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Design development and evaluation of 5-fluorouracil gel

Reshma Bhanu Dudekula*, Venkata Ramana Bachu, Venkata Badarinath Atluri

Dr. K. V. Subba Reddy Institute of Pharmacy, Kurnool, Andhra Pradesh, India – 518218

A B S T R A C T

Controlled Drug Delivery Systems (CDDS) in recent years there has been a growing interest in subject of drug delivery and design and evaluation of controlled release systems. These are more sophisticated systems can be used as a means of altering the pharmacokinetic behavior of drugs in order to provide twice or once a day dosage. The basic approach used in development of Floating insitu gel is the use of natural gums which provide instantaneous viscosity in the presence of fluid and there by releasing on floating with the help of bicarbonates in stomach. 5-Fluorouracil is an anti-neoplastic agent used in the treatment of many types of cancers. Floating insitu gel of 5-Fluorouracil was prepared by using Sodium alginate, Guar gum by general orderly mixing methods. Change in the concentration of sodium alginate made the drug release changed to the extent of understanding. FTIR studies revealed that there is no chemical incompatibility between the drug and other excipients used in the formulation development.

Keywords: 5-Fluorouracil, Anti-Neoplastic, Sodium Alginate, Guar Gum

A R T I C L E I N F O

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***Corresponding Author**
Reshma Bhanu Dudekula
Dr. K.V. Subba Reddy Institute of Pharmacy, Kurnool,
Andhra Pradesh, India – 518218
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1. Introduction

Controlled release dosage forms are the convenient means to obtain a reduction of daily administration of drugs with fast absorption and elimination. Many controlled release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for longer period of time as well as to reduce

side effects. Oral controlled systems are mainly grouped into reservoir and matrix types [1]. However, gastrointestinal motility, a vigorous and variable phenomenon, presents a major impediment to the effectiveness of controlled delivery system [2]. A significant obstacle, which may rise, is the narrow absorption window for drug absorption in the GIT, stability problem or the poor solubility of drug in the GIT fluids. GIT has versatile pH areas starting with strong acidic in stomach, less acid to slightly alkaline in intestine and alkaline in colon. The residence of dosage form in stomach determines the power of gastric movements during both the digestive and inter-digestive phase and it is usually upto 2 hours. The small intestine transit is unaffected by food and is constant at 3 hours [3]. In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [4]. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. In the formulation of the FDDS, polymers play an important role. They not only hold the formulation ingredients together but also give a floating property and sustained release. The most commonly used polymersare HPMC and sodium alginate. HPMC comes in various grades like Methocel K4M, Methocel K50M, Methocel K100M, Methocel E4, Methocel E50, Methocel E100 etc. Which have their own characteristics based on their molecular weight.

2. Materials and Methods

Materials: 5-Fluorouracil, Guar Gum, Sodium Alginate, Sodium Bicarbonate, Calcium Chloride and deionized water. All the materials and chemicals are of analytical grade.

Methods:

Preformulation Studies

Drug - Excipient compatability studies by FTIR[5]:

- The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product.
- The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, and easy to administer and safe by FTIR spectroscopy, Compatibility with excipient was confirmed by carried out IR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.
- Compatibilitystudywasperformedbypreparingcompatibilityblendsatdifferent ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 40^0 C/75% RH. Control samples were stored at 40^0C. The ratio of drug to excipients varies from 1:1 to 1:10 depending on the purpose of use, and the samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 40^0C for a period of15 days.

Formulation

Formulation of Floating Gel [6]

First of all, active material (5-Fluorouracil) was passed from sieve # 22 while other ingredients were passed form sieve # 40.Then Sodium bicarbonate and 5-Fluorouracil (50 mg) was added to it while stirring so that there was proper and homogenous dispersion of the active material in the solution. In around 30% water in other beaker was heated to NMT 60°C on hot plate and dissolved sodium alginate in it. Cool it to 40°C then guar gum is added by stirring. This solution was added to drug solution or vice-versa. This solution was mix well. Volume was adjusted to 100% with distilled water. Finally, the mixture was mixed well to get the final preparation.

Evaluation

Evaluation of Floating Gel

***In-vitro* Floating Ability (*In-vitro* Buoyancy) [7]**

The *in-vitro* floating study was carried out using 900 ml of 0.1N Hcl .The medium temperature was kept at 37°C. Ten milliliter formulation was introduced into the dissolution vessel containing medium without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on surface of the dissolution medium (duration of floating) were note.

