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FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE IN *SITU* GEL DRUG DELIVERY PATTERN OF IBUPROFEN

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ABSTRACT

The objective of the present work is to design and development of floating *in situ* gel containing Ibuprofen in order to achieve an extended retention in the upper GIT, which may enhance the absorption and thereby improved bioavailability. Floating *in situ* gel of Ibuprofen were prepared by ionic gelation method using Sodium Alginate, Gellan Gum, HPMC K 4M. The prepared *in situ* gel were evaluated for various parameters like physical appearance, *in vitro* gelation study, viscosity, *in vitro* floating study, drug content, water uptake by the gel, density, gel strength, *in vitro* drug release study, *in vitro* drug release kinetics and stability study. FT-IR study confirmed the drug-polymer compatibility. All Floating *in situ* gel formulations showed optimum pH in the range of 7.53 - 7.64 and optimum density of less than~1.004g/cm^3. Among all formulations, F3 (0.2% of Gellan gum) and F6 (0.2 % of HPMC K4M) showed shorter floating lag time and longer total floating time and also drug release rate (75.59% in 8hrs and 76.79% in 8hrs), hence it is considered as the best formulation. The data obtained in this study thus suggests that the floating *in situ* gel of Ibuprofen are promising for sustained drug delivery which can be used for reducing dosing frequency.

KEYWORDS

Ibuprofen, Sodium alginate, Gellan gum, HPMC K4 M, *Insitu gel* and Sustained drug delivery.

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INTRODUCTION

Oral drug delivery is one of the simplest routes of delivery of drugs for systemic effect. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit. Variable gastric emptying leads to no uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the

upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed[1]. These reasons are made the researchers to develop a drug delivery system which can be retained in stomach for longer duration. Dosage forms that can be retained in stomach for longer periods of time are called gastro retentive drug delivery systems (GRDDS). GRDDS are suitable and beneficial for such drugs by improving their absolute bioavailability, therapeutic efficiency, increase gastric residence time (GRT), possible reduction of the dose, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment[2]. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Improved bioavailability can be achieved by prolonged gastric retention, it also reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Floating drug delivery systems meant for gastric retention, float on the surface of the gastric fluids, due to their low density and produce a prolonged effect. Floating drug delivery system (FDDS) is an effective technology to extend the gastric residence time in order to improve the bioavailability of the drugs[3]. To achieve the sustained drug delivery, floating In-situ gel has been introduced. In-situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner keeps relatively constant plasma profiles. The in-situ gel dosage form is a liquid before administration and after it comes in contact with gastric contents gets converted to gel which floats on gastric contents[4]. The concept of floating *in situ* gel can also be utilized to reduce the irritant effect of weakly acidic drugs on the stomach by avoiding direct contact with the mucosa and providing a mean of getting low dosage for prolonged periods[4]. Ibuprofen (IBU) is a well-established nonsteroidal anti-inflammatory drug (NSAID) used for a variety of pain and inflammatory conditions such as musculoskeletal disorders (e.g. rheumatoid arthritis and juvenile rheumatoid arthritis).

Ibuprofen is classified by BCS as a Class II API as it presents low solubility and high permeability[5]. Being a weak acid, pKa 4.91, the drug is well absorbed from the upper portion of the duodenum. Therefore, a floating *in situ* system is expected to produce a sustained release of the drug[6].

Objective of the present study

- To carry out the preformulation studies
- To study drug and polymer compatibility by using FTIR.
- To formulate ibuprofen gastro retentive floating in situ gel.
- To carry out characterisation of floating *in situ* gel of Ibuprofen
- To carry out *In-vitro* evaluation of the prepared gastro retentive floating *in- situ* gel containing ibuprofen.
- To carry out the stability studies of selected formulations as per ICH guidelines.

MATERIAL AND METHODS

Materials

Ibuprofen (Apotex Research PVT. LTD. (Gift sample), Sodium alginate, HPMC K4M, Gellan gum, Calcium carbonate, Methyl paraben, Propyl paraben, Sodium sachharine (Yarrow chem products Mumbai).

Methods

Preparation of *insitu gel*

Methodology

Floating *in situ* gel of Ibuprofen was prepared by ionic gelation method.

