CODEN (USA): IJPB07 ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)
Journal homepage: www.ijpbr.in

Research Article DOI: https://doi.org/10.30750/ijpbr.6.4.10

Development, Characterization and bioavailability enhancement of oral floating sustained release beads containing Indomethacin

Rajesh Kumar Sharma*, Naresh kalra, Jayesh Dwivedi, G. Jeyabalan, Gurpreet Singh

Department of Pharmaceutical Sciences, Sunrise University Alwar, India

ARTICLE INFO:

Article history:
Received: 17 September 2018
Received in revised form:
22 November 2018
Accepted: 24 November 2018
Available online: 31 December 2018

Keywords:
Floating drug delivery system, *Gastro retentive*, Indomethacin

Abstract

The purpose of this research was to prepare and evaluate floating gastroretentive beads of Indomethacin an Non-steroidal anti-inflammatory agent for increased drug bioavailability. Floating beads were prepared by dripping Method using different polymers in varying ratios. The formulations were optimized on the basis of floating ability and *in-vitro* drug release. The floating beads were evaluated for micromeritic properties, entrapment efficiency, as well as in-vitro buoyancy study and drug release. Indomethacin was estimated in the formulation by using UV/Visible spectrophotometer (Shimazdu UV-1800) at 321 nm. The floating beads shows drug entrapment efficiency, buoyancy and yield the 72.55%, 60.2 and 74.3%respectively. *In vitro* drug release study confirms formulation I4 was the best formulation as it releases 99.28 % of Indomethacin at the end of 24 hrs in controlled manner.

Introduction

Indomethacin, 2-[1-(4-cholorobenzoyal)- 5-methoxy-2methyl-indol-3-yl] acetic acid, mol wt= 357.787g/mol (fig 1), a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties, is used to treat osteoarthritis and control acute pain. The use of indomethacin in the traditional pharmaceutical forms such as tablets and capsules requires administration of three or four unit doses per day. Most patients on this therapeutic regimen are elderly and are often on treatment of other disease states, such as hypertension, depression etc[1,2]. Oral administration is the most convenient and commonly employed route of drug delivery for the drug candidates who show absorption window in the GIT and proximal gut[3]. But it has limitation of less absorption, poor residence time and subsequently poor bioavailability which is the major obstacle to the development of oral delivery of such agents[4]. Due to this considerable attention has been focused on the development of Novel Drug Delivery Systems (NDDS) like microspheres, nanoparticles, liposomes, etc The objectives of the proposed research work is to select a foaming agent that enhances the formability and foam stability and thereby, enhances the gastric retention in the GIT. & to formulate a floating (GR) drug delivery system of indomethacin[5,6]. Floating drug delivery system[7] (FDDS) promises to be a potential approach for gastric retention. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Several approaches are currently used to prolong gastric retention time[8-10].

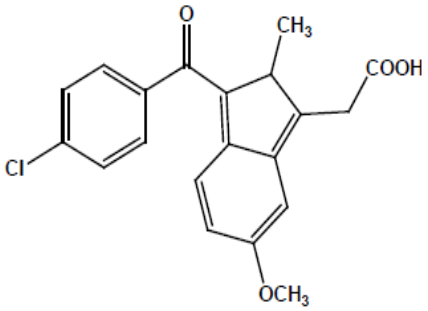

Figure 1: Structure of Indomethacin

***Corresponding Author: Rajesh Kumar Sharma,** Department of Pharmaceutical Sciences, Sunrise University, Alwar, Rajasthan, Chemistry, India. **E-Mail:** sharmapharma82@gmail.com

Materials and Methods

Materials: Indomethacin was received as a kind gift from Oniosome healthcare pvt. Ltd., Mohali. Sodium Alginate, Poloxamer 188 were procured from. Thomas Baker Pvt. Ltd., Mumbai Signet Chemical Corp. Pvt. Ltd., Mumbai. Methanol from Fihar Chemical Ltd., Ahmedabad.

Preformulation Studies

Preformulation studies are important for the development of dosage form for achieving the goal of designing optimum drug delivery system. The objective of Preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

Characterization of Indomethacin

The drug sample obtained was identified by various analytical techniques such as IR Spectroscopy, UV spectroscopy, melting point, partition coefficient and solubility etc. Melting point is the temperature at which a material melts at atmospheric pressure. Melting points are usually expressed as a range between when the material begins to melt and when it has completely melted.

