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Formulation and Characterization of Zingiberol Loaded Microsphere for Motion Sickness

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Abstract

The present research work involves the development of Zingiberol as the treatment of motion sickness. The Zingiberol microsphere was formulated by Ionotropic gelation method using different polymers in different ratio depending on RSM method. The prepared formulations were optimized on the basis of dependent variables like particle size (mg), entrapment efficiency etc. The SEM photographs of Zingiberol microsphere before dissolution shows the spherical and smooth surface whereas after dissolution the pores and crevices were shown which is indicating that the microsphere are showing drug release by diffusion mechanism. The microsphere formulations were able to sustain the release of drug both *in vitro* and *in vivo*. In the stability studies no significant change in drug entrapment release characteristics of the microspheres.

Keywords: Zingiberol, Microspheres, Ionotropic gelation method, Evaluation parameters.

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1. Introduction

Motion sickness is a condition in which a disagreement exists between visually perceived movement and the vestibular system's sense of movement. Depending on the cause, it can also be referred to as sea sickness, car sickness, simulation sickness or air sickness. Dizziness, fatigue and nausea are the most common symptoms of motion sickness Spite syndrome, in which a person feels fatigue or tiredness, is also associated with motion sickness [1]. Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres. Microspheres are multi-particulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers. Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 µm consisting of techniques for the preparation of microspheres provides multiple options to control as drug, administration aspects and to enhance the therapeutic efficacy of a given the drug. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and

convenience. Such systems often use macromolecules as carriers for the drugs [2,3].

Zingiberol is a anti emetic drug, used for short term treatment of motion sickness. It is effective in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs, and Motion Sickness including cisplatin, and has reported anxiolytic and neuroleptic properties. Ginger (*Zingiber officinale*) is a flowering plant whose rhizome, ginger root or ginger, is widely used as a spice and a folk medicine. Ginger is in the family Zingiberaceae, to which also belong turmeric (*Curcuma longa*), cardamom (*Elettaria cardamomum*), and galangal. Ginger originated in the tropical rainforests from the Indian subcontinent to Southern Asia where ginger plants show considerable genetic variation [2]. Zingiberol is a highly specific and selective serotonin 5-HT_3 receptor antagonist, with low affinity for dopamine receptors. The 5-HT3 receptors are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema in the medulla. Serotonin is released by the enterochromaffin cells of the small intestine in response to chemotherapeutic agents and may stimulate vagal afferents (via 5-HT3 receptors) to initiate the vomiting reflex. It is thought that Zingiberol antiemetic action is mediated mostly via antagonism of vagal afferents with a minor contribution from antagonism of central receptors. [4]

2. Material and methods

Zingiberol was obtained as a gift sample from Bioprex Labs, Pune. Sodium Alginate was obtained from Salus Pharmaceuticals, Baddi, H.P. Methyl cellulose was obtained from Bsdk Chemic Pvt. Ltd. Calcium Chloride, Calcium Carbonate, Citric Acid, Methanol, and Hydrochloric acid etc. were purchased locally. All chemicals were used as laboratory grade.

2.1 Preparations of floating alginate beads [5, 6]

Sodium alginate solutions of different concentrations were prepared by dissolving required amount of alginate in 400 ml of deionized water under gentle agitation. Zingiberol acid and calcium carbonate were dispersed in alginate solution under constant stirring for uniform mixing. The dispersion was solicited for 80 minutes to remove any air bubbles. The resultant dispersion was dropped through a 32 gauge syringe needle into 500 ml of 6% (w/v) calcium chloride solution containing 10% (v/v) citric acid at room temperature. Then the beads formed were allowed to remain in the stirred solution for 70 min. The beads were filtered, washed with plain water and subsequently oven-dried at 80ºC for 1 hour. A schematic representation of prepared microsphere by Ionotropic Gelation Method was shown in Fig. 1 and the composition ratio was given in table 1.

Table 1:- Composition of Zingiberol loaded Microsphere.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zingiberol powder (mg)	800	800	800	800	800	800	800	800	800
Sodium alginate (mg)	600	800	800	700	700	700	100	600	700
Methyl cellulose(mg)	900	800	700	200	800	700	900	800	700
$CaCO_3$(mg)	100	100	100	100	100	100	100	100	100
$CaCl_2$ Solution (%)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

