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Formulate and evaluate triamcinolone loaded microsponges for colon drug delivery

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Abstract

The study aims to formulate and evaluate in-vitro and pharmacokinetic analyses of microsponges loaded with triamcinolone for colon drug delivery. This study intended to deliver drugs specifically to the colon by creating microsponges filled with triamcinolone. Eudragit RS 100 was used as a polymer to make the microsponge formulations in a quasi-emulsion solvent diffusion technique. It was observed that a time-dependent polymer blocked up to four hours of measurable drug release. At pH 6.8, the pH of the colon, Eudragit RS 100, a sustained release polymer, was found to be present, leading to maximum release. The drug: polymer ratio significantly influences the drug release rate. It has been demonstrated that the highest drug release occurs with a more fantastic drug: polymer ratio. Other microsponges are stable under storage conditions. The produced microsponges have been shown to have a more extended retention period in the colon and good mucoadhesion qualities, indicating that they would be the best dosage form for colon targeting. Microsponges provide the colon with an adequate dosage and, more precisely, controlled release because of their porosity.

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INTRODUCTION

When more significant regional drug levels are possible than with conventional modes of administration, site-specific drug delivery is preferred. As a result, adverse effects associated with high systemic medication levels are reduced or eliminated. Site-specific medication delivery can be defined according to the degree of specificity in the delivery procedure. Individual organs (or tissues) are targeted during delivery [1]. Targeting a specific cell type (s) within a tissue. Intracellular targeting involves engineering the incorporation of drug and drug carrier constructs

via specific transport channels to deliver them to various intracellular compartments in target cells. A controlled drug delivery system that provides the drug continuously over a particular period with predictable and reproducible kinetics and an identified mechanism of release. New research activities have focused on selectively delivering drugs to the colon via oral route. In recent years, there has been a lot of research on the subject of colonic medication delivery. Several things have sparked this curiosity [2].

METHODOLOGY

Pre-formulation studies:

Before developing a microsponge dosage form, it is crucial to ascertain a few basic physical and chemical characteristics of the drug molecule both by itself and in combination with excipients. Pre-formulation is the name for this initial stage of learning. The main goal of the pre-formulation is to produce data that will help the formulator create mass-producible, stable, and bioavailable dosage forms [3].

Drug-polymer identification studies (Compatibility studies):

FTIR spectroscopy was used to characterize the drug and polymer compatibility. The medication and polymer were physically mixed (1:1) to test for compatibility, and the mixture was then subjected to FTIR analysis [4]. If the FTIR spectra of mixes exhibit similar peaks to those of pure drug and polymer, then there is no interaction between the two.

Preparation of Triamcinolone loaded microsponges.

MICROSPONGE CHARACTERIZATION:

Morphological examination (SEM):

Scanning electron microscopy visualized the surface morphology and structure (SEM). After applying the gold coating, samples were scanned randomly for particle size and surface morphology using a Zeiss DSM 982 Gemini, India [5].

CHARACTERIZATION OF TRIAMCINOLONE-LOADED MICROSPONGES:

Production yield:

Using the weight of the dried microsponge (W1) and the total of the initial dry weight of the starting ingredients (W2), the production yield percentage was computed using the following formula [6]:

$$\% \text{ Production Yield} = \frac{\text{W1}}{\text{W2 x 100}}$$

Particle size:

Optical microscopy measured the prepared microsponges' particle size and size distribution. A calibrated optical microscope (Olympus Pvt. Ltd., India) was used to count between 200 and 300 microsponges to determine the particle size [7].