Polymers was dissolved in around 40ml water. Then 2g $CaCO_3$ was added to it while stirring so that there was proper and homogenous dispersion. Ibuprofen was dissolved in this solution. In around 30ml water in other beaker was heated to NMT 60^{o}C on hot plate and to it sodium alginate was dissolved. It was cooled to 40°C. This solution was added to HPMC solution. This solution was mixed well. Final volume was made up to 100ml with distilled water. Finally, it was stirred and mixed well to get the final preparation.

Preformulation Studies

Organoleptic Properties[7]

The colour, odour and taste of the drug were characterized and recorded.

Solubility studies[8]

Preformulation solubility analysis has been done to select a suitable solvent system to dissolve the drug and to test the solubility in the dissolution medium to be used.

Solubility of ibuprofen was determined various solvents like water, ethanol, methanol, acetone etc.

Melting Point[8]

Melting point determination of the drug sample has been done by an open capillary method.

SPECTROSCOPIC STUDIES

Determination of λmax

The stock solution of Ibuprofen (100µg/ml) is prepared by using 0.1N Hydrochloric acid pH 1.2. This solution was appropriately diluted with 0.1N Hydrochloric acid pH 1.2 to obtain 10µg/ml. This solution was scanned between 200-400nm in UV visible spectrophotometer, to obtain λmax.

Standard Calibration Curve of Ibuprofen

Standard stock A (1000µg/ml)

Standard stock solution B (100µg/ml)

Aliquots of 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml, 3ml from standard solution C was diluted to 10ml with 0.1N of HCl to give concentration of 5, 10, 15, 20, 25, 30µg/ml. The absorbance of these solutions will be measured with UV-VIS spectrophotometer at λmax (221nm)[9].

Drug excipeint compatibility study

The FTIR spectra of the drug with polymers were compared with the standard FTIR spectrum of the pure drug. For determining the compatibility of drug with polymers, IR spectra of pure ibuprofen, pure polymers such as Gellan gum, HPMC K4M, physical mixture of drug and polymer were taken[10].

CHARACTERIZATION OF THE PREPARED FLOATING *INSITU* GEL

Physical appearance and pH

All the prepared alginate based *in situ* solutions of Ibuprofen were checked for their physical appearance. The pH of the developed gel base was measured on a standardized digital pH meter at room temperature by taking adequate amount in a 50ml beaker[11].

Determination of viscosity

The viscosities of formulation are determined by brook field viscometer.

In vitro floating study:

10ml of the prepared in situ gelling formulation were withdrawn with disposable syringe and transferred into the dissolution vessel containing simulated gastric fluid. The time taken by the formulation to emerge on the medium surface (floating lag time, FLT) and the total time formulation constantly floated on the dissolution medium surface (duration of floating, TFT) were recorded[12].

***In vitro* gelation study**

5ml of the simulated gastric fluid (0.1N HCl, pH 1.2) in a 15ml test tube maintained at 37ºC followed by the addition of 1ml of the formulation using a pipette. The pipette was positioned facing the surface of the fluid in the test tube and slowly the formulation was released from the pipette. When the formulation came in contact with the gelation medium, it was quickly converted into a gel-like structure. On the basis of stiffness of gel as well as the duration, for which the gel remains as such the *in vitro* gelling capacity was investigated[13].

The *in vitro* gelling capacity was mainly divided into three categories based on gelation time and time period formed gel remains.

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for 12 hours

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

Measurement of gel strength

30g of the gel was taken in a 50ml beaker and a 50g weight was placed on the centre of the surface of the gel and allowed to penetrate through the gel. The total time taken by the 50g weight to penetrate down 5cm through the gel was noted for all the formulations. The same method was followed for 6 times for each fresh formulation and average time was noted[14].

Measurement of density of gel

30ml of the *in situ* formulation was poured into a beaker containing 50ml of 0.1N HCl. 10ml of the gel formed was taken in measuring cylinder and weight of the gel was measured. By using the gels weight and volume, density of the gel was calculated. This method was followed for all the formulations[15].