Figure 1: Photograph of floating Ability of 5-Fluorouracil gel

Determination of Drug Content [8]

Accurately, 10 ml of in-situ gel from different batches were measured and transferred to 100 ml of volumetric flask. To this 50-70 ml of 0.1 N Hcl was added and sonicated for 30 min. Volume was adjusted to 100 ml. Complete dispersion of contents were ensured, visually and filtered using Whatman Filter Paper. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1 N Hcl. Contents of 5-Fluorouracil was determined

spectrophotmeterically at 266 nm using double beam UV-Visible spectrophotometer.

Estimation of 5-Fluorouracil by UV Spectroscopy

Standard Solution: Accurately weighed 100 mg of 5-Fluorouracildissolved in 100 ml 0.1NHcl to get a solution containing 1000 mcg/ml.

Stock Solution:

From the standard solution, a stock solutions was prepared to give 10,20 30,40, 50 and 60 in 100 ml volumetric flasks. The volume was made upto the mark with 0.1N Hcl. These The absorbance of prepared solutions of5-Fluorouracil in0.1N Hcl were measured at 266 nm in UV spectrophotometer against an appropriate blank (0.1N Hcl).The absorbance data for standard calibration curves are given in table-00.standard calibration curve yields a straight line, which shows that the drug follows Beer's law in the concentration range of 10-50 mcg/ml.

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Theoretical drug content

Theoretical drug content was determined by calculation assuming that the entire 5-Fluorouracil present in the polymer solution used gets entrapped in 5-Fluorouracil floating gel

Actual drug content

Procedure: Practical drug content was analyzed by using the UV Spectrophotometer, by taking weighed amount of 5-Fluorouracil floating gel.

***In-vitro* Gelling Capacity [9]**

To evaluate the formulations for their *in-vitro* gelling capacity by visual method, colored solutions of gel forming drug delivery system were prepared. The *in-vitro* gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N Hcl,) in a 10 ml borosilicate glass test tube and maintained at 37±1ºC temperature. One ml of colored formulation solution was added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which the formed gel remains as such. The *in-vitro* gelling capacity was graded in three categories on the basis of gelation time and time period for which the formed gel remains.

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for 12 hours

(+++) Gelation immediate remains for more than 12hours.

PH Measurement [10]

The pH was measured in each of the solution of sodium alginate based In situ solutions, using a calibrated digital pH meter at 27°C.

Measurement of Water Uptake by the Gel [11]

The water uptakes by the gel of the selected formulations of sodium alginate were determined by a simple method. In this study the in situ gel formed in 40ml of 0.1 N Hcl (pH 1.2) was used. From each formulation the gel portion from the 0.1 N Hcl was separated and the excess Hcl solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10 ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated and reported.

***In-vitro* Drug Release Studies and Drug Release Kinetics for Floating Gel [12]**

In vitro dissolution studies of 5-Fluorouracil floating beads and floating gel were carried out in USP1 tablet dissolution test apparatus-II employing a basket at 50 rpm using 900ml of 0.1N Hcl at 37±0.5ºC as dissolution medium. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 281nm using UV-Visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicate. The results of in vitro release profiles obtained for all the 5-Fluorouracil formulations were fitted into four models of data treatment as follows:

Figure 2: Dissolution Apparatus

- Cumulative percent drug released versus time (zero-order kinetic model).
- Log cumulative percent drug remaining versus time. (First-orderkineticmodel).
- Cumulative percent drug released versus square root of time (Higuchi'smodel).
- Log cumulative percent drug released versus log time (Korsmeyer-Peppasequation).

Zero Order Kinetics: A zero-order release would be predicted by the following equation.

$At = A_0 - K_0t$ …1

Where:

At = Drug release at time t

A0 = Initial drug concentration

K0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if

The plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

First Order Kinetics: A first-order release would be predicted by the following equation

$\text{Log } C = \text{Log } C_0 - Kt/ 2.303 \ldots 2$

Where:

C = Amount of drug remained at time t

C_0 = Initial amount of drug

K = First-order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slope values.

Higuchi's Model:

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = Kt_{½} \ldots 3$$

When the data is plotted according to equation-3 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to K.

Korsmeyer and Peppas Model:

The release rates from controlled release polymeric matrices can be described by the equation (5) proposed by korsmeyer *et al*.