Drug entrapment efficiency:

Phosphate buffer (pH 6.8) was added to the 100 ml volumetric flask and 25 mg of crushed microsponges. The mixture was then agitated for 12 hours. Using a UV spectrophotometer 1700 (Shimadzu), the absorbance at 243 nm was measured after the solution had been stirred and filtered using Whatmann filter paper. Appropriate dilutions were then prepared from the filtrate. The following equation was used to determine the proportion of drug entrapment [8]:

Table 1 Formulation table of Triamcinolone loaded microsponges

S. No	Excipients	TMS 1	TMS 2	TMS 3	TMS 4	TMS 5	TMS 6	TMS 7	TMS 8
1.	Triamcinolone	0.1	0.3	0.5	0.7	0.9	0.11	0.13	0.15
2.	Ethyl alcohol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3.	Poly Vinyl Alcohol (%w/v)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
4.	Tri-ethyl citrate (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
5.	Water (ml)	50	50	50	50	50	50	50	50

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content x } 100}$$

In vitro Drug Release studies of Triamcinolone loaded microsponges:

The dialysis membrane method was used to conduct in vitro evaluation tests of topical gel. 6.8 pH phosphate buffer was added to the receptor compartment after the membrane had been soaked in 0.1 NHCl for 12 hours. On the membrane's surface, an equal amount of test vehicle (100 mg) was applied [9]. It was carefully placed on the cell to prevent air bubbles from getting trapped beneath the prepared membrane. The entire assembly was held at 37°C for twelve hours with a constant 600 rpm stirring speed. Four-millilitre aliquots of the drug sample were removed every hour and replaced with an equivalent volume of newly made buffer. Three duplicates of each experiment were run. The drug analysis was performed at 243 nm using a UV spectrophotometer [10].

Modeling of Dissolution Profile

The release kinetics of ketoconazole from the matrix tablets were explained in the current investigation by fitting data from the in vitro release to several equations and kinetic models. The kinetic models employed were the first order, Higuchi release, zero order equation, and Korsmeyer-Peppas models [11].

Kinetic Studies: Mathematical models

For the optimal formulation, the release rate of the drug from matrix systems was interpreted using a variety of release kinetic equations, including zero-order, first-order, Higuchi's equation, and Korsmeyer-Peppas equation. The highest correlation (r2) best fit was computed.

Zero-order model: The equation can illustrate drug dissolution from dosage forms that do not break down and release the medication gradually.

$$Qt = Q0 + K0t$$

First Order Model:

When the concentration of the dissolving species affects the dissolution rate, the first-order equation describes the release from those systems. The first-order equation that describes release behavior in general is as follows:

$$\text{Log C} = \frac{\text{Log Co} - \text{kt}}{2.303}$$

Higuchi model:

Higuchi created the first mathematical model 1961 that attempted to explain drug release from a system. It was first developed for planar systems and extended to various geometric configurations and porous systems. In a general way, the Higuchi model is expressed by following the equation

$$Q = K_H - t^{\frac{1}{2}}$$

Korsmeyer-Peppas model:

The Korsmeyer-Peppas model was fitted to the first 60% of drug release data to identify the mechanism of drug release.

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

Stability Study:

Stability studies were applied since the formulation of TMS5 had a high encapsulation efficiency. After being kept in glass bottles for a month at four, twenty-five, and fifty degrees Celsius, the Triamcinolone microsponges were analyzed every ten days to see if the percentage of drug concentration had changed [12].

RESULTS AND DISCUSSION:

Compatibility studies

IR studies

FTIR is used to record the infrared spectra of the pure Triamcinolone sample. This contrasts with the Triamcinolone standard functional group frequencies, displayed in **Table 2**.The formulation's FTIR spectrum is shown in **Figure 1-5.**

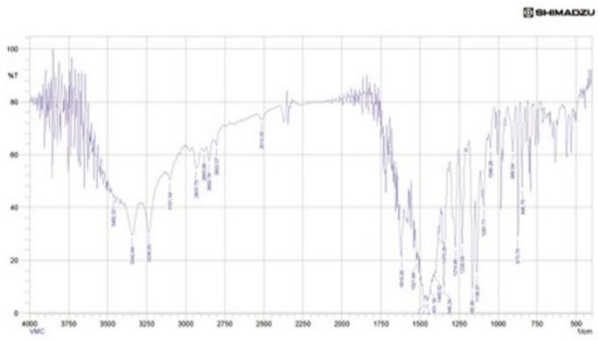


Figure 1 FTIR Spectra of Pure drug (Triamcinolone)

