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To Design and Study the Effectof Different Polymersand Their Composition Difference on Floating Oral In-Situ Gelling System of Amoxicillin.

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ABSTRACT: Amoxicillin trihydrate is a β-lactam antibiotic which is used in the eradication of H.Pylori infections. Oral floating in-situ gelling system of amoxicillin was prepared using two gelling polymers sodium alginate and gellan gum to eradicate H. pylori along withcross-linking agent$CaCO_3$. The floating oral in-situ gel undergoes gelation by ion sensitive mechanism. These formulations were prepared by using different concentration of sodium alginate, Gellan gum and in combination of both polymersin the range of 1.5%, 2% & 2.5%.All the obtained pre-formulation parameters were in compliance with the standard values. All the formulations exhibited instant gelation with stiff gel formation and good integrity, except the one with lowest SA level. WRT floating behaviour, all formulations floated for more than 10 hrs irrespective of their composition except the one with the lowest SA level. All the formulations took less than 1 min to float and the results of content uniformity and pH was satisfactory ensuring the safe useand the formulations possessed optimal viscosity which can help in easy administration of thespecified dose.Formulation F5 and F9 were selected as best formulation regarding CDR, in vitro gelling capacity and other factors. Formulation F5 & F9 follows Higuchi kinetic model.Physicochemical parameters were found directly proportional to the concentration of polymer but the percentage of CDR is inversely proportional to the concentration of polymers used in the formulation.From the designed set of experiments, it was proved that formulation containing Gellan gum controls the release rate of drug for longer duration and will be used for stomach specific and sustained action.

KEY WORDS: Amoxicillin trihydrate, H.pylori, Insitu gel, Gellan gum, sodium alginate, invitro drug release.

I. INTRODUCTION

Floating system is a novel process, which will increase the site-specific uptake and improves the absorption rate of the drug. The floating system is a low-density system, so it has enough ability to float on the acidic content of stomach. Floating system is meant for gastric retention because of sufficient buoyancy and low-density system it can releases drug for longer duration by controlled and sustained rate. The floating system is very useful for the API that has an absorption window in the upper part of the Gastro Intestinal Tract to produce the local effect in stomach. [1, 2]

The oral drug delivery system is considered as a one of the best route for drug administration. Different oral drug delivery system is prepared as an API reservoir and from them the active API molecule will release over a prolonged period of time with a predetermined release rate as well as controlled and sustained rate. In recent times the dosage forms are designed in such a way that they will be retained in the upper part of Gastro intestinal tract by using different techniques such as; Raft system, floating system, expanding system, swelling system, bio-adhesive system and lower density system. The system offers benefits such as the delivery of medication with short absorption periods in the small intestine and greater resistance duration in the small intestine, which supports the local effect in the upper part of the small intestine. E.g.: In treatment of the peptic ulcer disease [3, 4]

Helicobacter pylori is one of the most commonly found gram negative, pathogenic bacteria that are found in the stomach & responsible for the bacterial infections. It is associated with the development of serious gastro duodenal disorders, which includes the diseases like peptic ulcers, gastric lymphoma & acute chronic gastritis. Helicobacter pylori will be residing mainly in the gastric mucosa (or) at the interface between the mucous layer & the epithelial cells of the antral region of the stomach.

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Antibiotics that are required for the eradication of the H. pylori & its associated infections are generally given in high dose and more administration that is frequent is seen [5].

