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Low density multiparticulate system for pulsatile release of meloxicam

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Abstract

A blend of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release. A multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate (Florite RE®) and sodium alginate, for time and site specific drug release of meloxicam. Meloxicam was adsorbed on the Florite RE® (FLR) by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR powder was used to prepare calcium alginate beads by ionotropic gelation method, using 3^2 factorial design. Developed formulations were evaluated for yield, entrapment efficiency, image analysis, surface topography, mechanical strength, apparent density, buoyancy studies and dissolution studies. Entrapment efficiency of different formulations varied from 70% to 94%. Formulations show a lag period ranging from 1.9 to 7.8 h in acidic medium followed by rapid release of meloxicam in simulated intestinal fluid USP, without enzymes (SIF). Complete drug release in SIF occurred in less than 1 h from the formulations. The size of beads varied from 2.0 to 2.7 mm for different batches. Prepared beads were spherical with crushing strength ranging from 182 to 1073 g. Floating time was controlled by density of beads and hydrophobic character of drug. A pulsatile release of meloxicam was demonstrated by a simple drug delivery system which could be useful in chronopharmacotherapy of rheumatoid arthritis.

Keywords: Floating-pulsatile drug delivery system; Porous calcium silicate; Meloxicam; Rheumatoid arthritis

1. Introduction

Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are the widely used techniques for gastroretention (Akiyama et al., 1998; Nagahara et al., 1998; Singh and Kim, 2000); the latter have limitation of localized high drug concentration that could lead to irritation or ulceration.

Low density porous carriers have been used by researchers for formulation of FDDS (Yuasa et al., 1996a; Streubel et al., 2003). Porous carriers are low density solids with open or closed pore structure and provide large exposed surface area for drug loading. Their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse or dissolve in water, to completely hydrophobic ones, which float on water for hours. Due to wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes; some of these includes development of novel drug delivery systems like floating drug delivery systems, sustained drug delivery systems; improvement of solubility of poorly soluble drugs; enzyme immobilization etc. (Hanawa et al., 1996; Byrne and Deasy, 2002; Streubel et al., 2003; Ito et al., 2005). Examples of pharmaceutically exploited porous carriers include porous silicon dioxide (Sylysia®), polypropylene foam powder (Accurel®), porous calcium silicate (Florite®), magnesium aluminometa silicate (Neusilin®), porous ceramic, etc. Florite RE® (FLR) is a porous calcium silicate [$2CaO{\cdot}3SiO_2{\cdot}mSiO_2{\cdot}nH_2O$ ($1<m<2$, $2<n<3$)], and possess a lot of pores particularly of size 0.15 μm on its surface (Yuasa et al., 1996a). FLR has been used to adsorb oily and other drugs, as a compressive agent in pharmaceuticals and to improve solubility (Yuasa et al., 1994, 1996b; Kinoshita et al., 2003).

Pulsatile drug delivery system (PDDS) is based on principle of rapid release of a certain amount of drug within short

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time period after a predetermined off-release period, lag time (Kikuchi and Okano, 2002). Such novel drug delivery has been attempted for: (i) chronopharmacotherapy of diseases which show circadian rhythms in their pathophysiology (Sawada et al., 2004); (ii) avoiding degradation of active ingredients in upper GI tract, e.g. proteins and peptides (Rubinstein et al., 1997); (iii) for time programmed administration of hormones and many drugs such as isosorbide dinitrate, respectively to avoid suppression of normal secretion of hormones in body that can be hampered by constant release of hormone from administered dosage form and development of resistance (Parker et al., 1983; Goldenheim et al., 1987; Flaherty, 1989; Jimoh et al., 1995; Charloux et al., 1999; Terasawa et al., 1999); (iv) to avoid pharmacokinetic drug–drug interactions between concomitantly administered drugs (Sawada et al., 2003), etc. Meloxicam [4-hydroxy-2 methyl-*N*-(5-methyl-2-thiaolyl)-2H-1,2 benzothiazine-3-carboxamide 1,1-dioxide], is a practically water insoluble, preferential COX-2 inhibitor non-steroidal anti-inflammatory drug (NSAID) and used for rheumatoid arthritis and other joint pains (Roberts and Morrow, 2001). Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic–pitutary–adrenocortical axis (Crofford et al., 1997; Cutolo et al., 2003). Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness (Stehlin, 1997). A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system.

The majority of drugs are preferentially absorbed from the upper part of the small intestine (Rouge et al., 1996) hence, drug release at site of better absorption can improve therapeutic efficacy of drug. This is of more concern for drug delivery that is meant for pulse drug release after a lag period of 5–6 h following oral administration of dosage form. Oral pulsatile drug delivery systems that release drug after a lag period of 6–7 h usually release drug in large intestine (Niwa et al., 1995; Gazzaniga et al., 1995) however, the viscous contents of lower part of GI tract cause hindrance to the drug diffusion and also enzymatic degradation of some drugs makes it an unfavorable site for drug release (Basit and Lacey, 2001; Hoffman et al., 2004). Development of floating drug delivery systems involved complex techniques like intra-gastric floating device (Harrigan, 1977) or generation of gases (Umezawa, 1978). Disadvantages of floating drug delivery systems based on gas generation include controlling of in situ acid base reaction and in-turn drug release (Singh and Kim, 2000).

