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PREPARATION AND CHARACTERISATION OF MICROPARTICULATE DRUG DELIVERY SYSTEM OF DIACEREIN

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Abstract:

The objective of the present study was to prepare and evaluate the floating microspheres of Diacerein. Diacerein microspheres were prepared by ionotropic gelation method using polymers such as HPMC (K 100 M), Carbopol, Ethyl cellulose and sodium alginate. Totally 12 different formulations of Diacerein were prepared by using the above polymers. The microspheres were characterized for entrapment efficiency, floating property by in vitro wash-off test and in-vitro drug release. Theformulation F9 was selected as an ideal formulation based on the in vitro release profile which shows an extended drug release of 95% upto 12 hours 0.1N HCl buffer. Surface morphology (SEM analysis) and drug-polymerinteraction studies (FT-IR analysis) were performed only for the ideal formulation, F9. The microspheres were discrete, spherical in shape and had ideal surface morphology as confirmed by SEM and FT-IR studies indicated the lack of drug-polymer interactions in the ideal formulation, F9. The in vitro release data of all microsphere formulations were plotted in various kinetic equations to understand the mechanisms and kinetics of drug release. The ideal formulation, F9 followed first order kinetics and value of "n," is calculated to be 0.7187 indicated that the drug release shows Non-Fickian diffusion.

Keywords*: HPMC (K 100 M), Carbopol, Ionotropic gelation method, Diacerein, Sodium Alginate, Ethyl Cellulose.*

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INTRODUCTION:

Nowadays conventional dosage forms of drugs are rapidly being replaced by the new and novel drug delivery systems, among these sustained release or control release dosage forms are very popular in present day therapy [1]. Oral route of drug administration is the most suitable and commonly used method of drug delivery but this route more often produces gastric emptying rate that varies from person to person with a short stomach transit time and the existence of large absorption window in the upper small intestine for several drugs [2].

Floating systems are low-density systems that have adequate buoyancy to float over the gastric content and remain buoyant in the stomach without affecting gastric emptying rate for an extended period of time, which results in a augmented gastric retention time and a better control of fluctuation in plasma drug concentration [3,4]. After release of drug, the residual system is emptied from the stomach. These difficulties have encouraged researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period [5]. Attempts are being made to develop a drug delivery system which can provide therapeutically effective plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner [6,7].

Diacerein or Diacetylrhein comes under the class anthraquinone derivative. Chemically it is 9,10-dihydro-4,5-dihydroxy-9,10- dioxo-2-anthranoic acid diacetate1. Diacerein is thought to act via inhibition of interleukin-1Beta, a protein involved in the inflammation and destruction of cartilage that play a role in the development of symptoms of degenerative disease like osteoarthritis [8]. Diacerein is a short acting drug, practically insoluble in water. Oral bioavailability of Diacerein is about 35 to56%. Hence, the drug was selected for preparation of sustained release formulation. The study design was to prepare microsphere of Diacerein by ionotropic gelation method with HPMC and ethyl cellulose as polymers [9,10].

MATERIALS AND METHODS:

Materials

Diacerein was purchased from Hetero Drugs Pvt. Ltd. HPMC K100, Sodium Alginate, Carbopol, Ethyl cellulose was purchased from SDFL Chemicals, Mumbai.

Methods

FORMULATION OF FLOATING MICROSPHERES OF DIACEREIN

For Diacerein microspheres HPMC K100 and Sodium alginate were conceded over the sieve no 40. The floating microspheres were prepared by ionotropic gelation method [11,12]. It was then collected by filtration and allowed to dry in a desiccator for about 24 hours. The formed microspheres were then subjected to evaluation studies.