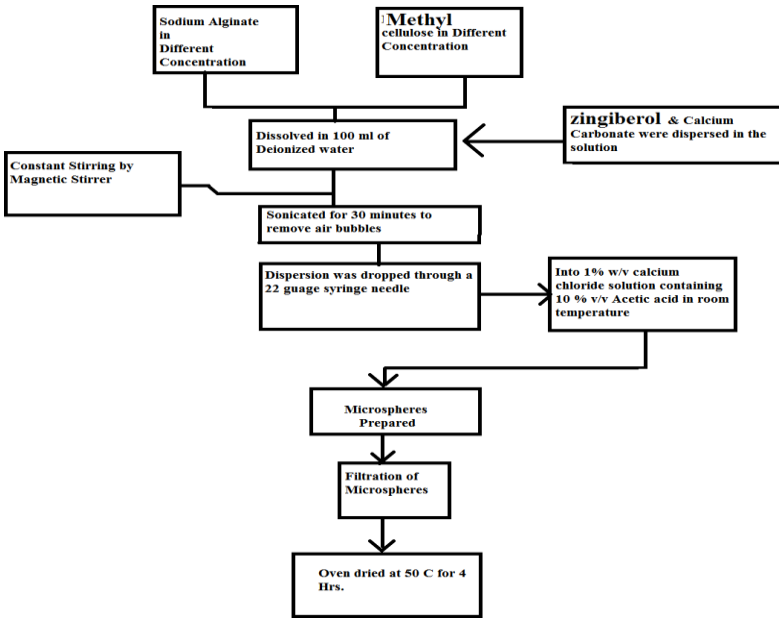


Fig. 1: Schematic represtation of Ionotropic Gelation Method

2.2 Evaluation study

2.2.1 Preformulation Studies [7]

The different types of preformulation studies like solubility, angle of repose, bulk density, tapped density, compressibility index, hausner ratio etc were evaluated which was shown in table 2.

2.2.2 Fourier-transform infrared spectroscopy (FTIR): [7,8]

Drug polymer interactions were studied by FT-IR spectroscopy. The infrared spectra of sodium alginate, Zingiberol acid and drug loaded beads were recorded on FT-IR (Shimadzu FTIR 8400S). The samples were prepared on KBr press and the spectra were recorded over the wave number range of 4,000 to 400 cm−1 (Fig 2 and Fig 3). The frequency range with their functional group was given on the table 3.

2.2.3 Preparation of standard curve of the drug in 0.1 N HCl buffer at 1.2 [8,9]

An accurately weighed quantity of Zingiberol acid equivalent to 10 mg was taken in a 100 ml volumetric flask and it is dissolved by using 5 ml of ethanol and volume was made to mark with 0.1 N Hcl at pH 1.2 to give a 100 µg/ml of the drug. The aliquot portion of standard stock solution of Zingiberol acid was diluted with 1.2 pH 0.1 N HCl buffer to obtain concentration 10 µg/ml. Appropriate dilutions was made for the drug from the standard stock solution and scanned in the spectrum mode from 200-600 nm. Zingiberol acid showed absorbance at 237 nm in 0.1 N HCl buffer 1.2.From the above stock solution 2,4,6,8 and 10 ml were taken and dilute up to 10 ml with 0.1 N HCl buffer pH 1.2 to get 2,4,6,8,10 µg/ml concentrated solution of Zingiberol acid. Absorbance of solution was measured at 237 nm in 1.2 pH 0.1 N HCl buffer solution. The graph was plotted for concentration vs. absorbance to get calibration curve of the drug (Fig. 4).

2.2.4 DSC Study

DSC Study [10] helps in assessing physical properties of the sample nature (crystalline or amorphous) and indicates any probable interaction amongst drug and excipients which was performed from Vins Biotech Pvt. Ltd. Bangalore (Fig. 5 & Fig. 6).

2.2.5 X – Ray Diffraction Method [10]:-

X – ray diffraction patterns of pure Zingiberol, physical mixture and combination of drug with polymer, calcium chloride was determined using a X-ray diffractometer equipped with rotating target X-ray tube and a wide angle goniometer which was performed from Vins Biotech Pvt. Ltd. Bangalore shown in Fig. 7.

2.2.5 Scanning electron microscopy (SEM) [10]:

The surfaces and cross-section morphologies of the beads were observed using a scanning electron microscope (SEM) (JSM-6490 LA, JEOL, Tokyo, Japan) operated at an acceleration voltage of 25 kV which was performed from Averin biotech Pvt. Ltd. Hyderabad given in Fig. 10.

2.2.7 Particle size analysis [8,9]

The particle size of microspheres was determined using an optical microscope with calibrated ocular micrometer. The mean particle size was calculated by measuring 100 particles of each formulation (Table 4).

2.2.8 Determination of drug encapsulation efficiency [11, 14, 15]

50 mg of beads from each formulation were weighed and crushed in a mortar and pastel and the crushed material was dissolved in 100 ml of 0.1 N HCl buffer at pH 1.2. This solution was mechanically agitated on shaker at 200 rpm for 2 hours. The resultant dispersions were filtered and analyzed at 237 nm using UV spectrophotometer (Shimadzu 1700, Japan). The encapsulation efficiency was determined by the following formula which is shown in table 5.