Partition coefficient is a measurement of drug's lipophilicity and its ability to cross cell membrane. Partition coefficient of Indomethacin were determined at 37 ± 0.5 °C by taking 5 ml of octanol which was saturated with 5 ml of water by using separating funnel. After shaking the system remained undisturbed for half an hour. About 100 mg of drug was added to this solution and shake again. Two layers were separate through separating funnel after 24 hr and filterer through Whatman grade filter, and the amount of Indomethacin solubilized, was determined by measuring the absorbance at 317 nm against reagent blank through double beam UV/Vis spectrophotometer[5].

Solubility study was carried out with different solvents such as, 0.1 N HCl, Phosphate buffer pH6.8, pH7.4, ethanol, methanol, DCM, Acetone in water bath shaker at 37^{o}C and kept it for 24 hours. Took 2 ml of each solvent in culture tube. Add excess amount of drug in 2ml, 0.1N HCl, Phosphate buffer pH6.8, pH7.4 Methanol, ethanol, DCM, Acetone solution using vortex shaker. Put the solution into water bath shaker for 48 hr at 37°C. After 48 hr centrifuge the sample at 10000 rpm followed take the supernatant and diluted with buffer if required. Scan the sample in UV spectroscopy between 200-400nm.

Fourier Transform Infrared Spectrophotometric was used for structure analysis of drug. The potassium bromide (KBr) disc technique[11].

Preparation of foam solution using different foaming agents

Sodium alginate was dissolved in distilled water at a concentration of 1.5% w/v. Different foaming agents in varied amount was then added into sodium alginate solution and agitated vigorously for 20min at 2600pm. Foams were immediately transferred into a graduated cylinder for continued observation.

Preparation of Alginate/Poloxamer floating beads dripping Method

Floating beads of indomethacin was prepared by dripping method using poloxamer 188 as foaming agent and sodium alginate as foam stabilizer. Sodium Alginate was dissolved in double distilled water at a concentration of 0.5 to 2.5%w/v, poloxamer 188 was then added into sodium alginate solution while stirring at 2600 rpm held by mechanical stirrer (REMI Mumbai) equipped with three blade propeller, at room temperature. The whole system was stirred for 20 minutes to completely form the foam solution. Drug (75 mg) was added into foam solution under vigorous stirring condition continuously. The foam solution was pumped using a syringe of 0.5 into 1% CaCl2 (100 ml). The distance between the edge of the needle and the surface of the CaCl2 medium was about 10 cm. The beads formed were left in the solution with gentle stirring for 10 min at room temperature to be cured. The beads were collected, washed with distilled water twice and oven-dried subsequently (40^{o}C).

Table 1: Composition of different formulation Indomethacin

Batch No.	Sodium Alginate (%w/v)	Poloxamer 188 (g)	Indomethacin (g)	% w/v $CaCl_2$ Solution	rpm
I1	1.5	0.15	0.075	0.5%	2600
I2	2	0.15	0.075	0.5%	2600
I3	2.5	0.15	0.075	0.5%	2600
I4	1.5	0.15	0.075	1%	2600
I5	2	0.15	0.075	1%	2600
I6	2.5	0.15	0.075	1%	2600
I7	1.5	0.15	0.075	2%	2600
I8	2	0.15	0.075	2%	2600
I9	2.5	0.15	0.075	2%	2600

Evaluation of floating beads of Indomethacin

Percentage entrapment efficiency (EE %) and Drug Loading (%)

10 mg of floating beads were weighed and was dissolved in 10 ml of methanol with agitating at room temperature for 12 hours. Then it was filtered through wattmann's filter paper. The filtrate was assayed by spectrophotometrically at maximum wavelength. The drug loading (%) and entrapment efficiency (%) was calculated according to following relationship.

% Drug Loading = Weight of drug loaded in beads in gms / Weight of quantity of beads in gms

EE (%) = WA/Wr Where:

WA = Actual drug content

Wr = theoretical drug content

Percentage (%) yield

The prepared floating beads were collected and weighed. The measured weight was divided by the total weight of all the excipients and drug. The % yield was calculated using following formula.

% yield = Total bead weight/Total weight of all excipients

Percent Floating

Beads 100 of each batch were placed in 100 ml of 0.1 N HCl, agitated at 100 rpm and temperature was maintained at 37±2ºC. The number of sinking beads was observed visually after 24 hours. The percentage of floating beads was calculated according to
the following equation:

F (%)= NF/NT×100 Where:

F= Floating percent

NF = Number of floating beads

NT = Total number of beads.