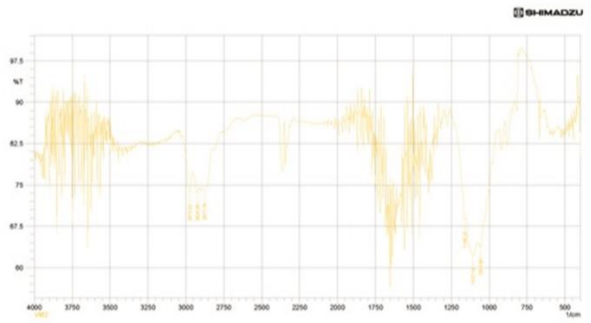


Figure 2 FTIR Spectra of Ethyl alcohol

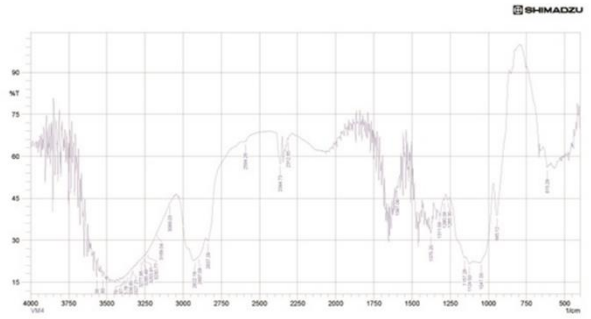


Figure 3 FTIR Spectra of Poly Vinyl Alcohol

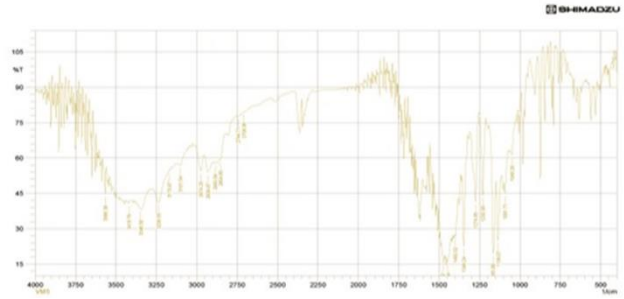


Figure 4 FTIR Spectra of Tri-ethyl citrate

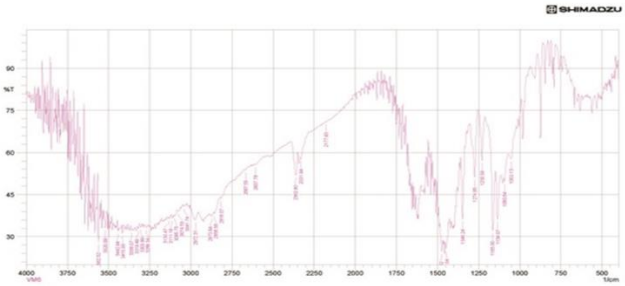


Figure 5 FTIR Spectra of Drug + EA + PVA+ Tri-EC

MICROSPONGE CHARACTERIZATION:

Morphological examination (SEM):

SEM was used to examine the microsponges' shape using the quasi-emulsion solvent diffusion approach (**Figure 6**). The microsponges were homogeneous, spherical, and free of drug crystals. Their form influences the surface area and surface area per unit weight of spherical microsponges. The irregular shape of the particles may impact the dissolution rate in the dissolution environment.

The agitation's speed affected how well the medication and polymer dispersed into the aqueous phase. When the stirring speed was low, less energy was produced, and the particles stuck together because no emulsion droplets formed, resulting in uneven particle shapes.

