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Development and Evaluation of Colon Specific Drug Delivery System of Capecitabine Minitabs

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ABSTRACT

The present study aimed to develop a colon-specific drug delivery system (CSDDS) for Capecitabine using maltose as a triggering agent. The system was designed to release the drug specifically in the colon, leveraging the interaction between maltose and colonic microflora. The core minitabs were formulated using Capecitabine, maltose, and other excipients, followed by coating with Eudragit E-100 and Eudragit L-100 polymers to achieve pH-dependent release. The formulation was evaluated for physicochemical properties, in-vitro drug release, and stability. The results demonstrated that the optimized formulation (Batch C-12) showed minimal drug release in acidic pH (1.2) and significant release in colonic pH (6.8) in the presence of ceacal content, achieving 93.45% drug release at 8.5 hours. Stability studies confirmed the formulation's robustness under accelerated conditions. The study concludes that maltose-based CSDDS is a promising approach for targeted delivery of Capecitabine to the colon.

INTRODUCTION

Colon-specific drug delivery systems (CSDDS) have gained significant attention for their ability to deliver drugs directly to the colon, minimizing systemic exposure and reducing side effects. Capecitabine, a prodrug of 5-fluorouracil, is widely used in the treatment of colorectal cancer. However, its systemic administration often leads to severe side effects. Targeted delivery to the colon can enhance therapeutic efficacy while minimizing adverse effects.

Maltose, a disaccharide, has been explored as a potential triggering agent for CSDDS due to its ability to interact with colonic microflora, leading to acid production and subsequent drug release. This study focuses on developing a maltose-based CSDDS for Capecitabine, utilizing a multi-layered coating approach to ensure pH-dependent release and colon-specific delivery.

MATERIALS AND METHODS

Materials

Drug: Capecitabine
Excipients: Maltose, Microcrystalline Cellulose, Magnesium Stearate, Cross Carmellose Sodium
Polymers: Eudragit E-100, Eudragit L-100, Hydroxypropyl Methylcellulose (HPMC)
Solvents: Phosphate buffer (pH 6.8, 7.4), 0.1 N HCl (pH 1.2)
Methods

Preformulation Studies:

Characterization of Capecitabine (melting point, UV, IR spectroscopy)
Drug-excipient compatibility studies using FT-IR
Solubility studies in different pH media

Formulation of Core Minitabs:

Direct compression method was used to prepare core minitabs containing Capecitabine, maltose, and other excipients.
Evaluation of powder blend for flow properties (angle of repose, bulk density, tapped density, Carr's index, Hausner ratio).

Coating of Minitabs:

Core minitabs were coated with Eudragit E-100 (4%, 6%, 8%, 10%, 12%) and HPMC (2%) as a barrier layer.
Final coating with Eudragit L-100 (2%, 4%, 6%, 8%, 10%) for enteric protection.

Evaluation of Minitabs:
Physicochemical properties (thickness, diameter, weight variation, hardness, friability, disintegration time, drug content).

In-vitro drug release studies in different pH media (pH 1.2, 6.8) with and without ceacal content.

Stability Studies:
Accelerated stability studies at 40°C and 75% RH for 3 months.

RESULT AND DISCUSSION

Preformulation studies :

Characterization Of Capecitabine:
Characterization of Capecitabine was carried out by conducting various physiochemical test including melting point determination, spectral analysis such as UV spectrum and IR spectrum for Capecitabine.

Description:
Capecitabine was found to be white hygroscopic crystalline powder, no characteristics odor.

Melting point:
The melting point of Capecitabine was determined by open capillary method and Melting point was found to be 114-117°C. This value is similar to reported value 115°C- 120°C.

Spectroscopic Studies:

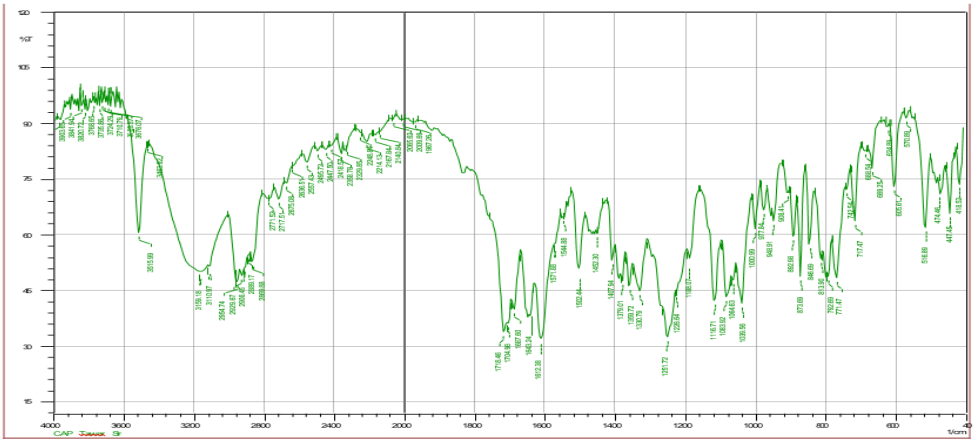


Fig no: FTIR studies of Capecitabine

UV Spectroscopy (Determination of λ max):

