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Formulation and *In Vitro* Evaluation of Tropisetron Loaded Microspheres

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ABSTRACT

Tropisetron is a 5-HT_3 (5-hydroxytryptamine$_3$) receptor antagonist used for the prevention of chemotherapy-induced nausea and vomiting. In the present study, ethyl-cellulose, sodium alginate and HPMC K15M loaded microspheres of tropisetron were successfully prepared by ionic gelation technique. All the formulations were evaluated for various parameters such as drug content, entrapment efficiency, *in vitro* dissolution study, release kinetic study and stability study. The *in vitro* dissolution studies showed that tropisetron microspheres formulation F10 have better sustained effect over a period of 12 hours which contains all three polymers having a perfect controlled release. The mechanism of release was determined by various kinetic equations such as zero-order, first-order, Higuchi, Hixon Crowell, Korsmeyer-Peppas and finding the R^2 values of the release profile corresponding to each model. Thus, in the present study, *in vitro* drug release kinetic of the best formulation followed zero order release kinetic model and the drug release mechanism was anomalous diffusion. The results of the current study clearly indicate a promising potential delivery system of the tropisetron microsphere as an alternative to the conventional dosage form.

Keywords: Microsphere, tropisetron, ethyl cellulose, sodium alginate, HPMC K15M.

1. INTRODUCTION

To administer any drug in the body, oral drug delivery system is the most preferable route.[1] Therefore, there are large numbers of controlled or sustained release methods for oral administration of drug. Orally administered drugs generally depend on its solubility and absorption. These drugs exhibit poor aqueous solubility and low bioavailability. Micro-sizing of such drugs enhances the oral absorption and bioavailability.[2]

Microspheres can be best described and defined as nearly spherical particles containing measurement sizes from 1 to 1000 µm. They are free-flowing particles having quick onset of action for drugs that are completely but slowly absorbs and this system is used by many researchers for sustained release of drug in the stomach or upper GIT. The main goal for preparing microspheres is for controlled release of the drug.[3,4]

Tropisetron is a serotonin (5-hydroxytryptamine; 5-HT) antagonist that is primarily used in the prevention of nausea and vomiting. Tropisetron blocks the action of serotonin receptors at the 5-HT_3 receptor which

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helps in suppression of chemotherapy and radiotherapy that produce nausea and vomiting. The half-life of antiemetic action after a single dose of tropisetron is 6-8 hours; the requirement of clinical use for a single dose is of 5-10 mg to be taken once a day.[5] Tropisetron monotherapy is effective for the control of acute and to a lesser extent, delayed nausea and vomiting in patients receiving moderately to severely emetogenic chemotherapy.[6] Thus, a controlled release dosage form of tropisetron is advantageous. Hence an effort has been made to formulate microspheres of tropisetron using polymers for controlled release profile of drug ionic gelation technique. This technique of microencapsulation has been used for changing the site of absorption.

To prepare microspheres of tropisetron, sodium alginate as a gelling agent was used as it upholds better stability with boosted pharmacological action, HPMC K15 M was used as a binder & thickener. Ethyl cellulose used as matrix former for microsphere and calcium chloride was used as cross-linking agent. This method has been used for discovering new polymeric substances developing the new chemical entities which are preferable for continuous drug release, therapeutic efficacy improvement and its safety of drug.[7-9]

2. MATERIAL & METHODS

2.1 Chemicals and Reagents

The chemicals and reagents used in the present study are represented in Table 1.

2.2 Instruments and Equipment

The instruments and reagents used in the present study are presented in Table 2.

2.3 Pre-formulation Studies

The general objective of pre-formulation studies is to create useful information of stable development and bioavailable dosage forms. A thorough understanding of physical and chemical properties can eventually give rise to formulation design, support molecular modification, and authenticate without significantly impeding combination development.

2.3.1 Identification of Drug

The pure drug was evaluated physically for its appearance and solubility. In a dry petri dish, 1 gm of sample drug was observed for conformability of specification. Solubility test was performed for selection of satisfactory solvent for dissolving the drug and also with different excipients which are needed for microsphere formulation.

2.3.2 Determination of λ_{max} Absorption Maxima

Tropisetron was dissolved in phosphate buffer with a pH of 6.8 and 0.2 N HCl with a pH of 1.2, and it was further diluted with the same solution. The absorbance maxima were measured using a UV spectrophotometer in the 200-400 nm range.