Determination of drug content

The formulation of 10ml equivalent to 300mg of drug was added to 80ml of 0.1N HCl, pH1.2 and stirred for 1h on magnetic stirrer. The solution was filtered, suitably diluted to 100ml with 0.1N HCl and drug concentration was determined using UV Visible Spectrophotometer at 221nm against a suitable blank solution[16,17].

$$\text{Drug content (\%)} = \frac{\text{Concentration from the std graph} \times \text{DF}}{1000} \times 100$$

DF=Dilution factor

***In vitro* dissolution study**

The dissolution studies were conducted in triplicate by using a type II (paddle method) dissolution apparatus. The dissolution medium used was 900ml of 0.1 N HCl (pH 1.2), maintained at 37ºC. The stirring rate was adjusted to 50rpm. At predetermined time intervals, 10mL samples were withdrawn and replaced by fresh dissolution medium, filtered through Whatman filter paper, diluted, and assayed at maximum absorbance using UV-Visible Spectrophotometer[18].

Stability studies

The stability study of the floating *in situ* gel was determined by *in vitro* buoyancy, drug content, *in-vitro* drug release study. The selected batch was packed in an aluminium foil and was kept in a Petri dish at room temperature (25 ± 2ºC and 60 ± 5% RH) an accelerated temperature (40 ± 2ºC and 70 ± 5% RH) for a period of 90 days[19-22].

RESULTS AND DISCUSSION

The aim of the study was to formulate and characterise the floating *in situ* gel of Ibuprofen by ionic gelation method by using different concentrations of sodium alginate and gellan gum and HPMC K4M. A total of six formulations were prepared and evaluated. Formulations F1-F3 were prepared with different concentration of gellan gum and formulations F4-F6 were prepared with different concentration of HPMC K4M. The prepared floating *in situ* were subjected to pH, *in vitro* gelation study, viscosity, *in vitro* floating study, drug content, water uptake by the gel, density, gel strength, *in vitr*o dissolution study, Release kinetics studies and stability study. The λmax and calibration curve were plot for the drug. It showed maximum absorbance at 221nm. The FTIR studies for drug and drug with polymer showed no possible interaction. The drug content was found to be in the range of 77.14% ± 0.13 % to 86.80% ± 0.03%. The percentage cumulative drug release of the formulation (F1-F3) ranged from to 75.59% to 90.58%, formulation (F4-F6) ranged from 76.79% to 91.92%. The density of the all the formulation was lesser than density of gastric contents. Hence promotes the floating of in situ gel in the stomach. The formulation F3 and F6 exhibited good gel strength which is observed in very higher values of 73 sec and 69 sec which has the higher concentration of gellan gum and HPMC K4M. Gel strength signifies the capacity of the gelled mass to withstand the peristaltic movement *in vivo*. Short-term stability studies of the formulations indicate that there are no significant changes in the appearance, drug content, percentage cumulative release, floating and dissolution parameter values after 90 days of storage at 25 ± 2ºC with 60 ± 5% RH and 40 ± 2ºC with 70 ± 5% RH.

Table No.1: Formulation design for Ibuprofen floating *in situ* gel

S.No	FC	Ibuprofen (gm)	Sodium alginate (gm)	Gellan gum (mg)	HPMC K4 M (mg)	$CaCO_3$ (gm)	Methyl paraben %	Propyl paraben %	Sodium saccharine %	Distilled water q.s (ml)
1	F1	3	2	100		2	0.02	0.2	0.2	100
2	F2	3	2	150		2	0.02	0.2	0.2	100
3	F3	3	2	200		2	0.02	0.2	0.2	100
4	F4	3	2		100	2	0.02	0.2	0.2	100
5	F5	3	2		150	2	0.02	0.2	0.2	100
6	F6	3	2		200	2	0.02	0.2	0.2	100

Table No.2: Calibration Curve for Ibuprofen

S.No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.02 ± 0.002
3	10	0.041 ± 0.017
4	15	0.062 ± 0.010
5	20	0.084 ± 0.011
6	25	0.106 ± 0.012
7	30	0.128 ± 0.015

Table No.3: Drug content

S.No	Formulation code	Drug content (%)	Gel Strength (sec)	3 Density (g/cm)
1	F1	81 ± 0.09	61 ± 0.13	0.666 ± 0.0120
2	F2	83.17 ± 0.14	68 ± 0.10	0.679 ± 0.0091
3	F3	86.60 ± 0.03	73 ± 0.22	0.689 ± 0.0102
4	F4	77.14 ± 0.13	49 ± 0.03	0.657 ± 0.0021
5	F5	79.04 ± 0.02	51 ± 0.51	0.657 ± 0.0062
6	F6	82.69± 0.01	69 ± 0.01	0.663 ± 0.0126