Encapsulation efficiency = (AQ/TQ) X 100

Where AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads.

2.2.9 Buoyancy test [12, 13]

The obtained beads were studied for buoyancy12 and floating time using USP Apparatus II (paddle type). 300 mg beads of each batch were placed in 900 ml of 0.1 N HCl buffer (pH 1.2) containing 0.02% w/v Tween 80 and agitated at 50 rpm, temperature was maintained at 37ºC shown in table 5**.**

2.2.10 Swelling Index Studies [13, 15]

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of microspheres was determined by placing the microspheres in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37±0.5°C. After 0.5, 1, 2, 3, 4, 5, and 6h, each dissolution basket containing microspheres was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula shown in table 5.

Swelling index

= (Wet weight of microspheres – Dry weight of microspheres)/Dry weight of microspheres.

2.2.11 Zeta Potential [10]

The zeta potentials of Zingiberol loaded floating microspheres formulations are presented here. The zeta potentials of all the formulations are found to be ranging from 8.64 mV to 17.6 mV shown in table 6.

2.3 *In vitro* dissolution studies [11, 15]

In vitro dissolution studies of all the prepared formulations were performed using USP apparatus II

(paddle type) in 0.1 (N) Hcl medium at pH 1.2. The temperature was maintained at 37ºC and stirred at a speed of 50 rpm. The collected samples were filtered and analyzed at 237 nm using UV- visible spectrophotometer. The data obtained for percent drug release was fitted to various release kinetics model. The percent of drug release was determined as a function of time. All methods of this experiment were performed in triplicate manner for each batch and average value is taken.

3. Results and discussion:

The obtained micromeritic properties are given in the table 2. The angle of repose data shows within the range of 27.58± 0.15 to 29.69± 0.19 indicating good flow properties. The tapped density values ranged between 0.50 ± 0.07 to 0.59 ± 0.04 g/cm3. The result of car's index range from 12.23±0.6 to 15.60±0.21% suggests excellent flow characteristics of the microspheres and Hausner ratio from 1.11±0.04 to 1.18±0.12 % which indicates good flow property of microspheres.

Table 2 :- Evaluation Study of Preformulation Parameters (Mean ± SD).

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)
F1	0.35±0.045	0.55± 0.09	16.90±0.2	1.13±0.06	26.06± 0.31
F2	0.42±0.045	0.56 ± 0.07	13.28±0.6	1.10±0.02	37.35± 0.15
F3	0.47±0.044	0.50 ± 0.09	12.58±0.8	1.14±0.05	28.44± 0.846
F4	0.45±0.045	0.52 ± 0.04	14.19±0.1	1.19±0.03	22.37± 0.13
F5	0.41±0.044	0.51± 0.01	16.48±0.6	1.15±0.08	29.62± 0.52
F6	0.49±0.045	0.58 ± 0.04	11.48±0.8	1.13±0.07	29.32± 0.19
F7	0.57±0.045	0.54 ± 0.04	13.48±0.8	1.25±0.09	28.59± 0.49
F8	0.46±0.041	0.50 ± 0.10	12.60±0.21	1.13±0.06	28.06± 0.41
F9	0.43±0.041	0.53± 0.11	15.35±0.54	1.16±0.14	27.52± 0.17

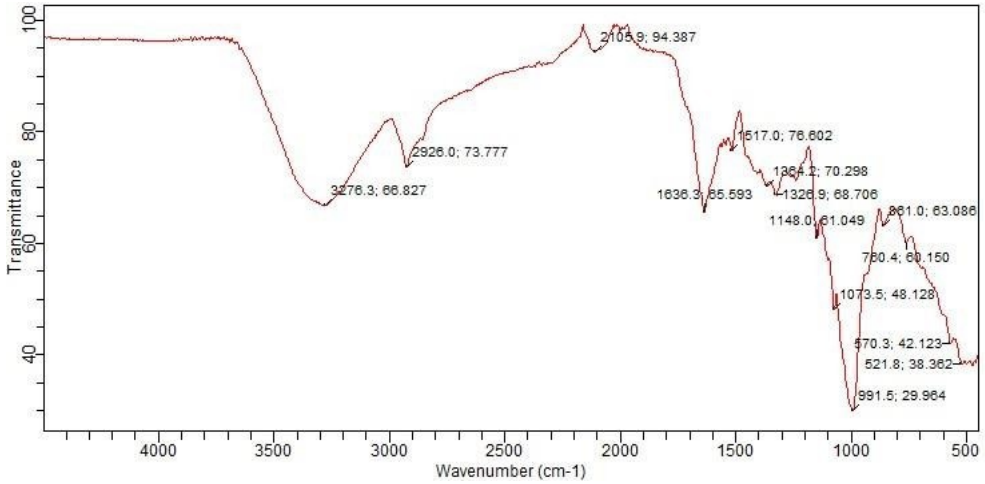


Fig. 2: FTIR spectra of Pure Drug, Zingiberol.