2.3.3 Standard Calibration Curve of Tropisetron

2.3.3.1 By using 0.2 N HCl Buffer of pH 1.2

100 mg of tropisetron was accurately weighed and dissolved in 100 ml of 0.2 M HCL of pH 1.2. This is called as primary stock solution. From the above primary stock solution, 1 ml solution was transferred into 100 ml volumetric flask by using the pipette and then the volume was made up to 100 ml with 0.2 N HCl of pH 1.2 i.e., the concentration of 10 µg/ml as secondary stock solution. To prepare a final solution, the secondary solution was further diluted with pH 1.2 HCl to get an aliquot solution of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, and 10 µg/ml as the final solution. After this, the absorbance was measured using a UV spectrophotometer at 284 nm against HCl pH 1.2 as a blank solution. The calibration curve was plotted in the Figure 1.

2.3.3.2 By using Phosphate Buffer of pH 6.8

100 mg of tropisetron was accurately weighed and dissolved in 100 ml of phosphate buffer of pH 6.8. This is called as primary stock solution. From the above primary stock solution, 1 ml solution was withdrawn by using a pipette and then transferred into 100 ml volumetric flask, made up to volume with phosphate buffer pH 6.8 i.e., a concentration of 10 µg/ml as secondary stock solution. To prepare the final solution, the secondary solution was additionally diluted with phosphate buffer to get aliquot solution of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, and 10 µg/ml as the final solution.

Table 1: Chemicals and reagents

S. No.	Materials	Manufacturer
1	Tropisetron	Dr. Reddy's Lab, Hyderabad, India
2	Sodium alginate	SD Fine Chemicals, Boisar, India
3	Ethyl cellulose	Essel Fine Chemicals, Mumbai, India
4	HPMC K15M	SD Fine Chemicals, Boisar, India
5	Ethanol	SD Fine Chemicals, Boisar, India
6	Calcium chloride	Otto Chime Pvt Ltd., India

Table 2: Instruments and equipment

S. No.	Instrument/Equipment	Manufacturer
1	Electronic Balance	Citizen CTG-302, USA
2	UV & Visible Double Beam Spectrophotometer	Analytical Technology Ltd., India
3	Dissolution Test Apparatus	Lab India, India
4	FT-IR Spectrophotometer	Schimadzu, Japan
5	pH Meter	Hanna Industries, Italy
6	Magnetic Stirrer	Remi Equipment Pvt. Ltd., India
7	Differential Scanning Calorimeter	Agilent Technology, USA

The absorbance was measured using UV spectrophotometer at 284 nm against phosphate buffer of pH 6.8 as a blank solution. The calibration curve was plotted in the Figure 1.

2.3.4 Fourier Transforms-Infrared Spectroscopy (FT-IR) Studies

The spectrum was recorded from IR-spectral studies, and analysis was carried out for the pure drug, excipients separately, as well as both mixed together (i.e., drug and excipients). A small amount of sample was taken, compressed under high pressure in a disc, and the sample's peaks in the range of 4000 to 500 cm^{-1} were recorded.

2.3.5 Differential Scanning Calorimetry (DSC) Studies

The Differential Scanning Calorimetry (DSC) Studies were carried out for pure drug tropisetron and optimized formulation. The obtained peaks were compared which usually indicated the fusion point of the sample.[10-12]

2.4 Formulation of Microsphere by Ionic Gelation Technique

Microspheres were prepared using the ionic gelation method. Tropisetron was weighed accurately and dissolved in a solution of sodium alginate using distilled water. HPMC K15M and ethyl cellulose were added to get a viscous aqueous solution by stirred continuously. In a beaker, 4% calcium chloride solution was taken. With the help of a syringe needle, the drug and excipient were dispersed dropwise in the form of beads by continuously stirred using a magnetic stirrer at 50 rpm. The formed tropisetron microspheres were kept for 1 hour in calcium chloride solution. After a certain time period, the solution was removed and separated using Whatman filter paper, dried at room temperature and stored in desiccators (Table 3).[13]

2.5 Evaluation of Microspheres

The microspheres of tropisetron were prepared and characterized for different properties like particle size analysis, entrapment efficiency study, percentage yield, *in vitro* drug release study, drug content, FTIR, DSC, etc.