Table No.4: Percentage cumulative drug release (%CDR)

S.No	Time	Percentage cumulative drug release (%CDR)					
		F1	F2	F3	F4	F5	F6
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	0.25	13.48	3.63	3.23	8.82	6.81	4.09
3	0.5	17.01	7.10	6.48	13.36	8.40	5.26
4	0.75	21.25	13.72	13.35	18.06	14.40	11.08
5	1	30.41	22.79	20.18	24.52	22.05	21.16
6	2	40.71	30.15	27.70	32.54	28.89	25.42
7	3	53.50	39.74	39.13	39.44	36.60	34.41
8	4	60.86	49.97	45.41	46.37	41.86	43.29
9	5	66.75	58.87	54.74	58.83	53.65	52.21
10	6	75.81	68.90	62.40	70.40	65.09	60.22
11	7	84.41	80.82	69.92	82.77	75.12	69.43
12	8	90.58	88.14	75.59	91.92	86.64	76.79

Table No.5: Pre-Formulation Studies

S.No	Formulation code	Physical appearance	pH	Gelling capacity	Viscosity (cps)	Floating lag time (sec)	Total floating time (hrs)
1	F1	Creamy white	7.53± 0.01	+++	1210 ± 0.01	7	> 24
2	F2	Creamy white	7.54 ± 0.01	+++	1370 ± 0.01	7	> 24
3	F3	Creamy white	7.56 ± 0.03	+++	2920 ± 0.2	5	> 24
4	F4	Creamy white	7.63 ± 0.01	+++	771 ± 0.03	6	> 24
5	F5	Creamy white	7.63 ± 0.04	+++	979 ± 0.32	5	> 24
6	F6	Creamy white	7.64 ± 0.03	+++	1570 ± 0.25	4	> 24

Table No.6: Formulation Studies

S.No	Formulation code	Time (Days)		Appearance	pH	Drug Content (%)	Gelling Capacity	Floating lag time	% CDR at time 8hour
1	F3	0		Creamy white	7.56	86.60	+++	5	75.59
2	F6	0		Creamy white	7.64	82.69	+++	4	76.79
3	F3	30	At 25 ±2°C/ 60±5%RH	Creamy white	7.64	82.69	+++	4	76.79
			At 40±2°C/ 70±5%RH	Creamy white	7.53	86.12	+++	5	74.83
4	F6	30	At 25 ±2°C/ 60±5%RH	Creamy white	7.52	82.12	+++	5	76.18
			At 40±2°C/ 70±5%RH	Creamy white	7.38	81.73	+++	6	75.83
5	F3	90	At 25 ±2°C/60± 5%RH	Creamy white	7.49	85.61	+++	6	74.23
			At 40± 2°C/70±5% RH	Creamy white	7.41	85.13	+++	7	73.95
6	F6	90	At 25 ±2°C/60± 5%RH	Creamy white	7.35	82.07	+++	5	75.89
			At 40±2°C/ 70±5% RH	Creamy white	7.27	81.79	+++	6	75.65