Table 1: FORMULATION TABLE OF DIACEREIN

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
API	50	50	50	50	50	50	50	50	50	50	50	50
Sodium Alginate	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K100	25	50	75	100	--	--	--	--	--	--	--	--
Carbopol 934 P	--	--	--	--	25	50	75	100	--	--	--	--
Ethyl cellulose	--	--	--	--	--	--	--	--	25	50	75	100
$NaHCO_3$	30	30	30	30	30	30	30	30	30	30	30	30
$CaCl_2$ (g)	5	5	5	5	5	5	5	5	5	5	5	5

EVALUATION OF FLOATING MICROSPHERES OF DIACEREIN:

Pre formulation Parameters

Melting point:

The purity of the obtained drug sample was determined by associating the melting point of the obtained sample with that of the official standards [13].

Drug-Excipient Interaction studies:

FT-IR:

The infrared spectra of the pure medicine Diacerein and optimised formula were captured between 400 and 4000 cm. An FTIR spectrophotometer was used to obtain the IR spectra using the KBr disc method [14].

Post formulation parameters

Percent yield:

The percentage yield of Diacerein in the formulated product is determined by using the formula:

$$\frac{\text{Weight of the formulation}}{\text{Theoretical weight of drug and polymer}} \text{ X100}$$

Particle size:

The test is performed to determine the uniformity of the prepared formulation. The particle size of each formulation was determined using optical microscopy technique were diameter of 100 particles each was recorded to determine the average particle size of each formulation [15].

Floating lag Time:

When microspheres are added to a dissolution medium that simulates stomach fluid without pepsin, at pH 1.2, temperature 37 ºC, and paddle rotation of 50 rpm, the time it takes for the microspheres to upsurge to the surface of the liquid is measured using a timer [16].

Total floating time:

The time engaged by the microspheres to float continually on the surface of the gastric fluid without pepsin, at pH 1.2, temprature37 ºC, paddle rotation at 50 rpm, it is measured using stopwatch [17].

Determination of swelling index:

A dose unit's swelling index was calculated by examining its weight increase. By adding the microspheres to 10ml of 0.1N HCl in a petri dish, the swelling index of a microsphere was calculated. Each microsphere was taken out after every hour for a total of up to 12 hours, blotted with tissue paper to remove any extra water, and weighed on a balance. For each time point, the experiment was carried out three times [18]. The swelling index was derived from the equation and expressed as a percentage

$$\textbf{Swelling index (S.I)} = \{(Wt\text{-}Wo/Wo\} \times 100$$

Where

Wt = Weight of microspheres at time t

Wo = weight of microspheres before immersion.

Drug Entrapment Efficiency:

The drug entrapment efficiency of the prepared formulations was assessed by taking 20mg of the prepared microspheres and triturating with 100ml of 0.1N HCl and allowed to stand [19]. The concentration of the drug present is calculated by recording the absorbance and concentration of each formulation.

$$\frac{\text{Concentration of drug in sample}}{\text{Total concentration of drug}}$$

Drug Dissolution studies:

The rotating paddle method of the USP XX1V apparatus was used to conduct the dissolution test. A 50 rpm stirring speed was used. The dissolution medium (900ml) contained 0.1 N HCL. The temperature was kept at 37± 5°c.At regular intervals, 5 ml samples were taken out, filtered, and replaced with 5 ml of fresh dissolving medium [20]. A double beam UV spectrometer was used to analyse the collected samples for the presence of diacerein at 268 nm after being appropriately diluted with dissolving fluid as needed.

Shape and Surface Morphology (SEM):

Scanning electron microscopy was used to study the microspheres' morphology [21].

Kinetics and Mechanism of Release Analysis

Data from drug release investigations conducted in vitro were plotted in several kinetic models to evaluate release kinetic [22].

Zero order equation

$$\% \text{ drug released} = kt$$

First order equation

$$\text{Log \% unreleased} = kt/2.303$$

Korsmeyer – Peppas equation

$$M_t / M_\infty = kt^n$$

where M_t / M_∞ signifies the portion of drug release at time t,

k is the release rateconstant and

n is the diffusion coefficient.

or

Log drug released = log k + n log t

Higuchi equation

% drug released = $kt^{0.5}$

STABILITY STUDIES:

The stability studies of optimized formulations F9 was achieved at accelerated condition of 40˚C ± 2˚C, 75% RH conditions for a time of 1 month. The microspheres were withdrawn at every week and evaluated for the percent entrapment efficiency [23]. Samples were analysed after 1 month for their entrapment efficiency.