2.5.1 Determination of Particle Size

By using calibrated optical microscopy method, the particle size was determined with the help of a stage micrometer and ocular micrometer.[14]

2.5.2 Percentage Yield

By using the following equation, percentage yield can be calculated,

$$\% \text{ yield} = \frac{practical\ yield}{theoritical\ yield} \times 100$$

Table 3: Composition of prepared tropisetron microspheres

S. No.	Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Tropisetron	100	100	100	100	100	100	100	100	100	100
2	Sodium Alginate	400	400	100	200	350	350	-	450	450	300
3	Ethyl Cellulose	400	100	400	350	200	350	450	-	450	300
4	HPMC K15M	100	400	400	350	350	200	450	450	-	300
5	Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Total (mg)	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**

Note: q.s. = quantity sufficient

2.5.3 Drug Entrapment Efficiency

Accurately weighed 100 mg of tropisetron microsphere were added to phosphate buffer of pH 6.8 and kept for 24 hours. After this, it was shaken well. Aliquots of 5 ml were diluted, analyzed using UV spectrophotometer and percentage entrapment efficiency was calculated by dividing the practical drug content by theoretical drug content.[15]

2.6 *In-Vitro* Dissolution Study

Accurately weighed 150 mg tropisetron microspheres were suspended in 900 ml of HCl buffer of pH 1.2 for about 2 hours. The sample was withdrawn from dissolution medium at ½ hour time interval each using a 5 ml syringe and analyzed using a UV spectrophotometer. After that, the microsphere residue from the dissolving media was filtered and suspended for around 5 hours in 900 ml of pH 6.8 phosphate buffer. At each 1-hour interval, the sample was taken out of the dissolving media using a 5 ml syringe, and it was then examined using a UV spectrophotometer.

2.7 *In-Vitro* Drug Release Kinetics

The dissolution profile of all batches was evaluated with various models such as zero order, first order, Higuchi, Hixon Crowell, and Korsemeyer-Peppas to ascertain the kinetics of drug release.

2.8 Short Term Stability Studies

Stability testing was done to ensure the quality, safety, and efficacy of drug products. In the present study, stability testing was carried over a period of up to 90 days i.e., 3 months for selected microsphere formulation. The selected formulation was examined for the physical appearance and *in vitro* accelerated testing at 40°C±2°C and 75%±5% RH for 3 months.[16]

3. RESULTS

3.1 Identification of Drug

The tropisetron drug was physically found to be crystalline white powder. Tropisetron is essentially insoluble in acetone but soluble in water and ethanol. This drug was soluble in both 0.2 N HCl buffer (pH 1.2) and phosphate buffer (pH 6.8).

3.2 Determination of λ_{max}

The λ_{max} of the tropisetron dissolved in 0.2 N HCl of pH 1.2 and phosphate buffer pH 6.8 was found to be 283 nm. The absorbance of tropisetron standard solutions was measured at 284 nm against HCl pH 1.2 and phosphate buffer pH 6.8 ranging from 2 to 10 g/ml. Figure 1 illustrates the calibration curves that were plotted respectively with concentration vs absorbance. The resultant curves were discovered to be linear in the 2-10 g/ml range at a λ_{max} of 284 nm. The regression coefficients for pH 1.2 and pH 6.8 were determined to be 0.997 and 0.996, respectively.

3.3 FTIR Studies of Tropisetron

FTIR spectra of the pure drug and the physical combination of the drug and polymer utilized in the formulations were taken to confirm the compatibility of the substances used to create the various formulations of the tropisetron microsphere. From the studies, it was found that