The main reason for the above problems is because of the low concentration of the antibiotic, which will be reaching the bacteria under the mucosa, the instability of the drug in the lower pH of gastric fluid & shorter residence time of the antibiotic in the stomach, which will lead to the incomplete eradication of the bacteria H. pylori. Amoxicillin is a semi-synthetic penicillin, which is orally absorbed & categorized as a broad-spectrum antibiotic. It is widely used to treat a number of bacterial infections, this also include the treatment of gastric H. pylori infection & its complete eradication when it is combined with a secondary antibiotic & an acid-suppressing agent [6].The add on advantages of this delivery system is; it will reduce the dosing frequency of the dosage form and improves the patience compliance and also it will helps in providing the local action directly to the targeted site. [7]

Compared with the traditional formulations, IN – SITU gels are administered as low viscosity solutions & under the sensitive environment, the polymer changes its conformation producing a gel form, so it can not only increases the contact time between the drug and the absorptive sites in the stomach, but also the drug releases slowly and continuously, hence, it will be useful especially for those drugs which are used chronically. With this background, the present study is focused to develop a floating in-situ gel for the sustained delivery of AMOXICILLIN to improve its gastric residence time & there by reducing the dosing frequency and improving its bioavailability and also to determine the effect of different polymers and their composition difference on the floating oral in-situ gelling system.

II. EXPERIMENTAL SECTION

MATERIALS:

Amoxicillin was received as a gift sample from Ce-Chem Pharmaceuticals Pvt.Ltd (Bangalore). All other materials and chemicals used in the study were of Analytical grade.

METHOD:

Oral floating in-situ gel of Amoxicillin Trihydrate formulation coded F1-F9 were prepared by using below steps,

- Polymeric solution of different concentration 1.5% w/v, 2% w/v and 2.5 % w/v were prepared in around 30 ml deionized water & the solution was heated to 70°C while stirring it on the magnetic stirrer. Now appropriate amount of Guar gum, Bentonite and Sodium silicate is added to the beaker and the solution was heated to 90°C with stirring individually and cooled below 40°C.
- In another beaker Drug was dissolved in 10 ml of deionized water with continuous stirring and appropriate amount of calcium carbonate and sodium citrate is added to the beaker with continuous stirring.
- Now carefully add the drug solution in 2nd beaker to the 1st beaker containing polymeric solution at 40°C with continuous stirring and finally add the preservative (methyl paraben), colouring agent (sunset yellow) and sweetening agent (sodium saccharin) to the above solution. Then final volume was adjusted to 50 ml with deionized water with constant stirring.Now the resulting polymeric in-situ gelling system containing Amoxicillin trihydrate was transferred into the amber colored narrow mouth bottle and stored for further evaluation parameters.

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Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amoxicillin trihydrate	5%	5%	5%	5%	5%	5%	5%	5%	5%
Guar gum	1%	1%	1%	1%	1%	1%	1%	1%	1%
Sodium Alginate	1.5%	2%	2.5%	---	----	----	0.5%	1%	1.5%
Gellan gum	---	---	---	1.5%	2%	2.5%	1.5%	1%	0.5%
Calcium carbonate	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Sodium citrate	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
Bentonite	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
Sodium silicate	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
Methyl paraben	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Colouring agent.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Sodium saccharin	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Deionized water	upto 50ml	upto 50ml	upto 50ml	upto 50ml	upto 50ml	upto 50ml	upto 50ml	upto 50ml	upto 50ml

TABLE 1: Composition of Amoxicillin Oral Floating In-situ Gel.

Evaluation of the Dosage form:

Determination of pH:

The pH of all the formulations were measured by using a calibrated digital pH-meter at a room temperature and then the results were recorded as an average of three measurements.

Determination of viscosity:

Viscosity of all the samples was determined by using Brookfield Digital Viscometer LV- 4 spindle. 100ml of the formulation wastaken into sample holder and angular velocity increased gradually from 10 to 100 rpm. The torque value was found to be maximum at 100 rpm for the spindle LV-4, which has been selected for the entire study. The viscosity measurement was performed at room temperature.

Water uptake:

The in-situ gel which was formed in 50 ml of 0.1N Hcl (H 1.2) was used for this present study. The gel was separated from the buffer solution and it is blotted out using tissue paper; all the ideal formulations were prepared in the same way and it is weighed, it is considered as an initial weight of the gel. To this gel, 10 ml of the distilled water was added. After 30 minutes, the water is decanted and the gel is re-weighed. Now it is considered as final weight of the gel. By using the following formula, the water uptake was calculated.