The major objectives of the present study were to develop a simple, multiparticulate, floating-pulsatile drug delivery system using porous carrier for obtaining no drug release during floating time followed by pulse drug release in small intestine. A blend of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release (lag period). Additionally, multiple unit dosage forms provide many relative advantages over single unit dosage forms such as predictable GI transit time, greater product safety, etc. (Ritschel, 1991).

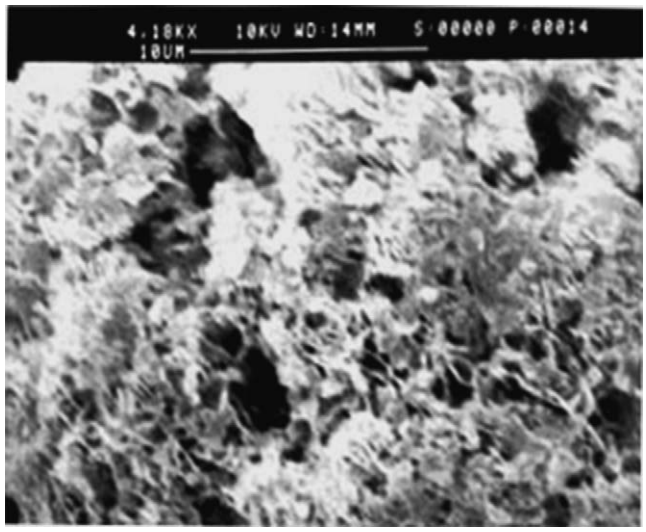

Fig. 1. SEM of Florite RE®.

Meloxicam is a low dose first line drug for symptomatic relief in rheumatoid arthritis hence; meloxicam was used as a model drug. Porous calcium silicate (FLR) possesses low density because of its porous nature (Fig. 1). Its hydrophilic nature improves dispersal of drug loaded powder in aqueous sodium alginate solution. Also, Florite® RE has a fine particle size of around 29 μm that allows extrusion of powder from needle bore. Hydrophobic or larger size carriers like Accurel® cannot be formulated as beads using simple techniques.

2. Materials and methods

2.1. Materials

Florite RE® (FLR) was a kind gift from Tokuyama Corporation (Yamaguchi, Japan). Sodium alginate (Protanal LF-240D; Signet Chem. Co., Mumbai, India) and meloxicam (Lupin Research Park, Pune, India) were supplied as a gift sample. All other chemicals were of analytical grade (Merck Ltd., Mumbai, India).

2.2. Adsorption of meloxicam over FLR

Accurately weighed quantity of meloxicam (200 mg) was dissolved completely in minimum quantity of chloroform, into a 500 ml round bottom flask. FLR (200/600/1000 mg) was dispersed into drug solution, with shaking. Chloroform was allowed to evaporate completely under vacuum in rotary evaporator (IKA® WERKE RV06ML, Stanfer, Germany) at a constant temperature and speed of 60 °C and 40 rpm, respectively. Collected free flowing powder was dried at 80 °C for 72 h.

2.3. Preparation of beads

The beads were prepared by the ionotropic gelation method (Acarturk and Takka, 1999). Three hundred and fifty milligrams

Table 1
Different batches with their respective composition (coded levels of factors), percent yield and percent entrapment efficiency

Batch code	FLR quantity (X_1)[a]	Concentration of sodium alginate solution (X_2)[b]	% Yield	Entrapment efficiency (%)
1	−1	−1	89.37 ± 7.87	82.14 ± 4.62
2	−1	0	92.67 ± 6.60	81.20 ± 4.84
3	−1	+1	100.17 ± 0.24	93.40 ± 0.34
4	0	−1	90.12 ± 9.19	72.99 ± 2.92
5	0	0	97.97 ± 2.08	70.29 ± 8.93
6	0	+1	100.25 ± 0.35	82.66 ± 5.38
7	+1	−1	98.50 ± 0.79	69.16 ± 4.87
8	+1	0	99.89 ± 0.31	68.20 ± 5.23
9	+1	+1	102.82 ± 3.99	71.11 ± 2.95
Control	+1	0	99.98 ± 0.58	–

[a] X_1 levels [200 mg (−1), 600 mg (0), 1000 mg (+1)].
[b] X_2 levels [0.5%, w/v (−1), 1.0%, w/v (0), 1.5%, w/v (+1)].

of drug adsorbed FLR powder was added to 10 ml of alginate solution (0.5/1/1.5%, w/v) and stirred for 4 min to form a uniform dispersion. Out of this, 8 ml dispersion was extruded through an 18 G (1.2 mm diameter) needle drop wise into 60 ml of stirred 0.054 M calcium chloride solution. The extrusion flow rate was approximately 4 ml/min. The gel beads formed were allowed to remain in the stirred calcium chloride solution for 10 min. Formed beads were then filtered, washed and dried at 40 °C for 24 h. A control batch using pure FLR without adsorbed meloxicam was also prepared using above procedure with 1% (w/v) sodium alginate solution.