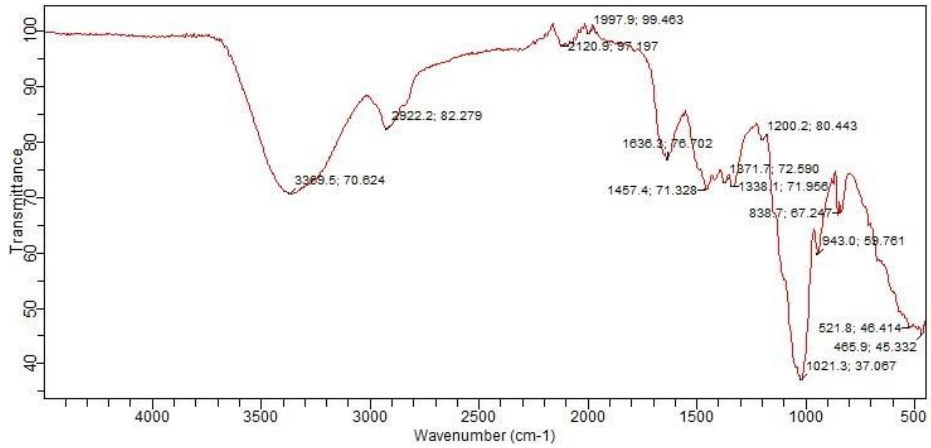


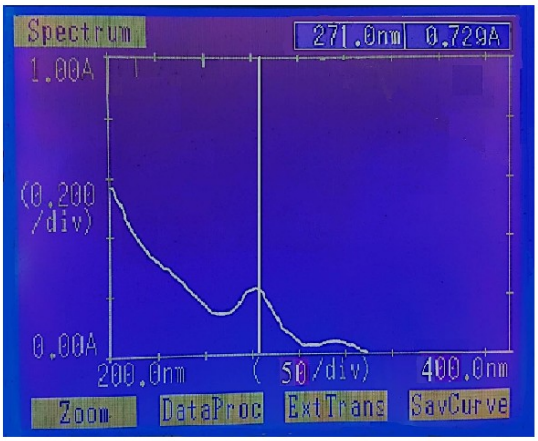
Fig. 3:- FTIR spectra of Drug, Zingiberol with polymer, Calcium Chloride

Table 3:- Frequency Range & Functional Group of IR

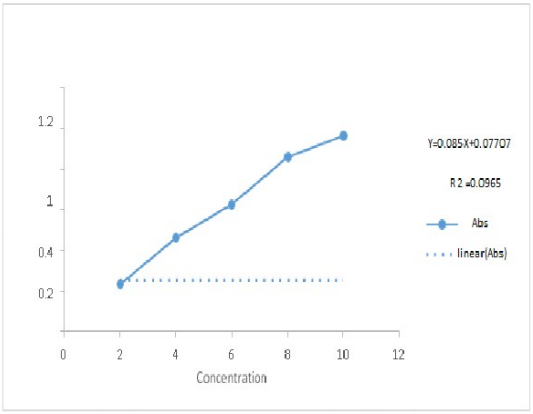
SL. No.	FREQUENCY RANGE (cm^{-1})	FUNCTIONAL GROUP
1	3675.36	Amide
2	2353	C–O bond
3	2260–2100	C=C Stretching bond of alkynes molecule
4	1535–1640	Diketones
5	1440–1470	Nitrosamine
6	1368	Iso propyl group
7	1270–1150	Ester carbonyl
8	1045, 1048	C–O bond
9	1035–1149	Polysaccharide
10	835–805	Aromatic compound
11	500–730	Halogen compound [Chloro-compound] (C-Cl)
12	490–620	Halogen compound [Iodo-compound](C–I)

The graph obtained of drug sample was compared with the graph of zingiberol given in IP and analytical profile of drug substances. The two graph match with each other it shows that the drug sample used is pure and stable. FTIR spectrum of zingiberol and the physical mixture of Zingiberol with other excipients were captured to examine chemical linkage formed during formulation of floating microsphere. These peaks were remaining unchanged or slight changes in the physical mixture of both components.