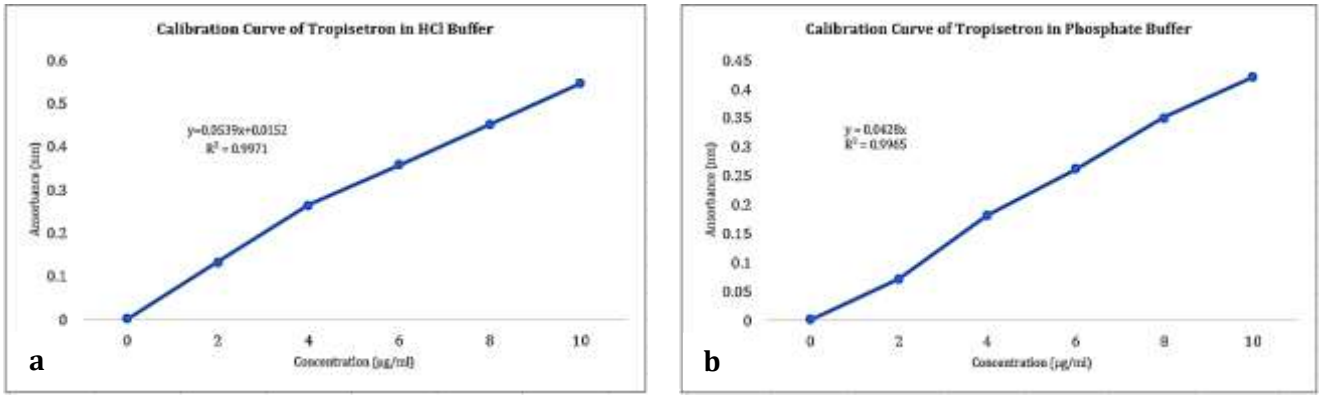

Fig. 1: Calibration curve of Tropisetron at λ_{max} 284 nm

Calibration curve of Tropisetron in (a) HCl buffer (pH 1.2) (b) Phosphate buffer (pH 6.8)

