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Formulation and characterization of capecitabine muco adhesive beads for the treatment of colorectal cancer

Malapati Lakshmi Sahithi[1], Venugopalaiah Penabaka*[1], Yadala Prapurna Chandra[2]

[1]Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346.

[2]Department of Pharmacology, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346.

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Abstract

This study focuses on the formulation and characterisation of Capecitabine muco-adhesive beads for the treatment of colorectal cancer. The alginate beads were synthesised using the ionotropic external gelation technique. To maximise encapsulation efficiency and control the release of Capecitabine from the alginate beads, precise formulation conditions were implemented. Results from in vitro dissolution studies revealed that formulations incorporating increasing concentrations of sodium alginate with SCMC released the drug more rapidly compared to those formulated with sodium alginate and HPMC. Moreover, beads prepared using a 2% w/v aluminum chloride solution as the gelling agent demonstrated greater rigidity compared to those formed with a 2% w/v calcium chloride solution. This highlights the importance of selecting an appropriate gelling agent to optimise bead structure and functionality. Further research is necessary to develop the most effective formulations of Capecitabine for improved therapeutic outcomes in colorectal cancer treatment.

∗Corresponding Author

Name: Venugopalaiah Penabaka
Phone: +91 8686353637
Email: pvenupharma@gmail.com

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INTRODUCTION

CONTROLLED DRUG DELIVERY : Rapid advancements are happening in the field of controlled drug delivery. Polymeric materials are no longer just used in traditional prosthetics for medical devices; they are now used in new ways in pharmacology and pharmaceuticals. Due to the early stages of their discipline, there is a lot of uncertainty in the scientific literature about what should be referred to as "controlled" drug delivery. This term, like many others, is now firmly established in the literature but is still frequently misinterpreted [1]. Controlled drug delivery involves accurately regulating the speed at which a specific drug dose is released from a delivery system (usually consistently for an extended

period) without requiring frequent, repetitive dosing, whether through oral or parenteral administration. Drug release that remains steady for an extended period is governed by zero-order kinetics, independent of concentration. Orally taken tablets and most types of injections (except for continuous i.v. infusions) initially release the drug quickly, followed by a gradual decline in a first-order manner, where the rate depends on concentration. This continues until another dose is given to keep the drug concentration in the blood at therapeutic levels [2].

MATERIALS AND METHODS:

MATERIALS:

Capecitabine is a gift sample from Drugs India, Hyd. The other polymers such as Sodium alginate (Himedia), Sodium carboxy methyl cellulose (Fischer scientific), Hydroxyl propyl methyl cellulose (Paxmy), Aluminum chloride (Drugs India), Calcium chloride (Microfine chemical).

METHODS:

Method of preparation

Preparation of sodium alginate beads:

Alginate beads were created using the ionotropic external gelation method. In this process, sodium alginate, HPMC, and SCMC were dissolved in distilled water with agitation in ratios of 1:0.5 and 2:0.5. The drug was then added to this mixture, followed by the drug suspension being introduced into a solution containing varying concentrations of CaCl2 and AlCl3 and cured for 15 minutes. Using a syringe with a needle, the drug suspension was added dropwise into this solution. The resulting beads were filtered through Whatman paper filters, washed twice with deionized water, and dried at 45°C for 48 hours. The dried beads were then encapsulated with a dose equivalent to 500 mg.

METHODOLOGY FOR EVALUATION OF MUCOADHESIVE BEADS

Determination of the organoleptic properties of Capecitabine:

Measuring organoleptic properties is typically challenging because there are no standardized laboratory tests for these attributes and it requires experienced personnel. This study evaluated the following organoleptic properties: physical appearance, odor, and taste. The Capecitabine powder samples were examined and assessed using sensory evaluation methods involving sight, smell, and taste [3].

Pre-evaluation parameters

Drug-Excipient compatibility study:

FT-IR spectroscopy

A Japanese Shimadzu 8400S FT-IR spectrometer was used to obtain FT-IR spectra. The samples were first ground and thoroughly mixed with potassium bromide, an infrared-transparent matrix, at a 1:5 ratio (Sample: KBr). The Mixture was compressed using a hydraulic press under 5 tonnes of pressure for 5 minutes, and scans were performed with a resolution of 4 cm^{-1} over the 4000 to 400 cm^{-1} range [4], [5].