The calibration curve of Zingiberol in pH 1.2 obeyed Beer's Lambert's law within the concentration range of 2-10 µg/ml of Zingiberol. Low RSD (Relative Standard Deviation) ensured reproducibility of the method. The regression coefficient value is 0.0965 with Y value of 0.08 at 0.07703which indicates the linearity of the method.



(A) Over-Spectrum of λ_{max}



(B) Calibration curve of Zingiberol

Fig. 4: Preparation of Calibration Curve of Zingiberol using 0.1 (N) Hcl Buffer

DSC was performed for the drug alone and also with the excipients shown in Fig. 5 & 6. 10 mg of sample was weighed and subjected for DSC & thermogram obtained presented in figures according to the thermogram performed from Vins Biotech Pvt. Ltd. Bangalore. Zingiberol presented a sharp endothermic peak corresponding to the melting point of the drug slight variation in endothermic peak value observed of Zingiberol & excipient physical mixture. X-ray diffraction patterns given in Fig. 6 showed that pure extract was amorphous in nature of drug changed to crystalline form.

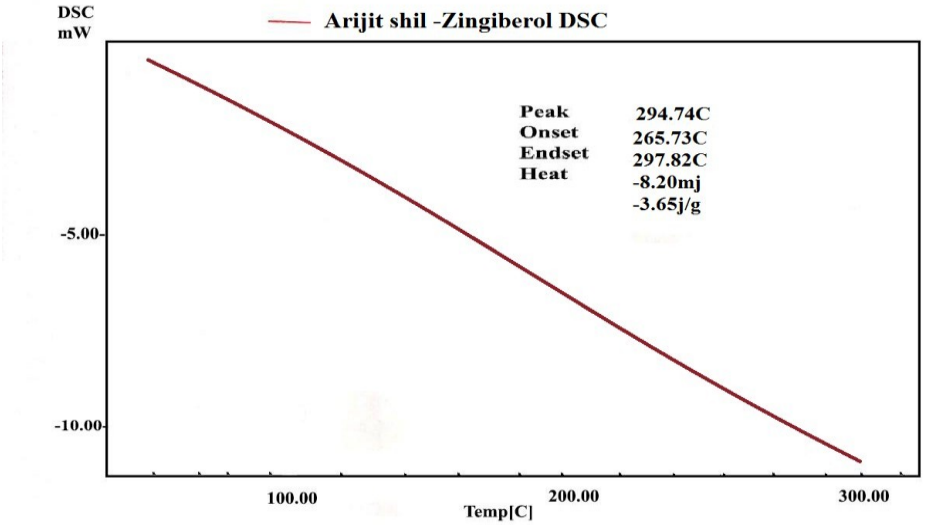


Fig. 5:- DSC of Zingiberol Drug

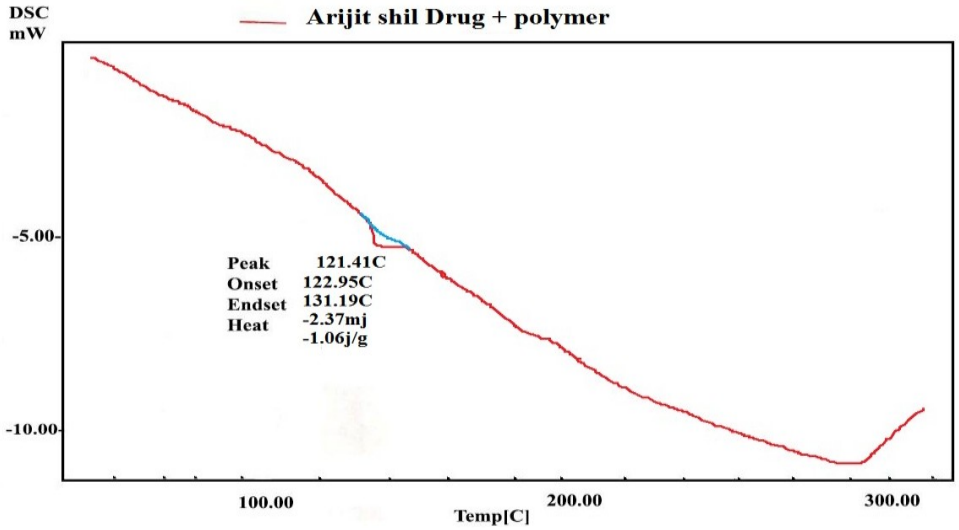


Fig. 6:- DSC Study of Physical Mixture of Drug with Polymer

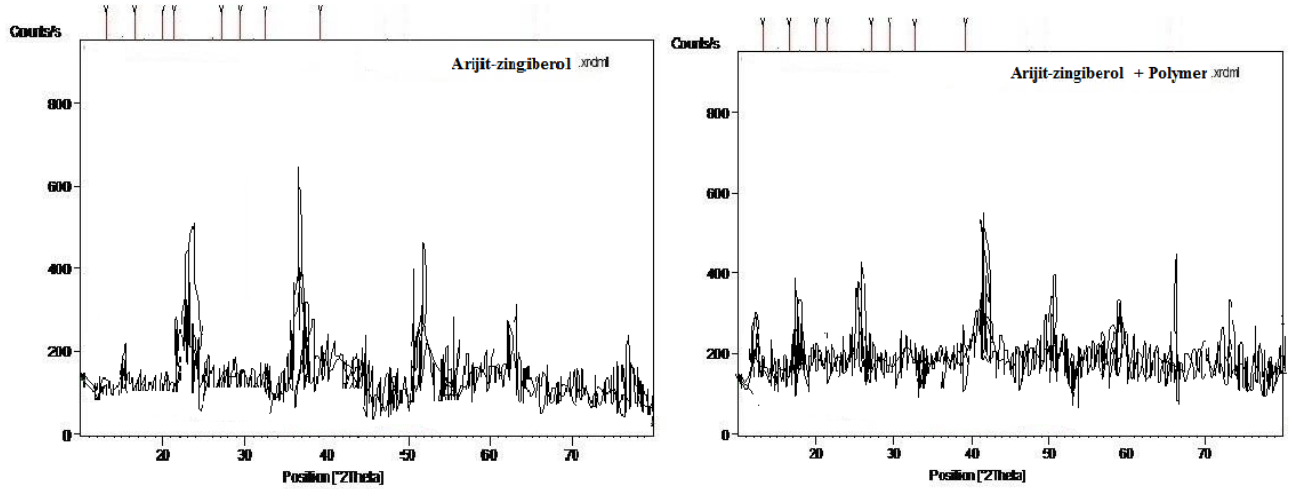


Fig. 7:- X-Ray Diffraction Study of Pure Drug, Zingiberol & Mixture of Drug with Polymer

Particle size analysis can be determined by sieve analysis method and optical microscopy. The mean diameter of prepared microsphere ranges from 601±0.85 to 718±0.63 µm shown in table 4.

Table 4:- Particle Size Analysis