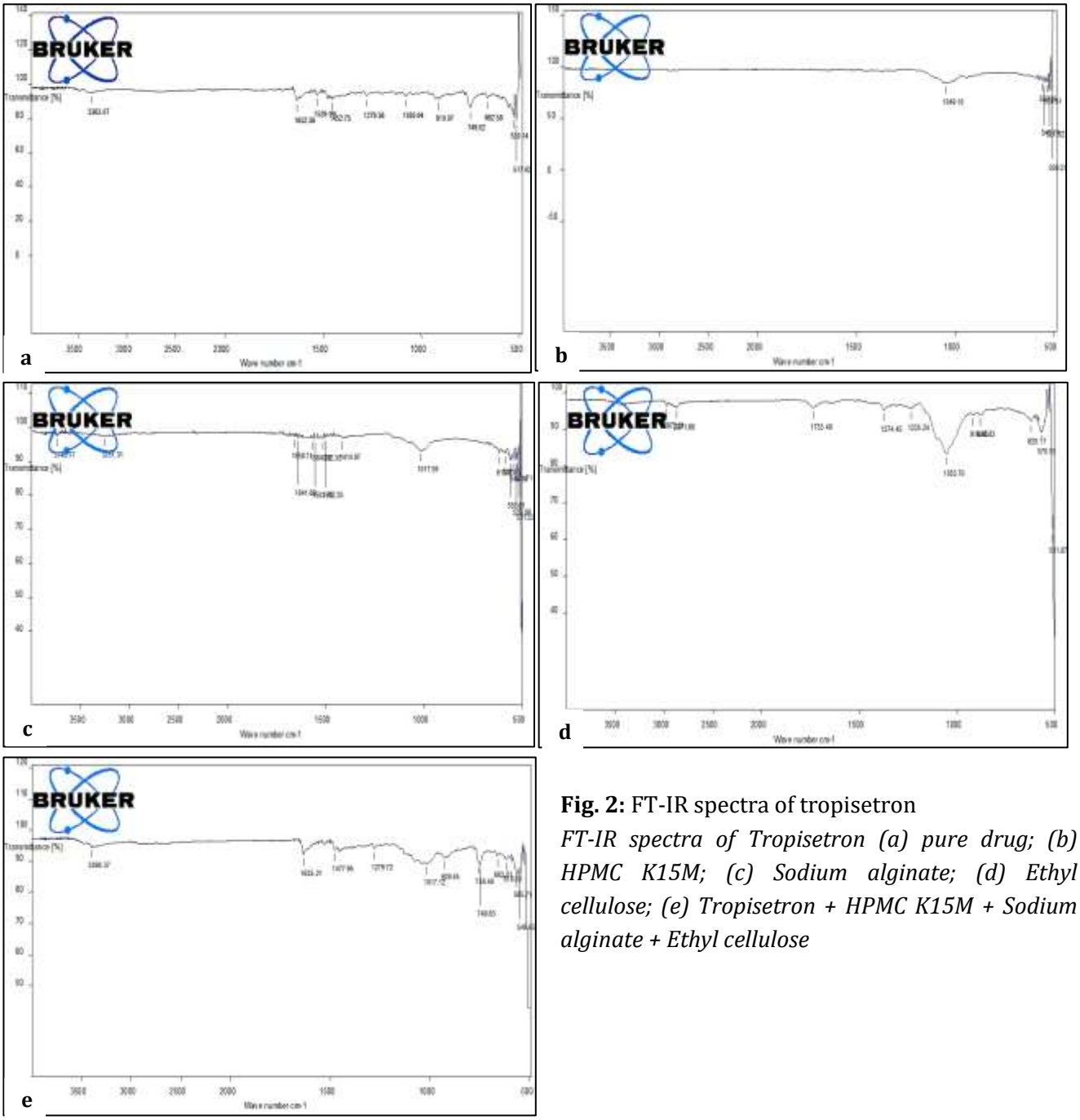

Fig. 2: FT-IR spectra of tropisetron

FT-IR spectra of Tropisetron (a) pure drug; (b) HPMC K15M; (c) Sodium alginate; (d) Ethyl cellulose; (e) Tropisetron + HPMC K15M + Sodium alginate + Ethyl cellulose

the major peaks did not shift, indicating that tropisetron and the numerous substances employed in the formation of diverse microsphere formulations did not interact. As a result, stable formulations for investigation are possible when the drug and excipients work well together. Figure 2 shows the FTIR spectra of tropisetron, different polymers employed, and the physical mixing of medication and polymer for microsphere formulation.

3.4 DSC Studies of Oxybutynin HCl

DSC thermogram of pure drug tropisetron and physical mixture of polymer used for optimized formulation were observed that the endothermic peak appeared between 198.2^{0}C and 199.3^{0}C respectively which indicate that the physical mixture of optimized formulation is thermodynamically stable by the addition of tropisetron. From the DSC studies, it was observed that the formulation is thermodynamically stable as it required marginally more heat than pure drug because of existence of different excipients with drug. No shifting of peaks from endothermic to exothermic was also noticed. The DSC thermogram of tropisetron and physical mixture of polymer used for optimized formulation is shown in Figure 3.

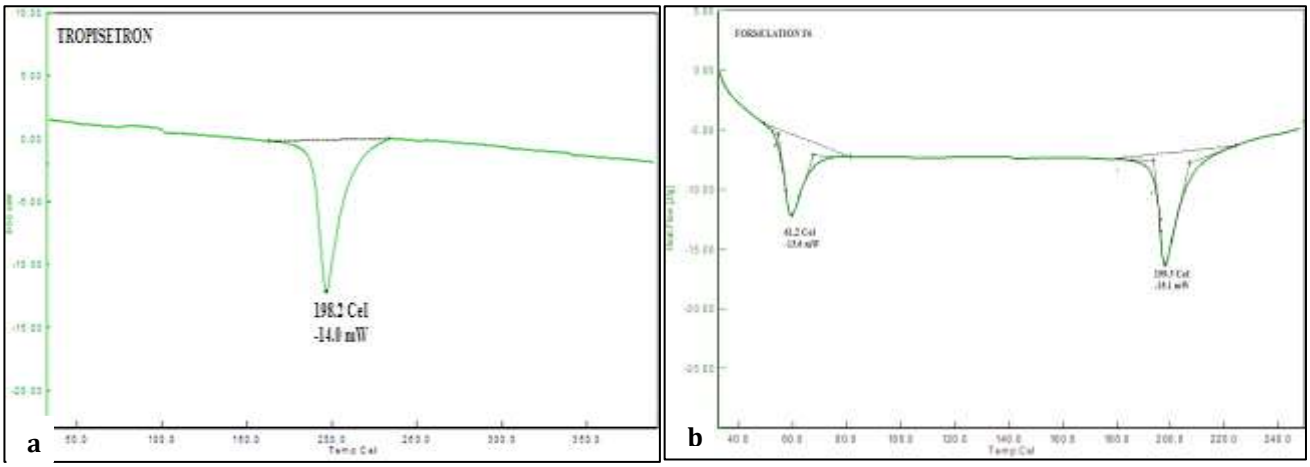

Fig. 3: DSC spectra of tropisetron

DSC spectra of Tropisetron HCl (a) pure drug; (b) prepared microsphere formulation.