2.4. Factorial design

Calcium alginate beads containing meloxicam adsorbed FLR were prepared based on the 3^2 factorial design. Quantity of FLR used to adsorb meloxicam (X_1) and concentration of sodium alginate solution (X_2) were selected as two independent variables. Three levels determined from preliminary studies of each variable were selected and nine possible batches were prepared using different levels of variables (Table 1). A polynomial equation (Eq. (1)) was used to study the effect of variables on different evaluation responses (Y), where the coefficients in the equation (β_0, β_1, β_2, β_{12}) were related to the effects and interactions of the factors.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2 \quad (1)$$

where β_0 is the arithmetic mean response of nine batches, β_1 and β_2 coefficients of factor X_1 and X_2 and β_{12} the coefficient of interaction of X_1 and X_2. The interaction (X_1X_2) shows how the dependent variable changes when two or more factors are simultaneously changed. UNISTAT® (Statistic version, Meglon, USA) was used to obtain values of coefficients in the equation and f statistics were used to identify statistically significant terms (Bolton, 1997).

2.5. Evaluation of beads

2.5.1. Yield and entrapment efficiency

Beads were weighed after drying and percent yield was calculated. For determination of entrapment efficiency (EE) 10 mg beads were dissolved in 100 ml of phosphate buffer (pH 7.6) by shaking on rotary shaker (Steelmet Industries, Pune, India) at 200 rpm overnight. The solution was filtered using 0.45 μm pore size filter and after sufficient dilution with phosphate buffer (pH 7.6) analyzed spectrophotometrically at 359 nm (JASCO-V500, Japan). Entrapment efficiency was calculated by Eq. (2),

$$\text{EE} = \left(\frac{\text{actual drug content in beads}}{\text{theoretical drug content in beads}} \right) \times 100 \quad (2)$$

2.5.2. Image analysis and surface topography

The images of beads were captured using a stereomicroscope (Carl Zeiss, Germany) attached with a digital camera (WAT-202, Watec, Japan). The captured images were analyzed using Biovis Image Plus software (Expert Tech Vision, India). Twenty beads of each batch were analyzed. Average diameter and different shape factors such as circulatory factor and roundness were determined. Circulatory factor is ratio of equivalent to actual perimeter of the particle.

Beads were coated with a thin gold-palladium layer by sputter coater unit (VG-Microtech, UK) and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (Cambridge, UK) operated at an acceleration voltage of 10 kV.

2.5.3. Mechanical strength

Crushing strength of five beads from each batch was determined using mercury load cell method (Jarosz and Parrott, 1983).

2.5.4. Buoyancy of the beads

Apparent density of different batches was determined using mercury porosimeter (Autoscan 60 porosimeter, India), without application of external pressure and attached software (Quntachrome, India). To determine floating characteristics, sample beads ($n = 30$) were initially dipped into 900 ml of simulated gastric fluid USP (without enzymes) filled in USP 26 type II dissolution apparatus (Electrolab TDT-06P, Mumbai, India) for 1 min. Then the medium was stirred at 100 rpm (Kawashima et al., 1991). Temperature of medium was maintained at 37.5 ± 0.5 °C. At hourly intervals, stirring was stopped for 2 min and the number of settled particles was counted visually.

2.5.5. Drug release studies

Two sets of dissolution studies were performed using USP 26 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). Drug loaded beads equivalent to 7.5 mg pure drug, filled in '0' size hard gelatin capsule were used for all dissolution studies. Volume of dissolution medium (900 ml), stirring speed (100 rpm) and temperature of medium (37 ± 0.2 °C) were kept same for all dissolution studies.

In one set of dissolution studies, simulated gastric fluid without enzymes (SGF) was used as dissolution medium and dissolutions were performed for 6 h. The second set of dissolution studies were performed using SGF for time period equivalent to floating time which varied for each batch and then subsequently in simulated intestinal fluid, without enzymes (SIF) till complete release of drug.

Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41, concentration of meloxicam was determined in samples spectrophotometrically (JASCO-V500, Japan) at 245 and 259 nm, respectively, for SGF and SIF. Analysis of data was done using 'PCP Disso v2.08' software (Poona College of Pharmacy, Pune, India).