The angle of Repose:

The angle of Repose, also known as the critical angle of Repose, is the maximum inclination angle of a slope relative to the horizontal at which a granular material begins to slide or shift. This angle ranges from 0° to 90°. Good 25-30, Passable 30-40, Very Poor >40, and Excellent <25 [8].

$$\tan\theta = \frac{h}{r}$$

Table 1 Various formulations of mucoadhesive drug delivery system were made as given in the table

Ingredients	CPT-1	CPT-2	CPT-3	CPT-4	CPT-5	CPT-6	CPT-7	CPT-8
Capecitabine	2gm	2 gm	2 gm	2 gm	2 gm	2 gm	2 gm	2 gm
Sodium Alginate	2gm	4gm	2gm	4gm	2gm	4gm	2gm	4gm
SCMC	-	-	0.5g	0.5g	-	-	0.5gm	0.5gm
HPMC K15	0.5gm	0.5gm	-	-	0.5gm	0.5gm	-	-
Aluminium chloride	-	-	-		2%w/v	2%w/v	2%w/v	2%w/v
Calcium chloride	2%w/v	2%w/v	2%w/v	2%w/v	-	-	-	-

$$\theta = \tan^{-1}\frac{h}{r}$$

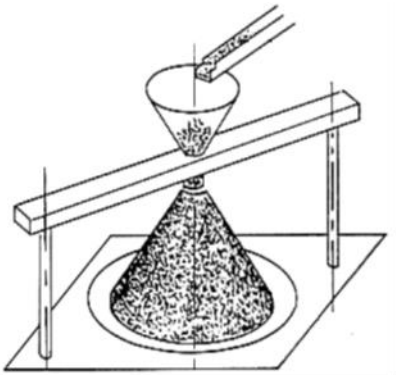

Figure 1 Funnel method for the angle of Repose

Bulk Density

The bulk density of a powder is the mass of an untapped powder sample divided by its volume, which includes the voids between particles; the bulk density is computed using the following formula, and the measured volume is called the bulk volume [9].

$$\text{Bulk Density} = \frac{\text{Powder Weight}}{\text{Bulk Volume}}$$

Tapped Density

When the powder sample is mechanically tapped into a container, the higher bulk density is called "tapped density." The final tapped volume is Vb if the difference between Va and Vb is less than 2%. After that, the following formula is used to determine the tapped density.

$$\text{Tapped density} = \frac{Powder\ Weight}{Tapped\ Volume}$$

Carr's Index (Compressibility Index)

It is a crucial parameter for characterizing the properties of powders and granules. It can be determined using the following equation.

$$\text{Carr's index} = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \text{X } 100$$

Hausner's Ratio

Hausner's ratio is a key characteristic for assessing the flow properties of powders and granules. It can be calculated using the following formula.

$$\text{Hausner's ratio} = \frac{Tapped\ Density}{Bulk\ Density}$$

Post-evaluation parameters

Drug Content

To determine the drug content beads equivalent to a 250 mg dose were triturated and dissolved in 100 mL of a 7.2 pH phosphate buffer. The solution was then analyzed spectrophotometrically at 260 nm [6], [7].

Drug loading:

The dosage necessary to dissolve 250 mg of mucoadhesive beads in 100 mL of phosphate buffer with a pH of 7.2 was used to calculate the drug loading. After passing through 45 µm filter paper, the solution was subjected to spectrophotometric analysis at 260 nm. A formula was used to compute the medication loading;

$$\%\ \text{drug loading} = \frac{\text{Amount of drug in beads}}{\text{Amount of beads}} X\ 100$$

Percentage encapsulation efficiency

The formula used to compute percentage encapsulation efficiency was:

$$\%\ \text{encapsulation efficiency} = \frac{AQ}{TQ\ X\ 100}$$

Microscopical characteristics of beads

A Motic microscope examined 50 muco adhesive beads of Capecitabine to determine their particle size. The mean size of the particles was computed.

SEM of beads

The alginate beads of Capecitabine were morphologically characterized using a scanning electron microscope (Model Jeol JSM-5200). To get cross-sectional views, bead cuts sharpened with a razor were utilized. Before microscopy, the samples were coated with gold-palladium to a thickness of 200 Aº. The working conditions were 20 KV for the accelerating voltage. Images were captured between 7000- and 12000-times magnification [8].

Swelling studies

The characteristics of bead swelling were investigated. Only batches with entrapment efficiency greater than 50% and good drug content were selected. After obtaining and weighing a sample from the drug-loaded beads, it was placed in the USP dissolving apparatus II wire basket. At 370 degrees Celsius, the beaded basket was set inside a beaker that contained 100

milliliters of pH 7.2 phosphate buffer. The beads were removed at predetermined intervals and weighed. Afterward, the swelling ratio was calculated using the formula below [9]:

$$\text{Swelling ratio} = \frac{\text{weight of wet beads}}{\text{weight of dried beads}}$$

In-vitro dissolution studies

900 cc of phosphate buffer (pH 7.2), kept at 37±0.50C and agitated at 50 rpm, were used in a USP Type II dissolution apparatus to study the dissolution of capecitabinemuco sticky beads. Periodically, samples were taken, and a new dissolving medium was added. These samples were examined using a UV spectrophotometer (UV-1700, Pharmaspace, Shimadzu) to determine their medication. Only batches with good drug content and drug entrapment efficiency of greater than 50% were chosen for the release study [10].