CHARACTERIZATION OF TRIAMCINOLONE-LOADED MICROSPONGES:

Production yield:

A range of 43.07 ± 1.72 % to 63 ± 1.94 % was seen in the Triamcinolone microsponges' manufacturing yield. According to the viscosity nature of the slurry, some agglomerates formed, and the polymer adhered to the container, causing product loss. Because in high drug-to-polymer ratios, there was relatively less polymer available per microsponge, the formulation prepared with a drug-polymer ratio of 7:1. Smaller-sized microsponges were likely produced when there was less polymer surrounding the drug in high drug-polymer ratios, which also resulted in a thinner polymer wall.

Particle Size:

The size of the microsponges is consistent. The manufactured microsponges had particle sizes ranging from 464 ± 12.5 to 83.21 ± 14.2 (**Table 3**). The diameters of microsponges influence the effectiveness of encapsulation and the drug release rate. Particle size was shown to decrease

Table 2 Interpretations of FTIR

Functional Groups	Pure Drug	Ethyl Alcohol	Poly Vinyl Alcohol	Tri – Ethyl Citrate
-N-H- (Amines)	3462.22	2924.24	3327.21	3236.55
C-H Stretch (Aromatics)	3236.55	2974.23	2922.16	2974.23
-N=N- (Azo Group)	348.24	1107.14	945.12	932.14
C-H Rocking (Alkanes)	873.75	1056.99	615.29	834.72