3. Results and discussion

3.1. Process design and preparation of beads

Calcium alginate beads offer a simple multiparticulate pulsatile drug delivery system for macromolecules and drugs because of its highly pH dependent characteristics of swelling and drug release (Kikuchi and Okano, 2002; Pillay and Fassihi, 1999). To limit bulk volume the quantity of FLR was restricted to maximum of 1 g for adsorption of 200 mg of meloxicam. Preliminary study to obtain beads was carried out using 0.1–2% (w/v) sodium alginate solution and 1–5% (w/v) calcium chloride solution as cross-linking medium. It was observed that 0.5–2% (w/v) sodium alginate solution containing 35 mg/ml of drug adsorbed FLR, extruded in 1% (w/v) calcium chloride solution produced beads with instantaneous floating ability. An attempt was also made to obtain alginate beads containing pure drug without FLR using above formulation and processing parameters but friable discs in place of spherical beads were produced. On the other hand, beads containing pure FLR were easily formed using same procedure. This indicate that hydrophilic nature of FLR causes greater contact between solid particles and sodium alginate solution needed for bead formation, whereas hydrophobic nature of meloxicam did not allowed optimum contact of drug particles and sodium alginate solution. The concentrations of sodium alginate solution used in present study were also lower than usually used by researchers (2%, w/v or above) to prepare alginate-drug beads (Ostberg et al., 1994; Whitehead et al., 1998; Pillay and Fassihi, 1999). The yield and entrapment efficiency of different batches of beads were found in the range of 89–103% and 68–94%, respectively (Table 1). Percent yield of beads was observed to increase with increase in both the quantity of FLR and concentration of sodium alginate maybe due to increased bonding and encapsulation of particles in beads.

3.2. Image analysis and morphology of beads

The beads of all the batches were spherical with roundness and circulatory factor close to 1.0 (Table 2). The scanning electron microscope images of beads (batches 2 and 8) illustrate the spherical shape with thin and incomplete calcium alginate surface coat (Fig. 2). Also beads containing higher quantity of FLR (Fig. 2c) were more spherical and smooth surfaced compared to beads containing lesser quantity of FLR (Fig. 2a), keeping alginate concentration constant. This is also supported by roundness and circulatory factor data of batch 8 beads that showed lowest circulatory factor and high roundness (Table 2). Beads with less FLR quantity showed surface deposition of meloxicam crystals (Fig. 2b) which are very scanty on surface of beads containing higher quantity of FLR (Fig. 2d).

The size of beads varied from 2.0 to 2.7 mm for different batches. Keeping other factor constant, the bead size was found to increase with increase in FLR quantity in formulation and decrease in concentration of sodium alginate but former showed major effect (Fig. 3) as also depicted by sign and value of coefficients in Table 3. This increase in bead size may result because of low density of FLR.

Table 2
Results of different evaluation parameters for beads batches

Batch code	Average diameter (μm)	Roundness	CF[a]	MS[b] (g)	Apparent density (g/cm^3)	FT[c] (h)
1	2208.67 ± 137.87	0.825 ± 0.036	1.221 ± 0.068	262.09 ± 15.80	0.183 ± 0.016	4.17 ± 0.38
2	2004.37 ± 159.13	0.826 ± 0.024	1.208 ± 0.086	707.21 ± 78.89	0.340 ± 0.062	2.25 ± 0.43
3	2129.14 ± 39.98	0.797 ± 0.034	1.181 ± 0.064	1073.10 ± 56.61	0.347 ± 0.009	1.92 ± 0.14
4	2586.35 ± 61.66	0.835 ± 0.031	1.210 ± 0.073	208.57 ± 9.02	0.119 ± 0.012	7.34 ± 1.15
5	2426.36 ± 127.78	0.856 ± 0.016	1.152 ± 0.047	591.13 ± 32.36	0.213 ± 0.020	5.0 ± 0.85
6	2344.58 ± 65.35	0.771 ± 0.085	1.198 ± 0.073	905.78 ± 18.04	0.325 ± 0.045	3.83 ± 0.14
7	2649.39 ± 71.22	0.833 ± 0.025	1.149 ± 0.109	182.47 ± 27.78	0.114 ± 0.006	7.83 ± 0.76
8	2551.49 ± 113.78	0.856 ± 0.016	1.120 ± 0.060	490.84 ± 17.99	0.177 ± 0.011	6.92 ± 0.14
9	2500.42 ± 45.71	0.797 ± 0.028	1.123 ± 0.054	762.20 ± 19.57	0.208 ± 0.044	4.92 ± 0.14
Control	2358.11 ± 57.07	0.838 ± 0.029	1.149 ± 0.079	586.19 ± 11.11	0.145 ± 0.009	3.67 ± 0.38

[a] Circulatory factor.
[b] Mechanical strength.
[c] Floating time.

