Original Research Article

DEVELOPMENT AND EVALUATION OF *IN SITU* GELLING GASTRORETENTIVE FORMULATIONS OF MELOXICAM

ABSTRACT:

The aim of this study was to develop a novel gastro retentiveoral floating in situ gelling system for controlled release of Meloxicam. Meloxicam is NSAIDs inhibits cyclooxygenase (COX) synthesis having analgesic and antipyretic effects. Four polymer based floating *in situ* gelling systems of Meloxicam were prepared by dissolving varying concentrations of different ingredients including sodium alginate, HPMC K100 M, calcium carbonate, sodium citrate. The prepared gels were characterized for solution viscosity, pH, gelling capacity, floating lag time, floating duration and in-vitro release study. All the formulations showed instant gelation maintaining integrity for at least 12 hr.

The study demonstrated that a stomach specific *in-situ* gel of Meloxicam could be prepared using floating mechanism to increase the residence time of the drug in stomach andimproved bioavailability and thus improved patient compliance.

Keywords: Novel gastro retentive, floating *in situ* gelling system, Meloxicam.

INTRODUCTION:

Gastro-retentive *in situ* gel forming system provides the controlled drugdelivery within stomach. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange[1].

The *in situ* gel dosage form is a liquid before administration but converts into a gel that floats on gastric contents as it comes in contact with it. It consist of a solution of low viscosity that on coming in contact with the gastric fluids, undergoes change in polymeric conformation viscous gel having density lower than the gastric fluids thus floats on the surface of the gastric fluids[2].

This low density gel formation provides gastro retention to prolong the contact time, as well as it arrange continuous and slow drug release. To produce sustained release formulation of an oral liquid formulation could be successfully augmented substantially through a strategy of liquid in situ gelling system[3]. Advantages of in situ gel forming systems includes ease of administration and reduced frequency of administration, improved patient complianceand comfort and improved bioavailability[4].

Furthermore solid dosage forms are associated with swallowing problems for geriatric, pediatrics and bedridden patient and chances of accidental burst release[5]. Gastroretentive liquid dosage forms i.e. *in situ* gel formulations may be helpful to overcome these limitations. The oral use of liquid pharmaceutical has generally been justified on the basis of ease of administration to those individuals who have difficulty swallowing solid dosage forms and better patient compliance[6].

Meloxicam is a NSAID belonging to the class of oxicams[7]. Meloxicam inhibits cyclooxygenase (COX) synthesis. It has analgesic and antipyretic effect and used in the treatment of rheumatoid arthritis, osteoarthritis, dental pain, post-traumatic and post-operative pain, inflammation and swelling[8,9].

The aim of the present study is to develop in situ gelling gastroretentive formulations of meloxicam sustained drug release, ease of administration and patient compliance.

MATERIALS AND METHODS:

Materials:

Sodium alginate, calcium carbonate and calcium chloride were supplied by Logus Investment Limited (Lagos,Nigeria), Sodium citrate and Methyl paraben were obtained from Honeystones Nigeria Limited, Lagos,Nigeria. HPMC K100M and Carbopol 940 weresupplied by Krispine Nig Ltd (Nigeria).

Preparation of *in situ* gel

Specified quantity of Meloxicam, Sodium citrate, calcium carbonate, calcium chloride, methyl paraben, carbopol 940 and HPMC were weighed accurately.

Accordingly, in about 30 ml of deionized water, HPMC K100M was allowed to hydrate overnight. Meloxicam was then dissolved in the HPMC K100M solution and $CaCO_3$ (gas generating agent) was added to it while stirring to facilitate dispersion. Sodium alginate solutions were prepared by adding to 60 ml of deionized water containing sodium citrate and calcium chloride and heating to 60^0C while stirring on a heating magnetic stirrer (Finlab, Nigeria Ltd). After cooling to below 40^0C, it was added to the HPMC K100M solution while stirring to achieve uniform dispersion. Solution of methy paraben and carbopol 940 wereadded and mixed properly. Finally, the formulations were adjusted to volume, filled and stored in amber colored bottles until further testswere done[10].

Table 1: Compostion of Meloxicam floating *in situ* gel formulations.

Ingredients	Formulation code			
	G1	G2	G3	G4
Meloxicam (mg)	100	100	100	100
Sodium Alginate (% w/v)	2	2	2	1
HPMC K100M (% w/v)	0.5	0.6	1	0.8
Calcium carbonate (% w/v)	1	2	1	2
Sodium citrate (% w/v)	0.5	0.5	0.5	0.5
Methyl paraben (% w/v)	0.2	0.4	0.6	0.5
Calcium chloride(% w/v)	0.15	0.15	0.15	0.15
Carbopol 940	0.5	-	0.7	-
Distilled water (up to ml)	50	50	50	50

Evaluation of in situ gel formulations

1. Determination of pH:

The pH values of all *in situ* gel formulations of Meloxicam weremeasured using a calibrated digital pH-meter (Ms026, Mon Scientific, Nigeria) at room temperature and results were recorded as average of three measurements[11].