3.5 Evaluation of Tropisetron Microsphere

3.5.1 Particle Size

Average particle size of prepared microspheres as determined by optical microscopy with the help of stage micrometer and ocular micrometer as shown below in Table 4. The mean particle size of microspheres for all formulation ranges from 281±3.23µm (F6), to 524±3.28 µm (F3). The particle size showed uniformity in particle size with little deviation (Table 4).

3.5.2 Percentage Yield

The percentage yield of formulation F1 to F10 was calculated and the yield was found to be between 86.9% and 92.3% respectively. The results of all formulations F_1 to F10 of prepared microsphere are shown in Table 5. All the formulation showed remarkable yield. The reduction in yield is due to loss of material during formulation of microsphere (Table 5).

3.5.3 Percentage of Drug Content

As per result, F10 shows maximum value of drug content i.e., 99.67% and F3 contained 92.83% of drug. A comparison of % drug content is shown in Table 6. The parentage drug content showed remarkable results according to specification. All the formulation showed percentage drug content more than 90%.

3.5.4 Drug Entrapment Efficiency

The results of % drug entrapment efficiency values are shown in Table 6. As shown in the table, F10 has shown maximum value for % drug entrapment efficiency i.e., 98.71% and F1 has shown minimum value for % drug entrapment efficiency i.e., 91.78% (Table 6).

Table 4: Average particle size of prepared tropisetron microspheres

S. No.	Formulation	Average Particle Size (μm) ± SD
1	F1	364±2.31
2	F2	353±3.42
3	F3	524±3.28
4	F4	442±2.65
5	F5	388±2.43
6	F6	281±3.23
7	F7	445±2.21
8	F8	511±2.42
9	F9	520±1.98
10	F10	497±1.65

Table 5: Percentage yield of prepared tropisetron microspheres

S. No.	Formulation	Theoretical Yield (mg)	Practical Yield (mg)	Percentage Yield (%)
1	F1	1000	886	88.6
2	F2	1000	905	90.5
3	F3	1000	859	85.9
4	F4	1000	894	89.4
5	F5	1000	912	91.2
6	F6	1000	858	85.8
7	F7	1000	874	87.4
8	F8	1000	933	93.3
9	F9	1000	880	88.0
10	F10	1000	883	88.3

Table 6: Percentage of drug content and entrapment efficacy of prepared tropisetron microspheres

S. No.	Formulation	Drug Content (%)	Entrapment Efficacy (%)
1	F1	94.14	91.78
2	F2	95.52	94.58
3	F3	92.83	92.95
4	F4	96.47	95.37
5	F5	91.75	93.53
6	F6	96.23	93.25
7	F7	97.47	95.24
8	F8	98.56	94.56
9	F9	98.84	96.56
10	F10	99.67	98.71

The entrapment efficiency indicates to what extent the polymers can be able to hold the drug in the microsphere and to what extent the drug is entrapped in microsphere. All the formulation shows more than 90% entrapment efficiency which can be said to be remarkable and can fit to pharmacopeial specifications.

3.6 *In Vitro* Dissolution Studies

Comparative *in vitro* drug dissolution data of formulation F1 to F10 are shown in Table 8. By using a USP dissolution apparatus, dissolution studies were performed on all the ten formulations of Tropisetron microspheres in 0.2 M HCl of pH 6.8 for remaining 10 hours was used

