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Formulation, Characterization, and *in vitro* Evaluation of Chlorzoxazone Floating Microspheres

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Abstract

Chlorzoxazone is a centrally acting agent for painful musculoskeletal conditions. Chlorzoxazone microspheres were facilitated by preparing floating dosage form which could increase its absorption by increasing the gastric residence time and to achieve sustainable drug release. Chlorzoxazone floating microspheres were prepared by emulsion solvent evaporation method in 10 different formulations (F1-F10) using Ethyl cellulose and HPMCK15 as polymers, tween 80 as surfactant, Ethanol and Dichloro methane were used as solvents. The influence of formulation factors (drug-polymer, stirring speed, concentration of surfactant and solvent ratio) on particle size, encapsulation efficiency and *in-vitro* release characteristics of the microspheres were investigated. The prepared formulations were evaluated with pre-compression parameters like bulk density, compressibility index, hausner ratio, angle of repose and post-compression parameters like drug content, percentage yield, drug entrapment efficiency, floating lag time, total floating time, and in-*vitro* drug release. All the formulation possesses good flow property, start to float within 40 sec. with a total floating time for not less than 12hrs. *In-vitro* drug release and floating behavior were studied in stimulated gastric fluid at pH 1.2 was found to 54.27% and 85.06% of the optimized formulation F9. The yield and percentage entrapment efficiency of microspheres was obtained up to 81.48% and 84.47%. Kinetic studies of the optimized formulation (F9) showed that the drug release follows Higuchi model and Peppa's plot stated non-fickian diffusion controlled.

Keywords

Chlorzoxazone, Floating microspheres, Skeleton muscle relaxant, Solvent evaporation method

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1. INTRODUCTION:

The traditional drug delivery system retains the concentration of medicines within the therapeutic range when taken many times a day, which leads to major fluctuation in the amount of drug. Gastro retentive drug delivery system is one of the successful methods with extended clinical effects and reduced frequency of dose. Several methods of gastric retention have been developed. Of these floating dosage forms have been found to be best. Floating drug delivery system have lower bulk density than gastric fluid so that buoyant in the stomach for long period without affecting gastric emptying time [1-3]. Chlorzoxazone (CHZ) is a centrally acting muscle relaxant that inhibits muscle spasm. The common side effects are drowsiness, dizziness and headache. Its effect begins within an hour after an oral dose and lasts for 3-4 hours. The usual oral dose is 500mg three or four times daily. CHZ is a good choice for formulation as a gastro retentive dosage form and it's coming under BCS class II with low solubility and high permeability and it's Pka value is 3.3 [4-6]. The increase in gastric residence time helps increase its solubility and hence its absorption. The present study aims in designing floating microspheres of Chlorzoxazone using Ethyl cellulose and HPMCK15 to achieve floating sustained release profile suitable for oral administration.

2. MATERIALS AND METHODS:

Chlorzoxazone, Ethyl cellulose and HPMCK15 were obtained from SKN Pharmaceuticals Pvt.Ltd. Tween 80 was procured from Apex Pharmaceuticals, India. Methanol and Dichloromethane was obtained from Universal Scientific Appliances, Madurai. All other chemicals were used of analytical grade.

MATHODS:

2.1Determination of (λ) max of Chlorzoxazone in acid buffer pH 1.2

The absorption maxima (λmax) of chlorzoxazone was determined by scanning the diluted concentration of drug solution in buffer solution (10µg/ml) between 200-400 nm. The obtained spectrum exhibited the absorption maxima (λ max) at 282nm in acid buffer pH 1.2.

2.2 Calibration of Chlorzoxazone in 0.1N HCL

10mg of drug is accurately weighed and transferred to 10ml standard flask and dissolved in 10ml of methanol. From this solution 1ml is taken and diluted to 10ml using acid buffer pH 1.2 from the stock solution various dilutions were prepared to get concentration, 5-25µm /ml. These dilutions were analyzed at 282 nm using UV-spectrophotometer (shimadzu 1700, Japan). Calibration curve of concentration v/s absorbance was plotted and data was subjected to linear regression analysis on the maximum absorbance (λ max)282nm [7,8].

2.3 Drug-Excipient compatibility study

The drug-excipient compatibility studies of pure drug and physical mixture of drug with polymer were performed using FT-IR spectroscopy (FTIR, Shimadzu RXI, Japan) by the KBr Disc method. The samples were scanned between 4000 cm^{-1} and 400 cm^{-1}. The spectrum of pure chlorzoxazone was compared with the spectrum of physical mixture [7].