Sl. No	Formulation code	Mean particle size µm (±s.d.)
1	F1	808±0.23
2	F2	701±0.85
3	F3	696±0.44
4	F4	650±0.59
5	F5	627±0.66
6	F6	998±0.43
7	F7	503±0.72
8	F8	649±0.78
9	F9	668±0.15

The particle size of drug loaded formulations were measured by an optical microscope fitted with calibrated ocular and stage micrometer and particle size distribution was calculated. 50 particles in five different fields were examined.

The drug entrapment efficiency increased from 68.78±0.65 to 77.13±0.78 % , % yield range between 75.9 to 90.11 % , Experimental Drug loading ranges between 27.78 to 55.82, Buoyancy ranges between 64 to 89%, and swelling index ranges between 30.25 to 38.33 % shown in table 5.

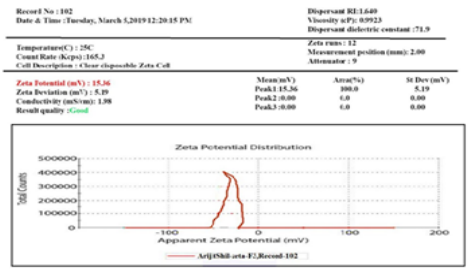
The zeta potentials of Zingiberol loaded floating microspheres formulations are presented on the table 6. After experimenting, F4 and F9 are shown the better combination depending on the pH of the medium and the concentration of formulations given in Fig. 8.

Table 5: Determination of Physical Properties of prepared Formulations

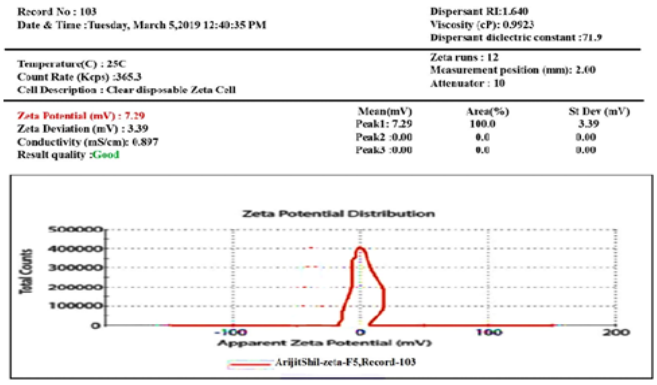
Sl. No	Formulation Code	% Yield	Drug Loading		% Buoyancy	% Drug Entrapment Efficiency	% Swelling Index
			TDL	EDL			
1	F1	79.24	33.21	25.61	69	73.45±0.96	32.36
2	F2	68.69	66	51.11	69	78.67±0.63	38.46
3	F3	76	55	34.16	76	83.32±0.48	31.89
4	F4	81	76.26	54.49	88	76.38±0.69	30.12
5	F5	89.36	69.78	48.36	88	69.28±0.45	37.74
6	F6	94.21	48.37	36.11	71	64.54±0.85	39.75
7	F7	73.54	45.19	30.06	68	65.49±0.23	37.75
8	F8	78.58	59.34	38.26	74	82.48±0.38	32.46
9	F9	92.78	38.36	29.45	99	67.13±0.78	36.94

