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DESIGN AND CHARACTERIZATION OF IN SITU GEL SYSTEM OF MELOXICAM

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KEYWORDS:

Meloxicam, *In-situ* gel, HPMC K200M, Sodium alginate, Floating, Optimization.

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ABSTRACT

The present study involves the formulation and evaluation of floating *in-situ* gel containing Meloxicam for the treatment of arthritis. In the FTIR and DSC study for compatibility of Meloxicam with polymers, there are no significant changes observed so it is confirmed the absence of drug-polymer interactions. The gastric floating *in-situ* gel was prepared by using Sodium Alginate, HPMC K 200 M & other ingredients. The prepared situ gel of Meloxicam was evaluated for pH, gelling capacity, floating lag time, total floating time, drug content, viscosity, *in-vitro* drug release. An optimization study was carried out by using was 3^2 factorial designs to find the effect of independent variables, *i.e.*, amount of Sodium Alginate (X1) and HPMC K 200 M (X2) on dependent variables *i.e.*, floating lag time & % CDR. The results showed that all the formulations exhibited a very short floating lag time. Most of the formulations floated within 1 min. All the formulations exhibited a basic pH in the range of 6.7 to 7.9 which is suitable for oral consumption and gastric delivery. Increasing the calcium carbonate content in the formulation simultaneously increased the viscosity at all polymer concentrations. The comparing G1 to G9 formulations it was observed that the drug release pattern of formulation G1 is about 99.25% at the end of 12 h & have sufficient gelling property, viscosity & floating lag time so it is selected as an optimum batch. 3^2 full factorial design optimization technique was successfully used in the development of this *in-situ* gel.

INTRODUCTION:

Oral drug delivery is the most popular route of drug administration but conventional oral dosage form has many problems like short gastrointestinal transit time, fluctuation in blood plasma concentration, low bioavailability so there is a need for novel drug delivery like Gastroretentive drug delivery (GRDDS) [1, 2]. GRDDS can be defined as a system which remains in the stomach for a sufficient period of time and releasing active moiety in a controlled manner and finally metabolized in the body [3]. Gastro retentive drug delivery system plays a vital role among novel drug delivery systems [4]. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size, and thus patient compliance [5]. Over the last two decades, numbers of GRDDS have been designed to prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery. In GRDDS most popular one is *in-situ* gel [6]. The gastro-retentive *in-situ* gel-forming system provides controlled drug delivery within the stomach. *In-situ* gel formation occurs due to one or a combination of different stimuli like pH change, temperature modulation and solvent exchange [7].

In-situ is a Latin word which means 'In its original place or in position'. Extensive researches focused on the development of new drug delivery systems with improving efficacy and bioavailability together, thus, reducing dosing frequency to minimize side effects. As a progress, they design *in-situ* forming polymeric delivery systems sparked by the advantages of easy administration, accurate dose as well as prolong the residence time of the drug in contact with mucosa compared to conventional liquid dosage form, improved patient compliance and comfort [8]. *In-situ* gel formation occurs due to one or a combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo *in-situ* gel transition upon administration [9].

Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a 3D network of interconnected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified as chemical gels that arise when strong covalent bonds hold the network together and physical gels when hydrogen bonds, electrostatic and Vander walls interaction maintain the gel network [10, 11]. Gastroretentive floating *in-situ* gel refers to a polymer solution of low viscosity which upon coming in contact with the gastric fluids; undergoes a change in polymeric conformation and a viscous strong gel of density lower than the gastric fluids is

produced. The gelation can be triggered by temperature modulation, pH change, and ionic cross-linking. *In-situ* gels can be administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes [12]. Meloxicam is one of the most effective non-steroidal, anti-inflammatory drugs of the Meloxicam derivative which also having antipyretic and analgesic activity in numerous types of pains such as used in the treatment of rheumatoid arthritis and osteoarthritis [13]. The main objective of the present work is the formulation and evaluation of Floating *in-situ* gel containing Meloxicam for the treatment of Arthritis.