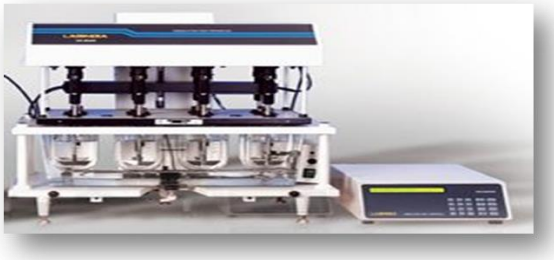

Figure 2 Lab India dissolution apparatus (DS-8000)

Mathematical modeling for drug release profile

To define the drug release mechanism, the total Amount of Capecitabine released from the formed tablets at various time intervals was fitted into several kinetic models, including the Higuchi, First Order, Zero Order, and Korsemayer-Peppas models [11], [12].

Zero-order kinetics

It describes a mechanism in which the drug's release rate is independent of its concentration.

$$Q_{ts} = Q_0 + k_0\, t$$

First order kinetics

It explains how drugs are released from systems where the rate of release is influenced by concentration.

$$\text{Log}\, Q_t = \text{Log} Q_0 + k_1 \frac{t}{2.303}$$

Higuchi model

It explains how the square root of time is proportional to the fraction of drug release from a matrix.

$$\frac{Mt}{M\alpha} = k_H\, t^{\frac{1}{2}}$$

Korsemayer-Peppas model

The potent law effectively characterizes the release of drugs from slabs, cylinders, and spheres by asserting that the relationship between the fractional Amount of drug release and the release time is exponential [13].

$$\frac{Mt}{M\alpha} = Kt^n$$

$$Log\, [\frac{Mt}{M\alpha}] = log\, K + n\, Log\, t$$

RESULTS AND DISCUSSION:

Capecitabine's mucoadhesive beads were made vi a the ionotropic external gelation process.
Sodium alginate has been utilized in this procedu re in a variety of ratios, including 1, 2% w/v, 0.5 % w/v of HPMC, 0.5% w/v of SCMC, and 2% w/v of calcium chloride and 2% w/v of aluminum chlo ride as gallant solutions.
The same method was used to prepare eight othe r formulations, and the following outcomes were attained.

Table 2 Pre-formulation studies for Capecitabine

S.NO	Capecitabine	Testing
1	white, odorless powder	Organoleptic properties
2	26 mg/mL at 20ºC in water	Solubility
3	0.45gm/cm^3	Bulk density
4	0.59gm/cm^3	Tapped density
5	22.5 %	Compressibility index
6	1.29	Hausner's ratio
7	26^0.5^1	Angle of Repose

Incorporation efficiency:

The findings were summarized in Table and showed a progressive rise in incorporation efficiency with an increase in sodium alginate

Table 3 Post-formulation studies of Capecitabine mucoadhesive beads

Formulations	Tapped density(g/ml)	Bulk density(g/ml)	Angle of repose(⁰)	Carr's index(%)	Hausner's ratio (%)
CPT-1	0.740	0.715	21.80	3.38	1.034
CPT-2	0.867	0.849	18.77	2.04	1.02
CPT-3	0.808	0.788	20.30	2.5	1.025
CPT-4	0.884	0.821	18.26	7.14	1.07
CPT-5	0.608	0.583	22.29	4.08	1.043
CPT-6	0.633	0.565	24.70	10.75	1.12
CPT-7	0.668	0.628	19.29	5.88	1.06
CPT-8	0.665	0.628	27.02	5.55	1.06

Table 4 Post-formulation evaluation tests

Formulations	Percentage yield (%)	Drug entrapment efficiency (%)	Swelling index(%)
CPT-1	76.8	57.23	55
CPT -2	98.4	74.13	61
CPT -3	86.8	63.25	51
CPT -4	81.4	71.34	58
CPT -5	75.2	75.27	41
CPT -6	91.2	97.24	33
CPT -7	72.5	81.53	21
CPT -8	98.5	91.71	22

concentration. The formulations that were crosslinked with Al3+ exhibited higher incorporation efficiencies overall. This could be attributed to the production of bigger beads in these formulations, which trap a higher concentration of medication.