Water uptake (%) = [Final weight – Initial weight] / [Initial weight]* 100

DRUG CONTENT:

Prepared 10 ml of the in-situ gel (containing equivalent to 500 mg of amoxicillin trihydrate) from different batches were measure and transferred to a 100ml volumetric flask of 0.1N HCL solution and stirred vigorously for 1 hour by using a magnetic stirrer. From this solution 1ml of sample was withdrawn and diluted to 10 ml with 0.1 N Hcl solution and the solution was then filtered using What-man filter paper and the drug content is determined by using U.V Visible Spectrophotometer at 272 nm against a suitable blank solution.

Gelling time:

Gelling time was determined by mixing each of the 5ml formulation with 0.1 N HCl (approx. 50 ml) pH 1.2 in a beaker and the gelation was assessed by visual examination. The time required for the detection of gelation of in situ gelling system is noted down as gelling time and the integrity of gel was also observed.

Gel strength:

50 ml of the formulation was placed in a 100 ml graduated cylinder and gelled by adding pH 1.2 buffer. Weight of 50 gm was placed onto the gel surface for measuring gel strength. Then gel strength, which is an indication of the ability of formed gel to maintain its integrity was measured, as time in seconds. The time taken by the weight to penetrate 5 cm down through the gel was noted down as gel strength.

In-Vitro Gelling Capacity:

The in-vitro gelling capacity of prepared formulations was measured by using visual method.5 ml of the gelation solution i.e. 0.1N Hcl of pH 1.2 was placed in a 15 ml borosilicate glass test tube and it was maintained at 37±0.5ºC temperature.One ml of the formulation solution was added to gelation solution by using pipette. The gelling capacity of the resulting solution is evaluated on the basis of stiffness of the gel formed.

Floating Behaviour:

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The time which is taken by the gel to reach the top from the bottom position of the dissolution flask is termed as **Floating lag time / buoyant time**. The floating lag time of the gel was determination by performing an visual inspection in a USP dissolution test apparatus, which contains 500 ml of 0.1 N Hcl (pH of 1.2) at temperature 37±0.5^0 C.

In vitro Drug Release:

In-vitro drug release studies were carried out by Type II USP dissolution test apparatus by using paddleand 500ml of 0.1N Hydrochloric acid as dissolution medium with 75rpm and temperature of 37 ± 0.5°C. Samples of 1ml volume were withdrawn at specified time intervals and diluted with 10 ml of 0.1N Hcl buffer and absorbance was measured by using a UV-Visible spectrophotometer at 272nm.

Drug release kinetic studies:

The drug release kinetic studies were done by various mathematical models and the model that best fits the release data is selected based on the regression coefficient (R^2) value in various models. The model that gives high 'R^2' value is considered as the best fit of the release data.

Stability studies:

The selected formulation will be subjected to stability studies as per ICH guidelines.

III. RESULTS AND DISCUSSIONS

1. Determination of absorbance maximum of Amoxicillin Trihydrate:

Absorbance maximum (λmax) of Amoxicillin trihydrate was determined using stock solution 0.1 N Hcl (ph 1.2). The solution was scanned over the wavelength range of 400 nm to 200 nm using UV-spectrophotometer against same dilutions as blank. The highest peak that is obtained from the spectrum analysis is been considered as an absorbance maxima and it was found to be 272.37 **nm**