MATERIALS AND METHODS:

Materials: Meloxicam was obtained from Shree Swami Samarth Ayurvedic Pharmacy Jalgaon (Allopathic division). HPMCK 200 M, Sodium alginate, Calcium Carbonate, Trisodium citrate, Propylparaben, Calcium chloride and Carbopol 934 was purchased from Research Lab Fine Chem Industries, Mumbai. All other ingredients used were of analytical grade.

Drug and DSC - Excipient Compatibility Study: FTIR and DSC studies were conducted to know the compatibility between drugs and excipients.

FTIR: Infrared Spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug & other excipients used in the formulation. 1 mg of the sample was powdered & intimately mixed with 10 mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler & the spectrum was recorded by scanning in the wavelength region of 4000-400 cm^{-1} in an FTIR spectrophotometer. The IR spectrum of the drug compared with that of the physical mixture to check for any possible drug- excipient interaction.

Differential Scanning Calorimetry Analysis: Method for estimating the physical interaction between drugs and polymers used for the formulation of the different dosage forms is a thermal analysis by DSC. In the present studies, the DSC analysis of drug and Polymers were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer-drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in an aluminum crucible and heated at a constant rate of 10 ºC/min over a temperature range of 40 to 300 ºC. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

Methods:

Preparation of *in-situ* Gel: Specified quantity of Meloxicam, trisodium citrate, sodium alginate, calcium carbonate, calcium chloride, Propyl Paraben, Carbopol 934 and HPMC K 200M were weighed accurately [14, 15, 16]. Accordingly, in about 30 ml of deionized water, HPMC K200M was allowed to hydrate overnight. Meloxicam was then dissolved in the HPMC K200M solution and CaCO3 (gas generating agent) was added to it while stirring to facilitate dispersion. Sodium alginate

solutions were prepared by adding the remaining amount of deionized water (up to 50 ml) containing sodium citrate and calcium chloride and heating to 60 ºC while stirring on a heating magnetic stirrer. After cooling to below 40 ºC, it was added to the HPMC K200M solution while stirring to achieve uniform dispersion. The solution of methylparaben and Carbopol 934 was added and mixed properly. Finally, the formulations were adjusted to volume, filled and stored in amber-colored bottles until further tests were done.

Optimization by Using Full Factorial Designs: In the present study, a 3^2 full factorial design was employed to find the effect of independent variables, *i.e.*, amount of Sodium Alginate…(X1) and HPMC K 200M (X2) on dependent variables *i.e.* Floating lag time & % CDR.

TABLE 1: LAYOUT OF 3^2 FULL FACTORIAL DESIGN BATCHES G1-G9 OF FLOATING *IN-SITU* GEL

Batch No.	X1	X2
G1	-1	-1
G2	-1	0
G3	-1	1
G4	0	-1
G5	0	0
G6	0	1
G7	1	-1
G8	1	0
G9	1	1

TABLE 2: TRANSLATION OF CODED VALUE IN AN ACTUAL UNIT

Coded Value	Sodium Alginate % (X1)	HPMC K 200 M % (X2)
-1	1	0.5
0	2	1
1	3	1.5

TABLE 3: OPTIMIZATION BATCHES AS PER FACTORIAL DESIGN

	Batches								
Ingredient									
	G1	**G2**	**G3**	**G4**	**G5**	**G6**	**G7**	**G8**	**G9**
Meloxicam (Mg)	100	100	100	100	100	100	100	100	100
Sodium alginate (% w/v)	1.0	1.0	1.0	2.0	2.0	2.0	3	3	3
HPMC K200M (% w/v)	0.5	1.0	1.5	0.5	1.0	1.5	0.5	1.0	1.5
Calcium Carbonate (% w/v)	2.0	1.0	2.0	1.0	1.0	2.0	1.0	2.0	1.0
Trisodium citrate (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propyl paraben (% w/v)	0.5	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6
Calcium chloride (% w/v)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Carbopol 934 (% w/v)	-	0.5	-	0.7	-	0.5	-	0.7	-
Distil water (ml)	50	50	50	50	50	50	50	50	50

Evaluation of Optimized Batches of *in-situ* Gel Formulations:

Determination of pH 17-24: The pH values of all *in-situ* gel formulations of Meloxicam were measured using a calibrated digital pH-meter at room temperature, and results were recorded.