RESULTS AND DISCUSSION:

Determination of Purity:

The determination of purity was done by performing melting point study compared with that of the official standards. The melting point of the drug Diacerein was found to be 230 ℃.

COMPATIBILITY STUDIES

The free drug and the microspheres' FT-IR spectra were both captured. The drug-excipient compatibility experiments show that there are no physical alterations in the drug and polymer mixes. To determine whether there had been any changes in the frequency of functional groups in microspheres with respect to the respective functional group of the drug, the IR spectra of the drug, drug-excipient mixture, and microsphere formulation were compared.

The fact that the main IR absorption peaks in the drug's spectrum were similar to those in the spectrum of the microspheres suggests that there is no contact amid the drug and the polymer, according to spectral studies. The fact that both the polymer and the preparation technique did not alter the drug stability is supported by the similar peaks that correspond to the functional groups and characteristics. The photos below display FTIR graphs of diacerein and an optimised formulation.

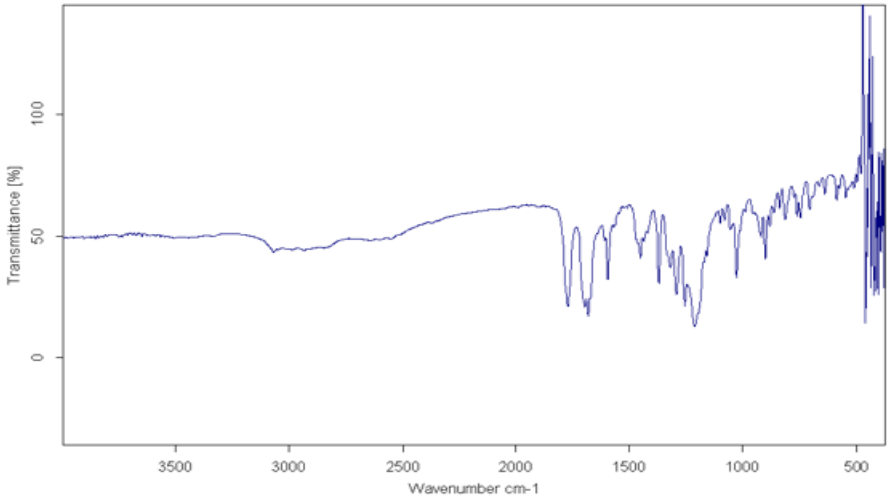

Figure 1: FT- IR spectra of the pure drug

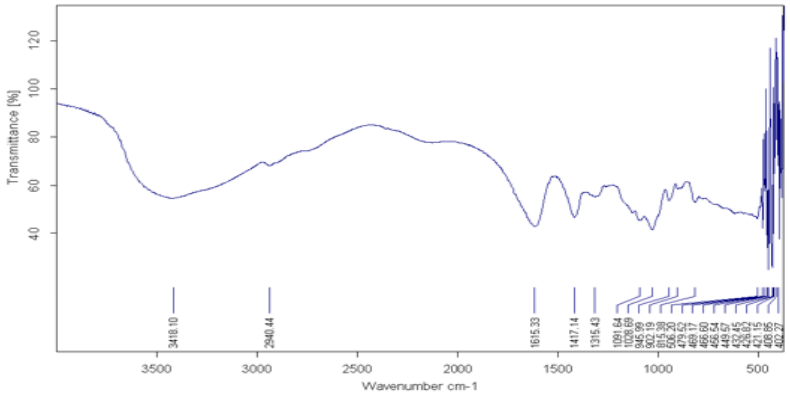

Figure 2: FT- IR spectra of the Optimized formulation

PERCENTAGE YIELD

As the drug: polymer ratio augmented, the percentage yield also increased. The low yield in some formulations may be due to adhesion of microspheres to the beaker throughout the formulation process or microspheres misplaced during the washing process. The % yield of Formulations F1 to F12 was between 13% to 30%.