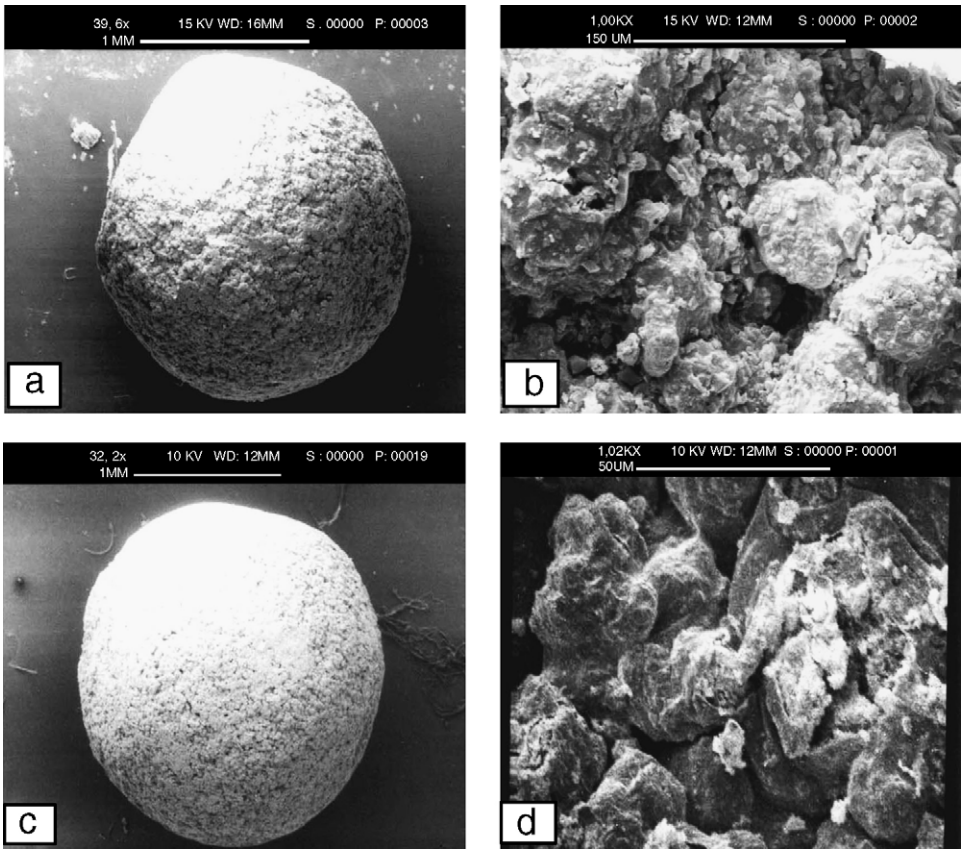

Fig. 2. SEM of beads: (a) and (b) of batch 2; (c) and (d) of batch 8.

3.3. Mechanical strength

Beads prepared by using 1.0% (w/v) and 1.5% (w/v) sodium alginate solutions showed higher crushing strength ranging from 490 to 1073 g probably due to greater bonding of increased strength with increase in concentration of alginate (Fig. 4). Higher mechanical strength of beads is important for avoiding breaking and distortion of beads during capsule filling or normal handling especially at the time of large batch production. It is also reflected by the value of coefficient (β_2), shown in Table 3. The opposite effect of FLR quantity (β_1) and interaction of it with alginate concentration (β_{12}) on crushing strength of beads may be attributed to increase in bead size with increase in FLR quantity keeping alginate solution concentration constant (Fig. 5) that probably resulted into weaker and insufficient alginate binding of solid particles. As compared to beads of batch 8 that contained 83.34% FLR out of total powder loaded the beads containing pure FLR showed smaller size and higher mechanical strength (Fig. 5). This indicates that size and mechanical strength of beads were not only affected by FLR quantity but also by hydrophobicity of powder loaded in beads. The hydrophobicity of drug probably did not allow stronger bonding between

Table 3
Estimation of regression coefficients for different response variables

Coefficient	Response					
	Average diameter (μm)	Mechanical strength (g)	Apparent density (g/cm^3)	Floating time (h)	DR* in SGF at 6 h	DR* in SIF at 5 min
β_0	2402.00$^{\$}$	589.00$^{\$}$	0.24$^{\$}$	5.20$^{\$}$	9.12$^{\$}$	56.20$^{\$}$
β_1	227.00$^{\$}$	−101.00$^{\$}$	−0.06$^{\$}$	1.89$^{\$}$	3.82$^{\$}$	7.28$^{\$}$
β_2	−78. 40	348.00$^{\$}$	0.08$^{\$}$	−1.44$^{\$}$	−1.77$^{\$}$	−26.92$^{\$}$
β_{12}	−17.40	−57.80$^{\$}$	−0.02	−0.17	−0.51	−6.41$^{\$}$
β_{11}	−112.00	11.20	0.01	−0.72	−0.42	−1.49
β_{22}	75.70	−30.70$^{\$}$	−0.03	0.28	0.01	−3.32
R^2	0.966	1.000	0.942	0.973	0.965	0.998
F	17.13	3010.44	8.26	21.87	16.71	378.40
P	0.021	0.000	0.046	0.014	0.021	0.000

DR*: drug release.
$^{\$}$ Statistically significant at $P < 0.05$.