Gelling Capacity of Formulations: Accurately measured 10 mL of the formulation was added to 100 mL of 0.1 N hydrochloric acid (pH 1.2) at 37 ºC in a beaker with mild agitation that avoids breaking of formed gel.

The *in-vitro* gelling capacity was graded in three categories on the basis of the stiffness of formed gel, gelation time and the time period in which, formed gel remains without a change. (+) Gels after a few min, dispersed rapidly. (++) Gelation immediate remains for a few hours. (+++) Gelation immediate remains for an extended period.

Determination of Viscosity:

Viscosity of the prepared *in-situ* gel formulations of Meloxicam was determined using a brook field viscometer. Viscosity was measured at different angular velocities (from 20 to 100 rpm) using spindle number 2 at room temperature.

Determination of Drug Content:

Accurately, 10 mL of a formulation containing the equivalent of 100 mg Meloxicam from different batches were measured and transferred to a 100 mL 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 was ensured visually and the dispersion was 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 Meloxicam were measured at maximum absorbance at 242 nm using UV 1800 -Visible Spectrophotometer at (SHIMADZU, Japan).

***In-vitro* Floating Study:**

The *in-vitro* floating study was determined by means of USP dissolution apparatus II having 500 ml of simulated gastric fluid (0.1 N HCl) maintained at 37±1 ºC with a paddle speed of 50 rpm. 10 ml of the prepared *in-situ* gelling formulations were withdrawn with a disposable syringe and added into the dissolution vessel containing simulated gastric fluid. The time the formulation took to emerge on the medium surface (Floating lag time, FLT) and the time the formulation constantly floated on the dissolution medium surface (duration of Floating, TFT) were recorded.

***In-vitro* Drug Release Study:** The release rate of Meloxicam from *in-situ* gel formulations was determined using USP dissolution testing apparatus type-II at 50 rpm. The dissolution medium was used 900 ml of 0.1 N HCl, and the temperature was maintained at 37 ºC. 1 mL of the sample of the solution were removed at the pre-determined interval for analysis and replace with 1 ml of fresh 0.1 N HCl. The drug concentration of each sample was determined spectrophotometrically at 242 nm.

RESULTS AND DISCUSSION:

FT-IR study of Drug: FT-IR spectra of the pure drug confirms its identity as Meloxicam and formulation showed no interaction of excipients with the drug and hence, it was concluded that the drug is compatible with the excipients used. As shown in **Fig. 1** and **2**.

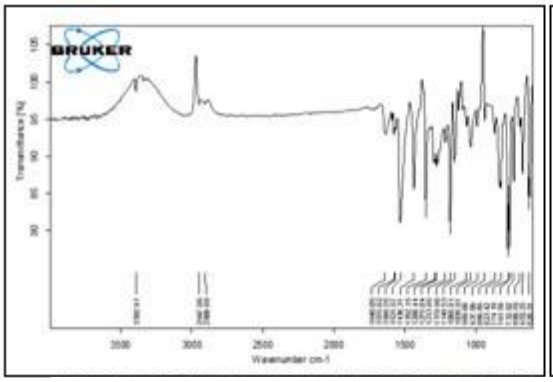
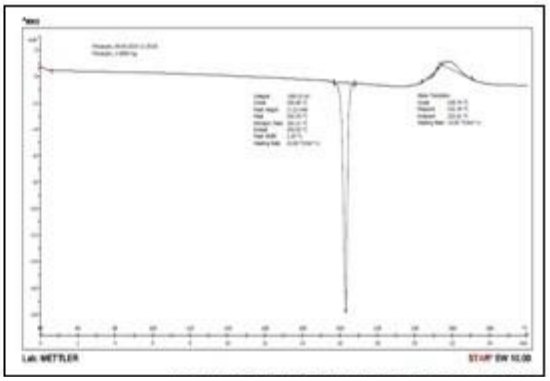