2.4 Preparation of chlorzoxazone floating microspheres:

Chlorzoxazone Microspheres were prepared by emulsion (Oil-in-water emulsion) solvent evaporation method. Drug and polymers (ethyl cellulose, HPMCK15) were dissolved in mixture of DCM and ethanol. This solution was poured into 200 ml water containing twenty-80 and subsequently stirred at different stirring speed using mechanical stirrer for specified time (2hrs) to allow the volatile organic solvent to evaporate. The microspheres formed were filtered, washed with water and dried overnight at room temperature. Amount of solvents (DCM, methanol) were changed in formulations (F1, F4 and F5), changes of stirring speed (rpm) in formulations (F1, F2, F3). Polymer and surfactant concentration were changed in formulations (F9, F10) and F6, F7, F8. To obtain the effects of the variables on floating microsphere of chlorzoxazone was shown in Table no. 1 [8,9].

Table 1: Composition of chlorzoxazone floating microspheres

Ingredients	Formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Chlorzoxazone(gm)	2	2	2	2	2	2	2	2	2	2
Ethylcellulose(gm)	2	2	2	2	2	2	2	2	4	5
HPMC K15(gm)	1	1	1	1	1	1	1	1	1	1
Tween 80(% v/v ml)	2	2	2	2	2	4	2	1	2	2
Distilled water(ml)	200	200	200	200	200	200	200	200	200	200
DCM(ml)	20	20	20	25	15	20	20	20	20	20
Ethanol(ml)	10	10	10	15	10	10	10	10	10	10
RPM	600	800	700	600	600	600	600	600	600	600

3. Evaluation of floating microspheres [10,11]:

3.1 Micromeritics

Microspheres were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausner's ratio.

3.1.1 Particle size

The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 200-300 particles with the help of a calibrated ocular micrometer.

3.1.2 Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed amount of floating microspheres was placed into 10 ml measuring cylinder. (Values expressed in gm/cm3).

Bulk density =Weight of sample/Volume of sample

3.1.3 Tapped density

Accurately weighed amount of floating microspheres was placed in 10 ml measuring

Cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded (values expressed in gm/cm3).

Tapped density = Mass of the microspheres / Tapped volume of the microspheres

3.1.4 Carr's index (%)

The Carr's index is frequently used as an indication of the flow ability of a powder.

Carr's index (%) = [(Tapped density − Bulk density)/ Tapped density] × 100

3.1.5 Hausner's ratio

The Hausner's ratio is an indication of the compressibility of a powder. It is calculated by the formula,

Hausner's ratio = (Tapped density/Bulk density) × 100

It is an indication of the flow ability of a powder. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability.

3.1.6 Angle of repose (θ)

The angle of repose is indicative of flow ability. Approximately 1gm of microspheres were transferred into the funnel. The sample was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile. The angle of repose is calculated by

θ = tan-1 h/r

Where, θ is angle of repose, h is height of the pile; r is the radius of the pile.

3.1.7 Percentage yield

Percentage yield of buoyant microspheres was calculated by dividing actual mass of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and it is represented by following formula.

$$\% \text{ yield} = \frac{\text{Total weight of microspheres}}{\text{Total weight of drug + polymer}} \times 100$$

3.1.8 Percentage drug entrapment efficiency (%DEE) [12,13]

Microspheres equivalent to 250mg of drug were accurately weighted and crushed thoroughly. The powdered microspheres were dissolved and extracted in 10ml of 0.1 HCL and volume was made up to 100ml with 0.1 HCL. This resulting solution is then filtered through filter paper. Then 1 ml of this solution was withdraw and dilute to 10ml with 0.1 HCL. The absorbance of resulting solution was measured at 282nm using UV spectrophotometer against appropriate blank.

