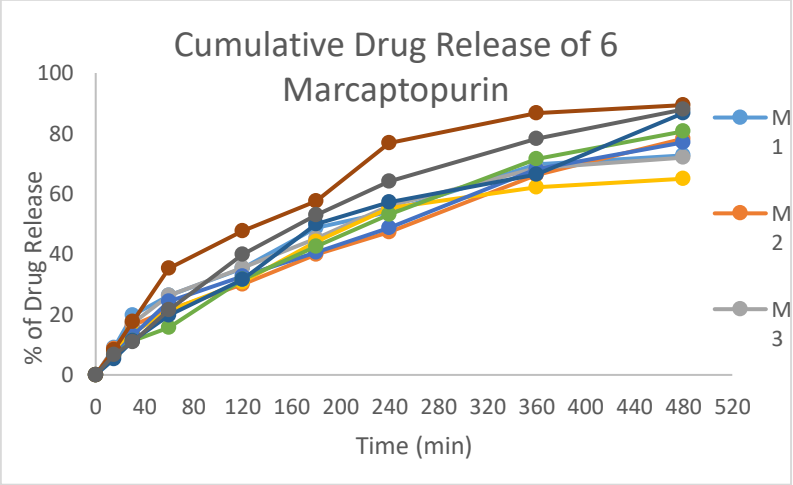

Fig. 1: Cumulative Drug Release Profile of Formulations of 6-Mercaptopurine (Formulation M1 - M9)

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Stability Study Profile of 6 – Mercaptoputin -Loaded Patches (M1–M9)

Stability studies of nine 6-mercaptopurine patch formulations (M1-M9) conducted under ICH guidelines at intermediate (25°C/60% RH) and accelerated (40°C/75% RH) conditions over 60 days revealed significant formulation-dependent performance variations. Initial drug content ranged from 67.28% (M7) to 93.25% (M4), with M4 demonstrating superior stability by retaining 91.27% and 90.43% drug content under intermediate and accelerated conditions, respectively. High-performing formulations (M4, M8, M5) maintained >87% drug content with minimal degradation, while moderate performers (M9, M2, M6) showed 79-87% retention, and poor performers (M1, M3, M7) exhibited concerning stability with <72% retention. Accelerated conditions showed marginally higher degradation rates (0.5-1.0% difference) compared to intermediate conditions, indicating overall formulation and consistent stability profile, shown in (table -3).

Table 3: Stability Study Profile of 6 Mercaptopurin -Loaded Patches (F1–F9)

Formulation Code	Initial % Drug Content	25 ± 2º C (60 ± 5% RH)			40 ± 2º C (75 ± 5% RH)		
		15 Days	30 Days	60 Days	15 Days	30 Days	60 Days
M1	70.41±1.99 %	69.31±0.75 %	68.22±0.93 %	67.79±0.49 %	68.99±0.42 %	68.05±0.76 %	67.59±0.45 %
M2	83.45±1.44 %	82.36±0.98 %	81.17±5.17 %	80.85±0.66 %	81.95±0.69 %	81.23±0.94 %	80.63±0.11 %
M3	74.48±0.56 %	73.29±0.98 %	72.98±0.42 %	72.05±0.74 %	72.98±1.33 %	72.17±0.81 %	71.79±0.02 %
M4	93.25±2.10 %	92.17±0.81 %	91.82±0.32 %	91.27±0.97 %	91.76±5.63 %	91.29±1.05 %	90.43±4.45 %
M5	89.05±0.38 %	88.99±0.42 %	88.41±2.32 %	87.79±2.25 %	88.13±0.76 %	87.63±1.92 %	87.09±1.54 %
M6	82.35±0.46 %	81.23±0.93 %	80.85±0.63 %	80.15±0.79 %	80.79±0.28 %	80.07±0.02 %	79.74±1.32 %
M7	67.28±0.84 %	66.94±0.71 %	66.34±1.07 %	65.98±3.06 %	66.25±0.90 %	65.73±1.42 %	64.92±0.37 %
M8	91.02±0.55 %	93.98±1.32 %	93.21±0.93 %	92.67±6.35 %	92.79±0.29 %	91.98±0.43 %	91.07±0.51 %
M9	90.01±0.54 %	89.76±0.51 %	84.11±0.75 %	83.91±0.39 %	88.89±0.39 %	88.37±0.98 %	87.71±0.21 %

Conclusion

In this researchs successfully created and tested gastrointestinal mucoadhesive patches containing the chemotherapy drug 6-mercaptopurine for colon cancer treatment. Using a solvent casting technique, developed nine different formulations with pectin and Eudragit S100 polymers to target the colon.

The patches showed promising properties, including a surface pH that minimizes irritation, strong mechanical durability, and uniform drug distribution. In vitro studies confirmed that the patches release the drug in a controlled, pH-dependent manner, making them ideal for localized treatment. Formulation M8 was identified as the most effective due to its superior drug release and mucoadhesive properties. Formulation M4 demonstrated the best long-term stability, retaining over 90% of its drug content under various storage conditions.

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This innovative patch system offers significant clinical advantages, such as targeted drug delivery to the colon, reduced side effects, and improved patient compliance. The study concludes that these mucoadhesive patches are a promising alternative to traditional oral medications for colon cancer, and further research is needed to confirm their therapeutic efficacy and safety in clinical settings.

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