Table 6:- Zeta Potential Study of Prepared Formulations.

Sl. No.	Formulation Code	Zeta Potential (mV)
1.	F1	11.23
2.	F2	12.12
3.	F3	15.36
4.	F4	10.78
5.	F5	7.29
6.	F6	9.54
7.	F7	10.89
8.	F8	12.64
9.	F9	13.21



Zeta Potential of F4



Zeta Potential of F9

Fig. 8: Zeta Potential of the best formulation

To describe the kinetic of drug release, release data was analyzed according to different kinetic models. The zero order, first order, higuchi model Korsmeyer – Pappas and Hixson crowell equation represent diffusion exponent, in all formulation it is in between 0.72 to 0.99, so it is normally said to follow non-fickian anamolous release shown in the Table 7. Comparative studies were also done in-between the different prepared formulations which was carried out on the Figure 9.

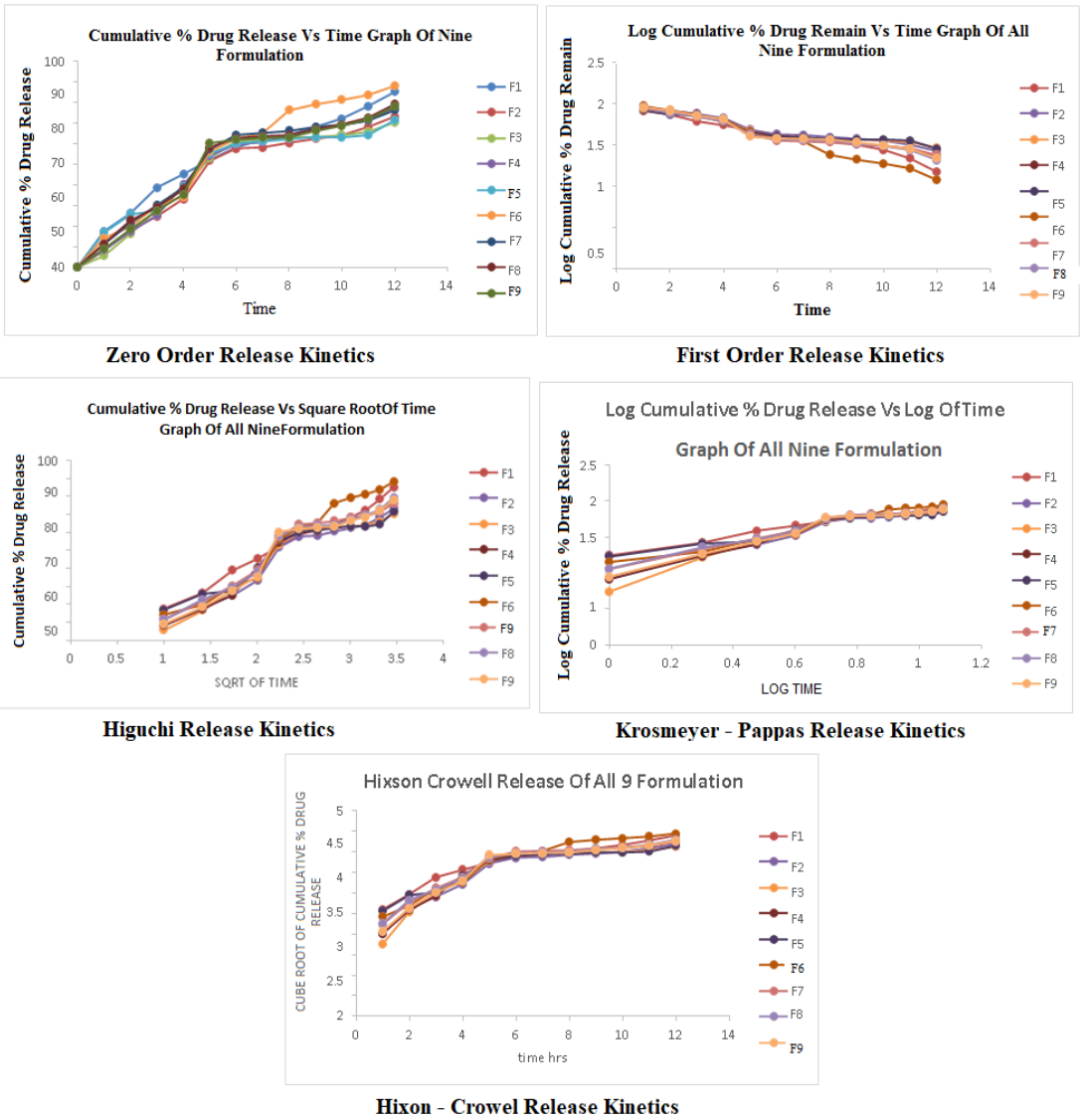
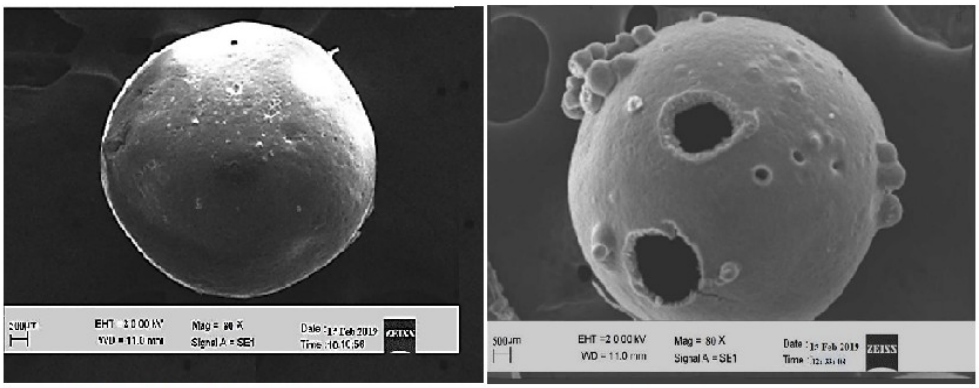