%DEE = (Actually drug concentration/Theoretical drug concentration) × 100

3.1.9 *In- vitro* percentage Buoyancy [14]

Floating behavior of prepared microspheres were carried out using stimulated gastric fluid 0.1 N HCL in a USP dissolution apparatus type-II (paddle). 50 milligrams of microspheres were spread over the surface of the dispersing medium (900 ml of 0.1 N HCL) containing 0.02% Tween 80 was agitated at 100 rpm for 12hrs and maintained at 37±5°C. The floating and settled portions of microspheres were collected separately. The microspheres were dried and weighed. The percentage of floating microspheres was calculated using the following equation,

$$\text{Percentage Buoyancy of microspheres} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of microspheres}} \times 100$$

3.1.10 *In-vitro* drug release studies of floating microspheres

The *In-vitro* release studies of developed floating microspheres were conducted in 0.1N HCL for 8 hours using USP type I dissolution apparatus. Accurately weighed samples of the microspheres were added in 900ml of the dissolution medium was used and stirred at 100 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval and analysed by any suitable analytical method, such as UV spectroscopy. [15,16]

3.1.11 *In- vitro* release kinetics

The mechanism of drug release from floating microspheres can be reported by studying the drug release kinetic models (zero order, first order, Higuchi's, Hixon-Crowell and Korsmeyer-peppas). The best fitted release kinetic model was selected on the basis of regression analysis [17,18].

RESULTS AND DISCUSSIONS:

Estimation of absorption maximum

The absorption maximum (λ max) of chlorzoxazone was determined by scanning the diluted concentration of drug solution in buffer solution (10µg/ml) in the range of 200-400 nm. Drug absorption maximum (λ max) was found to at 282nm in 0.1N HCL. Absorption maximum showed that drug sample was authenticated showed in figure 1.

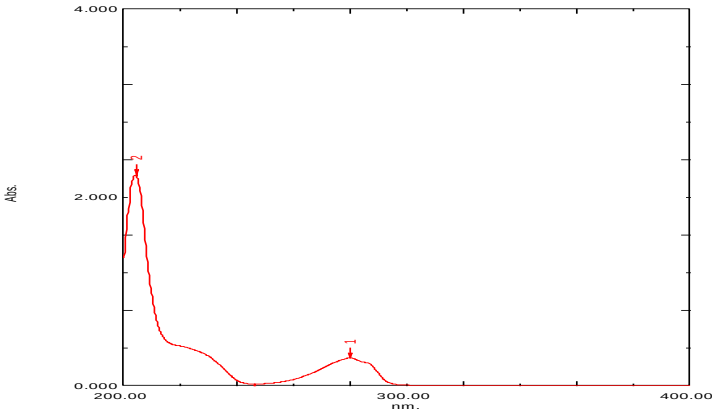


Figure 1: Absorption maximum of chlorzoxazone

Calibration of chlorzoxazone:

Quantitative estimation of drug sample was done by calibration curve which are prepared in 0.1N HCL concentration range of 5-25µm/ml and R^2 value was found to be 0.9967 respectively which indicated the linearity of the graph was shown in figure. 2.

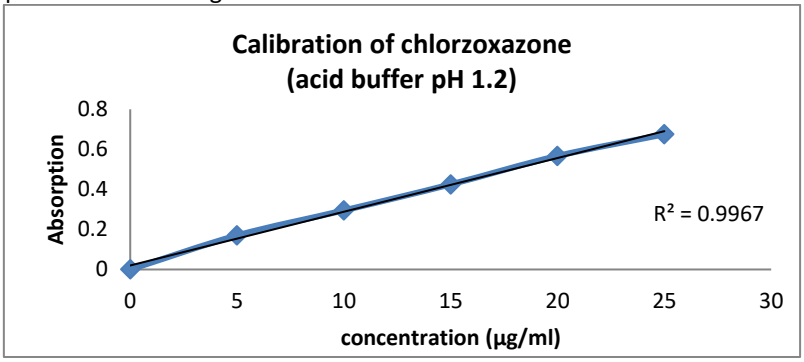


Figure 2: calibration curve of chlorzoxazone

Fourier transforms – infrared spectroscopy (FT-IR)
The FT-IR spectra of pure drug (chlorzoxazone) and physical mixture of the drug were given figure (3-5). After spectral analysis, no significant difference was observed in the characteristic peaks of pure drug chlorzoxazone and chlorzoxazone floating microspheres. Which proved that drug and excipients were compatible.