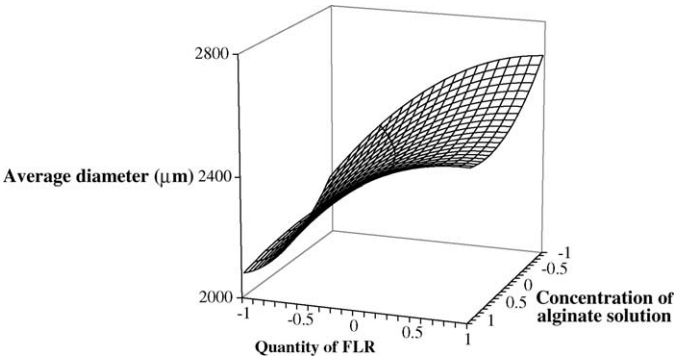

Fig. 3. Response surface plot showing effect of factorial variables on average diameter.

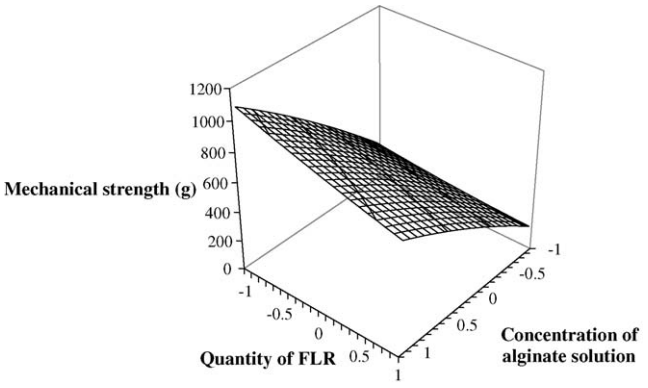

Fig. 4. Response surface plot showing effect of factorial variables on mechanical strength.

solid particles and alginate that resulted into larger bead size and reduced mechanical strength. The beads of control batch which are devoid of hydrophobic component (drug) probably formed stronger bonds with alginate and hence, produced smaller beads with higher mechanical strength. This is also supported by failure in preparing beads of pure drug.

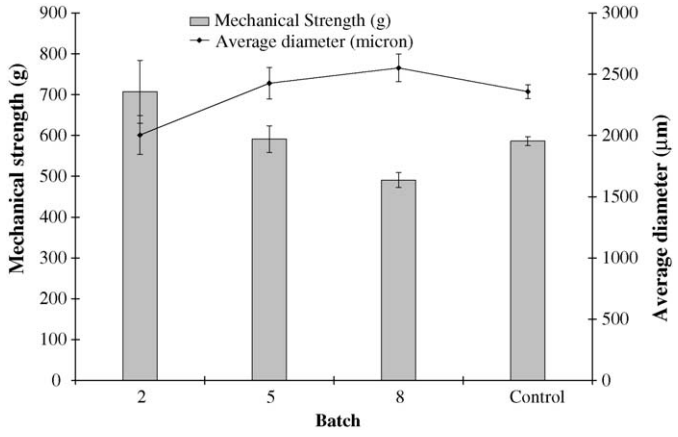

Fig. 5. Comparison of average diameter and mechanical strength of control batch with batches 2, 5 and 8.

3.4. Buoyancy of beads

Buoyancy of beads is directly related to performance of floating-pulsatile drug delivery system since lag time for beads is equivalent to their floating time. Instantaneous in vitro floating behavior was observed for beads of all batches, may be due to low apparent density provided by porous nature of FLR (Table 2). Floating time was determined as floating parameter; floating time is the time till all of the beads floated on medium. Floating time was primarily controlled by apparent density of beads, which on turn is affected by both quantity of FLR and concentration of sodium alginate solution (Fig. 6). Beads of batches containing higher FLR quantity and lower alginate concentration (batches 4, 7 and 8) showed floating time of greater than 6 h (Table 2). Floating behavior of beads could be explained on the basis of explanation given by Yuasa et al. (1996a) that polymer forms liquid bridges over pores present on surface of FLR and do not intrude completely into the pores which results into air trapped within granules. Similarly in our study, with the increase in FLR quantity in beads (at same alginate concentration) floating time increases and sinking rate decreases, probably because the number of air trapped pores in beads increases with increase in FLR quantity. Since the control batch does not include meloxi-