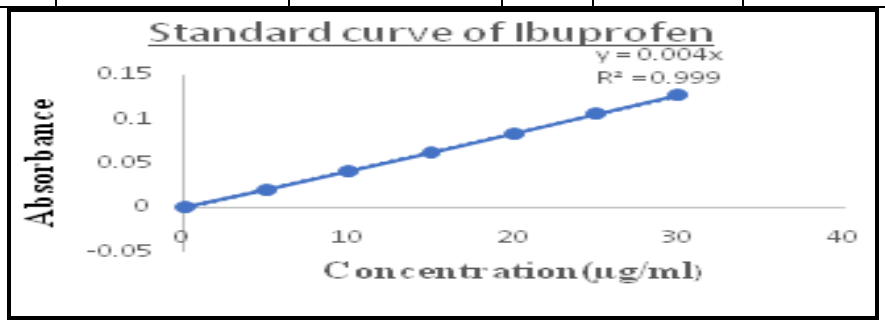

Figure No.1: Calibration curve of Ibuprofen

Drug excipient compatibility study by FTIR

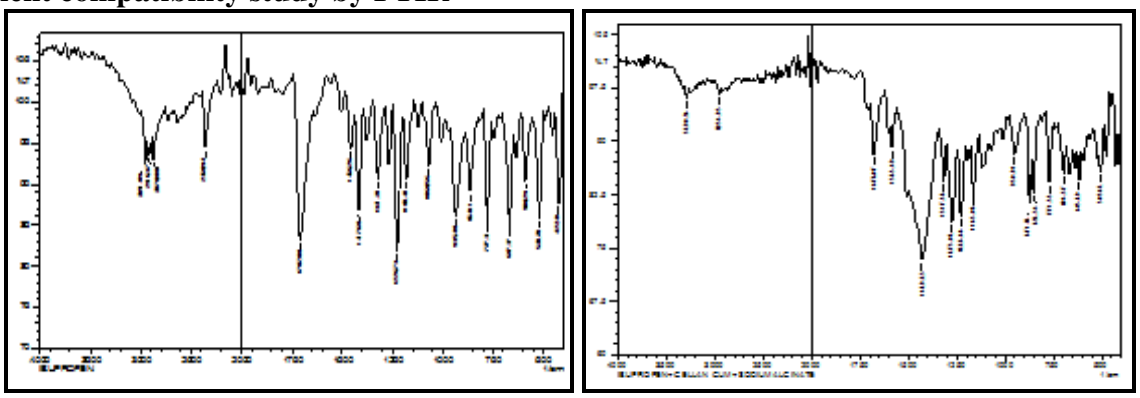

Figure No.2: FTIR spectra of pure Ibuprofen Ibuprofen + Gellan gum + Sodium alginate