Table 7: *In-vitro* drug release studies of prepared tropisetron microspheres

Time (Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F_{10}
0	0	0	0	0	0	0	0	0	0	0
1	16.4	13.4	9.7	11.4	14.1	14.4	7.3	16.8	8.5	11.3
2	25.4	21.6	13.5	19.6	22.2	24.4	11.0	25.2	16.2	18.5
3	34.5	28.5	24.7	26.5	27.5	32.4	20.4	33.5	23.3	26.3
4	44.5	39.7	34.5	35.7	39.3	43.1	27.5	42.7	31.4	37.7
5	58.4	53.5	42.6	51.3	47.2	55.5	36.9	57.6	40.6	45.7
6	68.7	62.4	48.4	58.4	55.5	65.0	44.6	65.8	47.7	52.3
7	77.5	70.6	56.5	68.6	61.9	75.4	51.4	75.7	52.2	58.4
8	89.6	84.4	66.4	80.5	73.5	86.4	60.6	91.4	64.8	69.7
9	97.3	90.6	76.4	89.4	81.2	95.5	67.4	99.8	72.5	79.8.
10	99.1	97.8	81.6	95.7	88.6	99.3	75.8	-	83.3	86.5
11	-	99.4	88.5	99.6	94.7	-	82.5	-	92.4	90.2
12	-	-	95.6	-	99.5	-	89.9	-	99.3	99.6

as the dissolution medium. It was noticed from above dissolution study that, by using higher concentration of sodium alginate, the controlled release profile of drug decreased, and maximum drug released up to 8 to 9 hours whereas by increased concentration of ethyl cellulose, slow release of drug is noticed as ethyl cellulose is hydrophobic in nature. By using adequate amount of all three polymers a perfectly controlled release effect is noticed up to 12 hours that is noticed in case of F10 formulation which contained 30% of all the three polymers (Table 7).

3.7 *In Vitro* Drug Release Kinetics

The *in vitro* release of drug data from the best formulations (F10) of Tropisetron Microspheres formulations were fitted to different kinetic models and regression coefficients were calculated. For the best formulation, the zero-order plots were found to be linear as indicated by their highest regression values. The release exponent 'n' for optimized formulations were found between 0.5 to 1 ($0.5 < n < 1$), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So, in present study *in vitro* drug release kinetic of the best formulation followed zero order release kinetic model and drug release mechanism is anomalous diffusion coupled with erosion.

3.8 Short Term Stability Studies

For the best formulation F10 was subjected to stability studies at 40°C/75% RH for up to 3months. The potency of prepared microspheres was under accelerated stability conditions was within 90% to 100%. There was no change in physical appearance and was chemically stable for 3 months (Table 8).

4. DISCUSSION

The ethyl-cellulose, sodium alginate and HPMC K15M loaded microspheres of tropisetron were successfully prepared by ionic gelation technique and based on its greater % yield, it was the ideal approach for preparing tropisetron-loaded microspheres. The formulation F10 has the highest milligram of drug content followed by other formulations. The particle size of a microsphere was determined by optical microscopy technique and all the batches of microspheres have given uniform size distribution.[17] The prepared microspheres had good spherical geometry with smooth as evidenced by the optical microscopy. The *in vitro* dissolution studies showed that tropisetron microspheres formulation F10 showed better sustained effect over a period of 12 hours. It was noticed from above dissolution study that, by using higher concentration of sodium alginate, the controlled release profile of drug decreased, and maximum drug released up to 8 to 9 hours whereas by increased concentration of ethyl cellulose, slow release of drug is noticed as ethyl cellulose is hydrophobic in nature. By using adequate amount of all three polymers, a perfectly