Table 2: Percentage yield of all formulations

FORMLATION	PERCENT YIELD
F1	13.70%
F2	13.90%
F3	17.80%
F4	24.08%
F5	16.37%
F6	19.80%
F7	24.20%
F8	17.90%
F9	26.70%
F10	21.80%
F11	13.80%
F12	28.60%

ANALYSIS OF PARTICLE SIZE

By using optical microscope, several formulations' particle sizes were evaluated. The range of 816 to 1292.7 m was found to be the typical particle size. According to the type of polymer employed to prepare the microspheres, the mean particle size greatly differed; this could be because the viscosity of the polymer solution varied. With an increase in polymer concentration, the microspheres' particle size and drug entrapment effectiveness both went up.

Table 3: Particle size analysis of all formulations

FORMULATION	AVERAGE PARTICLE SIZE
F1	797.6µm
F2	956 µm
F3	819.2 µm
F4	862.04 µm
F5	849 µm
F6	906 µm
F7	764.622 µm
F8	767.38 µm
F9	816 µm
F10	1292.7 µm
F11	1112 µm
F12	1216.7 µm

FLOATING LAG TIME:

When microspheres are added to a dissolution medium that simulates stomach fluid without pepsin, at pH 1.2, temperature 37 ºC, and paddle rotation of 50 rpm, the time it takes for the microspheres to rise to the surface of the liquid is measured using a timer. The floating lag time in the other formulations is less than 5 seconds, in contrast to the formulations F4, F10, F11, and F12 which showed no floating.

Table 4: Floating lag Time of all formulations

FORMULATION	FLOATING LAG TIME
F1	5 sec
F2	7sec
F3	5sec
F4	No floating
F5	5sec
F6	5sec
F7	5sec
F8	5sec
F9	5sec
F10	No floating
F11	No floating
F12	No floating

TOTAL FLOATING TIME:

At pH 1.2, 37°C, and a paddle rotation speed of 50 rpm, the time for the microspheres to float continuously on the surface of the stomach fluid without pepsin is measured using a stopwatch. According to the findings, the total floating time for formulations F7, F8, and F9 was high.

Table 5: Total floating time of all formulations

FORMULATIONS	TOTAL FLOATING TIME
F1	45 minutes
F2	40 minutes
F3	1 hour 25 minutes
F4	-
F5	48 Minutes
F6	2 hours51 minutes
F7	>3 hours
F8	>3 hours
F9	>3 hours
F10	-
F11	-
F12	-

DEGREE OF SWELLING:

Swellability is a characteristic that indicates how quickly a medication solution will be available for diffusion with higher flux. From the results, it can be inferred that as polymer concentration rises, so does swelling intensity.

The swelling index ranged from 5 to 40% for the various formulations from F1 to F12. The F12 formulation, which uses sodium alginate and HPMC as polymers, caused the most swelling.

Table 6: Swelling index of all formulations

FORMULATIONS	% swelling index
F1	5
F2	15
F3	5
F4	5
F5	3
F6	2
F7	35
F8	30
F9	10
F10	20
F11	10
F12	40

DRUG ENTRAPMENT EFFICIENCY:

Diacerein floating microspheres had a drug entrapment effectiveness that ranged from 27% to 110%. With an increase in the amount of the polymers, the produced microspheres' ability to trap drugs improved over time.

The viscosity of the dispersed phase increases as the polymer concentration rises. With increasing viscosity, the particle size grows exponentially. At the maximum polymer concentration, it would be anticipated that the higher viscosity of the polymer solution would reduce drug diffusion into the exterior phase, increasing entrapment efficiency.