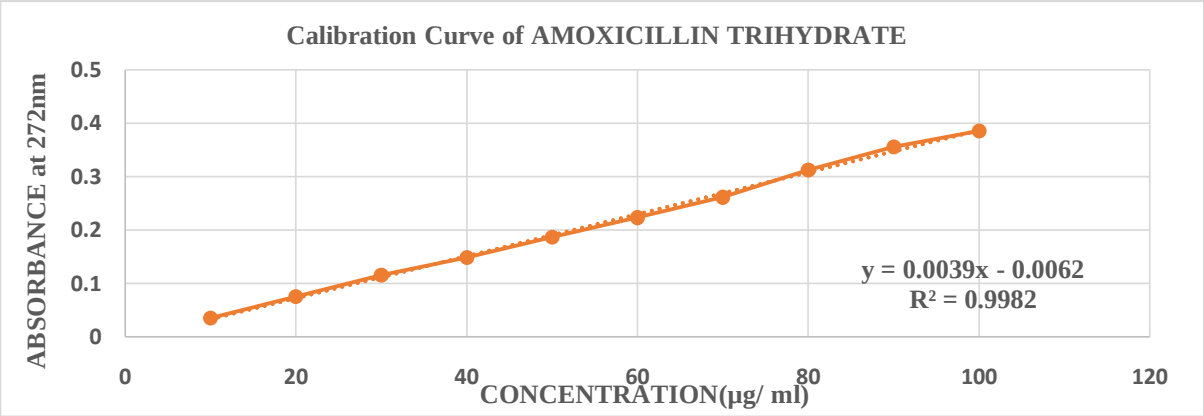

Fig.1 Calibration curve of Amoxicillin Trihydrate in 0.1N Hcl of pH 1.2

2. APPEARANCE:

All formulations were yellow-orange in colour. All formulations showed a smooth texture with good redispersibility with mechanical stirring indicating stability.

3. pH:

The pH of the formulations were found to be in the range of **7.00-7.5** which are well within the acceptable range i.e. 2.5 to 7.5.

4. VISCOSITY:

The formulation should have an optimum viscosity that will allow easy swallowing as a liquid, which then undergoes a rapid sol–gel transition due to ionic interaction.Results of viscosity studies shows that the viscosity of the formulations increased with an increase in polymer concentration and it is a consequence of increasing chain interaction with an increase in polymer concentration calcium carbonate which is the source of cations, increased the viscosity of the formulation.

The result obtained shows formulation consisting Gellan gum exhibit more viscosity in comparison to sodium alginate. The viscosity of all formulations was in the range of **22-34 cps** which was in the acceptable range. With this viscosity, a good flow of the suspension is seen and the pourability will be good.

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TABLE 2:ph and Viscosity of In-Situ Gelling formulations.

FORMULATION	pH	VISCOSITY(cps)
F1	7.1 ± 0.076	22 ± 0.50
F2	7.2 ± 0.100	24 ± 0.76
F3	7.5 ± 0.208	29 ± 0.52
F4	7.0 ± 0.322	27 ± 0.57
F5	7.2 ± 0.051	28 ± 0.47
F6	7.4 ± 0.044	34 ± 0.76
F7	7.3 ± 0.031	27.5 ± 0.32
F8	7.1 ± 0.060	26.2 ± 0.12
F9	7.3 ± 0.057	25.8± 0.27

5. WATER UPTAKE:

All the prepared formulations exhibited the property of water uptake due to the presence of polymers and also to the presence of the binder Guar gum and the values are seen in the range of 22.5% to 69.6 %. The release of the drug from the polymer matrix is highly dependent on the penetration of water into the matrix and simultaneously the release of drug will take place due to diffusion and as the concentration of the polymer increases, the water up taking capacity of the formulations also increases and up to some extent

6. DRUG CONTENT :

Drug content of the developed formulations that contains Amoxicillin trihydrate from F1 to F9 lies in the range of 96.2 ± 0.14% to 98.1 ± 0.8%, which were within the limit as specified in U.S.P. This study concludes that the drug is uniformly distributed in the formulation.

TABLE 3: Water Uptake and Drug Content of In-Situ Gelling Formulations.