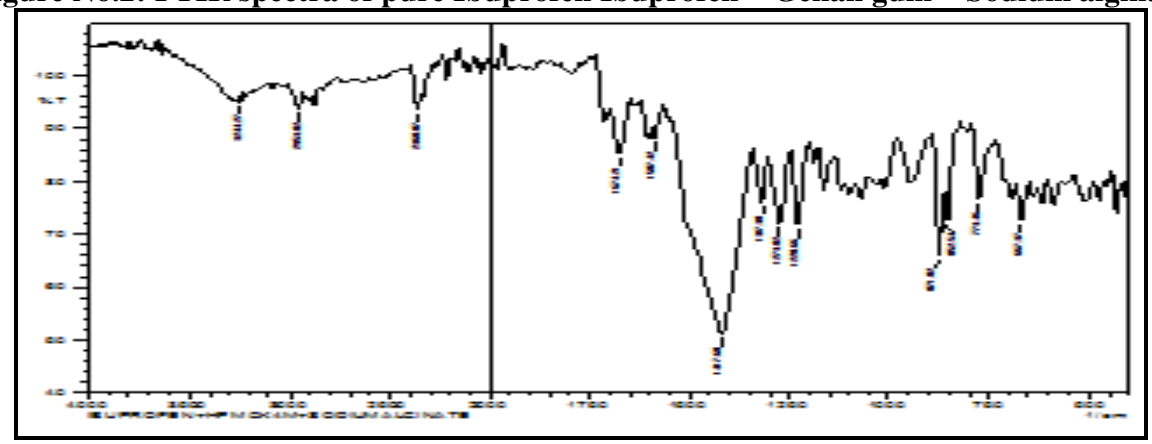

Figure No.3: Ibuprofen + HPMC K4M + Sodium alginate

Figure No.4: Prepared in situ gel of ibuprofen

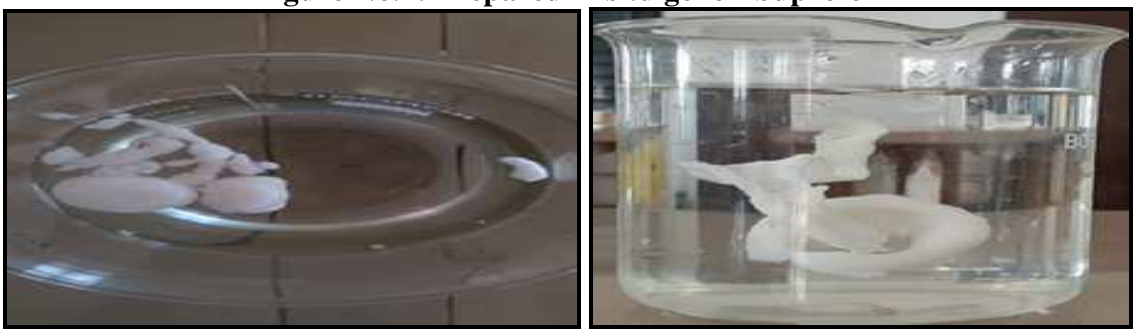

Figure No.5: Floating in situ gel

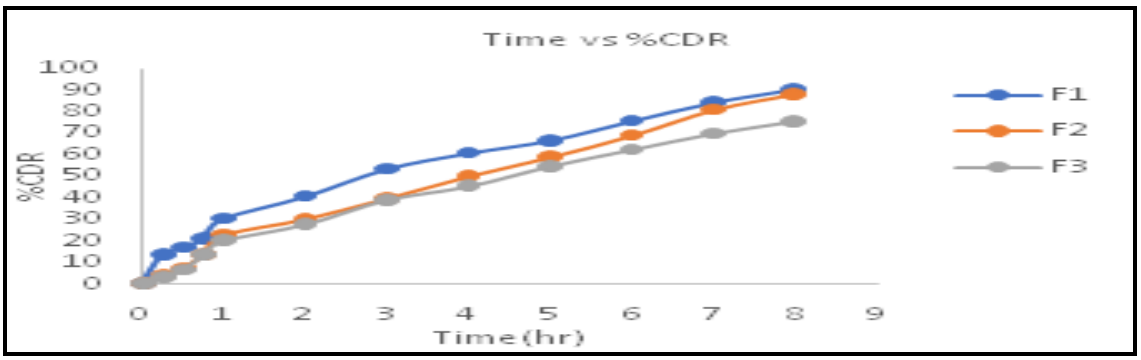

Figure No.6: *In-vitro* release profile of Ibuprofen *in situ* gel (F1-F3)

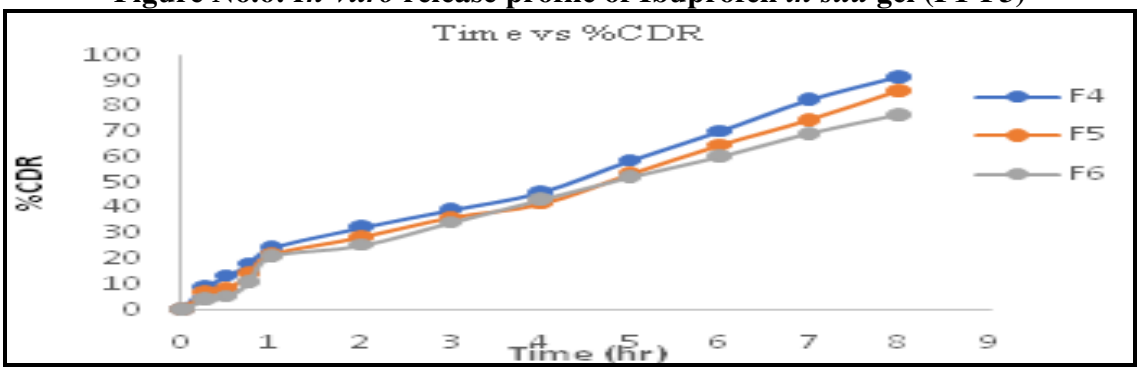

Figure No.7: *In-vitro* release profile of Ibuprofen *in situ* gel (F4-F6)

CONCLUSION

In vitro release studies showed that *in situ* gel containing higher concentration of polymer Gellan gum (0.2%) and HPMC K4M (0.2%) showed a larger degree of sustained release. It can be concluded that the developed formulation can be effective formulation with improved efficacy, prolonged and sustained release properties and patient compliance.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Faizi S M, Rathi P N, Tajane S V, Burghate R M, Wasankar S R. Drug delivery to absorption window through floating microspheres: A Review, *Res J Pharma Dosage Forms and Tec,* 4(3), 2012, 135-142.
2. Mangala B, Rana V, Jain A. Gastroretentive drug delivery system: An overview, *Asian Pacific J Health Sci,* 4(4), 2017, 140-154.
3. Rathode H J, Mehta D P, Yadav J S. A Review on stomach specific floating in-situ gel, *Int J Pharm Res,* 6(4), 2014, 19.
4. Das PS, Saha P. A review on approaches to achieve gastric retention of floating drug delivery system, *World J Pharm and Pharm Sci,* 6(7), 2017, 415-426.
5. Krishna S A, Anusha K. Preparation and evaluation of ibuprofen loaded microspheres, *Int J Ba and App Chem Sci,* 5(3), 2015, 30-38.

