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# Formulation and statistical optimization of multiple-unit ibuprofen-loaded buoyant system using $2^3$-factorial design

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ABSTRACT

This present investigation deals with the development and optimization of buoyant beads containing ibuprofen by emulsion-gelation method for gastroretentive delivery. The effect of three independent process variables like amount of sodium alginate, magnesium stearate, and liquid paraffin on drug entrapment, density, and drug release of buoyant beads containing ibuprofen was optimized using $2^3$ factorial design. The observed responses were coincided well with the predicted values, given by the optimization technique. The optimized beads showed drug entrapment efficiency of 83.07 ± 3.25%, density of 0.89 ± 0.11 g/cm$^3$, cumulative drug release of 35.02 ± 1.24% after 8 h, and floated well over 8 h in simulated gastric fluid (pH 1.2) with 4.50 min buoyant lag-time. The average size of all buoyant beads ranged from 1.43 ± 0.05 to 1.82 ± 0.14 mm. The buoyant beads were characterized by SEM and FTIR spectroscopy for surface morphology and excipients–drug interaction analysis, respectively. All these beads showed prolonged sustained release of ibuprofen over 8 h in simulated gastric fluid (pH 1.2). The ibuprofen release profile from these buoyant beads followed Korsmeyer–Peppas model over a period of 8 h with anomalous (non-Fickian) diffusion mechanism for drug release.



*Keywords:* Ibuprofen; Sodium alginate; Magnesium stearate; Buoyant beads; Sustained release; Optimization; Factorial design

## 1. Introduction

Oral administration is always the preferred means of drug delivery to the systemic circulation due to low cost of therapy, ease of administration, patient compliance, *etc.* Many attempts have been made to develop sustained release oral dosage forms with better clinical effects and reduced dosing frequency. However, the success of these conventional sustained release dosage forms for oral use is limited due to the inability to increase their residence time in the stomach and proximal portion of the small intestine (Sriamornsak et al., 2005). The variable and too rapid gastrointestinal transit can result incomplete drug release from the dosage form at the absorption site in the gastrointestinal tract (GIT) leading weaken efficacy of the administered dose. To overcome this restrictions, in various oral sustained release dosage forms have been designated to be retained in the gastric region for prolonged period and released incorporated drugs to increase their bioavailability (Nayak et al., 2010b). Many approaches have been reported in the literature for improved gastroretention for oral sustained release dosage forms, *viz.* floatation (Nayak and Malakar, 2011), bio- or mucoadhesion (Nayak et al., 2010a), sedimentation (Rouge et al., 1998), unfoldable, expandable, or swellable systems (Klausner et al., 2003), super porous hydrogel systems (Chen et al., 2000), magnetic systems (Fujimori et al., 1994), *etc.* Every approach has its own limitations. For example, swelling and expanding systems may show a hazard of permanent retention in the desired site and bioadhesive systems may result in irritation of mucous layer due to high-localized concentration of the incorporated drugs (Singh et al., 2010). In addition, single-unit gastroretentive systems such as tablets or capsules may exhibit the all-or-none emptying phenomenon (Kanivva et al., 1988). On the other hand, multiple-unit dosage forms may be an alternative since they have been shown to reduce the inter- and intra-subject variabilities in drug absorption as well as to lower the possibility of

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dose-dumping characteristics, *etc.* (Ishak et al., 2007; Elmowafy et al., 2009). Multiple-unit floating systems are designated to be remained buoyant on the gastric fluid due to their lower bulk density compared to that of the aqueous medium, thus retained in the stomach for prolonged period and the drug is slowly released (Sing and Kim, 2000). Various multiple-unit floating systems have been developed in various forms of principles such as air compartment multiple-unit systems (Iannuccelli et al., 1998), hollow microspheres (microballoons) prepared by emulsion solvent diffusion method (Sato et al., 2003; Jain et al., 2005), floating microspheres/beads based on low-density foam (Streubel et al., 2002; Yao et al., 2012), floating microspheres/beads based on gas formation technique (Sungthongjeen et al., 2006), and beads prepared by emulsion-gelation method (Malakar et al., 2012; Elmowafy et al., 2009; Bera et al., 2009; Sriamornsak et al., 2005).