Fig.1 FTIR OF PURE DRUG



DSC OF PURE DRUG

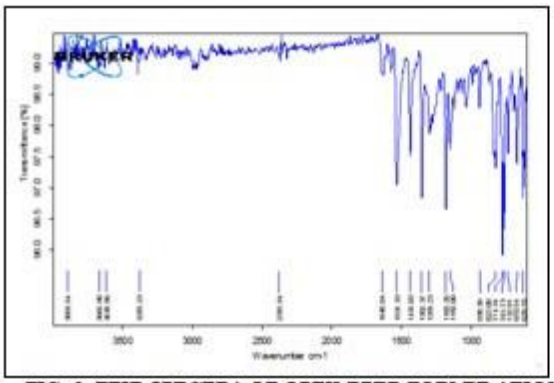


FIG. 2: FTIR SPECTRA OF OPTIMIZED FORMULATION

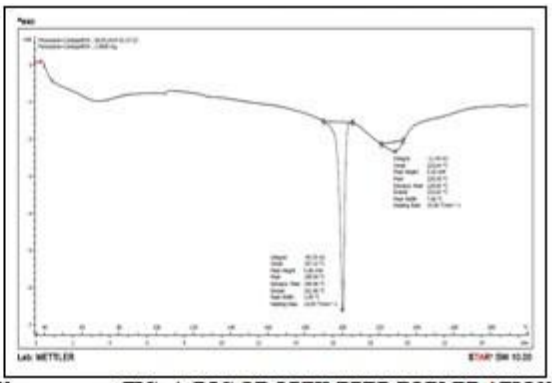


FIG. 4: DSC OF OPTIMIZED FORMULATION

The endothermic peak of the drug was found to be 200 ºC and which corresponds to the melting point is 198-202 ºC as reported in Pharmacopoeia. In physical mixture also Endothermic peak of the drug was found to be 200 ºC and which corresponds to the melting point is 198-202 ºC as reported in the pharmacopoeia. The drug, drug-excipients physical mixture studies reveal that there was no significant change in position of the peak in thermogram of the drug, drug-excipients was recorded. From **Fig. 4** of drug excipients compatibility study, it was concluded that the given drug was compatible with all the excipients and it was confirmed by FTIR & DSC study.

Evaluation of Optimized Batches G1-G9:

TABLE 4: CHARACTERISTICS OF PREPARED FLOATING *IN-SITU* GELS OF MELOXICAM

Code	pH	% Drug content	Viscosity (cps)	Gelling capacity	Floating lag time (Sec)	Floating duration (h)
G1	7.8	99.63± 0.09	49.46± 0.55	+++	24	12
G2	6.7	98.87± 0.25	79.46± 0.83	+++	22	12
G3	6.9	98.52 ± 0.39	91.33± 0.36	+++	18	12
G4	7.1	99.42± 0.22	101.96± 0.81	++	16	12
G5	7.3	98.53 ± 1.53	64.36±0.28	++	20	12
G6	6.8	98.04± 1.28	75.7± 0.53	+++	17	12
G7	7.4	97.82 ± 0.25	87.2± 0.76	+++	21	12
G8	7.9	99.34 ± 0.33	98.4± 0.74	+++	20	12
G9	7.6	98.67 ± 0.40	55.7± 0.91	++	20	Less than 12

Determination of pH: The pH of prepared formulations was measured using a calibrated digital pH meter at 35 °C. All the formulations exhibited a basic pH (>6) which is suitable for oral consumption and gastric delivery. The pH of optimized formulations G1 to G9 was in the range of 6.7 to 7.9.

Uniformity of Drug Content: Drug content determination was done for all batches of prepared *in-situ* gels. It was done to ascertain the drug distribution in the formulations. Since the prepared formulations are liquid in nature, uniform distribution of drug will benefit the patient in ensuring the availability of proper dose each time the dose is administered. From the results of drug content evaluation, it was found that the drug loading was uniform and there was the proper distribution of the drug in the *in-situ* gel formulations. The drug content in the formulations was in the range of 97.82 ± 0.25 to 99.63 ± 0.09% of the total amount of the drug added during the preparation. Hence, it can be concluded that the drug distribution was satisfactory in the prepared formulation.