Table 5 Microscopical Studies

Formulations	Particle Size(Mm)
CPT-1	0.198
CPT -2	0.281
CPT -3	0.276
CPT -4	0.321
CPT -5	0.295
CPT -6	0.321
CPT -7	0.313
CPT -8	0.385

Drug- Excipient Compatibility Studies (FT-IR):

Infrared spectroscopy was used to investigate the drug-polymer interaction. Utilizing Perkin Elmer-883 IR spectroscopy, the IR spectra were recorded between 500 and 3100 cm-1 for pure Capecitabine, 1020 to 3500 cm-1 for pure alginate, 650 to 3000 cm-1 for pure HPMC, 1000 to 3500 cm-1 for pure SCMC, and 500 to 1760 cm-1 for a mixture of Capecitabine with sodium alginate, HPMC, and SCMC in KBr pellets. By looking at the distinctive peaks in the data, it was determined that there is no incompatibility between the Capecitabine and other excipients.

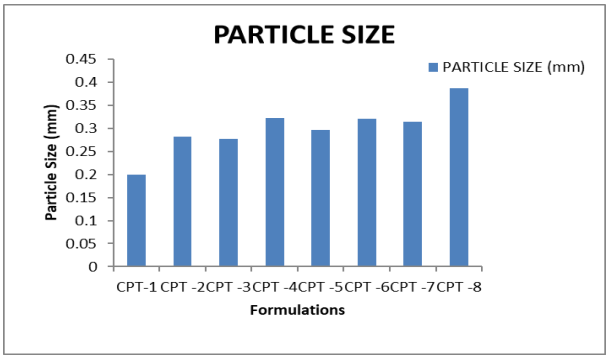

Figure 3 Microscopical studies

***In-vitro* dissolution:**

To investigate the impact of polymers on Capecitabine, several concentrations of sodium alginate—namely, 1, 2% w/v, 0.5% HPMC, and 0.5% SCMC—were combined with gellant solutions of calcium chloride (2% w/v) and aluminum chloride (2% w/v). These formulations' release profiles are displayed in Table and Figure. The findings showed that when the content of sodium alginate in the gellant solution increased in combination with aluminum chloride, the release was delayed.

Table 6 FT-IR Interpretation data for Capecitabine(drug)

Functional Group	Capecitabine(drug)		Sodium Alginate		HPMC
	Obtained	Observed	Obtained	Observed	Obtained
C–Br stretch (Alkyl halides)	610.60	690–515	1028.13	1250–1020	1159.95
C-N stretch (Aliphatic amines)	1109.54	1020-1250	1028.13	1250–1020	1159.95
C–H stretch (Alkenes)	3056.63	3100–3000	2888.13	3000–2850	965.19
C–O stretch (Aldehydes)	2813.94	2830–2695	3433.72	3500–3200	1727.60

Table 6 FT-IR Interpretation data for Capecitabine(drug) (Continued)

Functional Group	HPMC	SCMC		Data for Mixture	
	Observed	Obtained	Observed	Obtained	Observed
C–Br stretch (Alkyl halides)	1250–1020	1159.72	1300–1150	690–515	610.35
C-N stretch (Aliphatic amines)	1250–1020	1622.17	1650–1580	1250–1020	1037.60
C–H stretch (Alkenes)	1000–650	1622.17	1650–1580	1650–1580	1614.39
C–O stretch (Aldehydes)	1740–1720	1159.72	1300–1150	1300–1150	1158.74