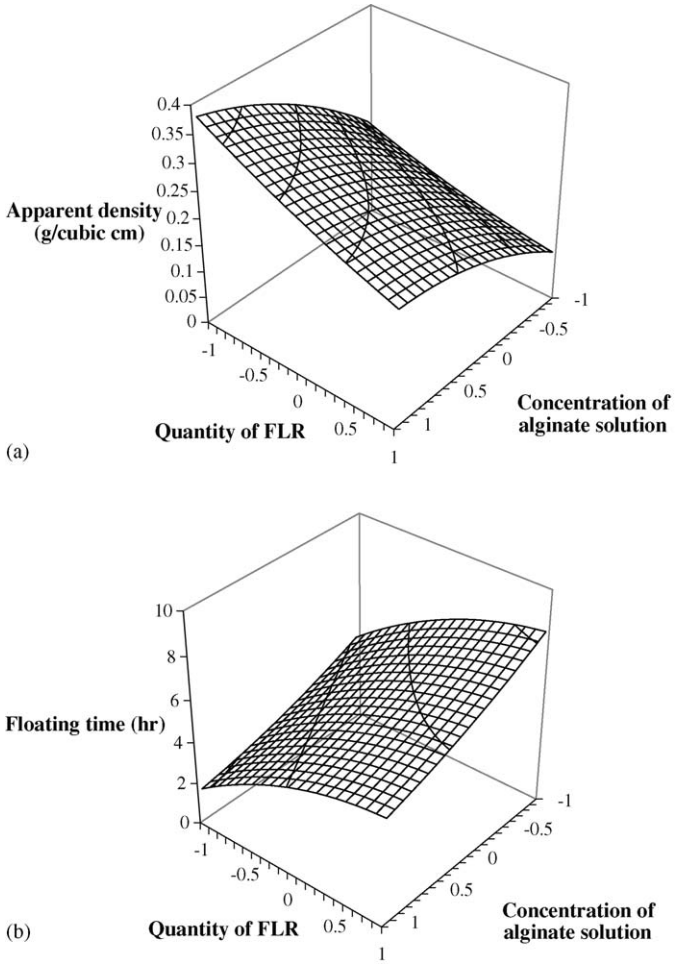

Fig. 6. Response surface plot showing effect of factors on: (a) apparent density and (b) floating time.

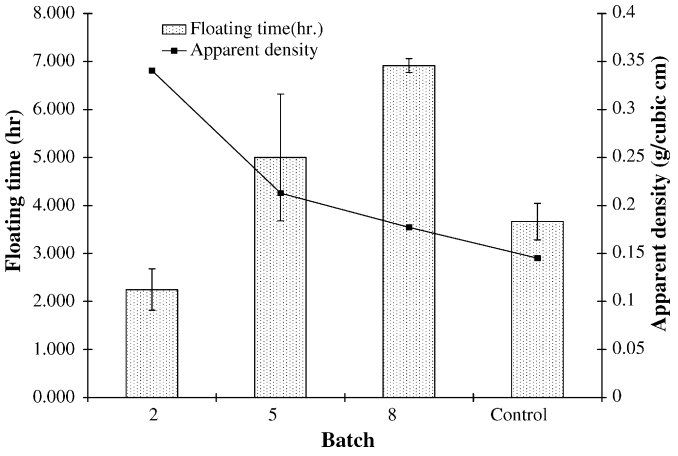

Fig. 7. Comparison of apparent density and floating time of control batch with batches 2, 5 and 8.

cam; a nonporous, denser solid component, therefore control batch beads incorporate higher proportion of FLR compared to drug containing beads that results in lower apparent density of control batch. Results presented in Fig. 7 show that with the increase in FLR quantity in beads, keeping alginate concentration constant (1%, w/v), apparent density of beads decreases and floating time increases except for control batch, for which apparent density is lowest but floating time is lesser than floating time of batches 5 and 8. This indicates that hydrophobic component in beads is not only affecting size and mechanical strength but also floating behavior of beads. Hydrophobic nature of meloxicam probably restricts the influx of aqueous medium into the pores of FLR and therefore delays removal of air trapped by aqueous medium.

3.5. In vitro drug release

Release studies in SGF for 6 h showed 4–15% cumulative drug release from beads of different batches (Fig. 8a). Comparatively lesser drug release at acidic pH is due to the lack of disintegration and swelling of alginate beads (Ostberg et al., 1994) and poor solubility of meloxicam in acidic media. The drug release was directly related to quantity of FLR and inversely related to concentration of sodium alginate (Table 3). The increase in drug release with increase in FLR quantity and reduction in alginate concentration, may be outcome of two factors; large surface area provided by FLR for drug adsorption and reduction in surface coating of alginate over beads, which thereby increase the effective surface area of surface deposited drug exposed to dissolution medium (Fig. 2b and d).

To simulate the pH variation of GI tract dissolution studies were performed first in SGF for time equivalent to floating time (round figure-hour) and then subsequently medium was replaced with fresh SIF having maintained temperature of $37 \pm 0.2\,^{\circ}C$ (Fig. 9). In SGF medium drug release from prepared batches over their respective floating time varied from 2.2% to 16.2%. All the batches of beads showed fast disintegration and drug release in SIF probably due to pH dependent swelling of alginate and solubility of meloxicam (Ostberg et al., 1994; Ghorab et al., 2004). Based on the morphology of beads (Fig. 2), rapid disintegration of beads in SIF was expected since concentration of sodium alginate solutions used were lower than required to encapsulate solid particles completely. Complete drug dissolution from beads of each batch occurred within 45 min in SIF, which would be useful in in vivo drug absorption from large surface area of small intestine. Small intestinal transit time for a drug formulation or for a meal is known to be almost constant at about 3 h (Davis, 2005). Although the drug release from