$Q = K_1 t^n \ldots . 5$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism. For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.8980.

3. Results and Discussion

Preformulation Studies

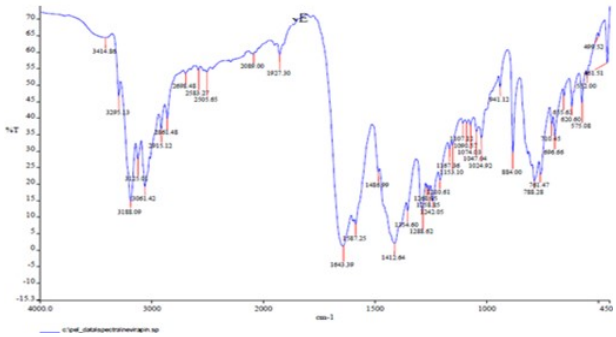


Figure 3: FTIR of 5-Fluorouracil

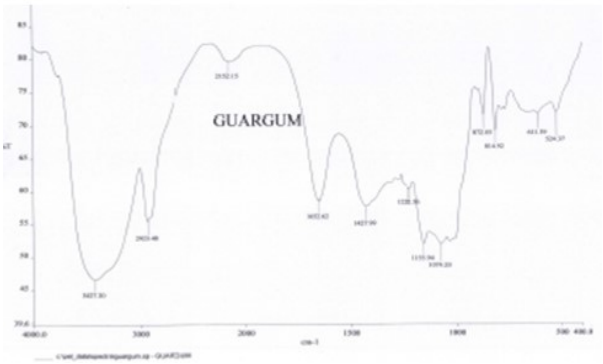


Figure 4: FTIR of Guar Gum

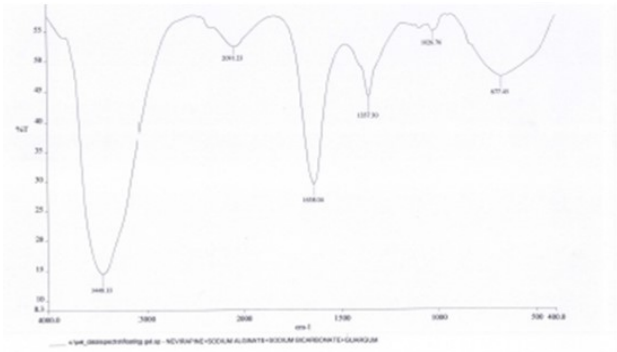


Figure 5: FTIR of 5-Fluorouracil Floating Gel

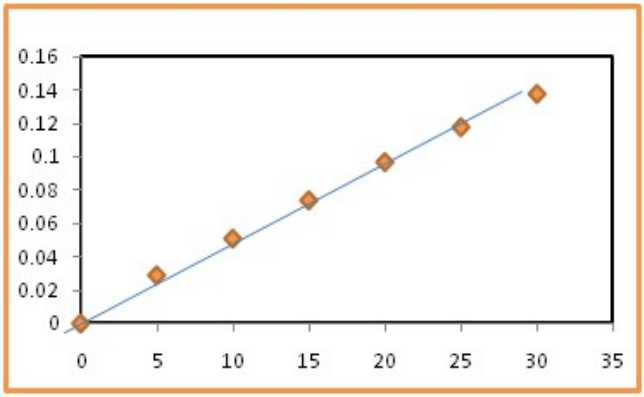
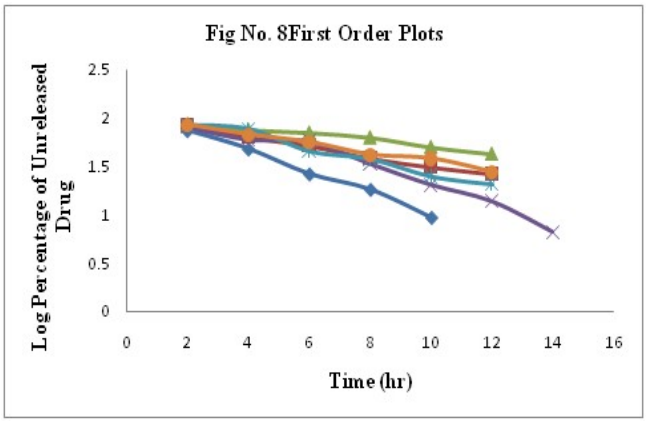
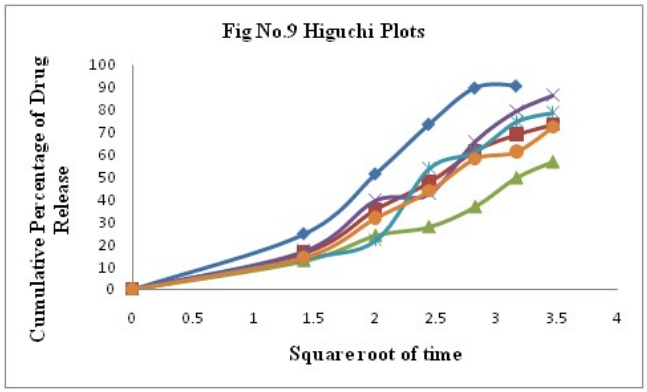
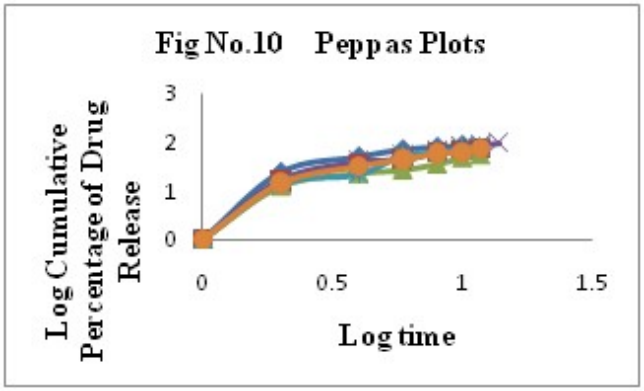


