Available online on 15.7.2017 at <http://ujpr.org>
Universal Journal of Pharmaceutical Research
 An International Peer Reviewed Journal
 Open access to Pharmaceutical research

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial Share Alike 4.0 License which permits unrestricted non commercial use, provided the original work is properly cited

Volume 2, Issue 3, 2017

Open Access

RESEARCH ARTICLE

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

Anyanwu NCJ, Adogo LY¹, Ajide B²

Department of Biological Science, Faculty of Science and Technology, Bingham University, Karu, Nigeria.

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.

Article Info: Received 1 May 2017; Revised 8 June; Accepted 5 July, Available online 15 July 2017

Cite this article-

Anyanwu NCJ, Adogo LY, Ajide B. Development and evaluation of *in situ* gelling gastroretentive formulations of Meloxicam. Universal Journal of Pharmaceutical Research 2017; 2(3): 10-13.

DOI: <http://doi.org/10.22270/ujpr.v2i3.R3>

Address for Correspondence:

Anyanwu NCJ, Department of Biological Science, Faculty of Science and Technology, Bingham University, Karu, Nigeria,
 E-mail: anyanwunneomacconfidence@gmail.com

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 exchange¹. 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 fluids². 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 system³.

Advantages of *in situ* gel forming systems includes ease of administration and reduced frequency of administration, improved patient compliance and comfort and improved bioavailability⁴. Furthermore

solid dosage forms are associated with swallowing problems for geriatric, pediatrics and bedridden patient and chances of accidental burst release⁵. 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 compliance⁶.

Meloxicam is a NSAID belonging to the class of oxicams⁷. 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 swelling⁸. It is practically insoluble in water. This low solubility in biological fluids, results into slower rate of absorption and poor bioavailability after oral administration⁹.

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 60°C while stirring on a heating magnetic stirrer (Finlab, Nigeria Ltd). After cooling to below 40°C , 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 done¹⁰.

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

1. 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 measurements¹¹.

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 0.1N HCl. Contents of Meloxicam was measured at

maximum absorbance at 362nm using UV-Visible Spectrophotometer (Biotech eng. UV-9200, UK)¹².

3. 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 change¹³.

(+) 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 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 temperature¹⁴.

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 $37 \pm 1^\circ\text{C}$ 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 recorded¹⁵.

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°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 362nm¹⁶.

Statistical analysis

Formulations were tested in triplicate, and each analysis was duplicated. Student's *t*-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 structure¹⁷. 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 agent¹⁸. 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 phases¹⁹. 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 concentration²⁰.

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 $\pm$ 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 buoyancy²¹.

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%).

CONCLUSION

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 the 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

The manuscript was carried out, written, and approved in collaboration with all authors.

ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Bingham University, Karu, Nigeria to provide necessary facilities for this work.

CONFLICT OF INTEREST

No conflict of interest associated to this work.