Evaluation of Optimized Formulation

Shape and Morphology Study

The shape and morphology study of optimized formulation was performed by Scanning Electron Microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminium stub. The stubs were then coated with platinum to a thickness under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The stub containing the coated samples was placed in SEM chamber. The samples were then randomly scanned, and photomicrographs were taken at acceleration voltage of 10 kV.

***In-vitro* drug release study**

The beads equivalents to weight containing 100mg of optimized formulation were immersed in dissolution medium. To assure the release of drug in solution at appropriate rate, dissolution test has been performed for optimized formulation in triplicate. The *in-vitro* release of optimized formulation from the beads was examined using USP Type I dissolution apparatus. 0.1 N HCl (SGF) (900 ml) was used as the dissolution medium and maintained at 37±0.5ºC at a rotation speed of 100 rpm. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and replaced by 5 ml of fresh dissolution medium. Samples were assayed spectrophotometrically at 278 nm after filtration through a 0.45 μm membrane filter (Millipore) against 0.1N HCl as blank.

Result and discussion

Pre-formulation Studies

Melting Point Determination (The melting point was observed with the capillary fusion method).

The melting point of Indomethacin was found to be in range 157-160^{0}C which is of the pure drug. Hence drug sample was free from any type of impurities.

Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P. The partition coefficient of indomethacin in Water: n-octanol was found to be 4.27± 0.12 this indicates that the drug is lipophillic in nature. Indomethacin is highly soluble in ethanol, methanol as followed by DMF in Table 2 .

Table 2: Solubility of indomethacin

Name of Solvent	Solubility of Indomethacin
0.1 NHCL	0.934±0.002
Phosphate buffer pH 6.8	1.564±0.012
Ethanol	22.307±0.008
Methanol	20.307±0.003
Phosphate buffer pH 7.4	0.105±0.007
DCM	25.43±0.002
Acetone	15.34±0.001

Standard curves of Indomethacin

Establishment of Calibration curve in methanol: Absorbance data for standard calibration curve is given in the Table 3. Using the absorbance of Indomethacin at varied concentrations, calibration curve was constructed. The calibration equation for straight line was observed to be y=0.01+0.032 with correlation coefficient of 0.995 this was used for the determination of concentration of unknown samples.

Table 3: UV calibration data of Indomethacin in methanol (λ_{max} = 317nm)

S. No:	Concentration (µg/ml)	Absorbance (mean±SD)
1	10	0.108
2	20	0.228
3	30	0.343
4	40	0.444
5	50	0.564
6	60	0.623
7	70	0.754
8	80	0.826
9	90	0.914

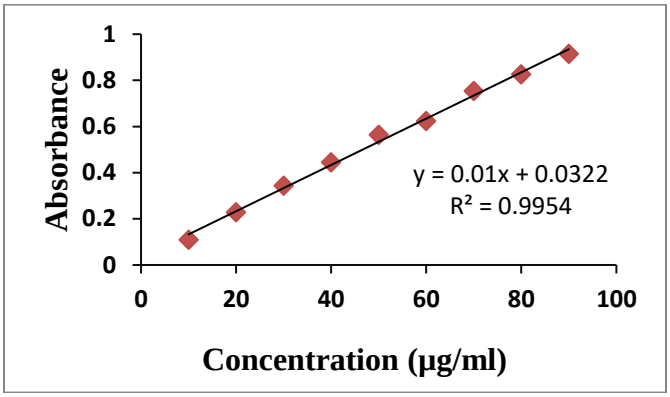

Fig.2: Standard calibration curve of Indomethacin in methanol (λ_{max} = 317nm)

Characterization of Indomethacin by FT-IR spectroscopy: The spectra obtained from FT-IR spectroscopy studied at wavelength from 4000cm^{-1} - 400cm^{-1} are shown in Fig 3