FORMULATION CODE	WATER UPTAKE (%)	DRUG CONTENT (%)
F1	22.5	97.7 ± 0.47
F2	27.1	98.1 ± 0.105
F3	35.8	97.8 ± 0.83
F4	51.2	97.4 ± 1.01
F5	62.4	97.0 ± 0.89
F6	69.6	97.4 ± 0.52
F7	56.8	96.8 ± 0.29
F8	40.4	96.2 ± 0.14
F9	31.2	98.1 ± 0.88

7. Gelling time:

Gelling time of the formulations were determined by mixing each of the formulation with 0.1 N Hcl pH 1.2 in a beaker and the gelation was assessed by visual examination. Gelling time found to be vary according to the concentration of the polymer used proportionally.

8. In-Vitro Gelling Capacity:

Though gelation occurred instantaneously, the nature of the gels formed was dependent upon the polymer and $CaCO_3$ concentration. Low sodium alginate concentration (F1) formed weak gels which would not be able to withstand peristaltic waves of the GI tract and could not last longer than 8 hour. F2 to F5 and F7 to F9 shows intermediate gelling capacity and F6 shows excellent gelling capacity along with good gel strength. The In-vitro gelling capacity of the gel will be increased with the increase in the polymer concentration and this is due to increased polymer chain interaction.

9. Gel strength :

Gel strength was determined after mixing the formulation with 0.1 N Hcl (100ml). Gelation occurs due to the ion cross linking of the polymer chains by the divalent cations. Gel strength was directly proportional to the gelling capacity of the formulations, which is again depended on polymer concentration. As the concentration increased the gel strength was also found to be increased proportionally. The result obtained shows formulation consisting Gellan gum exhibit better gel strength in comparison to sodium alginate.

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TABLE 4: Gel strength, Gelling time & Gelling capacity of in situ gelling formulations.

Formulation code	Gelling time* (sec)	In-vitro Gelling Capacity	Gel strength
F1	14	+	Poor
F2	08	++	Good
F3	04	+++	Good
F4	21	++	Good
F5	11	++	Good
F6	06	+++	Excellent
F7	19	+++	Good
F8	17	++	Good
F9	16	++	Good

Gel strength study (in sec):

Poor = less than 10 sec
Good = 10-30sec
Excellent = 31 sec and above.

In-vitro Gelling capacity:

Gels after few minutes, dispersed rapidly (+)
Gelation immediate remains for few hours (++)
Gelation immediate remains for extended period (+++)

10. Floating Behavior:

a. **Floating Lag Time**:

The floating lag time of all the prepared formulations from F1 to F9 was determined by using the 1.2 pH buffer of 0.1N Hcl and the floating lag time was found to be in between 12 to 36 sec for the formulations.W.R.T. Floating lag time, we can conclude that the higher polymer concentrations will helps in the shortening of the time that is been taken by the formulation to float completely over the surface of the dissolution medium in agreement with other reports. This may be due to the higher cross-linking density at higher polymer concentrations, which could effectively trap the $C0_2$ bubbles so that density of the gel is reduced rapidly to induce buoyancy.

b. **Floating Duration**:

The floating duration of all the prepared formulations from F1 to F9 was determined by using the buffer 0.1N Hcl (pH 1.2) and it was found out that all the formulations were able to float for more than the period of 10 hours except F1 formulation(08 hrs.).

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TABLE 5: Floating lag time & floating duration of in situ gelling formulations.

Formulation code	Floating lag time (sec)	Floating duration (hrs.)
F1	29	08
F2	18	>10
F3	12	> 10
F4	36	>10
F5	23	> 10
F6	17	>10
F7	30	> 10
F8	23	>10
F9	26	> 10

11. IN-VITRO DRUG RELEASE STUDIES :

The 2 optimized formulations i.e. F5 and F9 showed significant burst release where approximately, 40-50% of amoxicillin was released within the first hr. In addition to this, some lag time is required for the release of ca^{2+} ions from $Caco_3$ and cross linking of the calcium ions with the polymer i.e. Sodium alginate or Gellan gum will plays a major role in the formation of the stiff barrier gel. The release profiles also depicted that all formulations release 50% or more of amoxicillin within the first four hours and the remaining amount released at a steady rate that declined with time till the end of the dissolution study.Increasing concentration of polymer from 1.5% - 2.5% resulted in the reduction of amoxicillin release rate. Higher polymer concentration levels reduced the release rate presumably due to the higher polymer density formed that could serve as an effective barrier across which the drug had to diffuse. Gellan gum based formulations exhibit delayed release rate of Amoxicillin in comparison to sodium alginate based formulations.