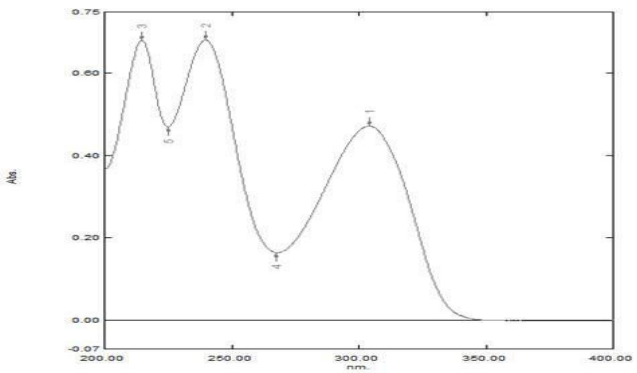


Fig No.: UV spectrum Capecitabine in Distilled Water

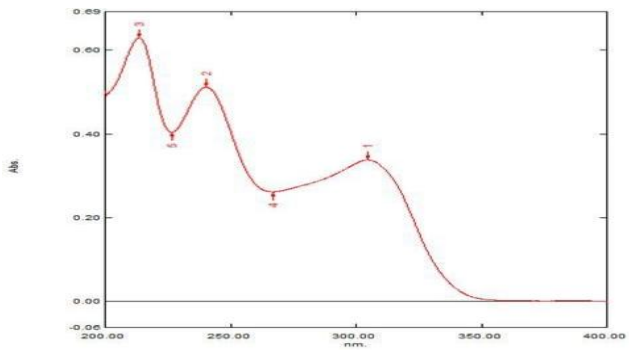


Fig No: UV spectrum Capecitabine in 0.1 N HCl

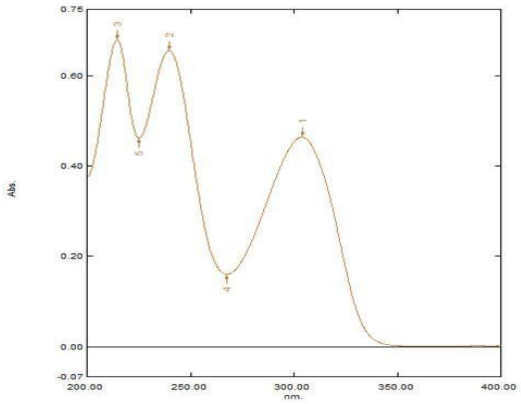


Fig No: UV spectrum Capecitabine in pH 6.8

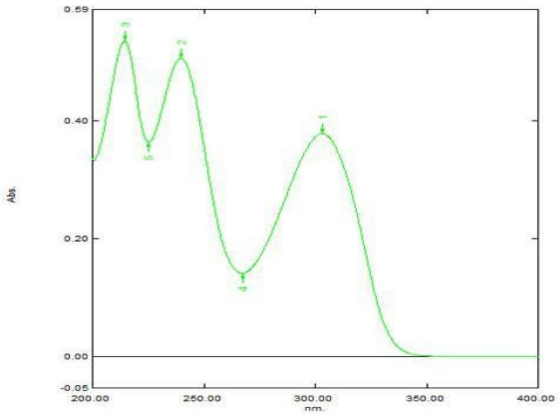


Fig No.: UV spectrum in Phosphate Buffer pH 7.4

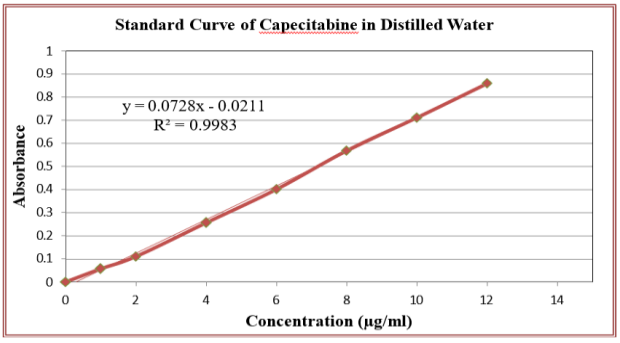


Figure : Calibration curve in Distilled Water

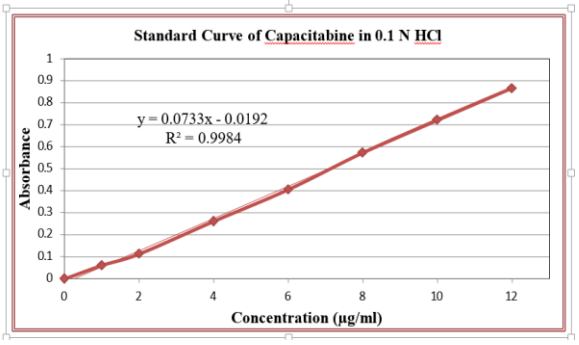


Figure No.: Calibration curve of in 0.1 N HCL

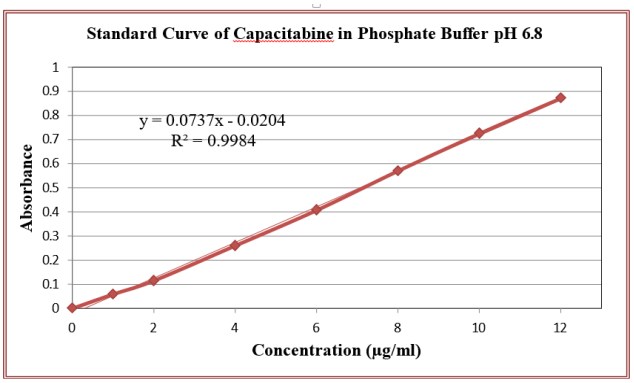


Fig No: Calibration curve in pH 6.8

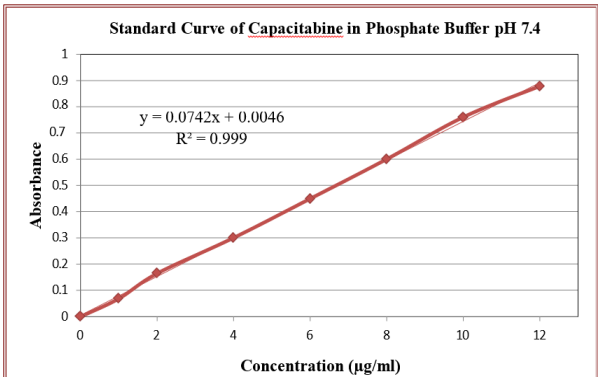