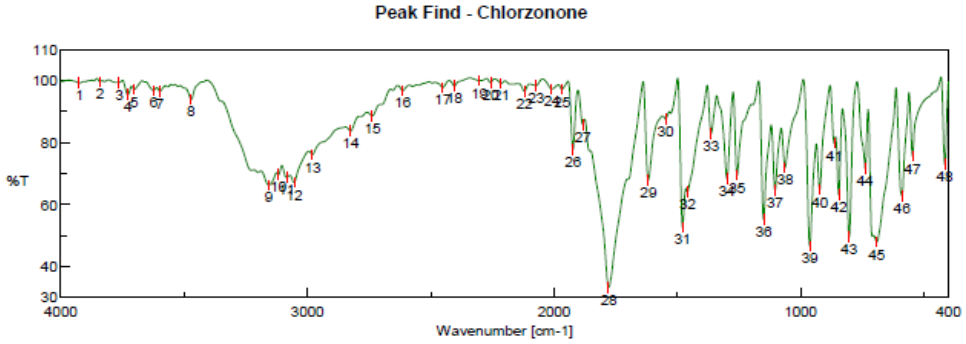


Figure 3: IR spectra of pure chlorzoxazone

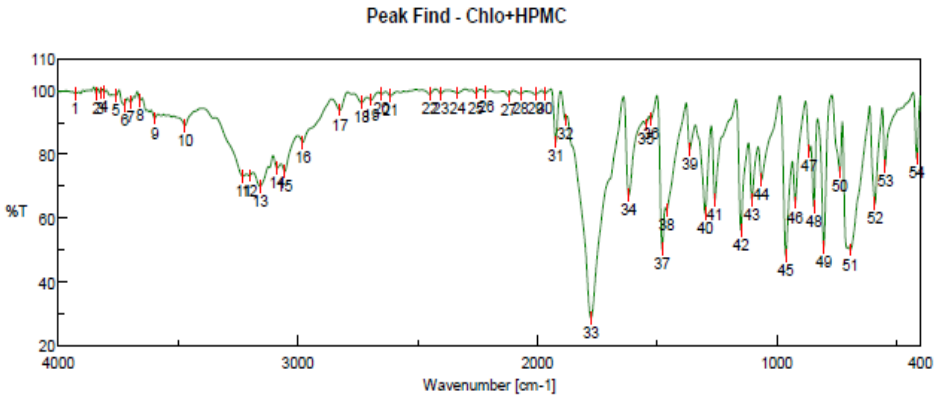


Figure 4: IR spectra of chlorzoxazone + HPMC K15

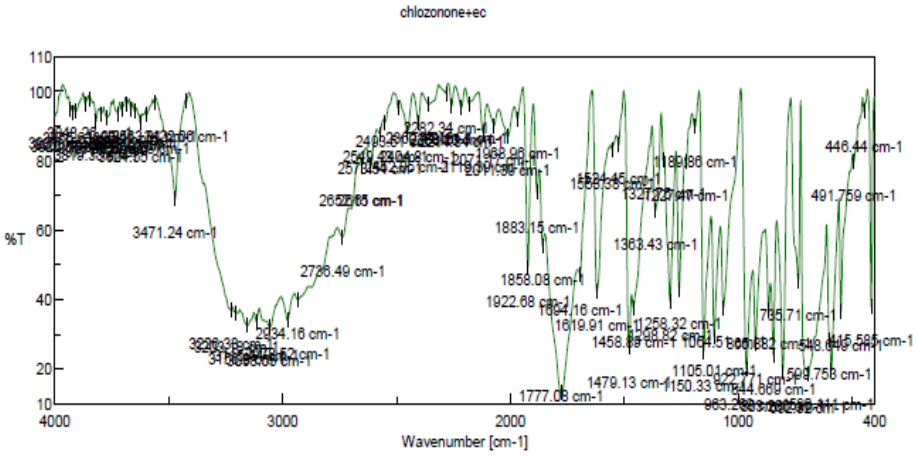


Figure 5: IR spectra of chlorzoxazone + ethylcellulose

Micrometric properties:
The rheological properties of formulations were expressed in terms of angle of repose, bulk density, tapped density, Carr's index, hausner's ratio as given in table 2 and 3. Angle of repose was in the range of 25.17± 0.04° to 46.06 ± 0.02° which shows good flow properties but needs some flow promoters. Bulk density, tapped density was found in the range of 0.1818± 0.02 to 0.2± 0.02 gm/ml and 0.1886 ± 0.05 to 0.222± 0.04 gm/ml respectively. The values of Carr's index and hausner's ratio for all formulations were less than 15 % and below 1.2, which showed good flowability. The mean particle size of the floating microspheres was found to be ranging from 99.9± 0.4 to 399.6±0.3 µm. the particle size were insignificantly decreased with increasing in stirring

speed which may be due to agitation speed (800 rpm) was not enough to break up the bulk of the polymer into more fine droplets due to relatively high viscosity of internal phase. In addition, it was found that the particle size of prepared microspheres decreased significantly as the concentration of the emulsifying agent increases in formulation F6.