2. **Determination of drug content**

Accurately, 10 mL of formulation containing the equivalent of 250 mg Meloxicam from different batches was measured and transferred to 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 metronidazole was measured at maximumabsorbance at 362nm using UV-Visible Spectrophotometerat (Biotech eng. UV-9200, UK)[12].

***3.* Gelling capacity of formulations**

An oral *in situ* gelling gastro retentive formulation should undergorapid 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. Accurately measured 10 mL of formulation was added to 100 mL of 0.1N hydrochloric acid (HCl, pH 1.2) at 37°C 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 stiffness of formed gel, gelation time and time period in which, formed gel remainswithout a change[13].

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for few hours

(+++) Gelation immediate remains for an extended period.

4. Determination of viscosity:

Viscosity of the prepared *in situ* gel formulations of Meloxicamwas determined using a rotational viscometer (Finlab Nigeria Ltd). Viscosity was measured at different angular velocities (from 20 to 100 rpm) using spindle number 2 at room temperature[14].

***5.* In vitro floating study:**

The *in vitro* floating study was determined by means of USP dissolution apparatus II (Erweka DT 600HH, Germany) having 500 ml of simulated gastric fluid (0.1 N HCl) maintained at 37±1 ^{0}C with a paddle speed of 50 rpm. Ten milliliters of the prepared *in situ* gelling formulations were withdrawn with 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 constantlyfloated on the dissolution medium surface (duration of floating, TFT) were recorded[15].

6. 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 temperature was maintained at 37^{o}C. 5 ml of solution containing the optimum quantity of sodium citrate, calcium chloride, in distilled water and loaded with drug was placed in petridish which was then float on dissolution media. Gelation was instantaneous on contact with simulated gastric fluid. One ml of sample of the solution were removed at pre-determined interval for analysis and replace with 1 ml of fresh 0.1N HCl. Thedrug concentration of each sample was determined spectrophotometrically at 362nm[16].

Table 2: Characteristics of *in situ* gel formulations of Meloxicam

Code	pH	% Drug content	Gelling capacity	Viscosity (cps)	Floating lag time (Sec)	Floating duration (hr)
G1	7.25±0.09	98.26±0.21	+++	165±0.43	24±0.47	12
G2	7.48±0.15	97.38±0.17	+++	192±0.37	22±0.35	13
G3	7.82±0.32	98.24±0.19	++	177±0.62	18±0.27	14
G4	8.12±0.49	96.43±0.25	+	210±0.55	20±0.08	12