Fig No. : Calibration curve in pH 7.4

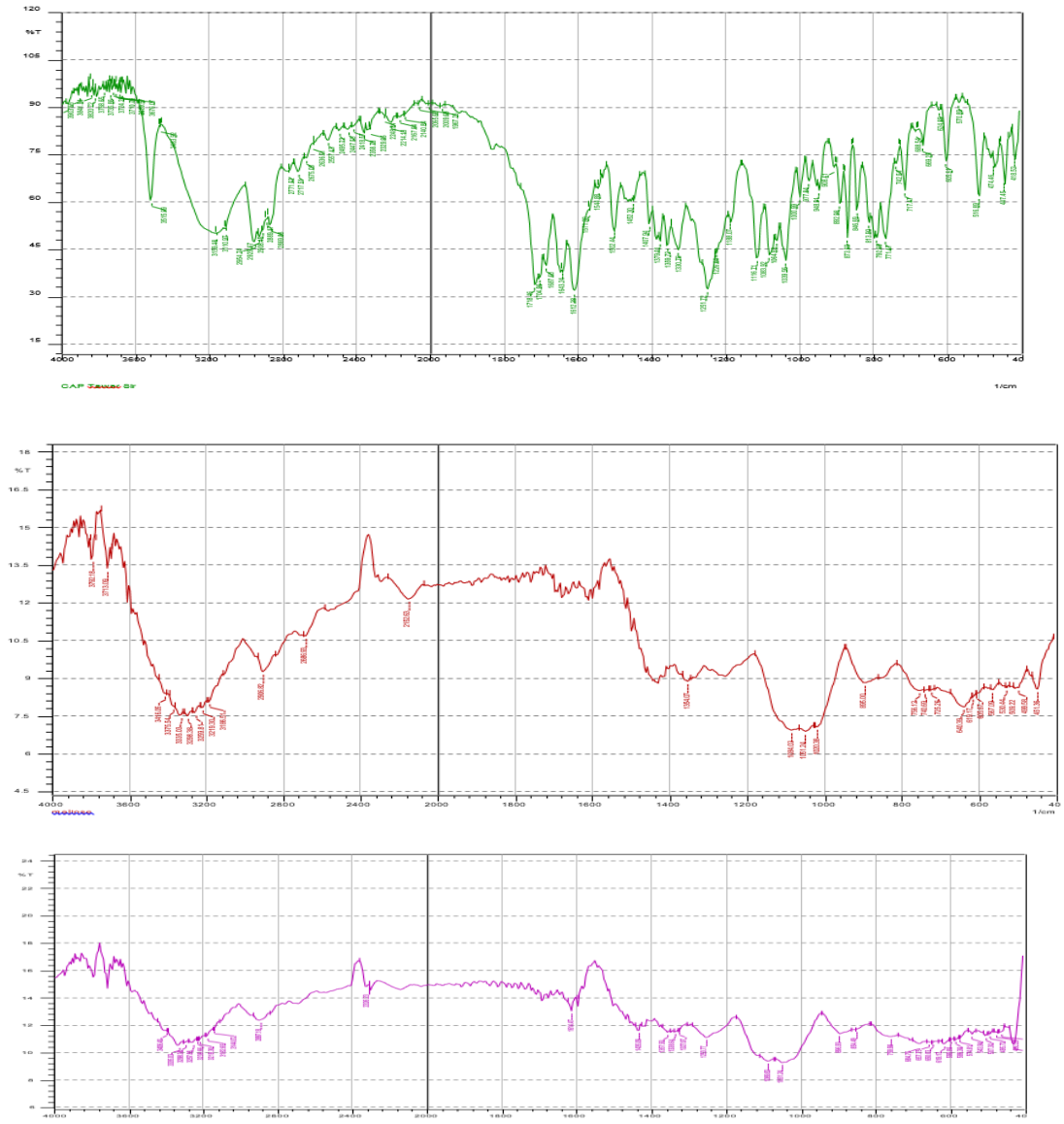
Determination of Solubility

Table No: Saturation solubility study of Capecitabine in different solvents.

Sr. No.	Solvent	pH	Average solubility* (mg/ml).
1	Distilled water	---	26
2	0.1 N HCl	1.2	22
3	Phosphate buffer	6.8	24
4	Phosphate buffer	7.4	23
5	Phosphate buffer	5.5	24

DRUG EXCIPIENT COMPATIBILITY STUDIES

Infrared Spectra Analysis



Formulation and evaluation of core Minitab
Formulation of Core minitab

Evaluation of Powder Blend

Table No.: Flow characteristics of physical mixtures of drug with excipients

Drug	Angle of Repose (Ø)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner Ratio
Capecitabine	30.54	0.345	0.405	14.81	1.17

Evaluation of Core Minitab

Table.: a) Physicochemical Parameters of minitabs

Formulation Code	Thickness (mm)	Diameter (mm)	Weight Variation	Hardness (kg/cm^2)
C-1 (Core minitab)	2.41	4.02	37.7	3.05

Table.: b) Physicochemical Parameters of minitabs

Formulation Code	Friability (%)	Disintegration Time (sec.)	Drug Content (%)
C-1 (Core minitab)	0.85	35	99.91

***In-Vitro* drug release studies**

Table No.: Dissolution Profile of Batch C-1 (Core minitab)

Sr. No.	Time in (min)	Cumulative % release
1	00	00
2	10	32.52
3	20	70.54
4	30	98.36