Table 2: Micromeritics properties of chlorzoxazone floating microspheres

Parameters	formulations				
	F1	**F2**	**F3**	**F4**	**F5**
Mean particle size (µm)	133.2±0.6	266.4±0.4	399.6±0.3	199.8±0.1	166.5±0.3
Particle shape	spherical	spherical	spherical	spherical	Spherical
Angle of repose (Θ)	34.24° ± 0.03	46.06 ° ± 0.02	35.53 ° ± 0.05	39.79 ° ± 0.06	33.02 ° ± 0.04
Bulk density (gm/ml)	0.1923±0.01	0.1818± 0.02	0.1851± 0.02	0.2083± 0.04	0.2± 0.02
Tapped density (gm/ml)	0.204± 0.05	0.1886± 0.05	0.1960± 0.03	0.2173± 0.02	0.2083± 0.04
Hausner's ratio	1.060±0.05	1.037±0.03	1.058±0.01	1.043±0.02	1.041±0.04
Carr's index (%)	5.7±0.013	3.60±0.022	5.56±0.042	4.1±0.032	3.9±0.012

Table 3: Micromeritics properties of chlorzoxazone floating microspheres

Parameters	formulations				
	F6	**F7**	**F8**	**F9**	**F10**
Mean particle size(µm)	99.9± 0.4	299.9± 0.5	266.4± 0.5	239.76± 0.3	166.5± 0.3
Particle shape	Spherical	spherical	spherical	spherical	spherical
Angle of repose (Θ)	34.21± 0.01	32.61± 0.03	31.79± 0.04	25.17± 0.04	27.02± 0.03
Bulk density(gm/ml)	0.1960± 0.02	0.2127± 0.04	0.2040± 0.03	0.2± 0.02	0.2040± 0.03
Tapped density(gm/ml)	0.2040± 0.02	0.222± 0.02	0.222± 0.02	0.222± 0.04	0.2173± 0.05
Hausner's ratio(%)	1.041±0.015	1.0437±0.030	1.088±0.31	1.11±0.23	1.065±0.04
Carr's index	3.9±0.015	4.1±0.013	3.6±0.021	9.9±0.012	6.5±0.014

Percentage yield:

The percentage yield of formulated microspheres was found to be in the range of 51.98 % - 74.42 %. Formulation (F9) has highest yield than other batches. The results were shown in table 4. The analyzed results for the prepared microspheres indicate that increase in polymer concentration caused a significant increase in percentage yield.

% Entrapment efficiency:

Entrapment efficiency of the formulated microspheres was in the range of 57 % - 81.4 %. Formulation (F9) showed good entrapment efficiency due to increasing polymer concentration. The results were shown in table 4.

Floating lag time and total floating time:

The floating lag time of the formulated microspheres was found to be in the range of 15- 40 seconds. Formulation (F1) floats quickly than other formulations. The results are shown in table 4 and figure 6. All the formulations were floated for more than 12 hours.

Figure 6: Chlorzoxazone floating microspheres

***In- vitro* Percentage buoyancy:**

Percentage buoyancy of formulated floating microspheres was in this range of 50-85%. Formulation (F9) has highest % buoyancy than other formulations. The results were shown in table 4. It was observed that the floating ability increased with increasing average particle size and also observed that the formulation prepared with high amount of ethyl cellulose showed better flow ability than other formulations due to the porous nature of ethyl cellulose polymer.

Table 4: Evaluation of floating microspheres

Formulations	% Yield	Floating lag time (secs)	Total floating time (hrs)	% Entrapment efficiency	% Buoyancy
F1	57.10±1.210	15 sec	>12hr	63.389±0.034	72.12
F2	57.05±3.120	38 sec	>12hr	66.10±0.052	50.42
F3	61.8±3.211	19 sec	>12hr	60.33±0.032	63.12
F4	74.42±4.321	27 sec	>12hr	67.11±0.036	65.35
F5	66.6±3.126	40 sec	>12hr	64.06±0.052	68.45
F6	51.98±2.243	33 sec	>12hr	54.57±0.041	73.21
F7	68.63±3.311	29 sec	>12hr	61.69±0.253	72.36
F8	71.73±4.215	31 sec	>12hr	54.42±0.621	60.10
F9	81.48±3.221	20 sec	>12hr	84.47±0.054	85.23
F10	72.37±1.324	25 sec	>12hr	74.57±0.024	79.12