Fig. 9:- Comparative study of different formulations accords to release kinetics model.

Table 7:- *In-Vitro* Release Kinetics Parameters for Zingiberol loaded Floating Microsphere.

Formulation Code	Zero Order		First Order		Higuchi Matrix		Korsmeyer Peppas		Hixson- Crowell	
	R^2	K0	R^2	K1	R^2	Kh	R^2	n	R^2	Khc
F1	0.9742	8.6934	0.9201	-0.0461	0.9736	46.358	0.932	0.97	0.8236	0.1592
F2	0.9892	7.0693	0.963	-0.0472	0.9824	27.239	0.917	0.5964	0.728	0.217
F3	0.9683	4.9823	0.9351	-0.0845	0.9906	26.257	0.919	0.7482	0.9269	0.121
F4	0.9531	6.8045	0.9836	-0.0901	0.9759	27.896	0.913	0.7566	0.945	0.134
F5	0.9587	5.7921	0.9461	-0.0561	0.9905	42.126	0.949	0.9372	0.919	0.1747
F6	0.9919	6.9245	0.9812	-0.0731	0.9833	21.563	0.920	0.8826	0.949	0.1327
F7	0.973	3.1102	0.9812	-0.0391	0.9654	28.125	0.962	0.4893	0.9136	0.1897
F8	0.9912	9.425	0.978	-0.0645	0.9831	28.763	0.916	0.8328	0.846	0.1321
F9	0.9899	5.2059	0.9787	-0.0478	0.9721	26.639	0.948	0.8358	0.915	0.1459



Before Dissolution Study **After Dissolution Study**

Fig. 10:- SEM Study of Zingiberol loaded microsphere at different time interval.

The SEM photographs of Zingiberol microsphere before dissolution shows the spherical and smooth surface whereas after dissolution the pores and crevices were shown in Fig. 10 which is indicating that the microsphere are showing drug release by erosion mechanism.

4. Conclusion

The present study was undertaken with an aim to formulate and evaluate Zingiberol microspheres by ionotropic gelation method. The Preparation contains nine formulations using different polymers i.e. Sodium Alginate and Microcrystalline cellulose in different ratios. The prepared batches of floating microspheres were evaluated for micromeritic studies like bulk density, tapped density, Carr's index (ci), Hauser's ratio, angle of repose, and evaluation studies like in vitro buoyancy, swelling index, drug entrapment efficiency and *in-vitro* release studies. The results from these studies could be used to optimize the design of clinical trials to enhance the efficacy of ginger in motion sickness.

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