Gelling Capacity of Formulations: An oral *in-situ* gelling gastro retentive formulation should undergo rapid sol to gel transition when it comes in contact with the gastric fluid. Also, to facilitate sustained drug release, the *in-situ* formed gel should preserve its integrity without dissolving for a prolonged period of time. It is the time taken by the prepared formulations (sol) to get converted into a gel state when placed in specific conditions (pH 1.2). The gelation time of the formulations should be less, so as to avoid drug release when the formulations are still in sol state. Once they are converted into a gel (*in-situ*) they possess a 3 dimensional network that can retard the drug release by increasing the diffusional path for the drug during diffusion/ release.

From the results, it was found that the formulations showed an immediate sol to-gel transition when placed in pH 1.2 buffer. Almost all the sol-gels responded to the study. This quick gelation of formulations can be attributed to the concentrations of both Carbopol 934 and calcium carbonate. It was noticed that as the concentration of Carbopol 934 increased, the gelation time decreased and the calcium carbonate also played a significant role in the gelation of sol-gels.

Floating Lag Time:

The time taken by the formulation to emerge on the medium surface (floating lag time) and the time for which the formulation constantly floated on the surface of the dissolution medium (duration of floating) are studied. When the formulation is placed in the medium, the CO2 released from the formulation was entrapped in the gel network producing buoyant formulation. Further, calcium ion reacted with HPMC K 2OOM produced a cross- linked 3-D gel network which swelled and entrapped with more CO2.

This entrapment in the network structure caused buoyancy and flotation for an extended period of time. Further, the gel network retarded the drug release and thus exhibiting sustained release pattern. All the formulations exhibited a very short floating lag time. Most of the formulations floated within 1 min after they were placed in the dissolution medium. Formulation G4 showed the least lag time of 16 sec,

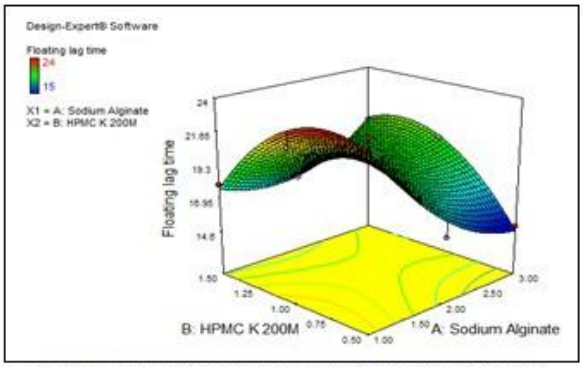


FIG. 5: A RESPONSE SURFACE PLOT SHOWING EFFECT OF CONCENTRATION OF INDEPENDENT VARIABLES ON THE FLOATING LAG TIME

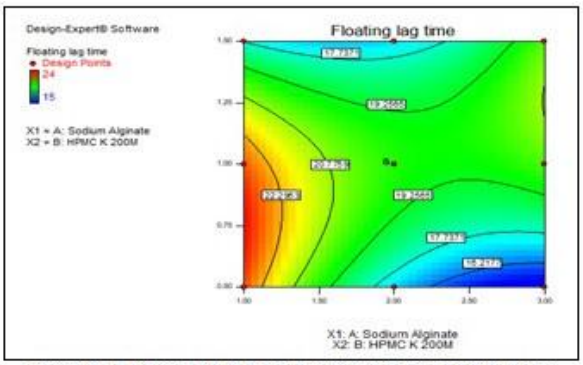


FIG. 6: A COUNTER PLOT SHOWING EFFECT OF CONCENTRATION OF INDEPENDENT VARIABLES ON THE FLOATING LAG TIME

whereas the formulation G1 showed about 24 sec. The variation in this lag time is mainly due to the

amount of calcium carbonate present in the formulations.

Mathematical relationship in the form of the polynomial equation for the measured response floating lag time was obtained and given in the equation below.