***In-vitro* drug release studies:**

All the formulations (F1-F10) were subjected to in-vitro drug release study. In addition, the choice of such formula F9 was allowed to study the effect of increasing the polymer concentration on the dissolution studies. The release rate of drug retarded by increasing the polymer concentration (EC), as shown in table 5 and figure 7 and 8. From the release data that had been obtained and discussed, formulation F9 was found to be the best formulation as it releases chlorzoxazone in a sustained manner with no burst and constant fashion over an extended period of time (after 8 hrs), which prolonged the gastric retention time at the upper part of GIT and thereby increasing the chlorzoxazone bioavailability.

Table 5: *In-vitro* drug release studies

Formulations	%Cumulative drug release at 8thhour
F1	**75.74 %**
F2	**71.6 %**
F3	**82.88 %**
F4	**74.71 %**
F5	**76.34 %**
F6	**90.8 %**
F7	**90.15 %**
F8	**95.79 %**
F9	**54.27 %**
F10	**59.46 %**

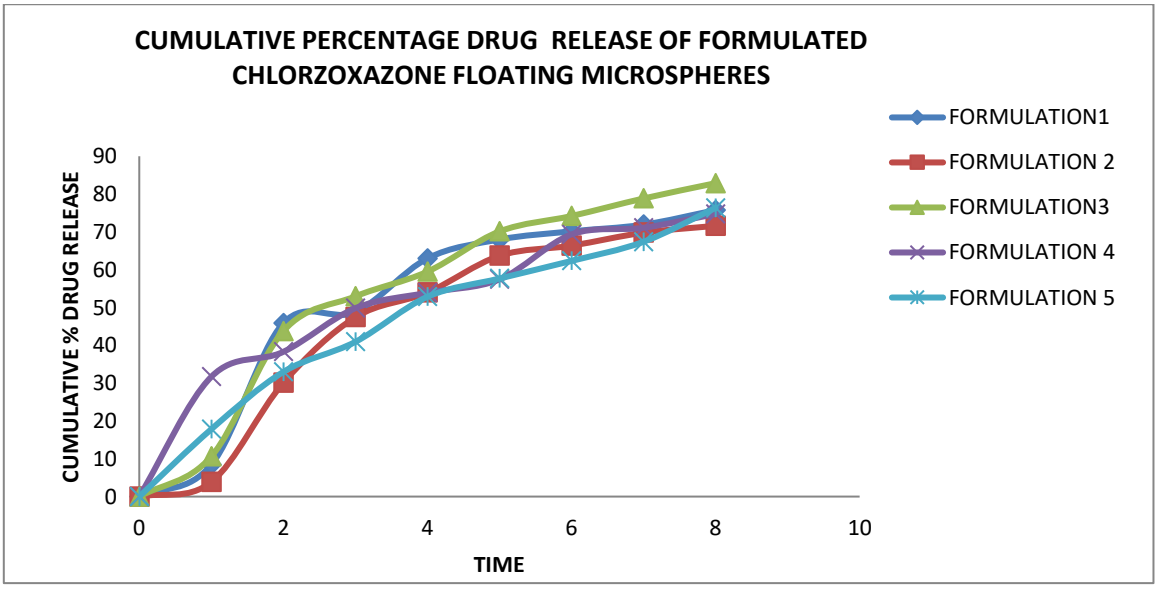


Figure 7: cumulative percentage drug release of chlorzoxazone floating microspheres