Table 7: % Entrapment efficiency

FORMULATION	% EE
F1	75%
F2	95%
F3	27.5%
F4	56.25%
F5	29.75%
F6	42.5%
F7	50%
F8	40%
F9	56%
F10	110%
F11	45%
F12	37.5%

***IN-VITRO* DRUG RELEASE STUDY:**

In-vitro dissolution study of Diacerein from prepared microspheres showed a biphasic mechanism. The release of Diacerein from microspheres was considered by an initial phase of burst effect (higher release), which was owing to the occurrence of drug particles on the surface of the microspheres shadowed by a second phase of moderate release. It has been pragmatic that the sustained release action was greater in formulations containing higher concentration of the rate controlling polymers. The *in vitro* release profile of Diacerein from microspheres displayed that with increasing the concentration of drug: polymer, the release of the Diacerein from the polymer matrix was retarded. The cumulative percent drug release of Optimized formulation F9 was found to be 95.45 % at 180 min.

Tables 8: *In-vitro* dissolution study Diacerein floating microspheres

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	10.90	12.72	6.36	10	12.72	20	21.81	9.09	9.09	9.09	10.90	8.18
10	22.72	17.27	10	12.72	15.45	23.63	28.18	19.09	16.36	13.63	12.72	10.90
15	27.27	20.90	15.45	14.54	22.72	29.09	27.27	20	19.09	26.36	18.18	151.45
20	33.63	29.09	30.90	16.36	27.27	37.27	33.63	31.81	20.90	33.63	21.18	36.36
25	40.90	37.27	38.18	19.09	30.90	54.54	60	46.36	46.36	55.45	28.18	71.81
30	47.27	44.54	46.36	36.36	38.18	60.90	71.81	72.72	79.09	62.72	42.72	73.63
45	62.72	50	57.27	47.27	45.45	60.90	73.63	73.63	80.90	71.81	55.45	75.45
60	80.90	64.54	65.45	55.45	51.81	62.72	80.90	73.63	84.54	72.72	66.36	84.54
120	82.72	64.54	66.36	65.45	55.45	62.72	81.81	73.63	86.36	73.63	79.09	82.72
180	82.72	64.54	71.81	70	55.45	62.72	82.72	73.63	95.45	73.63	84.54	88.18