Table 6: In-vitro drug release studies of in-situ gelling formulations

Time (hour)	% Cumulative drug release*								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	75.9	47.7	32.4	68.3	40.1	24.7	30.9	54.9	39.8
2	81.1	60.6	42.6	77.2	46.5	28.5	36.5	58.8	45.7
3	86.2	65.7	55.4	83.6	50.3	36.2	44.9	69.3	51.2
4	91.3	69.3	58.5	86.2	57.6	51.2	55.4	75.4	64.9
5	97.2	77.2	66.2	93.9	65.7	58.2	67.5	79.0	72.6
6		84.2	70.3	97.7	76.5	68.5	74.3	87.3	81.5
7		94.9	77.2		88.8	73.4	83.7	95.2	89.2
8			93.2		93.9	84.9	90.5		92.6
9						88.7			
10						96.5			

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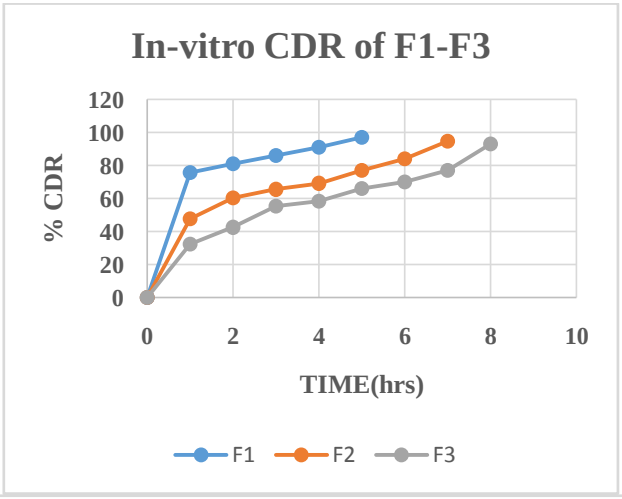