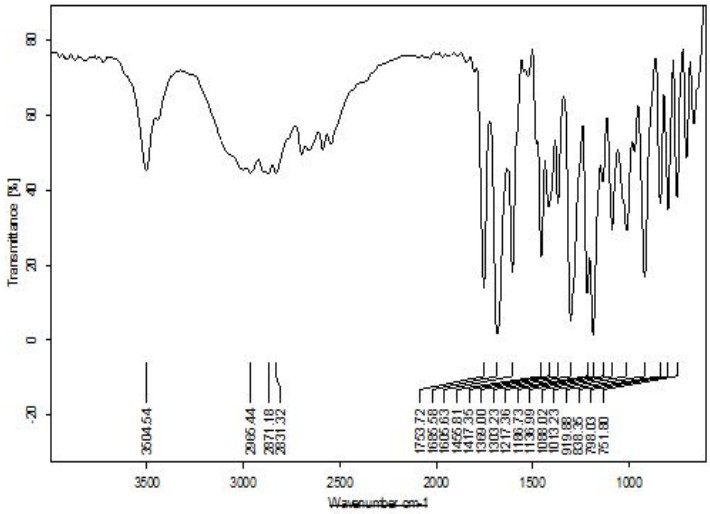

Fig.3: FT-IR spectrum of Indomethacin

Presence of characteristic peaks of Indomethacin the FT-IR spectra of physical sample (drug: polymer) indicates the absence of chemical interaction between drug and excipients are employed in the study.

Characterization of foam solution based on Foamability and Foam Stability: The data of formability and foam stability is shown in Table 4.

Table.4: Formability and Foam Stability

Poloxamer 188					
Amount (mg)	50	100	150	200	250
Foambility (%)	1.44±0.11	1.76±0.88	2.0±0.14	1.48±0.21	1.92±0.025
Foam stability (min)	10.0±4.0	22±3.0	32±2.0	50±3.0	60±3.0

Foam is defined as a dispersion of gas in a liquid or a solid. The presence of a foaming agent is essential for foam generation and stabilization. Foaming agents are ampiphilic substances; the hydrophilic part of a molecule is responsible for its solubility in water. When a foaming agent is added in water, the hydrophobic parts arrange themselves in a way to minimize the area of contact with water. This leads to their orientation at the air-water interface and formation of micelle in the bulk of liquid phase. When the foaming agent is absorbed into the air-water interface, the surface tension of water is lowered and surface pressure is increased. The rate of foaming agent adsorption depends on its diffusion rate, concentration and agitation in the bulk of liquid. Addition of some polymers leads to the formation of surface-polymer complex through interactions between polymer and surfactant, which contributes foam stability to formable formulations. In some homologous series of foaming agents, the maximum foaming stability is observed at a concentration equal to. Or near to the critical micelle concentration.

Table 5 Data representation of % yield and %EE of Indomethacin containing Sodium Alginate beads

Formulation code	**% Yield**	**% EE**	**Physical Appearance**
I1	62.6	70.875±0.005	Oval
I2	74.1	66.375±0.018	Round
I3	73.9	74.125±0.046	Oval
I4	67.5	68±0.013	Oval
I5	69.6	63.375±0.037	Round
I6	75.4	73.375±0.087	Round
I7	65.9	63.5±0.065	Oval
I8	72.1	68.25±0.022	Round
I9	68.1	73.375±0.034	Round

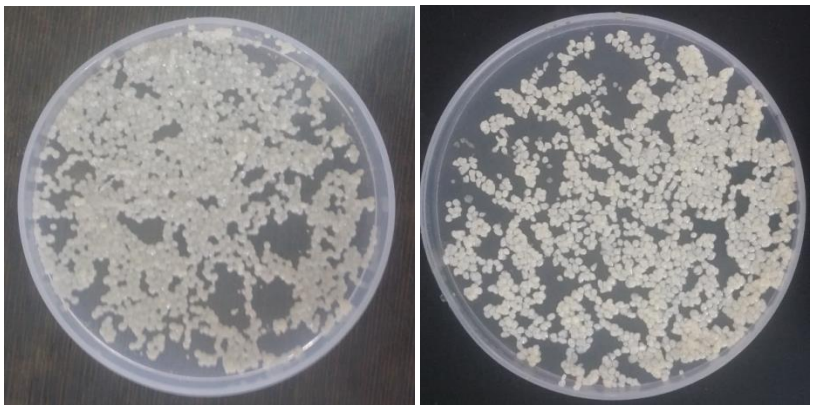

Figure 4: Beads of Indomethacin

***In-vitro* drug release:** Beads equivalent to weight 100 mg were taken and *in-vitro* dissolution study was carried out.