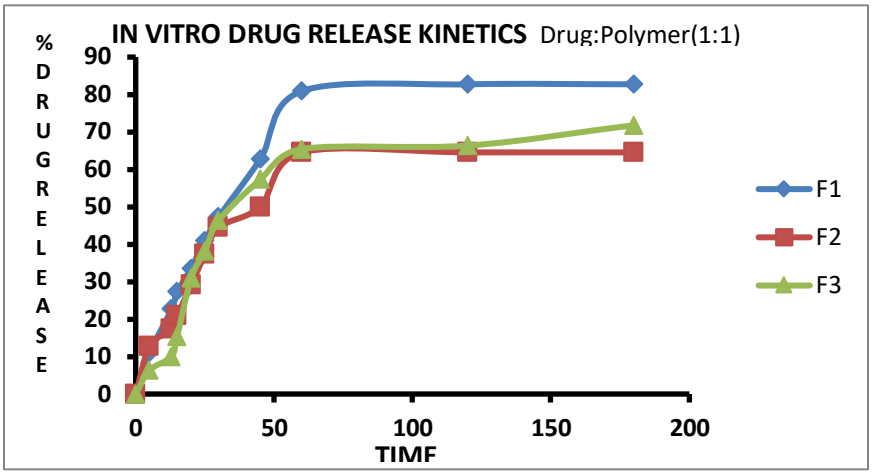

Fig 1: *In-vitro* dissolution study Diacerein floating microspheres F1-F3

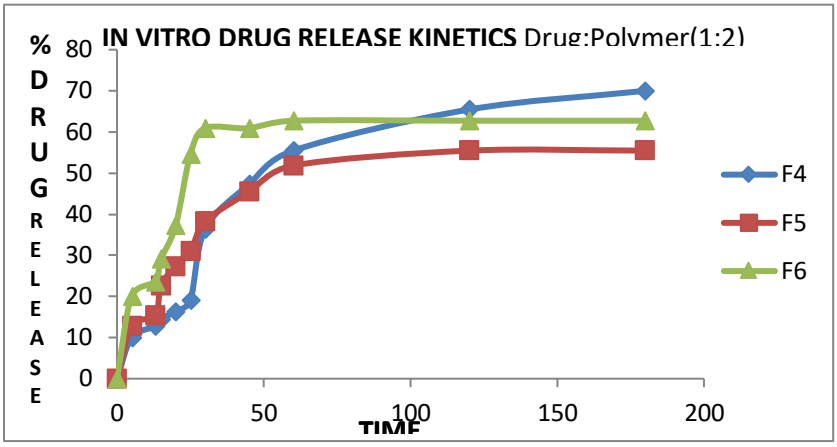

Fig 2: *In-vitro* dissolution study Diacerein floating microspheres F4-F6

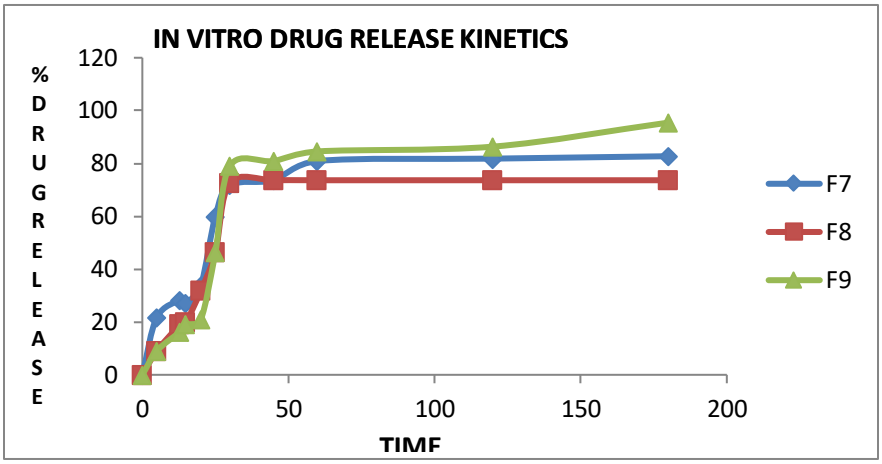

Fig 3: *In-vitro* dissolution study Diacerein floating microspheres F7-F9

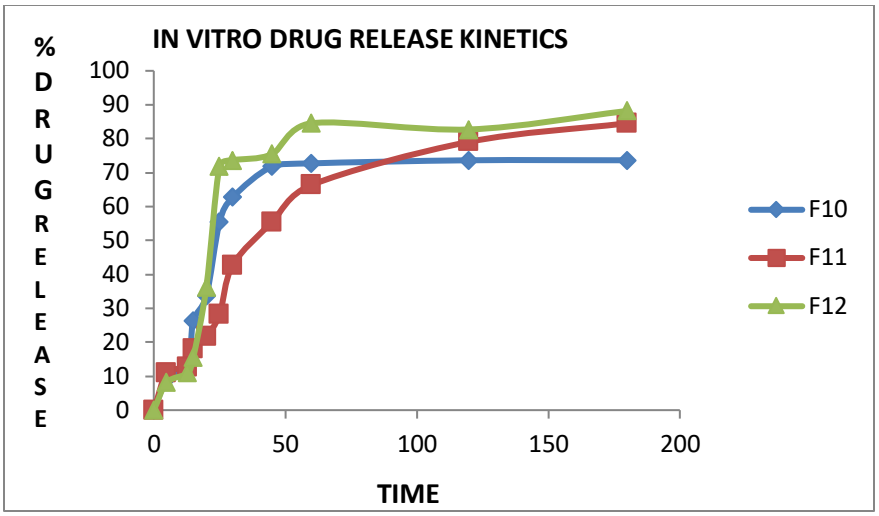

Fig 4: *In-vitro* dissolution study Diacerein floating microspheres F10-F12

KINETIC RELEASE MODELS:

Order of Release Kinetics of Formulations F1-F12:

For the purpose of understanding the linear relationship, or kinetic principles, the release data for diacerein were transformed into graphs. Regression analysis of the data was performed using statistical MS-Excel algorithms. A perusal to Table 9 considering the correlation coefficient (R^2) values obtained showed that all the formulations (F1 to F12) had highest R^2 values for First order plots indicating that the dissolution data fits into First order equation when compared to Zero order equation and R^2 values.

Tables 9: Release kinetics data

formulation	zero order	first order
F1	0.6334	0.7019
F2	0.682	0.777
F3	0.647	0.754
F4	0.7911	0.8808
F5	0.6468	0.713
F6	0.4219	0.4666
F7	0.528	0.6463
F8	0.5183	0.557
F9	0.5923	0.8181
F10	0.4991	0.5697
F11	0.8015	0.9343
F12	0.5031	0.6526

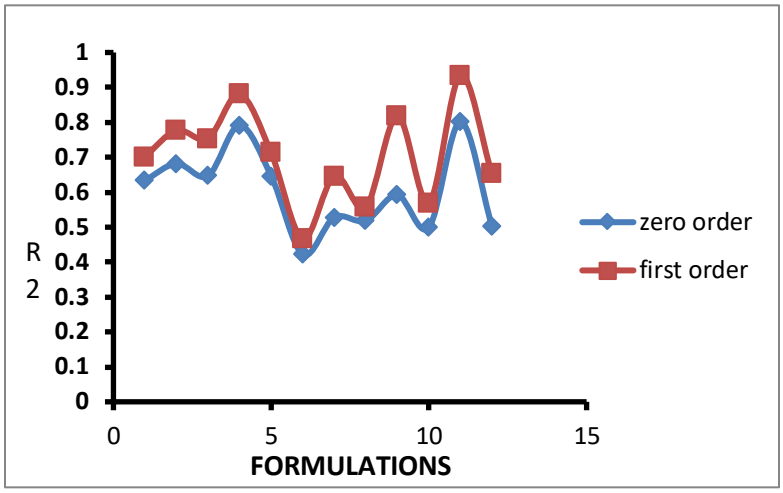

Fig 5: Zero order and First order plot release kinetics data

RELEASE MECHANISMS:

From the results obtained all the formulations (F1-F12) having the slope (n) value between 0.36 and 0.74. This indicates that these formulations follow release according to Fickian diffusion, while other formulations showed non fickian diffusion kinetics having 'n' value greater than 0.45 as shown in table 5.9.

Considering the correlation coefficient (R^2) values obtained from the different kinetic equations, the drug release from the most of the all formulations (F1 to F12) were found to follow first order and kosemeyers-peppas release model.

Table 10: Release kinetics mechanism data

formulations	Higuchi	Hixon crosswel	kosemeyers-peppas	N value
F1	0.8513	0.6816	0.8948	0.514
F2	0.8801	0.7526	0.9108	0.5757
F3	0.8424	0.7192	0.8472	0.722
F4	0.9128	0.8523	0.906	0.6402
F5	0.8692	0.6901	0.9089	0.4586
F6	0.6862	0.4527	0.766	0.3602
F7	0.7628	0.6007	0.7997	0.4359
F8	0.737	0.5584	0.8054	0.6312
F9	0.772	0.733	0.8195	0.7187
F10	0.733	0.5466	0.7829	0.6189
F11	0.9294	0.8951	0.9326	0.6654
F12	0.71	0.5963	0.7518	0.7415