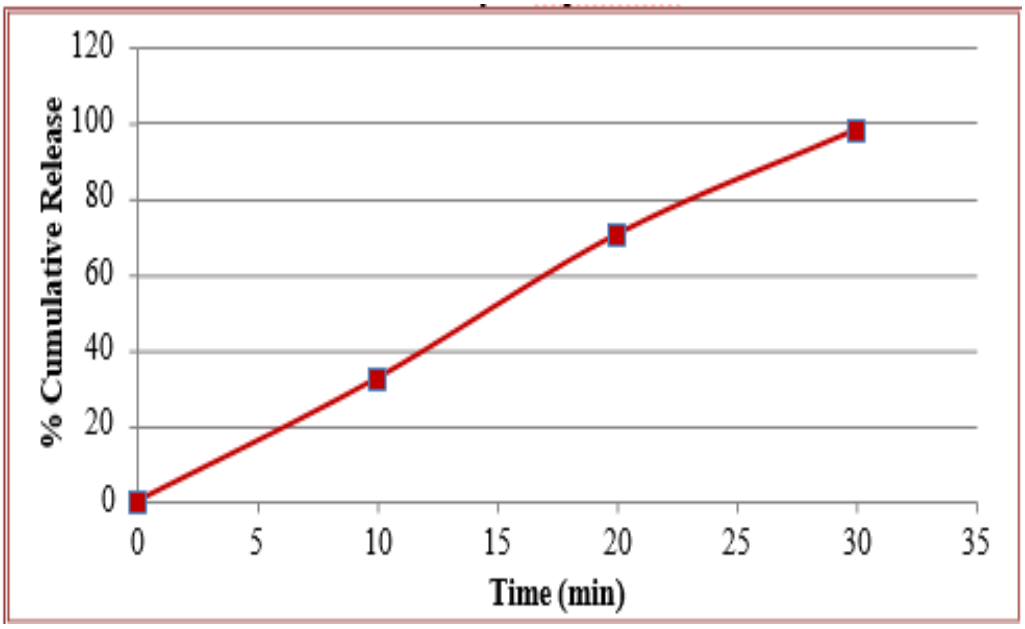


Figure No.: **Dissolution Study of Capecitabine from core minitabs in Phosphate Buffer solution pH 7.4**

HPTLC METHOD FOR ESTIMATION OF CAPECITABINE IN DEVELOPED FORMULATION

Selection of wavelength for densitometric evaluation band:

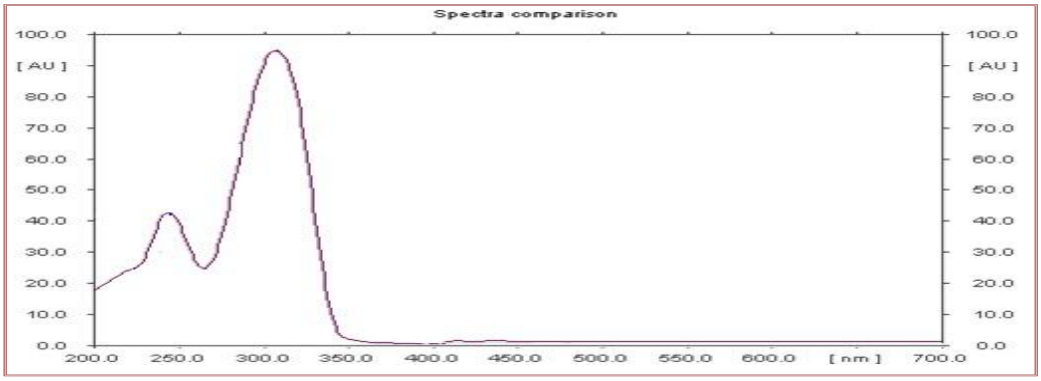


Figure No.: Spectrum of Capecitabine

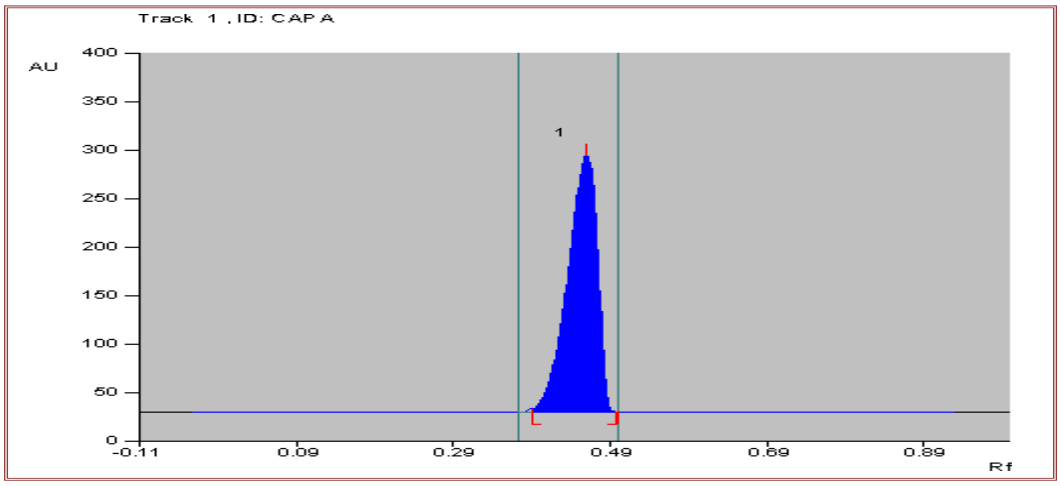


Figure No.: Typical Densitogram of Capecitabine (Rf = 0.4)

Study of Linearity Range:

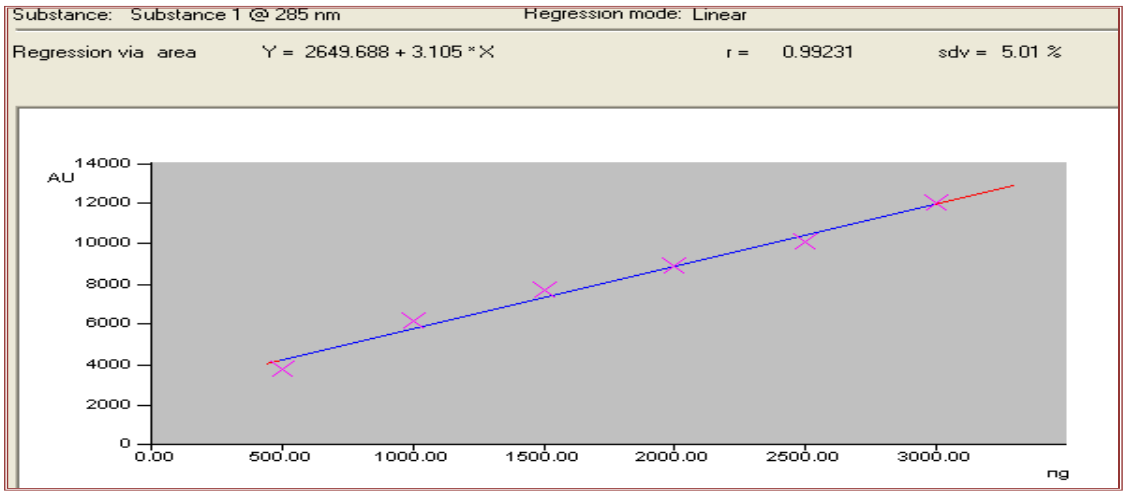


Figure No.: Standard Calibration Curve for CAP

Analysis of Formulation:

Table No.: The results of analysis of capecitabine formulation

Wt of Eight minitabs= 400.8 mg		Avg. wt of Minitab: 50.08 mg		
Sr. No.	**Weight of Minitabs Powder(mg)**	**Peak Area***	**Amount of CAP Estimated(mg/minitab)**	**% Label claim**
1.	133.6	8624	18.74	99.94
2.	132.8	8615	18.79	100.23
3.	133.9	8966	18.66	99.53
4.	134.2	8831	18.71	99.81
5.	133.5	8574	18.83	100.45
6.	133.6	8769	18.66	99.51
		Mean		99.91
		S.D. (±)		0.37
		R.S.D.		0.37

* Mean of four determinations

Formulation and evaluation of multi layered coated Minitab.