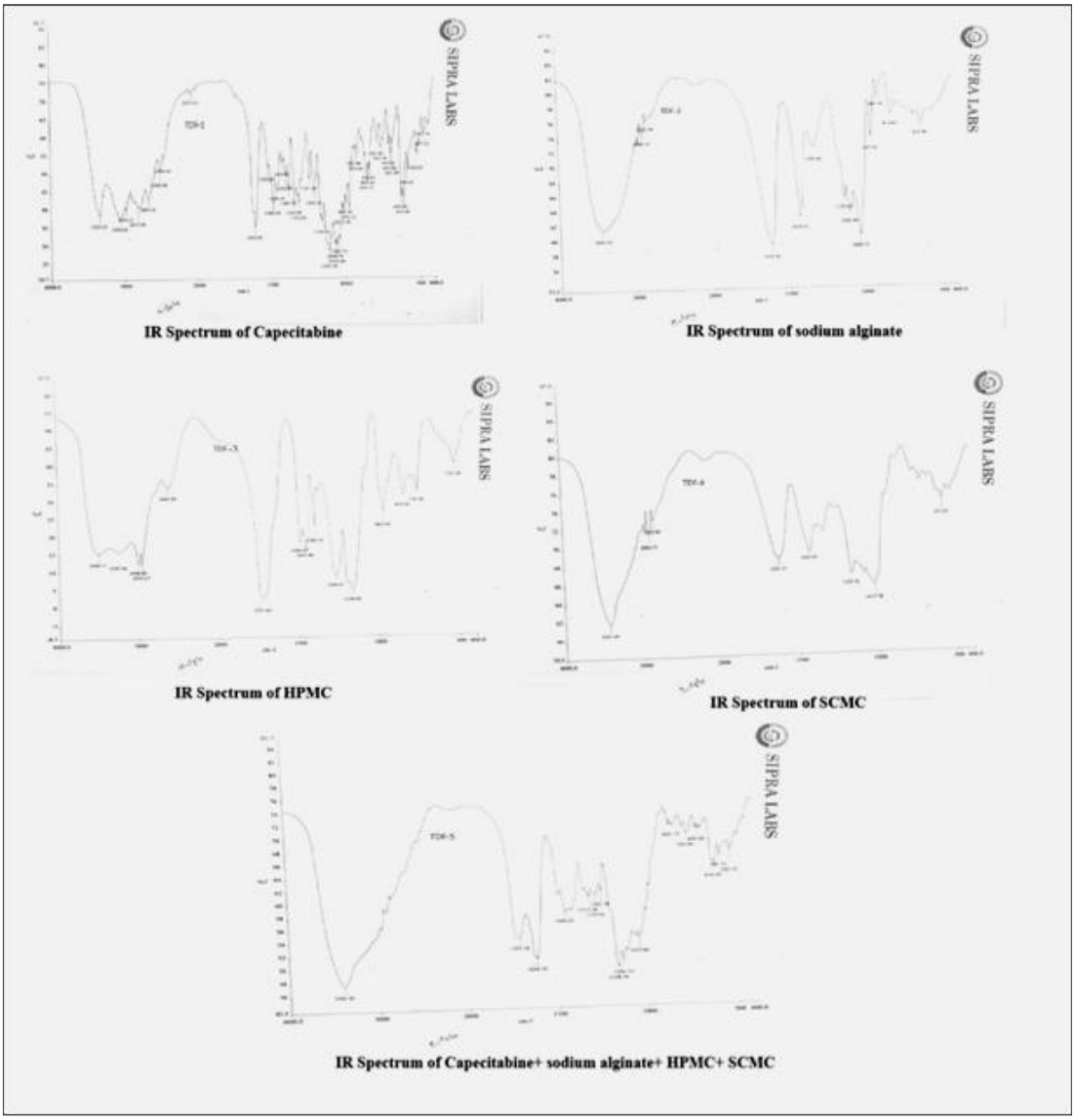

Figure 4 IR Spectrum of Capecitabine, sodium alginate, HPMC, SCMC, and Mixture

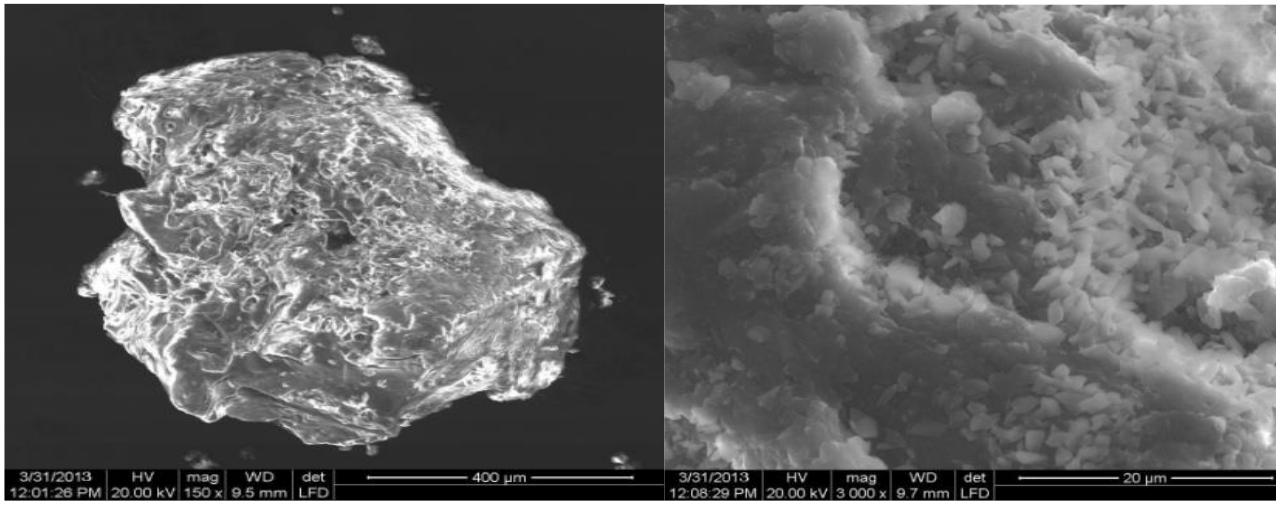

Figure 5 SEM Analysis of Capecitabine mucoadhesive beads using calcium chloride as a gallant solution(CPT-2)