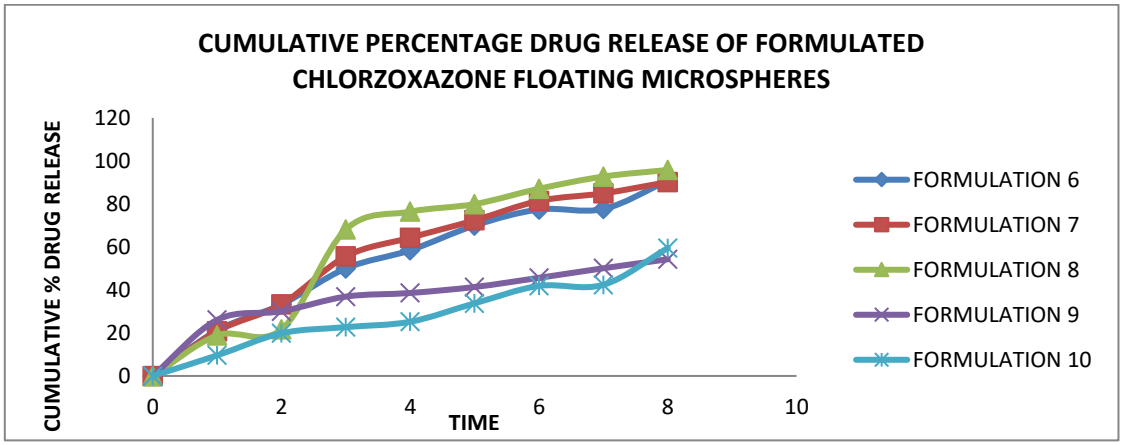


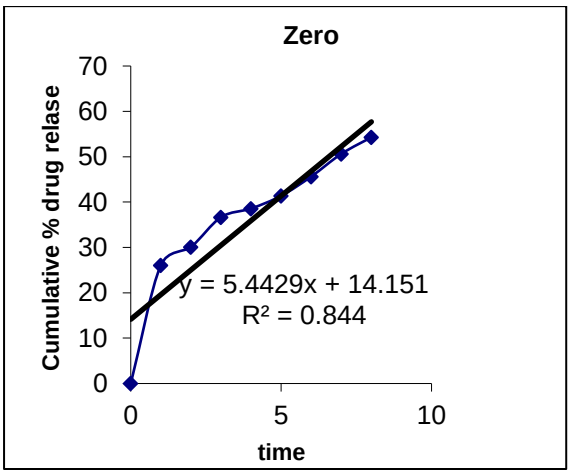
Figure 8: cumulative percentage drug release of chlorzoxazone floating microspheres

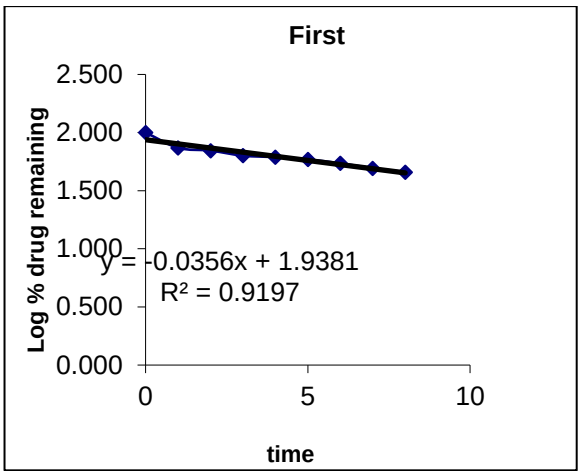
Release order kinetics:

The *in-vitro* release profiles from formulations were applied on various kinetics models. The best formulation (F9) fit with the highest correlation coefficient was observed in Higuchi model, indicating diffusion drug release principle. Further the 'n' value obtained from the korsmeyer plot suggests that the drug release from microspheres was anomalous non Fickian diffusion i.e. both diffusion and dissolution mediated drug release. The release kinetics of all formulated floating microspheres were shown in figure and Table 6.

Table 6: release order kinetics of formulated chlorzoxazone floating microspheres

formulations	Zero order R2 value	First order R2 value	Higuchi R2 value	Korsmeyer-Peppas model R2	n	Hixson crowell R2 value
F1	0.748	0.893	0.946	0.967	0.322	0.849
F2	0.850	0.915	0.971	0.919	0.583	0.918
F3	0.867	0.979	0.988	0.975	0.442	0.951
F4	0.964	0.924	0.901	0.963	0.793	0.942
F5	0.948	0.988	0.985	0.986	0.671	0.984
F6	0.954	0.950	0.977	0.989	0.701	0.993
F7	0.938	0.993	0.974	0.975	0.726	0.993
F8	0.879	0.971	0.908	0.868	0.878	0.966
F9	0.844	0.919	0.977	0.969	0.348	0.897
F10	0.883	0.970	0.989	0.978	0.431	0.951