Table.6 Percentage drug release of pure drug (Indomethacin) and I4 formulation

Time	Drug release of Pure Drug	% Drug release of I4 formulation
0	0	0
0.15	9.5±0.002	7.3±0.023
0.25	17.9±0.057	12.78±0.079
0.5	25.11±0.009	22.21±0.036
1	39.61±0.012	30.67±0.021
2	55.75±0.057	38.32±0.009
3	68.63±0.029	44.43±0.029
4	77.23±0.037	51.98±0.005
5	86.45±0.068	58.74±0.014
6	90.34±0.002	63.13±0.078
7	-	69.29±0.099
8	-	73.02±0.156
10	-	78.13±0.064
12	-	83.09±0.003
14	-	89.89±0.019
16	-	94.45±0.035
24	-	99.28±0.029

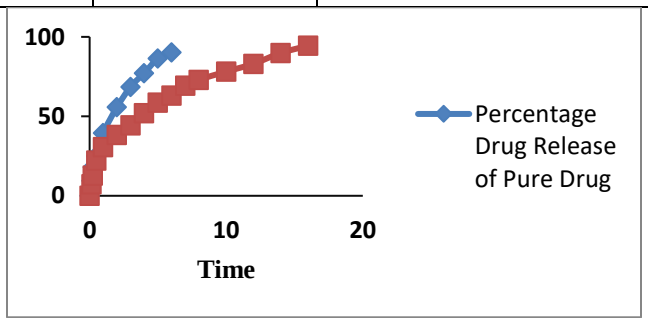

Fig 5: Percentage drug release of pure drug and I4 Formulation

Summary & Conclusion

The objective of the present study is to formulate and evaluate novel gastric floating

Inner-porous beads of Indomethacin using poloxamer 188 as foaming agent and sodium alginate as foam stabilizer. Sodium Alginate was dissolved in double distilled water at a concentration of 0.5w/v, 1%w/v and 2% w/v calcium chloride as cross linking agent by dripping method to prolong the gastric retention time, provide sustained release effect and prevent degradation of drug in acidic environment of stomach. Optimization of foaming agent was done on the basis of foamability and foam stability while stability increases up to 150 mg of surfactant and then foamability decreases. Drug release from the beads was sustained up to 24 hours. The cumulative % drug release of Indomethacin was found to be 99.28%.

References

1. Chen XQ, Jin YY, Tang G. New Pharmacology, 15th ed. People Health Publishing House. Beijing. 2003; 186–87.
2. Mason L, Edward J, Moore RA, McQuay HJ. Single dose oral indomethacin for the treatment of acute postoperative pain. Cochrane Database Syst. Rev. 2010; 4: 1–2.
3. Dixit N. Floating Drug Delivery System. Journal of current pharmaceutical research. 2011; 7(1): 6-20.
4. Suryawanshi. A. Floating Drug Delivery System- a review. American journal of pharmaceutical research. 2012; 2(1): 138-152.
5. Modi Kushal. Oral controlled release drug delivery system: an overview. International research journal of pharmacy. 2013; 4(3): 70-76.

6. Ruchi Taneja. Floating microsphere: a potential gastroretentive drug delivery system. International journal of comprehensive pharmacy. 2013; 04 (01): 1-9.

7. Park HJ, Choi BY, Hwang SJ, Park JB, Preparation of alginate beads for floating drug delivery systems: effects of CO_2 gas forming agents, Int J Pharm, 2002;239: 81-91.

8. Muriel P, Mourelle M, Prevention by siymarin of membrane alterations in acute CCl4 liver damage, J Appl Toxicol, 1990;10:275.

9. Satinder Kakar, Ramandeep Singh, Alok Semwal Drug release characteristics of dosage forms: a review, Journal of Coastal Life Medicine, 2014;2(4):332-336.

10. Rahman Z, Ali M, Khar RK, Design and evaluation of bilayer floating tablets of captopril, Acta pharm, 2006;56:49-57.

11. Yao H, Yao H, Zhu H, Yu J, Zhang L, Preparation and evaluation of a novel gastric floating alginate/poloxamer inner-porous beads using foam solution, Int. J. Pharm. 2012;422: 211-219.

12. Benigno MS, Marta MC, Amparo SN. Alfonso DG, a physico-chemical study of the interaction of ciprofloxacin and ofloxacin with polyvalent cations. Int J Pharm., 1994; 106(3): 229-354.

13. Satishbabu BK, Sandeep VR, Shrutirag R, Formulation and evaluation of floating drug delivery system of famotidine, Indian journal of pharmaceutical and sciences, 2010 nov-dec;72(6):738-744

Cite this article: **Rajesh Kumar Sharma, Naresh kalra, Jayesh Dwivedi, G. Jeyabalan.** Development, Characterization and bioavailability enhancement of oral floating sustained release beads containing Indomethacin. **Indian J. Pharm. Biol. Res.2018; 6(4):48-54.**