Figure 6: Calibartion Curve of 5-Fluorouracil

Dissolution Profiles of 5-Fluorouracil Floating Gel







Discussions

The Floating drug delivery system of gel of 5-Fluorouracil was prepared and evaluated to increase its overall bioavailability. In the present study 8 formulations with variable concentrations of Guar gum, Sodium alginate, Sodium bicarbonate and drug kept constant throughout preparation of formulations. In the present study 5-Fluorouracil floating gel also prepared by using polymer Sodium alginate with variable concentrations, Guar gum and drug kept constant. Floating gel formulations are prepared and evaluated invidually the floating ability and *in-vitro* drug release of floating 5-Fluorouracil gel.

Compatability study of Floating Gel

FTIR spectrum of 5-Fluorouracil, Sodium alginate, Guar gum and Floating Gel formulations were shown in **figures 3-5**. FTIR spectrum peaks were observed with individual compounds have remain unaffected in floating gel formulations indicates Gel formed were not a chemical reaction product, hence, the drug exists in original form and available for the biological action.

Evaluation Parameters of Floating gel:

In vitro floating studies were performed by placing floating gel in the beaker containing 900 ml of 0.1N Hcl maintained at a temperature of 37±0.5ºC. The floating lag time and floating time was noted visually. Floating lag time of gel for all the formulations ranges from 15 to 35 seconds. All the formulations shown less lag time to float. This parameter is shown in table 2 .All the formulations designed and shown to float 14 to 15 hrs to increase drug release for extended period of time. It is shown in table 6. All the formulations exhibited excellent floating ability, the different lag time observed due to different polymer concentration and drug content of the gel. Increase in polymer concentration, floating lag time also increased. Percentage Drug Content of floating gel ranges from 73.62 to 93.12.

Gelling capacity of the gel formulations was observed that all the formulations possess the ability to jellify due to the gums present in the formula and the gelling capacity was depend upon the quantity of the gum in the formulations. Increase in the concentration of Guar gum made the formulations more viscous and more ability to convert the material into strong gelling substance. Percentage Drug Content of floating gel ranges from 73.62 to 93.12 respectively; these parameters are shown in the table 4 .Drug content also affected by various parameters. On increasing % concentration of sodium alginate, the percentage of drug loading increased, but not at all other ingredients concentration.

The P^H of all the formulations ranges between 7.34 to 7.64 showing favorable values for drug release in gastric area. The property of residence of the drug and its stability is dependent of P^H which showed the supportable results. The drug release from the formulations was favoured by the values. Water uptake capacity of the gel was determined and produced satisfied results for the formulations to form enough viscous gels to release the drug and to float. Among all the formulations that is form G1-G8, as the concentration of gums increased the water uptaking capacity is also increased. The release of bicarbonates to be get floated depends on the water uptaking capacity of the gels.