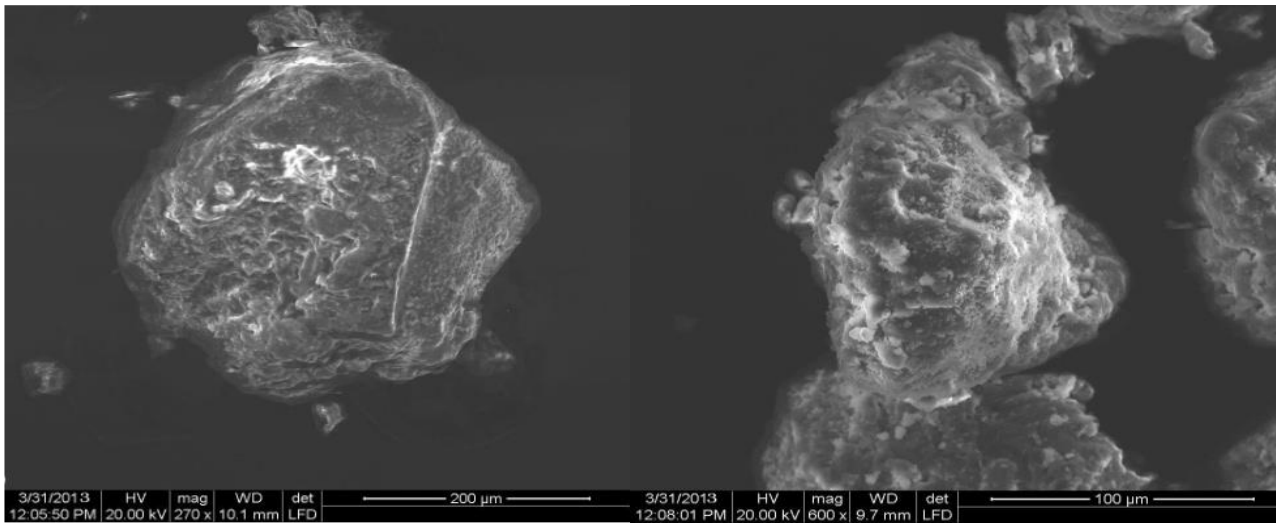

Figure 6 SEM Analysis of Capecitabine mucoadhesive beads using aluminum chloride as gellant solution (CPT-6).

Table 7 In-vitro drug release data for CapecitabineMucoadhesive beads

Sl.no	Medium	Time (Hrs)	CPT-1	CPT-2	CPT-3	CPT-4	CPT-5	CPT-6	CPT-7	CPT-8
1	7.4 pH phosphate buffer	1	9.7	9.5	10.8	9.9	9.2	8.2	9.5	8.2
2		2	20.4	17.9	23.7	20.5	15.8	20.2	16.5	20.4
3		3	29.2	24.8	38.4	28.2	22.4	25.8	24.8	28.6
4		4	38.5	35.8	44.5	36.5	30.8	32.5	38.4	33.8
5		5	48.7	46.8	52.6	42.7	42.4	47.8	48.9	41.8
6		6	52.4	58.7	68.7	56.9	55.8	53.6	56.3	58.5
7		7	65.1	66.5	73.4	63.2	64.7	60.2	62.5	68.2
8		8	77.9	75.6	84.3	75.6	72.3	66.4	69.4	74.8
9		9	85.6	84.6	98.0	84.7	85.4	76.9	89.8	80.5
10		10	97.4	89.5	-	97.5	92.5	80.3	97.4	92.8
11		11	-	98.6	-	-	98.2	92.4	-	97.8
12		12	-	-	-	-	-	98.8	-	-