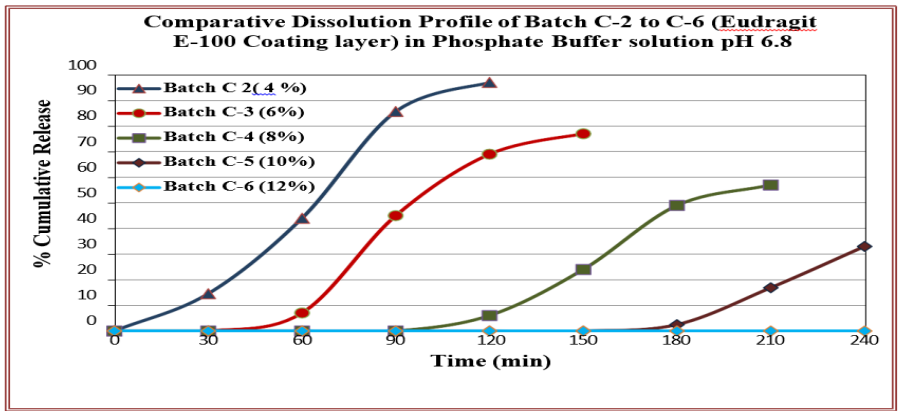


Figure No.: Comparative Dissolution Profile of Eudragit E-100 Coating Layer

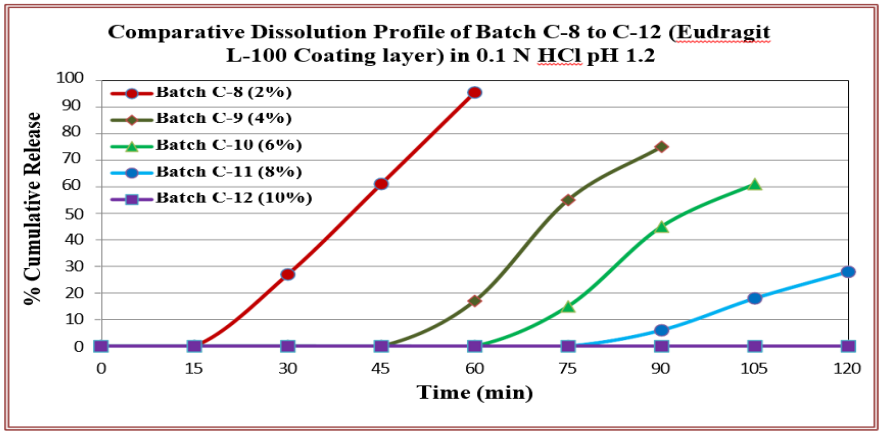


Figure No.: Comparative Dissolution Profile of Eudragit L-100 Coating Layer

Evaluation of Developed and Optimized Multilayered coated colon specificMinitabs

Table No: a) Physicochemical Parameters of Optimized Minitabs

Formulation Code	Thickness (mm)	Diameter (mm)	Weight Variation	Hardness (kg/cm^2)
C-12 (Optimized)	2.71	4.08	48.6	--

Table No.: b) Physicochemical Parameters of Optimized Minitabs

Formulation Code	Friability (%)	Disintegration Time (sec.)	Drug Content (%)
C-12 (Optimized)	--	--	99.59

Table No.: Cumulative % release of optimized batch without ceacal content

Dissolution Medium	Time (Hrs)	[Cumulative release (%)]
pH 1.2 buffer	0	0
	0.5	0
	1	0
	1.30	0
	2.0	0
pH 6.8 buffer	2.30	4.21
	3.00	5.64
	3.30	6.31
	4.00	7.98
	4.30	8.01
	5.00	9.71
	5.30	10.00
	6.00	11.43
pH 6.8 buffer without ceacal content	6.30	15.61
	7.00	25.23
	7.30	31.89
	8.00	39.79
	8.30	44.61

Table No. Cumulative % release of optimized batch (C-12) with ceacal content

Dissolution Medium	Time (Hrs)	[Cumulative release (%)]
pH 1.2 buffer	0	0
	0.5	0
	1	0
	1.30	1.22
	2.0	2.55
pH 6.8 buffer	2.30	3.56
	3.00	4.56
	3.30	6.02
	4.00	6.99
	4.30	7.55
	5.00	8.76
	5.30	9.99
	6.00	10.05
pH 6.8 buffer with ceacal content	6.30	48.78
	7.00	69.78
	7.30	93.33
	8.00	94.55
	8.30	96.57

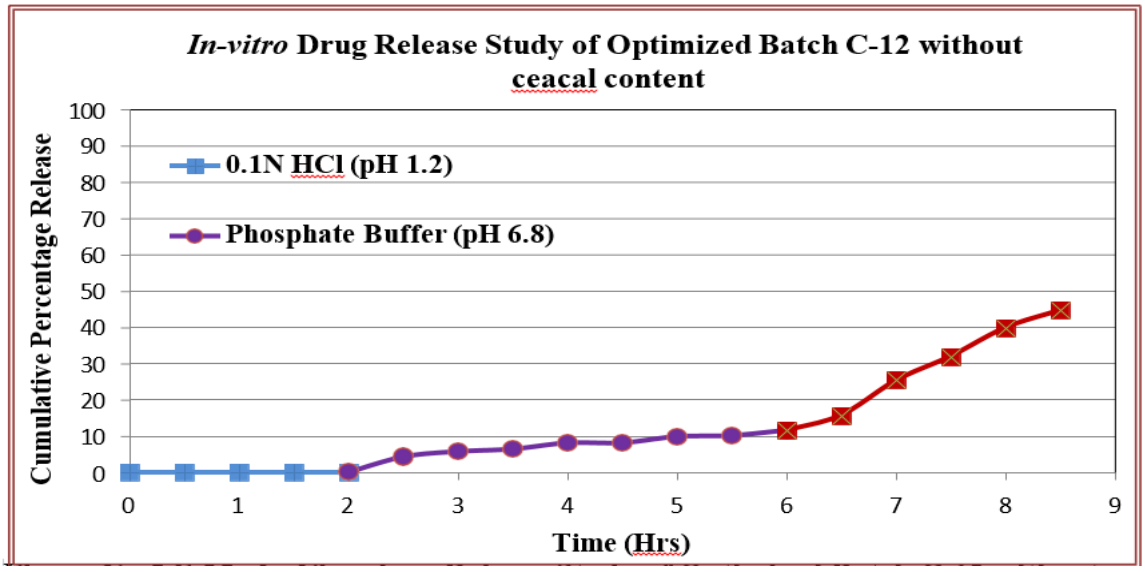


Figure No.: *In-Vitro* drug Release Study of Optimized Batch C-12 without Ceacal Content