In-vitro drug release studies of 5-Fluorouracil gel formulations was studied by USP 1 dissolution apparatus. Drug release was found to be highest G4. Drug release impeded in the following formulations G8 and G5.Cumulative release of 5-Fluorouracil was decreased with increase in sodium alginate concentration. The most retardant drug release effect observed indicates that the release rate is controlled by gel thickness: an increase in polymer ratio will increase the gel thickness surrounding the drug particles, thereby increasing the distance travelled by the drug through the gel causing a greater impedance to drug release. The release was found to be steady and extended upto14 hrs.

To ascertain the drug release mechanism and release rate, data of the above formulations were model fitted by using regression values. The models selected were Zero order, First order, Higuchi Matrix, Korsemayer Peppas, and Interpretation of data was based on the value of the resulting regression coefficients. The in vitro drug release showed the highest regression coefficient value for zero order models indicates diffusion to be the predominant mechanism of drug release. All the formulations follow zero order. In floating gel formulation, Most of the formulations shown n value > 0.5 it indicates drug release is by non ficknian mechanism. These data were shown in table3. .Among all formulation G4 and G8 was found to be the best formulation as it release 5-Fluorouracil in a

sustained manner with constant fashion over extended period of time (14hr).The evaluation parameters of floating gel of 5-Fluorouracil for the following parameters Floating lag time, Duration of floating, *in-vitro* drug release. Among floating gel formulations G4 is the best formulation..

Table 1: Formulation Table for Floating Gel

S.NO	Ingredients	G1	G2	G3	G4	G5	G6	G7	G8
1.	5-Fluorouracil	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
2.	Sodium alginate	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%
3.	Guar Gum	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
4.	Sodium bicarbonate	2%	2%	2%	2%	2%	2%	2%	2%
5.	Purified water	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Table 2: Calibration Curve of 5-Fluorouracil

Concentration (µg)	Absorbance (nm)
0	0
10	0.029
20	0.051
30	0.074
40	0.097
50	0.118
60	0.138

Table 3: Evaluation Parameters of Floating Gel

Formulation Code	Drug Content (%)	Floating lag time (min)	Duration of Buoyancy (hr)	P^H	Gelling Studies
G1	79.67	15	14	7.50	+
G2	88.62	20	15	7.54	++
G3	93.12	27	14	7.64	++
G4	75.74	30	14	7.51	+++
G5	78.91	35	14	7.42	+++
G6	73.62	32	14	7.34	+++
G7	74.56	22	14	7.38	+++
G8	76.82	26	15	7.46	++

Table 4: Water Uptake by the Gel

Formulation Code	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**	**G7**	**G8**
Initial weight (gm)	10	10	10	10	10	10	10	10
Time (hr)	% Water gain							
0	0	0	0	0	0	0	0	0
0.5	2.179	3.716	4.067	5.719	6.723	5.671	6.671	6.183
1	3.176	3.967	4.567	6.128	7.123	6.217	6.923	6.829
1.5	3.392	4.127	5.128	6.319	7.271	6.789	7.191	7.453
2	4.176	4.394	5.217	6.798	7.918	6.917	7.817	7.932

Table 5: In-vitro Drug Release of Floating Gel

	Time vs Cumulative Percentage of Drug Release						
FC	**2hr**	**4hr**	**6hr**	**8hr**	**10hr**	**12hr**	**14hr**
G1	24.612	51.32	73.47	89.69	90.61	-	-
G2	16.17	35.56	47.61	61.72	68.96	73.41	81.36
G3	12.62	23.910	27.73	36.712	49.61	56.72	68.34
G4	16.95	39.51	42.40	65.71	79.21	86.21	93.72
G5	13.71	21.67	53.67	61.21	74.61	78.67	87.12
G6	14.16	31.76	43.71	58.21	61.36	72.31	79.56
G7	13.23	29.66	39.99	56.58	62.20	69.31	78.62
G8	15.42	32.84	46.51	57.32	67.14	74.35	88.56