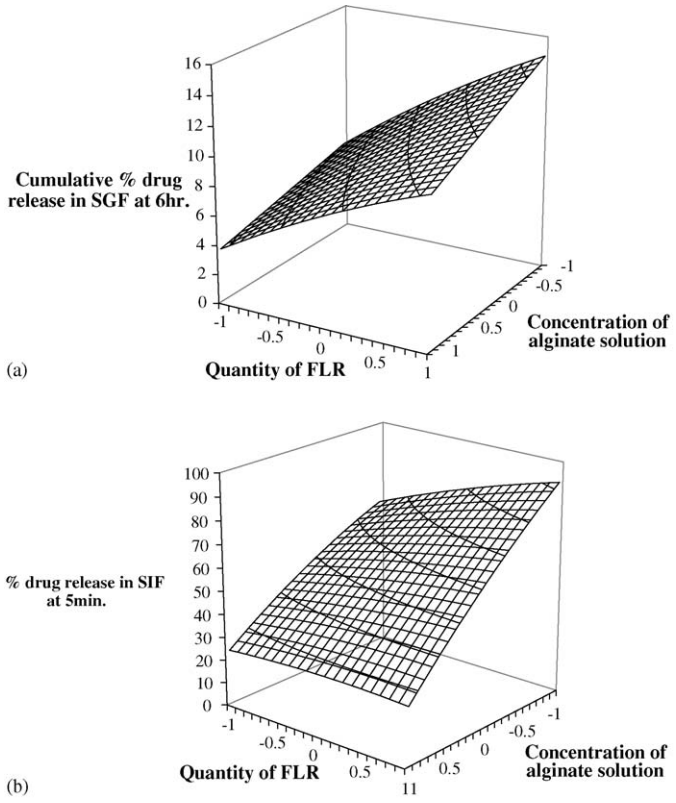

Fig. 8. Response surface plot showing effect of factors on drug release from beads in: (a) SGF at 6 h (b) SIF at 5 min.

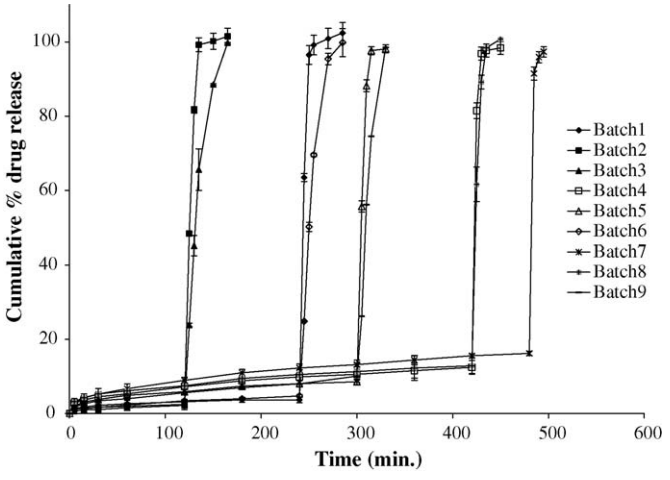

Fig. 9. Cumulative drug release profile of beads of different batches in SGF (for time equivalent to floating time of batch) followed by SIF.

beads of all batches was quiet rapid, the composition of bead shown significant effect on initial drug release in SIF (Table 3). As shown in Fig. 8b, the increase in concentration of alginate solution caused marked decrease in drug release in initial 5 min. Batches prepared by using 1.5% (w/v) sodium alginate solution (batches 3, 6 and 9) showed comparatively slower drug release than beads prepared by using 0.5% (w/v) or 1% (w/v) alginate solutions which showed more than 80% drug release within 10 min (Fig. 9). This marked effect of alginate concentration on initial drug release in SIF (Table 3) may be attributed to formation of stronger and thicker gel formation with increase in concentration of alginate that restrict the drug diffusion through the beads.

4. Conclusion

A new type of multiparticulate floating-pulsatile drug delivery system based on low density porous calcium silicate as drug carrier and pH responsive cross-linked alginate polymer has been developed. Developed formulations showed instantaneous floating with very less drug release in acidic medium followed by a pulse drug release in SIF. Quantity of porous carrier and concentration of sodium alginate solution significantly affected the performance of beads. By altering the amount of these two components in formulation floating time of beads could be controlled ranging from 1.9 to 7.8 h. Drug release from beads in acidic environment was influenced by both quantity of Florite RE® and sodium alginate concentration while initial drug release in simulated intestinal environment was primarily controlled by sodium alginate concentration. The developed system offers a simple and novel technique for pulse release of drugs in upper part of small intestine. Such work can be further extended using various excipients for variety of drugs suitable for chronopharmaceutical drug delivery.

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