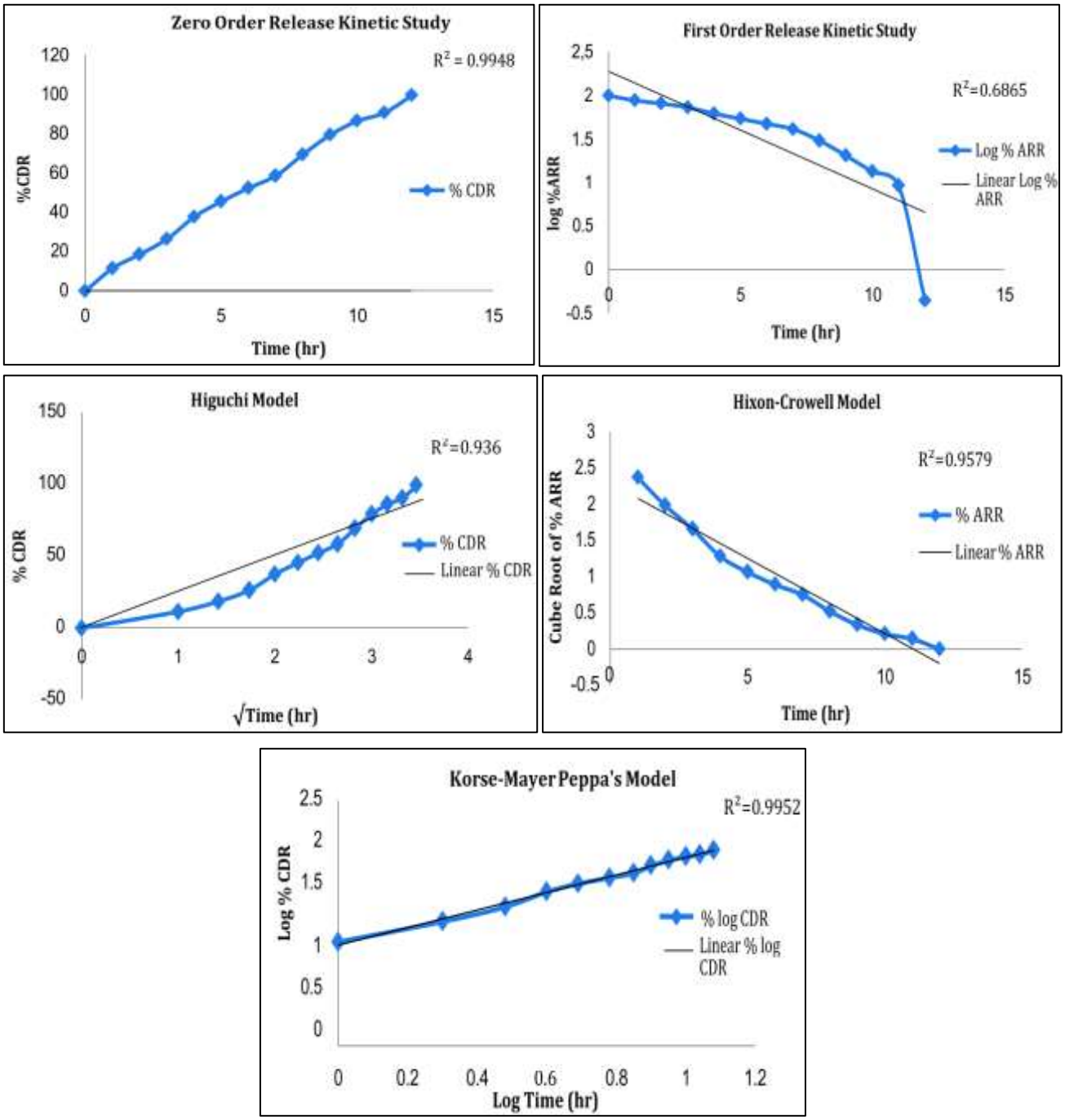

Fig. 4: *In vitro* drug release kinetic studies of tropisetron microspheres

Table 8: *In vitro* dissolution data of prepared tropisetron microsphere at accelerated stability conditions

S. No.	Formulation	Before Storage (%)	Stored at 40°C ± 2°C and 75% ± 5% RH		
			1st Month (%)	2nd Month (%)	3rd Month (%)
1	F10	98.12 ± 0.36	96.74 ± 0.45	94.67 ± 0.52	92.13 ± 0.48

All values were represented Mean±SEM.

controlled release effect was noticed up to 12 contained 30% of all the three polymers. The mechanism of release was determined by various kinetic equations such as zero-order, first-order, Higuchi, Hixon Crowell, Korsmeyer-Peppas and finding the R^2 values of the release profile corresponding to each model.[18] It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, in which the drug molecules must traverse so, the drug release of F10 formulation takes long time than other formulations.

5. CONCLUSION

In the present study, *in vitro* drug release kinetic of the best formulation followed zero order release kinetic model and drug release mechanism. Thus, the results of the current study clearly indicate a promising potential of the tropisetron microsphere as an alternative to the conventional dosage form as it enhances bioavailability of the tropisetron microsphere by bypassing the first pass metabolism and by producing sustained release effect for chemotherapy-induced nausea and vomiting. However, further clinical studies are needed to assess the utility of this system for patients suffering from nausea and vomiting.

Conflict of Interest: The author declared no competing interest.

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