Table 6: First Order Drug Release

	Time VS Log Percentage of Unreleased Drug						
FC	**2**	**4**	**6**	**8**	**10**	**12**	**14**
G1	1.877	1.687	1.42	1.26	0.972	-	-
G2	1.92	1.80	1.71	1.58	1.49	1.42	1.62
G3	1.94	1.88	1.85	1.80	1.70	1.63	0.63
G4	1.91	1.78	1.76	1.53	1.31	1.13	0.82
G5	1.93	1.89	1.66	1.58	1.40	1.32	1.10
G6	1.93	1.83	1.75	1.62	1.58	1.44	1.21
G7	1.91	1.79	1.66	1.63	1.54	1.51	1.28
G8	1.92	1.87	1.71	1.59	1.55	1.58	1.39

Table 7: Higuchi Drug Release

	Square root of time VS Cumulative Percentage of Drug Release						
FC	**1.41**	**2**	**2.44**	**2.82**	**3.16**	**3.46**	**3.74**
G1	24.61	51.32	73.47	89.69	90.61	-	-
G2	16.17	35.56	47.61	61.72	68.96	73.41	81.36
G3	12.62	23.91	27.73	36.71	49.61	56.72	68.34
G4	16.95	39.51	42.40	65.71	79.21	86.21	93.72
G5	13.71	21.67	53.67	61.21	74.61	78.67	87.12
G6	14.16	31.76	43.71	58.21	61.36	72.31	79.56
G7	14.16	31.76	43.71	58.21	61.36	69.31	78.62
G8	14.16	31.76	43.71	58.21	61.36	74.35	88.56

Table 8: Peppas Drug Release

	Log time VS Log Cumulative Percentage of Drug Release						
FC	**0.30**	**0.60**	**0.77**	**0.90**	**1**	**1.07**	**1.14**
G1	1.39	1.71	1.86	1.91	1.95	-	-
G2	1.20	1.55	1.67	1.79	1.83	1.86	1.88
G3	1.10	1.37	1.44	1.56	1.69	1.75	1.76
G4	1.22	1.59	1.62	1.81	1.89	1.93	1.97
G5	1.13	1.33	1.72	1.78	1.87	1.89	1.90
G6	1.15	1.50	1.64	1.76	1.78	1.85	1.86
G7	1.13	1.48	1.46	1.68	1.81	1.79	1.84
G8	1.14	1.39	1.52	1.56	1.79	1.81	1.82

Table 9: Drug Release Kinetics

FC	**Zero order**		**First order**		**Higuchi**		**Peppas**	
	R^2	**K_0%hr$^-$**	**R^2**	**K_1%hr$^-$**	**R^2**	**K_H%hr$^-$**	**R^2**	**n**
G1	0.966	30.754	0.9961	0.2187	0.9878	86.46	0.9838	0.32
G2	0.9768	22.32	0.9964	0.127	0.9946	75.68	0.9881	0.34
G3	0.992	13.004	0.9841	0.069	0.9806	44.069	0.9911	0.42
G4	0.9819	25.97	0.9793	0.1583	0.9887	88.06	0.9867	0.21
G5	0.9671	9.16	0.9876	0.0483	0.9768	31.07	0.9741	0.35
G6	0.9833	20.26	0.9931	0.1139	0.9913	68.69	0.9904	0.77
G7	0.973	19.32	0.9792	0.0395	0.9811	38.21	0.9812	0.61
G8	0.981	17.88	0.9813	0.0124	0.9825	41.52	0.9847	0.58

4. Conclusion

Floating gel of 5-Fluorouracil showed excellent floating ability, good buoyancy and prolonged drug release. Erosion and Diffusion was found to be the main release mechanism scale up leading to floating alginate gel beads of 5-Fluorouracil for effective management of metastatis. These beads were capable of reducing the frequency of administration and dose dependent side effects associated with the repeated administration of conventional 5-Fluorouracil Tablets. From the compatibility studies, it was concluded that, Sodium alginate, Guar gum 5-Fluorouracil were compatible and thus suitable for the formulation of 5-Fluorouracil floating gel. In vitro buoyancy studies were performed for all the formulations, by using 0.1N Hcl solutions .All the formulations were floated. The formulation containing Sodium bicarbonate showed more floating time. In vitro dissolution studies were also performed for all formulations. The formulations showed the sustained release for 16 has compared to floating gel. Thus all formulations of floating were identified as ideal batch based on its results. Finally, it was concluded that Floating alginate beads shown extended drug release by 14-15 hours floating. The developed floating gel of 5-Fluorouracil may be used in clinic for prolonged drug release for at least 16 h, thereby improving the bioavailability and patient compliance.

5. References

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