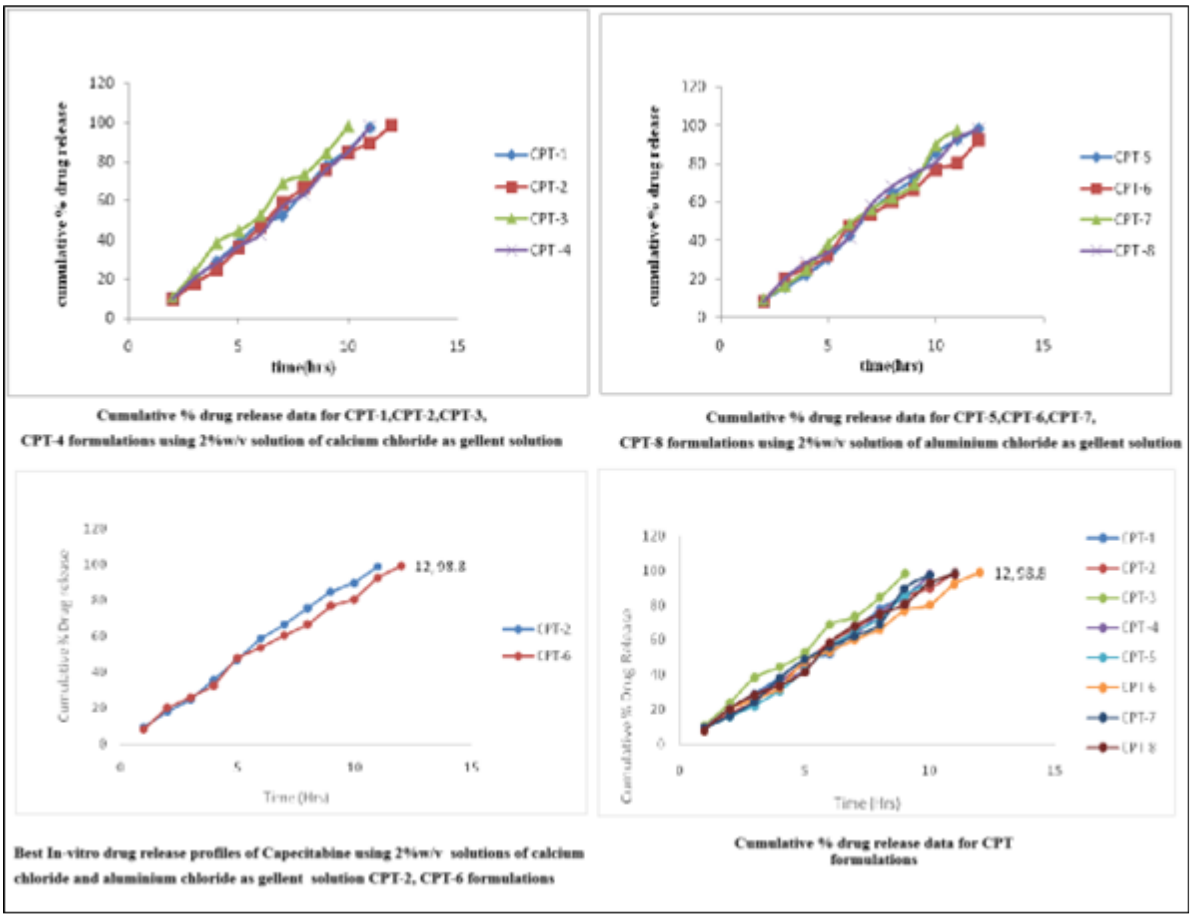

Figure 7 Cumulative % drug release data for CPT formulations

Table 8 In-vitro drug release kinetics data for formulation CPT-6

Zero-order		First order		Higuchi's data		Korsemayer-Peppas data	
Time (h)	% CDR	Time (h)	% Log CD Remaining	SQRT of time	% CDR	Log time	% Log CDR
1	8.2	1	1.9620	1.0	8.20	0	0.913
2	20.2	2	1.9020	1.414	20.20	0.30	1.305
3	25.8	3	1.8700	1.732	25.80	0.477	1.411
4	32.5	4	1.8290	2.0	32.50	0.602	1.511
5	47.8	5	1.7170	2.236	47.80	0.698	1.679
6	53.6	6	1.6660	2.449	53.60	0.778	1.729
7	60.2	7	1.5990	2.645	60.20	0.845	1.779
8	66.4	8	1.5260	2.828	66.40	0.903	1.822
9	76.9	9	1.3630	3.0	76.90	0.954	1.885
10	80.3	10	1.2940	3.162	80.30	1.0	1.904
11	92.4	11	0.8800	3.316	92.40	1.041	1.965

Table 9 Release Order Kinetic data of CPT-6

Formulation	Correlation Coefficient values (R^2)				Diffusion Exponent value (n)
	Zero Order	Korsemayer-Peppas	Higuchi	First order	
CPT-6	0.994	0.991	1.0	0.753	0.971