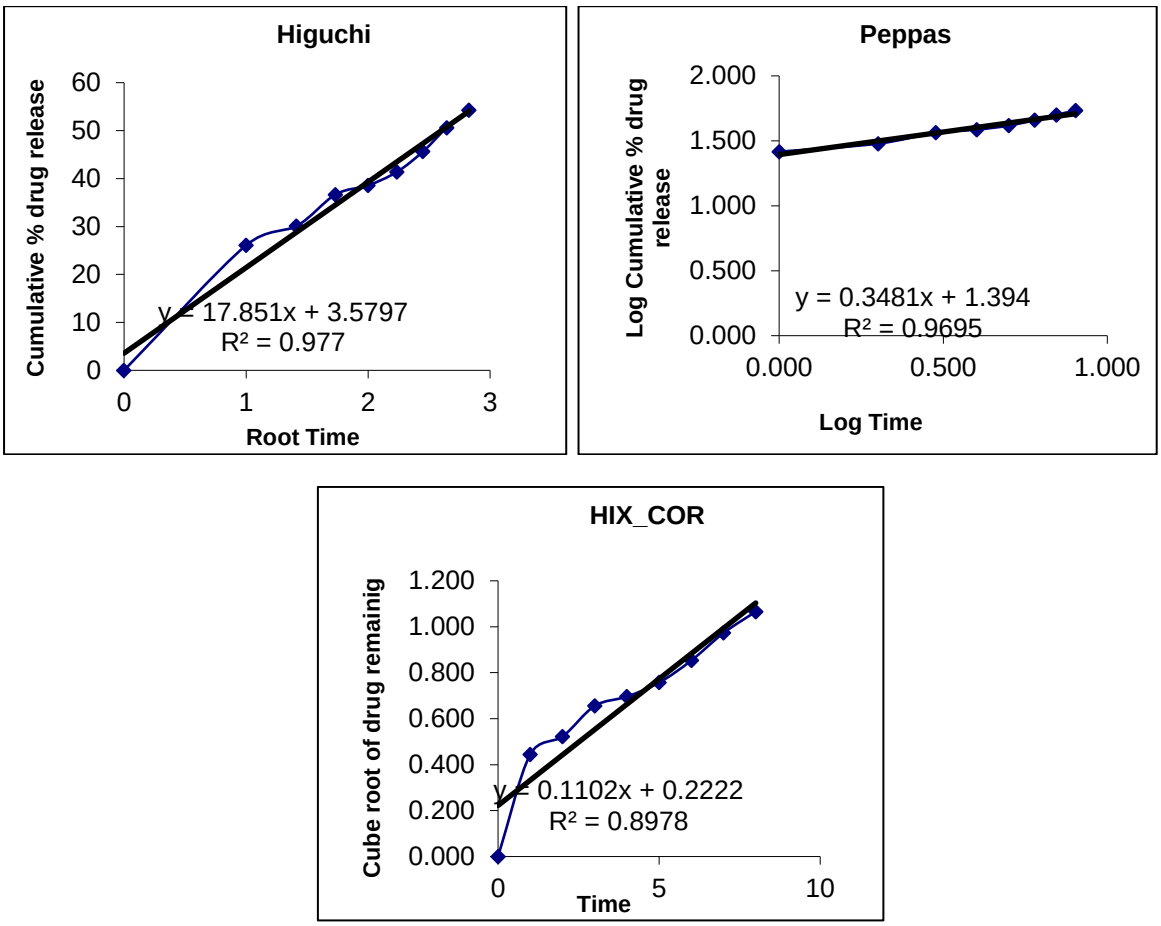


Figure 9 : Release order kinetics of best formulation (F9)

CONCLUSION:

Gastro retentive floating microspheres of chlorzoxazone were prepared by emulsion solvent evaporation technique, using ethyl cellulose and HPMC K15 in order to retain drug in body for longer period of time to increase bioavailability. Overall results suggest that most variables (polymer concentration, emulsifying agent concentration, type and volume of dispersed phase and stirring speed) had a significant effect on the physical characteristics along with the drug release profile of the formulated floating microspheres. On the basis of data obtained from *in-vitro* dissolution studies, it can be concluded that formulation F9 was promising formulation suitable for the sustained release of chlorzoxazone for gastro retention purpose that may be giving rise to enhance the bioavailability of the drug. Chlorzoxazone floating drug delivery system promises to be a potential approach for gastric retention used in the treatment of muscular pain by its muscle relaxing property.

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CONFLICTS OF INTEREST

There are no conflicts of interest regarding the publication of this article to disclose.

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