Floating Lag Time: +19.76, -1.50 * A, +0.000B, +2.75AB, +1.84 A^2, -2.66 * B^2

Duration of Floating: It is the total time duration where the formulation is constantly floating on the surface of the dissolution medium. The duration is considered once the formulation appears on the surface till it again sinks in the dissolution medium. This test is very important for an *in-situ* floating formulation since the formulations need to be floating until the drug release is complete from the unit. The study was conducted for a period of 12 hrs since the prolonged retention of the dosage form in the stomach is not intended as they may be forced away to the small intestine. All the formulations were studied for the duration of floating. Formulation G9 exhibited a floating duration of less than 12 h, whereas all other formulations were floating even after the study period *i.e.*, 12 h. The requirement of the formulations was to float for a period of 12 hrs which was achieved by all formulations except G9.

Viscosity Studies:

The rheological properties of *in-situ* gel containing different concentrations of Sodium alginate and HPMC K 200M were studied. Viscosity determination was done for all the formulations using Brookfield viscometer at 3 different rpm (20, 30 & 40 rpm) using spindle no. 63 at 25 °C.

From the observations, it was noticed that there was the *in-situ* gel demonstrated a considerable increase in viscosity with an increasing amount of sodium alginate. It was attributed to an increasing chain interaction with sodium alginate concentration. Similarly, an increase in the amount of calcium carbonate also increases the viscosity of the *in-situ* gels at all three sodium alginate percentage.

It could be due to the high concentration of finely dispersed particles of calcium carbonate in the gelling solution. Formulation G4 contained the concentration of HPMC K 200 M and hence exhibited higher viscosity amongst all other formulations. But the formulations G1 and G9 showed the formation of slimy and scattered gel on contact with 0.1N HCl due to their low viscosity.

***In-vitro* Drug Release Study:** *In-vitro* drug release studies were done for all floating *in- situ* gelling formulations. From the release data, it was observed that the concentration of polymers (Carbopol 934 and HPMC K 200 M) affected the drug release from the floating *in- situ* gels. The drug release profiles are depicted in **Fig. 9**. As the concentration of polymers increased, the amount of drug release decreased from the formulations. The comparing G1 to G9

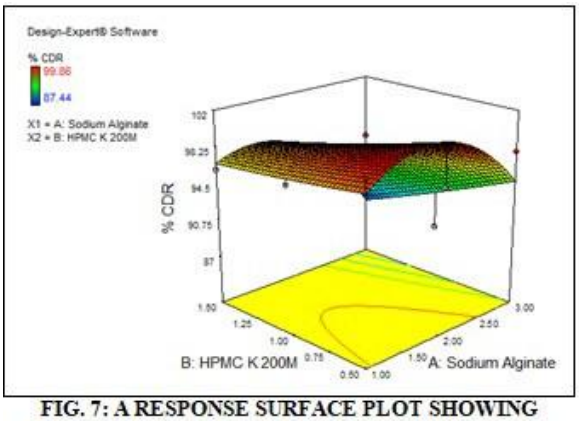


FIG. 7: A RESPONSE SURFACE PLOT SHOWING EFFECT OF CONCENTRATION OF INDEPENDENT VARIABLES ON THE % CDR

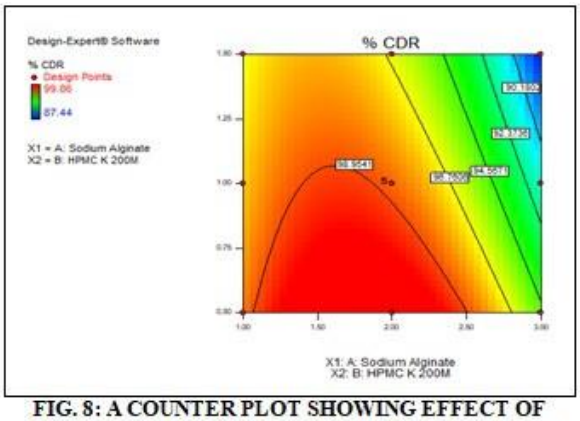


FIG. 8: A COUNTER PLOT SHOWING EFFECT OF CONCENTRATION OF INDEPENDENT VARIABLES ON THE % CDR

formulations it was observed that the drug release pattern of formulation G1 is about 99.25% at the end of 12 h.