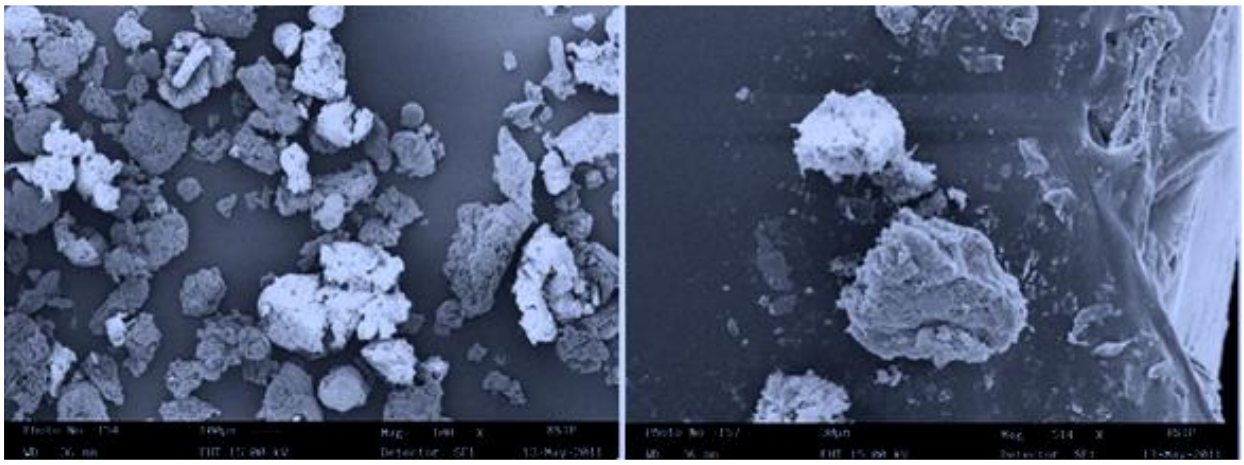


Figure 6 Scanning Electron Micro-Graphs

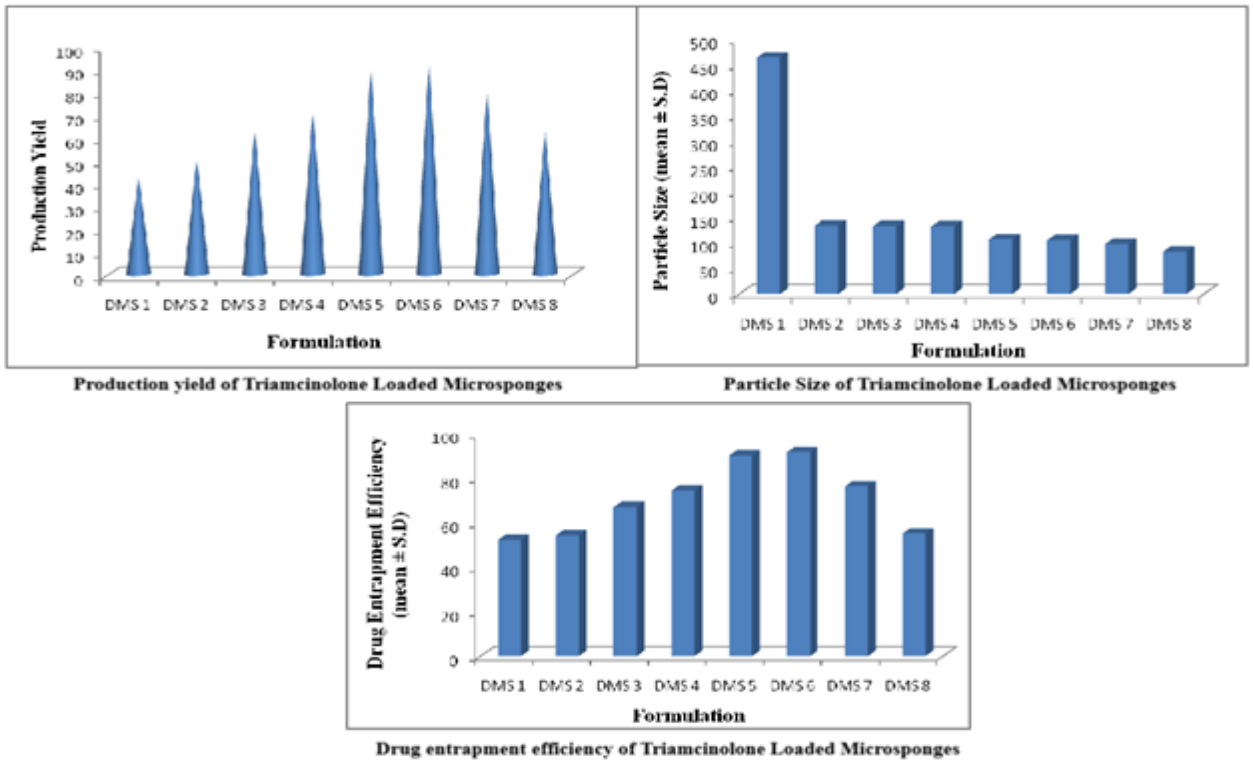


Figure 7 Characterization of Triamcinolone Loaded Microsponges

Table 3 Characterization of Triamcinolone Loaded Microsponges

Formulation Code	Production Yield (mean ± S.D)	Particle Size (mean ± S.D)	Drug Entrapment Efficiency (mean ± S.D)
TMS 1	43.07 ± 1.72	464.71 ± 12.5	52.42 ± 1.22
TMS 2	51.08 ± 1.07	134.64 ± 13.5	54.48 ± 0.85
TMS 3	64.3 ± 1.09	133.10 ± 17.2	67.05 ± 1.55
TMS 4	72.6 ± 1.11	132.22 ± 18.4	74.63 ± 0.62
TMS 5	92.04 ± 1.12	107.24 ± 9.8	90.33 ± 1.35
TMS 6	94.12 ± 1.37	105.61 ± 12.4	91.85 ± 1.65
TMS 7	81.32 ± 0.92	98.52 ± 11.4	76.55 ± 1.94
TMS 8	63.42 ± 1.94	83.21 ± 14.2	55.22 ± 1.77

