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RESEARCH ARTICLE

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

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Abstract

Objective: The aim of this study was to develop a novel gastro retentive oral floating *in situ* gelling system for controlled release of Meloxicam. Meloxicam is an NSAID that inhibits cyclooxygenase (COX) synthesis and has analgesic and antipyretic effects.
Methods: Four polymer based floating *in situ* gelling systems of Meloxicam were prepared by dissolving varying concentrations of different ingredients including sodium alginate, HPMC K100M, 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.
Results: The formulations possessed satisfactory pH value ranging from 7.25±0.09 to 8.12±0.49. All the formulations showed instant gelation maintaining integrity for at least 12 h. Maximum drug release was shown by formulations of batch G1 (94.38%).
Conclusion: The study demonstrated that a stomach specific *in-situ* gel of Meloxicam could be prepared using the floating mechanism to increase the residence time of the drug in the stomach and improve bioavailability and thus improve patient compliance.
Keywords: Floating *in situ* gelling system, Meloxicam, novel gastro retentive.

INTRODUCTION

Gastro-retentive *in situ* gel forming system provides the controlled drug delivery 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 arranges 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 compliance and 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]. It is practically insoluble in water. This low solubility in biological fluids, results into slower rate of absorption and poor bioavailability after oral administration[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

Meloxicam was obtained from Dabak Pharmaceuticals, Ogun State, Nigeria. 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 were supplied 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 remaining amount of deionized water (up to 50 ml) containing sodium citrate and calcium chloride and heating to 60ºC while stirring on a heating magnetic stirrer (Finlab, Nigeria Ltd). After cooling to below 40ºC, it was added to the HPMC K100M solution while stirring to achieve uniform dispersion. Solution of methyl paraben and carbopol 940 were added and mixed properly. Finally, the formulations were adjusted to volume, filled and stored in amber colored bottles until further tests were done[10].

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

Ingredients	Formulation code			
	G1	G2	G3	G4
Meloxicam (mg)	100	100	100	100
Sodium Alginate (% w/v)	2.0	2.0	2.0	1.0
HPMC K100M (% w/v)	0.5	0.6	1.0	0.8
Calcium carbonate (% w/v)	1.0	2.0	1.0	2.0
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 (% w/v)	0.5	-	0.7	-
Distilled water (up to ml)	50	50	50	50

Evaluation of formulations

Determination of pH

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

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 0.1N HCl. Contents of Meloxicam was measured at maximum absorbance at 362 nm using UV-Visible Spectrophotometer (Biotech eng. UV-9200, UK)[12].

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. 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 remains without a change[13].

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for 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 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].

***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°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 constantly floated on the dissolution medium surface (duration of floating, TFT) were recorded[15].

***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°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. The drug concentration of each sample was determined spectrophotometrically at 362 nm[16].

Statistical analysis

Formulations were tested in triplicate, and each analysis was duplicated. Student's -test using Graph Pad Prism software 5.0 version (Graph Pad Software Inc., San Diego, CA, USA) was used in the study and the values <0.05 were considered.

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 Ca^{2+} 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 floating agent[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 pH 4 to pH 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 h 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 was dependent upon the polymer and $CaCO_3$ concentration[20].

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

Code	pH	% Drug content	Gelling capacity	Viscosity (cps)	Floating lag time (Sec)	Floating duration (h)
G1	7.25±0.09	98.26±0.21	+++	165.00±0.43	24.00±0.47	12
G2	7.48±0.15	97.38±0.17	+++	192.00±0.37	22.00±0.35	13
G3	7.82±0.32	98.24±0.19	++	177.00±0.62	18.00±0.27	14
G4	8.12±0.49	96.43±0.25	+	210.00±0.55	20.00±0.08	12

Mean±SD, n=3, $p< 0.05$

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 h (Table 2). This indicates that the formulations could provide a sustained delivery of Meloxicam to the absorption window for more than 12 h as long as the gel was not depleted of the drug. Therefore, higher polymer concentrations imparted extra strength to the gels to remain buoyant at least for 12 h. 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].

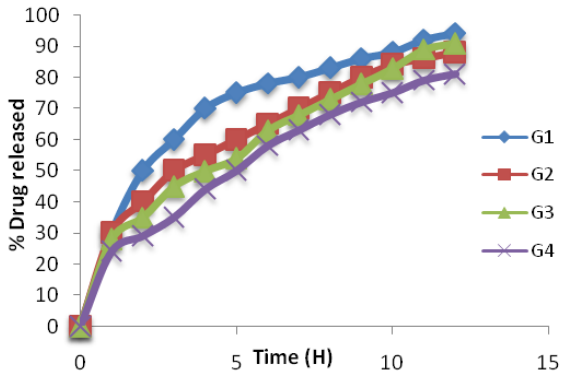

Figure 1: Cumulative *in-vitro* drug release of *in situ* gel formulations of Meloxicam

All the *in situ* gel formulations showed significant burst release where approximately, 24-30% of Meloxicam was released within the first h. 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 h. Maximum drug release was shown by formulations of batch G1 (94.38%).

CONCLUSIONS

In this research work, *in situ* gel formulations of Meloxicam were 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 h and slowly released Meloxicam during 12 h

period. It is concluded that Meloxicam could be targeted to stomach and be released slowly over a period of time and can improve bioavailability of the drug, dosing frequency and hence patient compliance.

AUTHOR'S CONTRIBUTION

Anyanwu NCJ: writing, review, and editing, data curation. **Adogo LY:** writing, review and editing, data curation. **Ajide B:** formal analysis, writing, review, and editing. All the authors approved the finished version of the manuscript.

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DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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