Mathematical relationship in the form of polynomial equation for the measured response % CDR was obtained and given in equation below. % CDR = +98.63, -3.08 * A, -2.19 * B, -1.28 * A * B, -4.23 * A2, +0.14 * B2. Responses observed for nine formulations were fitted to Design Expert software. Outcome of ANOVA is as shown in **Table 5** below.

TABLE 5: RESULT OF ANOVA

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Ade. Precision
Floating Lag time	69.08	5	13.49	25.37	Significant	0.9477	17.41
% CDR	198.61	5	37.12	4.18	Significant	0.7491	7.15

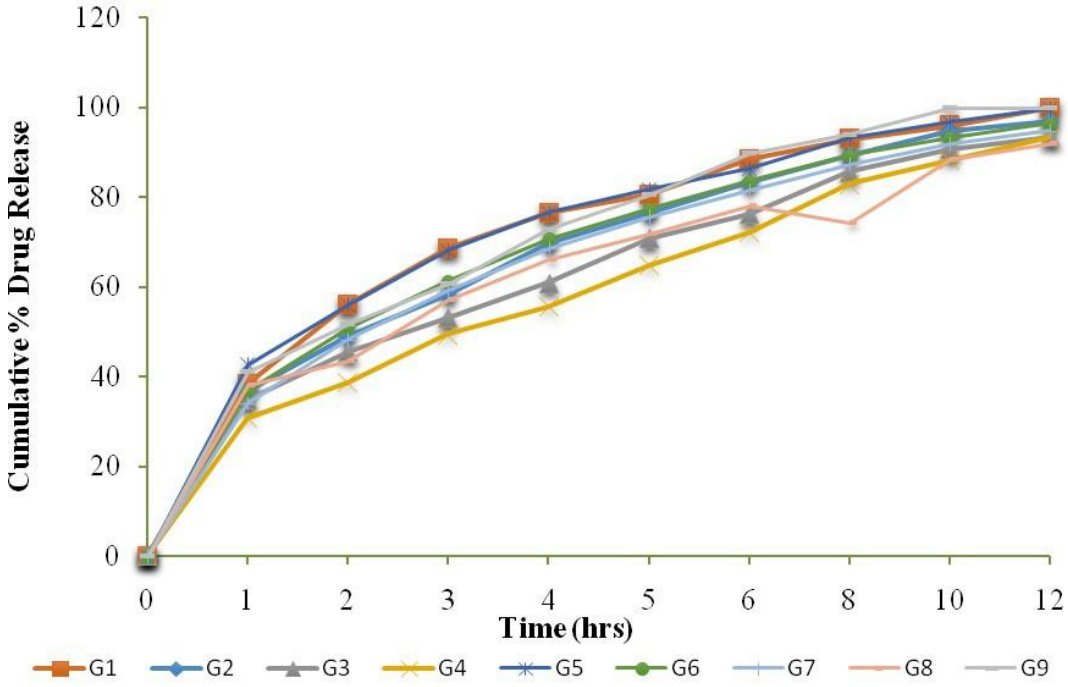


FIG. 9: *IN-VITRO* DRUG RELEASE PROFILE FROM MELOXICAM *IN-SITU* GELS (G1-G9)

CONCLUSION:

The aim & objectives of this work is design, develop & evaluate Floating *in- situ* gel containing Meloxicam for the effective management of Arthritis. The gastric floating *in-situ* gel was prepared by using sodium alginate, HPMC K 200 M & other ingredients. From the FTIR & DSC study, it was concluded that the compatibility of Meloxicam with polymers in the formulation blend. All the formulations exhibited very short floating lag time. The formulations G1 to G9 showed the formation of slimy and scattered gel on contact with 0.1 N HCl due to their low viscosity. Formulation G1 showed a drug release of about 99.25% at the end of 12 h & selected as an Optimized batch 3^2 Full factorial design and optimization technique successfully used in the development of *in-situ* gel.

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