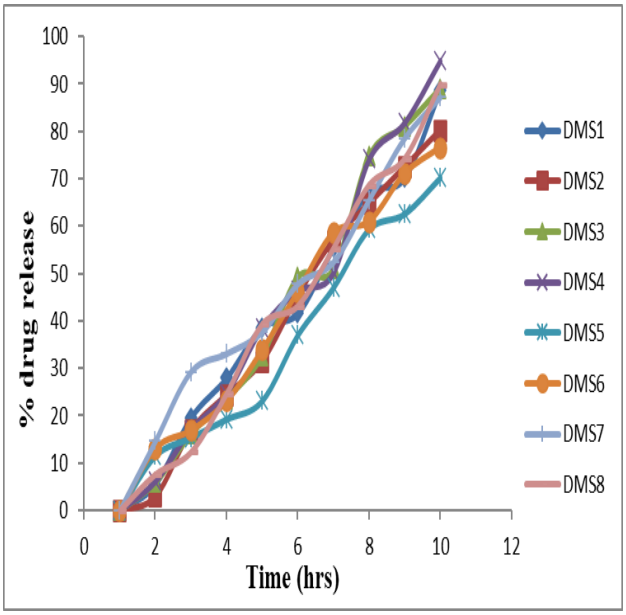
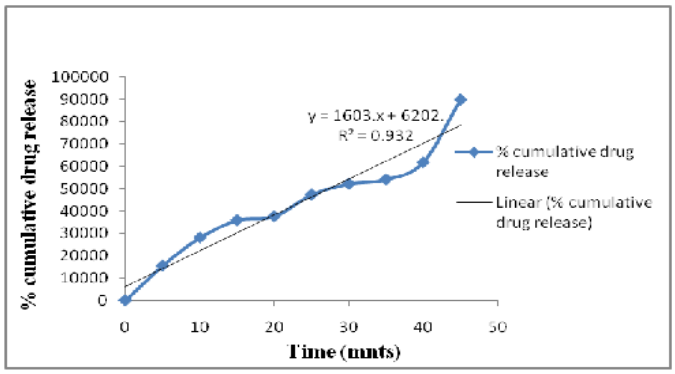


Figure 8 In vitro drug Release Studies of all formulations

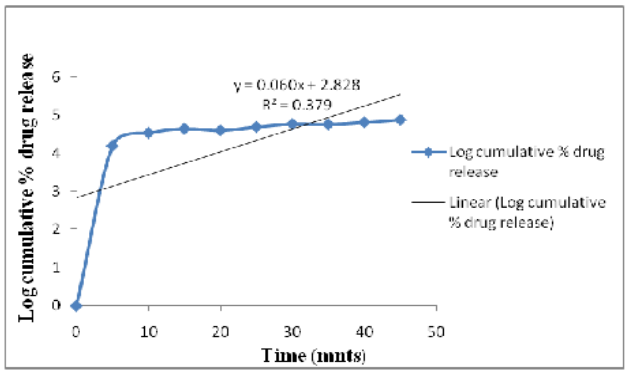
with an increase in the drug-to-polymer ratio. This may be because **Table 3** displays the impact of ethyl alcohol solvent volume on microsponges' dimensions. The outcome demonstrated that particle size reduced with increasing solvent volume. The relationship between the apparent viscosity of the dispersed phase and particle size was found to be exactly proportional. The decrease in solvent system viscosity resulted in a reduction of particle size from 107.24 ± 9.8 µm to 98.52 ± 11.4 µm when the solvent volume was increased from 5 ml to 15 ml.

Drug entrapment efficiency:

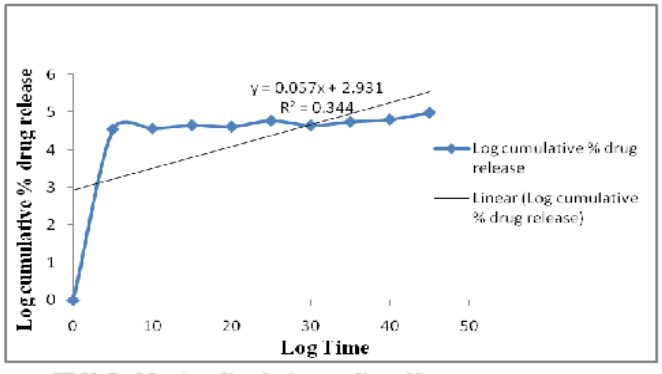
It was discovered that the microsponges' drug entrapment efficiency ranged from 52.42 ± 1.22 to 90.33 ± 1.35 percent. The formulations TMS5 and TMS6, with drug polymer ratios of 9:1 and 11:1, respectively, were shown to have the best drug encapsulation efficiency. The efficiency of encapsulation was reduced when the drug-polymer ratio increased more. This might result from a high concentration of drug molecules relative to low concentrations of polymer molecules, which would have reduced the polymer's capacity to coat the drug molecule and reduced the encapsulation efficacy (**Table 3 Figure 7**). The effectiveness of drug encapsulation was reduced as PVA concentration rose from 0.3% to 0.4% and 0.5%.



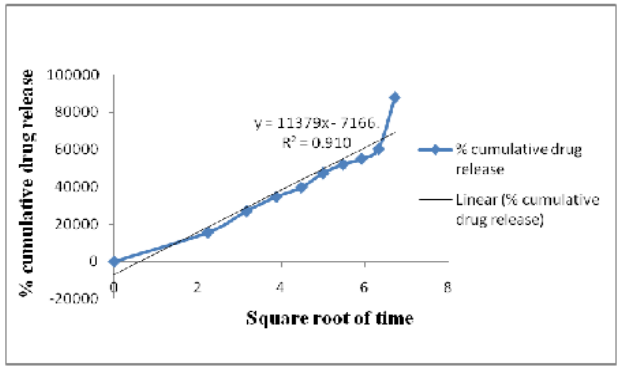
TMS 5 of *In vitro* dissolution studies of zero order kinetics



TMS 5 of *In vitro* dissolution studies of first order kinetics



TMS 5 of *In vitro* dissolution studies of korsmeyer peppas



TMS 5 of *In vitro* dissolution studies of Higuchi

Figure 9 TMS 5 of In vitro dissolution studies of Release Order Kinetics

Table 4 In vitro drug release studies of all formulations

Time (Hrs)	% of Drug release							
	TMS1	TMS2	TMS3	TMS4	TMS5	TMS6	TMS7	TMS8
1 Hrs	5.54	3.06	5.96	6.23	11.58	13.14	14.64	7.68
2 Hrs	19.62	16.96	16.24	17.06	15.42	16.98	29.32	12.36
3 Hrs	27.96	24.46	23.59	24.80	19.32	23.16	33.16	24.64
4 Hrs	38.68	31.58	32.64	38.64	23.16	33.94	37.72	39.32
5 Hrs	41.58	45.42	49.32	46.38	37.06	46.31	47.86	43.16
6 Hrs	55.42	57.06	50.91	50.22	47.08	58.64	52.48	55.32
7 Hrs	67.06	64.8	74.81	74.12	59.42	60.98	65.60	68.64
8 Hrs	70.19	72.48	81.10	81.86	62.64	71.11	78.62	74.19
9 Hrs	88.64	80.22	89.12	94.92	70.26	76.56	87.28	89.86

Table 5 Release order kinetics

Time	Zero Order	First Order	Korsmeyer-Peppas	Higuchi Model	
	% cumulative drug release	Log cumulative % drug release	Log cumulative % drug release	The square root of time	% cumulative drug release
0	0	0	0	0	0
5	15566	4.192	4.543	2.24	15560
10	28078	4.532	4.566	3.17	27050
15	35899	4.641	4.654	3.88	34700
20	37645	4.598	4.620	4.48	39720
25	47389	4.689	4.777	5	47420
30	52240	4.766	4.650	5.48	52144
35	54233	4.756	4.744	5.92	55123
40	61870	4.809	4.809	6.33	60432
45	89930	4.876	4.988	6.75	87993