+Poor, ++ Good, +++Very good

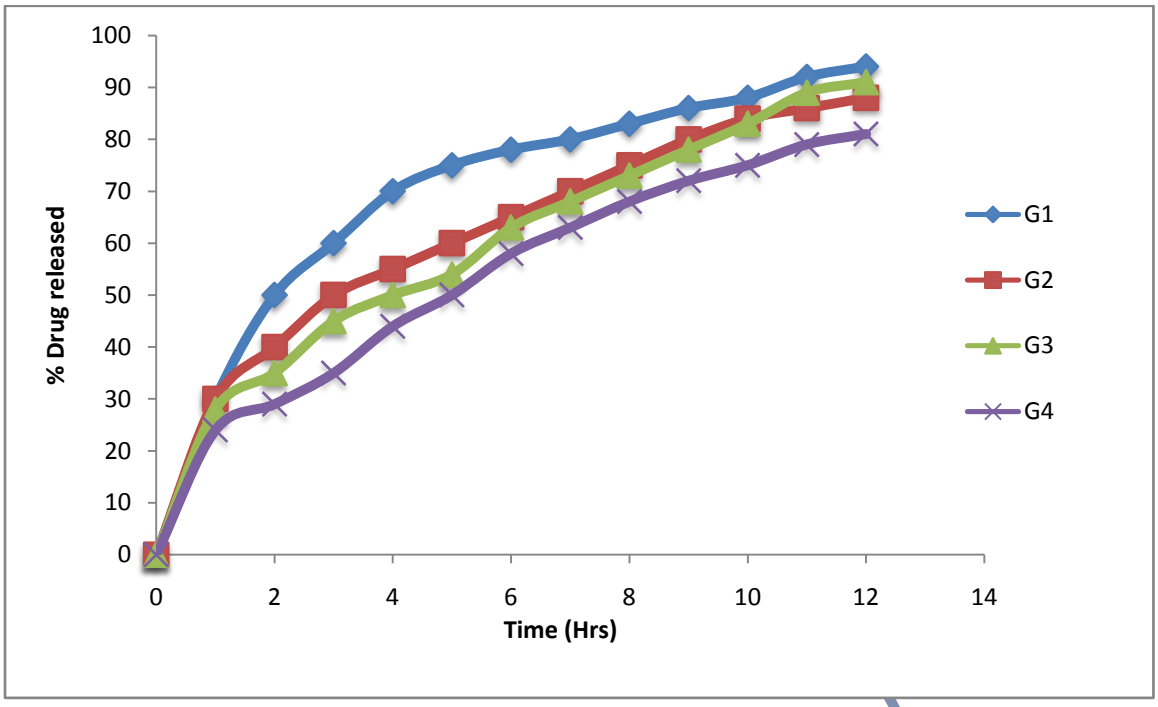

Figure : Cumulative in-vitro drug release of *in situ* gel formulations of Meloxicam

RESULTS AND DISCUSSION:

Four different *in situ* gel formulations of Meloxicam were prepared successfully by means of using different polymers and ingredients i.e. sodium alginate, HPMC K100M, calcium carbonate, sodium citrate in different ratio. Sodium alginate acts as a gelling agent. The free Ca2+ ions gets entrapped in polymeric chains of sodium alginate thereby causing cross linking of polymer chains to form matrix structure[17]. This gelation involves the formation of double helical junction zones followed by reaggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. $CaCO_3$ was incorporated as cross linker and floatingagent[18].

The formulations possessed satisfactory pH value ranging from 7.25±0.09 to 8.12±0.49 (table 2) which is suitable to maintain the formulations in a liquid state. Aqueous solutions of sodium alginate are most stable at pH range of 4–10. Below pH 3, alginic acid is precipitated from the alginate solution making the formulation unsightly containing gel and liquid phases[19].

In all the formulations, sol-to-gel transition occurred instantaneously at the formulation/simulated gastric fluid interface. This instantaneous surface gelation formed an enclosing membrane which entrapped the remaining liquid formulation at the center and the gel layer expanded to the center apparently due to slow diffusion of H^+ and Ca^{2+} ions. During preliminary tests, the gels tend to ooze when pierced in less than 1 hr of gelation and at the end of the test period the gels appeared solid throughout their dimensions. However, though gelation occurred instantaneously, the nature of the gels formed wasdependent upon the polymer and $CaCO_3$ concentration[20].

Low sodium alginate concentration (G4) formed weak gels (table 2) which would not be able to withstand peristaltic waves of the GI tract, and might be propelled to the intestine with stomach contents. Floating characteristics of prepared formulations were assessed in simulated gastric fluid (0.1 N HCl). All the formulations remained floating on the surface of the medium for at least 12 hr (table 2). This indicates that the formulations could provide a sustained delivery of Meloxicam to the absorption window for more than 12 hr as long as the gel was not depleted of

the drug. Therefore, higher polymer concentrations impartedextra strength to the gels to remain buoyant at least for 12 hr.

Higher polymer concentrations shorten the floating lag time taken to float completely over the surface of the dissolution medium. This may be due to the higher cross-linking density at higher polymer concentrations which could effectively trap the released CO_2 bubbles so that density of the gel is reduced rapidly to induce buoyancy[21]. All the *in situ* gel formulations showed significant burst release where approximately, 24-30% of Meloxicam was released within the first hr. This burst release may be because of dissolution of drug present at the surface of the formed gel that could have been released immediately upon contact with the 0.1N HCl. In addition to this, some lag time is required for the release of Ca^{2+} ions from $CaCO_3$ and cross linking of the guluronate residues of sodium alginate which plays a major role in the formation of barrier gel. The release profiles also depicted that all formulations release 81.56% (G4) or more of Meloxicam within the study of 12 hrs. Maximumdrug release was shown by formulations of batch G1 (94.38%).

CONCLUSION:

In this research work, *in situ* gel formulations of Meloxicamwere successfully developed and optimized stomach specific in situ gels which exhibit a unique combination of floatation and ionic gelation for prolonged residence in the stomach. Calcium carbonate added to the formulation provides calcium ions and carbon dioxide. Calcium ions, due to ion interactions with the polymer, help in gelation. Carbon dioxide entraps in the gel and facilitates buoyancy of the gel. The *in situ* formed gel preserved its integrity without dissolving or eroding for prolonged period to facilitate sustained release of drugs locally. The developed formulations met all prerequisites to become an *in situ* gelling floating system, gelled, and floated instantaneously in the pH conditions of the stomach. It was observed that the resulting gel remained buoyant for 14 hr and slowly released Meloxicam during the 12 hr period. It is concluded that Meloxicam could be targeted to stomach and be released slowly over a period oftime and can improve bioavailability of the drug, dosing frequency and hence patient compliance.

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