In recent years, buoyant alginate gel beads as multiple-unit systems have been developed to prolong the gastroretention (Bera et al., 2009). However, various floatable alginate gel beads suffer from rapid drug release, which can be overcame with the addition of further additives (Ishak et al., 2007; Whitehead et al., 2000). Buoyancy in the alginate gel beads can be imparted by incorporating various low density oils such as mineral oils, olive oil, linseed oil, sunflower oil, groundnut oil, castor oil, menthe oil, *etc.* (Bera et al., 2009; Fursule et al., 2008; Elmowafy et al., 2009; Singh et al., 2011). The buoyancy can also be imparted in alginate gel beads by incorporating magnesium stearate (Ishak et al., 2007), which is a low-density material. Nevertheless, the combined effect of two low-density materials like mineral oil and magnesium stearate incorporation on the floating and drug release properties of alginate beads is not reported until now. In the present investigation, we attempted to develop buoyant alginate beads by incorporating a low-density mineral oil (liquid paraffin) with another low-density material, magnesium stearate for floating delivery of ibuprofen.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with a short half-life (1.8–2 h), and commonly used in the treatment of arthritis, post-operative and dental pain (Eichie et al., 2009). As its duration of action is short, repeated administration of the same single dose is necessary during 24 h (Jha and Bhattacharya, 2008). Therefore, development of buoyant system containing ibuprofen was attempted to improve gastroretention with sustained drug release for prolonged period to minimize the dosing frequency and chances of side effects.

Pharmaceutical formulators often face the challenge of finding the appropriate combination of independent process variables (factors) that will produce the product with optimum properties (Nayak and Pal, 2011). However, this can be easily analyzed and understood using established statistical design of experiment tools such as factorial designs are considered the most effective in estimating the influence of individual process variables with minimum experimentation and time, where all factors are studied in all possible combinations (Joshi et al., 2010). Based on the factorial design of experiment, the optimization technique encompasses the generation of model equations for the investigated responses over the experimental design to determine the optimum formulation(s). The present investigation aims at developing a mineral oil-entrapped magnesium stearate-calcium alginate buoyant beads containing ibuprofen by ionotropically emulsion-gelation method as multiple-unit floating delivery systems using $2^3$ factorial design. The $2^3$ factorial design-based optimization was employed to investigate the effect of three independent process variables (factors), *i.e.*, amount of sodium alginate, magnesium stearate, and liquid paraffin on the properties of oil-entrapped magnesium stearate-calcium alginate buoyant beads containing ibuprofen, like drug entrapment, density, and drug release.

## 2. Experimental

### 2.1. Materials

Ibuprofen was purchased from B. S. Trader Pvt. Ltd., India. Sodium alginate (Central Drug House, India), calcium chloride (Merck Ltd., India), magnesium stearate (Loba Chemie, India), liquid paraffin (relative density = 0.84, Nice Chemicals Pvt. Ltd., India) were used. All chemicals and reagents used were of analytical grade.

### 2.2. Preparation of buoyant beads containing ibuprofen

The buoyant beads containing ibuprofen was prepared by emulsion-gelation method (Elmowafy et al., 2009). Briefly, required amount of sodium alginate was dissolved in 100 ml demineralised water with constant stirring. 500 mg of ibuprofen, required amount of magnesium stearate and liquid paraffin were added to sodium alginate solution. The final mixture containing sodium alginate, magnesium stearate, liquid paraffin and ibuprofen was homogenized for 10 min at 1000 rpm using a homogenizer (BL 232, BIO-LAB Instruments Mfg. Co., India) and stirring at 5000 rpm continuously for 30 min until the stable emulsion was formed. Then, the emulsion was dropped through 23 G needle into 5% (w/v) calcium chloride solution (100 ml), and the added droplets were retained for 15 min in the calcium chloride solution to complete the curing reaction. The prepared beads were filtered, washed twice with petroleum ether and kept the beads after drying at room temperature for 24 h. The dried beads containing ibuprofen were stored in desiccators until used.

### 2.3. Experimental design

$2^3$ (three-factor and two-level) factorial design was employed for optimization of the buoyant beads containing ibuprofen. Amount of sodium alginate ($X_1$, mg), amount of liquid paraffin ($X_2$, ml) and magnesium stearate ($X_3$, mg) were selected as independent variables (factors), which were varied at two levels (low and high). The drug entrapment efficiency (DEE, %), density (g/cm$^3$), and cumulative drug release after 8 h ($R_{8h}$, %) in simulated gastric fluid, pH 1.2 used as dependent variables (responses). Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA) was used for generation and evaluation of the statistical experimental design. The matrix of the design including investigated factors and responses are shown in Table 1.

For optimization, effects of various independent variables upon measured responses were modeled using following mathematical model equation involving independent variables and their interactions for various measured responses generated by $2^3$ factorial design is following:

$$Y = b_o + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3$$