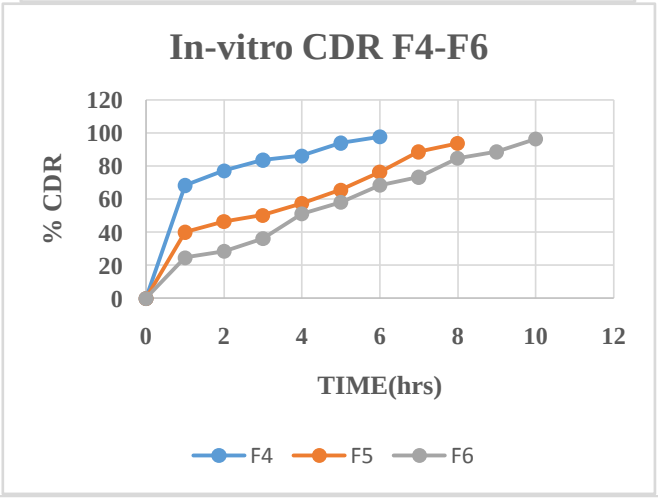

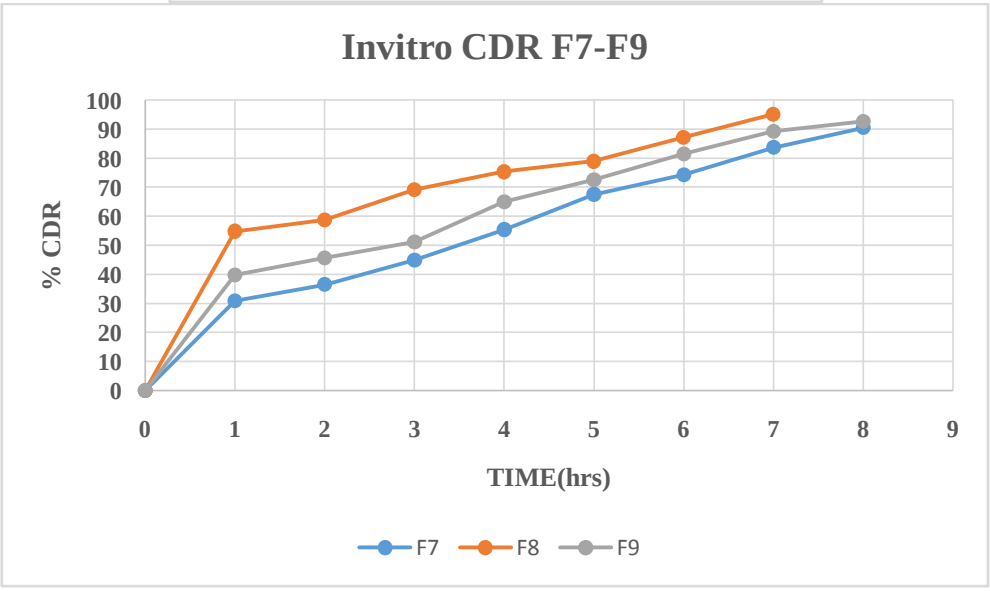

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12. KINETICS AND MECHANISM OF DRUG RELEASE:

From the tabulated data, we can observe that the drug release from the optimized formulations follows **Higuchi kinetic model** for drug release.From the data obtained from Korsmeyer-Peppas plot, the value of n was found to be higher than one (>1) which indicates that the mechanism of drug release is **Super case-2 transport**.

TABLE 7: Release Kinetics studies of in situ gelling formulations.

Code	Zero order	First order	Higuchi	Korsmeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	N	
F1	0.6353	**0.9236**	0.8756	0.1669	1.14	1st Order
F2	0.8145	0.892	**0.9665**	0.2295	1.17	Higuchi
F3	0.9087	0.8959	**0.9873**	0.2371	1.093	Higuchi
F4	0.6654	**0.9419**	0.8967	0.2044	1.21	1st Order
F5	0.9095	0.8877	**0.9589**	0.2284	1.08	Higuchi
F6	0.9699	0.8929	**0.9756**	0.6974	1.536	Higuchi
F7	0.9598	0.9123	**0.9729**	0.2497	1.12	Higuchi
F8	0.7706	0.89	**0.9467**	0.2235	1.17	Higuchi
F9	0.912	0.9639	**0.9871**	0.2319	1.10	Higuchi

IV. CONCLUSION

All the nine formulations of floating in-situ gelling system of Amoxicillin trihydrate were subjected to in-vitro drug release studies and also the other physiochemical parameters were subjected to evaluation studies.By considering all the evaluation parameters and their values, Formulation F5 and F9 were selected as Optimized formulations and the in-vitro drug release of these 2 formulations were found to be as **93.9 %** and **92.6 %** respectively in 8 hrs and these formulations were found to be following Higuchi kinetic model for drug release and follows Super case-2 transport mechanism.

By analyzing the results, we can conclude that the various properties of the prepared gelling system(such as gel strength & viscosity) were found to be directly proportional to the concentration of polymer that has been used in the formulation but the percentage of cumulative drug release is inversely proportional to the concentration of polymer. **Gellan gum** based formulations are considered to be the best formulations as compared to the Sodium alginate based formulations because of their effectiveness in controlling and sustaining the in-vitro drug release rate from the formulation but it has only one limitation i.e. it makes the formulation slightly more viscous than sodium alginate.

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