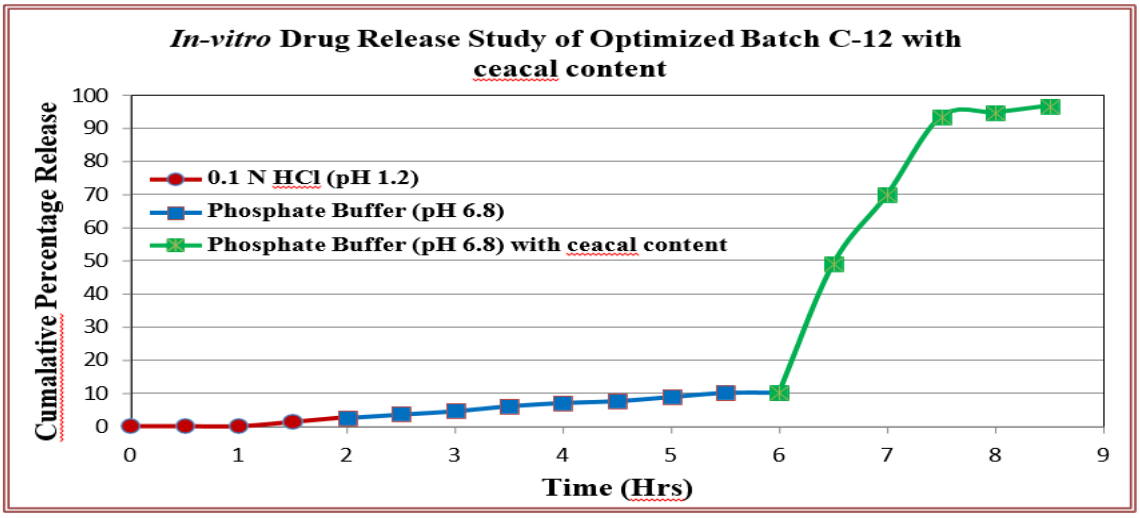


Figure No.: *In-Vitro* Drug Release Study of Optimized Batch C-12 with Ceacal Content.

Stability studies of optimized formulation:

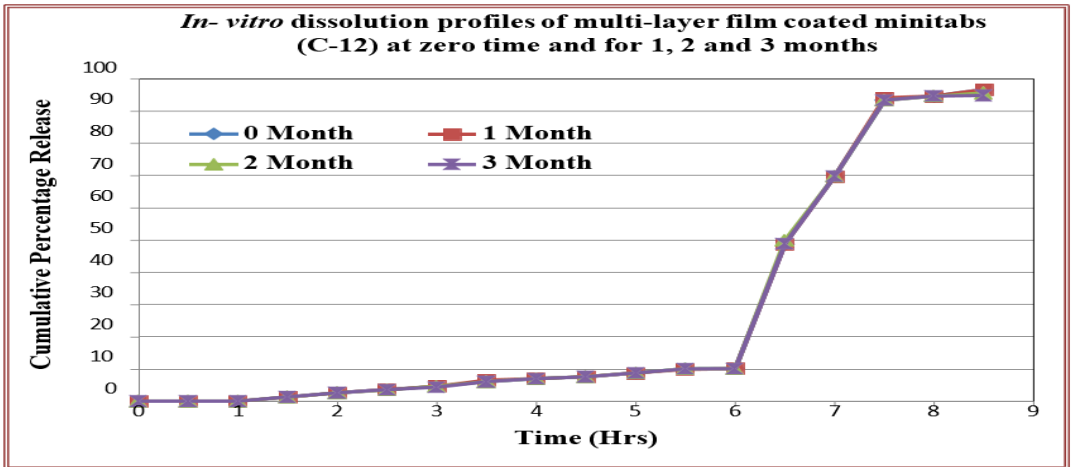


Figure No.: *In- vitro* dissolution profiles of multi-layer film coated minitabs (C12) at zero time and for 1, 2 and 3 months.

CONCLUSION

The developed maltose-based colon-specific drug delivery system for Capecitabine demonstrated successful pH-dependent release and targeted delivery to the colon. The optimized formulation (Batch C-12) exhibited minimal drug release in acidic conditions and significant release in colonic pH, facilitated by the presence of ceacal content. Stability studies confirmed the robustness of the formulation, making it a promising candidate for further clinical evaluation. This study highlights the potential of maltose as a triggering agent for colon-specific drug delivery systems.

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