6. Momoh M A, Kenechukwu F C, Gwarzo M S, Builders P F. Formulation and evaluation of ibuprofen loaded lipospheres for effective oral drug delivery, *Dhaka Univ J Pharm Sci,* 14(1), 2015, 17-27.
7. Bhowmik D, Yadav R, Jayakar B, Kumar K S. Formulation and evaluation the oral tablets ibuprofen, *The Pharma Innovation,* 1(9), 2012, 32-42.
8. Suchithra A B, Jeganath S, Nitish B. Formulation and evaluation of ibuprofen nanoparticulate gel, *Drug Invention Today,* 11(11), 2019, 2862-2870.
9. Shaikh S C, Sanap D, Bhusari D V, Jain S, Kochar P P, Sanchati V N. Formulation and evaluation of Ibuprofen gastro-retentive floating tablets, *Universal J Pharma Res,* 3(1), 2018, 19-25.
10. Suchithra A B, Jeganath S, Nitish B. Formulation and evaluation of ibuprofen nanoparticulate gel, *Drug Invention Today,* 11(11), 2019, 2862-2870.
11. Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanabe H, Attwood D. Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations, *Drug Development and Industrial Pharmacy,* 29(2), 2003, 113-119.
12. Kajale A D, Chandewar A V. Formulation and evaluation of oral floating In situ gel of Tramadol hydrochloride, *Pharm. Chem. J,* 3(2), 2016, 267-279.
13. Jayaswal B D, Yadav V T, Patel K N, Patel B A, Patel P A. Formulation and evaluation of floating *in situ* gel based gastro retentive drug delivery of cimetidine, *IJPRS,* 1(2), 2012, 327-337.
14. Wamorkar V, Varma M M, Manjunath S Y. Formulation and evaluation of stomach specific in-situ gel of metoclopramide using natural, bio-degradable polymers, *Int J Res Pharm Biomed Sci,* 2(1), 2011, 193-201.
15. Gulecha B S, Shahi S, Lahoti S R. Floating in situ gelling drug delivery system of verapamil hydrochloride, *Am J Pharm Tech Research,* 2(4), 2012, 954-969.
16. Gupta P, Gnanarajan, Kothiyal P. Formulation and evaluation of floating in situ gel based gastroretentive drug delivery of ciprofloxacin HCl, *IAJPS,* 2(9), 2015, 1298-1308.
17. Ramana B V, Jalalu S S, Clement S L, Chandra S S, Ademma G, Murthy K. Design and development of floating *in situ* gel of pantoprazole, *Der Pharmacia Lettre,* 8(8), 2016, 239-249
18. Thomas L M. Formulation and evaluation of floating oral in-situ gel of metronidazole, *Int J Pharm Pharm Sci,* 6(10), 2014, 265-269.
19. Bharathi A, Priyanka G, Aswini P V, Anusha N, Roja S. Formulation and evaluation of floating oral in situ gel of ofloxacin for stomach specific delivery, *World journal of Pharmacy and Pharmaceutical Sciences,* 4(12), 2015, 1144-1156.
20. Singh P A, Sharma M. Formulation and evaluation of floating stomach specific in situ gel of nizatidine, *International Journal of Pharmaceutical and Biological Archieves,* 5(1), 2014, 115-123.
21. Raghavendra M, Prasad R, Shelar U S. Controlled release ion sensitive floating oral in situ gel of prokinetic drug using gellan gum, *Indian Journal of Pharmaceutical Education and Research,* 49(2), 2015, 158-167.
22. Hetangi R, Vishnu P, Moin M. *In situ* gel as a novel approach of gastro retentive drug delivery, *Int J Pharm Life Sci,* 1(8), 2010, 440-447.

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