REFERENCES

- Jivani RR, Patel CN, Patel DM, Jivani NP. Development of a novel floating *in-situ* gelling system for stomach specific drug delivery of the narrow absorption window drug Baclofen. Iranian J Pharma Res 2010; 9(4):359-368. PMID: 24381600
- Kubo W, Konno Y, Miyazaki S, Attwood D. *In situ*-gelling pectin formulations for oral sustained delivery of paracetamol. Drug Dev Ind Pharm 2004; 30, 593-599. <https://doi.org/10.1081/DDC-120037490>
- Badgajar SD, Sontakke MA, Narute DR, Karmakar RR, Tupkay SV and Barhate SD. Formulation and evaluation of Sumatriptan Succinate nasal *in situ* gel using Fulvic acid as novel permeation enhancer. Int J Res Dev 2010; 2(8): 1-52.
- Varshosaz J, Tavakoli N and Roozbahani F. Formulation and *in vitro* characterization of ciprofloxacin floating and bio adhesive extended release tablets. Drug Dev 2006; 13(4), 277-285. <https://doi.org/10.1080/10717540500395106>
- Shamsuddin, Fazil M, Ansari SH, Ali J. Development and evaluation of solid dispersion of spironolactone using fusion method. Int J Pharm Investig 2016; 6(1): 63-68. <https://doi.org/10.4103/2230-973X.176490>
- Wamorkar V, Varma MM, Manjunath SY. Formulation and evaluation of stomach specific *in situ* gel of metoclopramide using natural, bio-degradable polymers. Int J Res Pharm Biomed Sci 2011; 2(1), 193-201.
- Singh G, Lanes S, Triadafilopoulos G. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Am J Med 2004; 117 (9): 100-6. <https://doi.org/10.1093/rheumatology/37.9.937>
- Engelhardt G, Homma D, Schlegel K, Utzmann R, Schnitzler C. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. Inflamm Res 1995; 44 (10): 423-433. <https://doi.org/10.1007/BF01757699>
- Kimble B, Black LA, Li KM, Valtchev P, Gilchrist S, Gillett A, Higgins DP, Krockenberger MB, Govendir M. Pharmacokinetics of meloxicam in koalas (*Phascolarctos cinereus*) after intravenous, subcutaneous and oral administration. J Vet Pharmacol Therap 2013; 36 (5): 486-493. <https://doi.org/10.1111/jvp.12038>
- Javadzade Y, Hamedeyazda S, Adibkia K, Kiafar F, Zarrintan MH, Bazregar-Jalali M. Evaluation of drug release kinetics and physicochemical characteristics of metronidazole floating beads based on calcium silicate and gas-forming agents. Pharm Dev Technol 2010; 15(4):329-38. <https://doi.org/10.3109/10837450903196843>
- Hasan MJ, Kamal BA. Formulation and evaluation of ranitidine hydrochloride as floating *in situ* gel. Int J Pharm Pharm Sci 2014; 6 Suppl 2:401-5.
- Garcia MS, Pedreno CS, Albero MI, Marti J. Spectrophotometric methods for determining meloxicam in pharmaceuticals using batch and flow-injection procedures, Euro J Pharm Sci 2000; 9, 311-316. [https://doi.org/10.1016/S0928-0987\(99\)00069-X](https://doi.org/10.1016/S0928-0987(99)00069-X)
- Jayswal BD, Yadav VT, Patel KN, Patel BA, Patel PA. Formulation and evaluation of floating *in situ* gel based gastro retentive drug delivery of Cimetidine. Int J Pharm Res Sch 2011; 1: 327-337.
- Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195(1-2): 125-135. [https://doi.org/10.1016/S0378-5173\(99\)00378-6](https://doi.org/10.1016/S0378-5173(99)00378-6)
- Kajale AD, Chandewar AV. Formulation and evaluation of oral floating *in situ* gel of Tramadol hydrochloride. The Pharmac Chem J 2016; 3(2):267-279
- Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13:123-33. [https://doi.org/10.1016/S0928-0987\(01\)00095-1](https://doi.org/10.1016/S0928-0987(01)00095-1)
- Thomas LM. Formulation and evaluation of floating oral *in-situ* gel of metronidazole. Int J Pharm Pharm Sci 2014; 6(10), 265-269.
- Osmond JD, Cruz PS, Faith M Uckun. Conceive a novel non contraceptive vaginal vehical for lipophilic microbicides. AAPS Pharm Sci Tech 2004; 6(1): 1-9. <https://doi.org/10.1208/pt060111>
- Mahagen Y, Patidhar V, Balaram Y, Gopkumar P, Sridevi G. Formulation and evaluation of floatable *in-situ* gel for stomach-specific drug delivery of carbamazepine. Pharm Pharm Sci 2014; 3(1):37-43.
- Goole J, Vanderbist F, Amighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm 2007; 334:35-41. <https://doi.org/10.1016/j.ijpharm.2006.10.018>
- Rohith G, Sridhar BK, Srinatha A. Floating drug delivery of a locally acting H₂-antagonist: an approach using an *in situ* gelling liquid formulation. Acta Pharm 2009; 59:345-54. <https://doi.org/10.2478/v10007-009-0021-z>