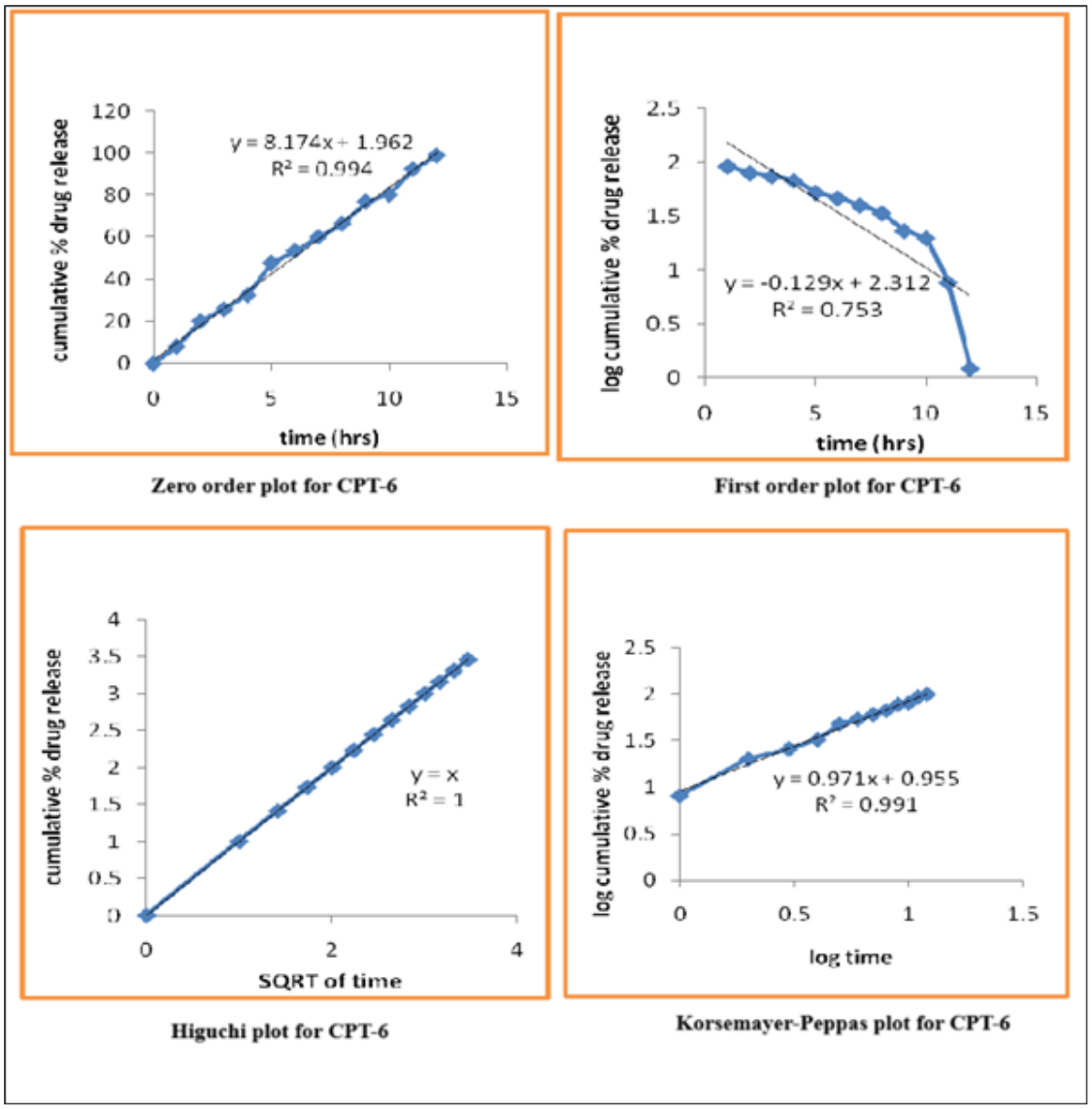

Figure 8 Release order kinetics of CPT-6

IN-VITRO DRUG RELEASE KINETICS

As a result, many model-dependent techniques (such as Higuchi, First order, Zero order, and Korsemayer-Peppas plots) were used to compare the dissolution profiles of each formulation (Tables and figures). According to the model's results, the "best-fit model" for all mucoadhesive beads contained in capsules has a zero order. This is because of a previous fact based on the R2 value found through model fitting. The results indicated that CPT-6 had a more significant release-delaying effect. The Korsemayer-Peppas release exponent (n) values of the capecitabine beads show Supercase 2 transport, as they are more critical than 0.85.

CONCLUSION

The study's findings led to the conclusion that formulation conditions must be carefully chosen to achieve high encapsulation efficiency and regulate the release of Capecitabine from alginate beads. According to in-vitro dissolving trials, formulations made with increasing sodium alginate concentrations with SCMC released the medication more quickly than those made with increasing concentrations of sodium alginate with HPMC. Furthermore, compared to beads prepared using calcium chloride 2%w/v as a gelling solution, the beads prepared using aluminum chloride 2%w/v as a gelling solution formed more challenging beads. More research must be done to

create the most effective Capecitabine formulations.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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