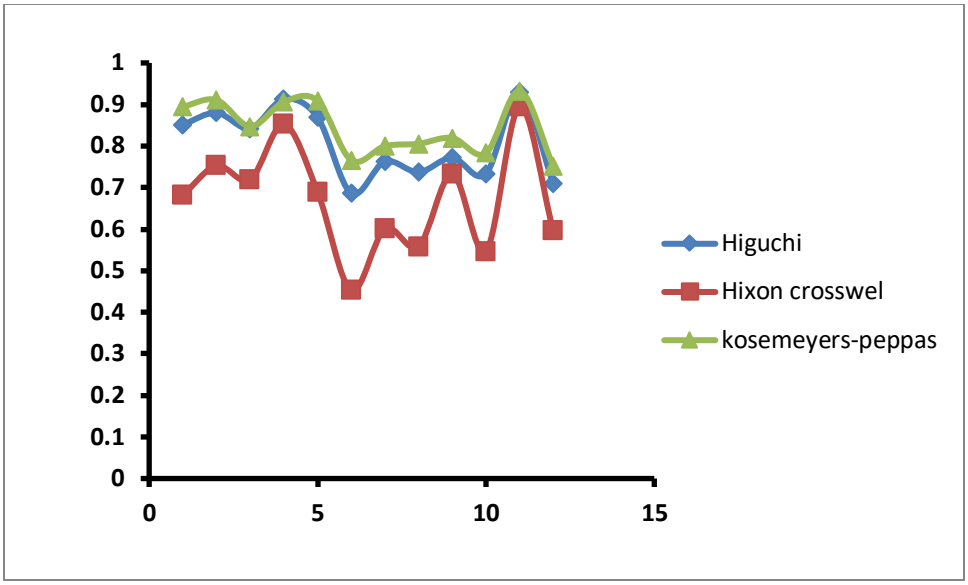

Figure 6: Release kinetics mechanism data

From the obtained release kinetics data, it can be observed that all formulations show first order kinetics i.e. rate of drug release is concentration dependent, followed by kosemeyers-peppas release mechanism, followed by non fickian diffusion properties with respect to n values obtained.

The optimised formulation F9 shows first order release kinetics, Kosmeyers-peppas model release mechanism with non-fickian diffusion property

STABILITY STUDIES:

The stability studies of optimized formulations F9 was accomplished at accelerated condition of 40˚C ± 2˚C, 75% RH conditions for a period of 1 months. The microspheres were withdrawn at every week and assessed for the percent entrapment efficiency. Samples were analyzed after 1 months for their entrapment efficiency. The entrapment efficiency of the optimized formulation at the end of a months stored at accelerated stability conditions 40 $\pm$ 2 ^{o}C, 75 $\pm$ 5 % RH was 80.08 %. Also, there was no change in physical appearance and colour change in the formulations. This showed that the formulations are stable at the stored conditions. Therefore shelf-life of the optimized formulation F9 in all possibility is expected to be more than two years.

CONCLUSION:

The current work involves the formulation and in-vitro estimation of floating microspheres_containing Diacerein for sustained release. By means of polymers such as Sodium alginate and HPMC K100M for the sustained release matrix. Diacerein has absorption window in the upper part of the GI tract. Due to this reason this formulation was designed as floating microspheres. Floating may enhance the absorption of Diacerein. There was no physical incompatibility among the drug and other excipients, according to pre-formulation investigations for drug excipient compatibility. The percentage yield, particle size, swelling index, entrapment effectiveness, floating time, and total floating time of each formulation were all assessed. According to the findings, the final mixture of the two medicines and excipients exhibited sustained release characteristics. All of the formulations' drug content and drug release were evaluated, and all estimated parameters were determined to be in limits, indicating that all of the prepared formulations were effective. For buoyancy characteristics such floating lag time & total floating time, all formulations underwent testing. With the exception of F4, F10, F11, and F12, all formulations produced good outcomes. Drug release in vitro tests were conducted on all formulations. The improved formulation F9 produced the superior result.

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