Table 6 Release kinetics of Triamcinolone loaded microsponges (TMS1 to TMS5)

Model	Equation	TMS 1		TMS 2		TMS 3		TMS 4		TMS 5	
		R^2	m	R^2	m	R^2	M	R^2	m	R^2	M
Zero order	Mo-Mt= kt	0.655	69.4	0.939	1123	0.007	15.93	0.202	72.88	0.928	1414
First order	InM= InMo	0.494	0.061	0.540	0.067	0.257	0.038	0.352	0.044	0.438	0.062
Higuchi's Matrix	$M_0 - M_t = kt1/2$	0.516	4508	0.767	7420	0.023	212.0	0.189	515.5	0.803	9618
Korsmeyer -Peppar	log (M_0-M_t)= log k + n log$t$	0.835	2.354	0.884	2.545	0.572	1.709	0.663	1.813	0.806	2.517

Table 7 Release kinetics of Triamcinolone loaded microsponges (TMS6 to TMS8)

TMS 6		TMS 7		TMS 8	
R^2	m	R^2	m	R^2	M
0.917	15.49	0.949	154.4	0.932	1603
0.481	0.052	0.465	0.051	0.379	0.060
0.798	1057	0.848	1067	0.344	0.057
0.835	2.032	0.827	2.033	0.910	11379

Table 8 Stability Conditions at 4 ± 1 oC, 25 ± 1oC, and 50 ± 1oC

Storage Condition	4 ± 1 oC	25 ± 1oC	50 ± 1oC
Room temperature	99.88 ± 0.07	99.76 ± 0.25	99.66 ± 0.16
Refrigerated temperature	98.60 ± 0.19	98.47 ± 0.07	98.32 ± 0.21

In-vitro drug release studies:

In vitro, drug release studies were conducted in a pH progression medium. 0.1N HCl was used for the first two hours of medication release. Phosphate buffer saline pH 7.4 was used for two hours after the drug release, and then phosphate buffer pH 6.8 was used for the remaining four hours. **Figure 8** presents the release profiles determined for TMS 1 through TMS 8 formulations. Research has shown that when the drug-polymer ratio rises, so does the drug release. This could be because the polymer concentration was maintained at the same level for every formulation despite the drug molecules' concentration rising. This led to a decrease in the thickness of the polymer coat encircling the microparticles. Due to the non-encapsulated Triamcinolone in the formulation, the release displayed an initial burst effect.

Stability Studies:

Stability studies were applied since the formulation of TMS 5 had a high encapsulation efficiency. After being kept in glass bottles for a month at 4 ± 1 oC, 25 ± 1oC, and 50 ± 1oC, the Triamcinolone microsponges were analyzed every ten days to see if the percentage of drug concentration had changed. Between 5 ± 1oC and 40 ± 1oC, the percentage drug content ranged from 99.88 ± 0.07 to 98.60 ± 0.19, 25 ± 1oC to 98.47 ± 0.07, and 40 ± 1oC to 99.66 ± 0.16 to 98.32 ± 0.21. According to degradation phenomena, there was a decrease in drug content, although it was still within allowed bounds. It was discovered that the optimised TMS5 formulation was stable when stored.

CONCLUSION

It was noted that a time-dependent polymer prevented any detectable drug release for up to four hours. Eudragit RS 100, a sustained-release polymer, was shown to be present at pH 6.8, which is the pH of the colon, resulting in maximum release. The drug: polymer ratio has a significant impact on the rate of drug release. A more extensive drug: polymer ratio was shown to result in the highest drug release. In storage conditions, additional microsponges remain stable. The generated microsponges have been found to have good mucoadhesion properties and a longer retention duration in the colon, suggesting that they would be the ideal dose form for colon targeting. Due to their porosity nature, microsponges offer the colon a sufficient dose and, more precisely, controlled release.

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Conflict of Interest: The Author declares that there is no conflict of interest.

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