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FORMULATION AND EVALUATION OF DOMPERIDONE LOADED MINERAL OIL ENTRAPPED EMULSION GEL (MOEG) BUOYANT BEADS

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Abstract: Alginate based mineral oil entrapped emulsion gel (MOEG) buoyant beads of domperidone were prepared by emulsion gelation technique. The prepared beads were evaluated for particle size, surface morphology, buoyancy, actual drug content and entrapment efficiency. Effect of different oils (castor oil, olive oil and linseed oil) and oil concentrations (10%, 15% and 20%, w/w) on uniformity, homogeneity and integrity of the beads was also studied. Density of the formulated beads was found to be ranging between 0.101 and 0.182 g/cm^3. The results of the *in vitro* drug release indicated that linseed oil showed to be good release retardant compared to castor oil and olive oil. Moreover, the beads formulated using 15%, w/w linseed oil were more uniform in shape, exhibited maximum buoyancy and minimal oil leakage. Diffusion exponent (n) value varied from 0.4855 to 0.7710 indicating anomalous drug release behavior involving swelling, diffusion and/or erosion of the polymer matrix.

Keywords: MOEG beads, domperidone, emulsion gelation, buoyancy

Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in absorption zone and reduce the efficiency of administered dose because a majority of the drug is absorbed in stomach or upper part of small intestine. The controlled gastric retention of solid dosage form may be achieved by mucoadhesion, floatation, sedimentation, expansion, modified shape system and simultaneous administration of pharmacological agents (1). Gastro-retentive floating drug delivery system has bulk density lower than gastric fluid and thus remains buoyant in the stomach without affecting the gastric emptying rate for prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at desired rate from the system. Floating drug delivery systems offer important advantages as they are less prone to gastric emptying resulting in reduction in intra and inter subject variability in plasma drug levels, effective for the delivery of the drug with various absorption windows, reduced dosing and increased patient compliance, reduced C_{max} and improved safety profile for the drug with side effect associated with C_{max}. Various approaches to induce buoyancy in cross linked beads are reported, which include freeze-drying, entrapment of gas or gas forming agents and use of volatile oils or fixed oils (2, 3).

Domperidone is a dopamine D_2 receptor antagonist and is used as a prokinetic agent for treatment of upper gastrointestinal motility disorders (4). After oral administration, domperidone is rapidly absorbed from the stomach and the upper part of the gastrointestinal tract (GIT) with fewer side effects. It is a weak base with good solubility in acidic pH but significantly reduced solubility in alkaline medium (5).

The present investigation was designed to formulate and evaluate mineral oil entrapped emulsion gel (MOEG) buoyant beads of sodium alginate as delivery system of domperidone. The drug loaded beads were prepared by emulsion gelation technique

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using castor oil, olive oil and linseed oil in different concentrations (10%, 15% and 20%, w/w). The formulated beads were evaluated for particle size, surface morphology, density, actual drug content, encapsulation efficiency, buoyancy, uniformity, integrity and *in vitro* drug release.

EXPERIMENTAL

Materials

Domeperidone was received as a gift sample from Helios Pharmaceuticals, India. Sodium alginate was purchased from Qualigens Fine Chemicals, India. Olive oil, castor oil and linseed oil were procured from Yarrow Chemicals, India. Calcium chloride was purchased from Loba Chemicals, India. All other chemicals were of analytical grade and were used as such.

Methods

Preparation of domperidone loaded sodium alginate MOEG beads

Doperidone loaded MOEG beads were prepared by emulsion gelatin method (6). In this method pre gelation liquid of sodium alginate solution (2%, w/v) was prepared. Mineral oil in the concentration (10%, 15% and 20%, w/w) was then added to the polymer solution. To ensure emulsion stabilization, the mixtures were homogenized at 10000 rpm using a homogenizer (Remi-motors, RQ-122, Vasai , India) for 20 min with the addition of emulsifier Span 80. Domperidone was then dispersed in the formed emulsion in the fixed drug:polymer ratio (1:1, w/w). The bubble free emulsion was extruded, using a 20 gauge syringe needle into 100 mL of gently agitated 0.1 M (1%, w/w) $CaCl_2$ solution at room temperature. The emulsion gel beads were allowed to stand in the solution for 60 min before being separated and washed with distilled H_2O. The beads were dried under vacuum at ambient temperature and were stored in desiccator. The composition of different batches of the drug loaded alginate beads are given in Table 1.

Study of homogeneity and uniformity/integrity of beads

In order to achieve uniformity in bead size and density it is essential that synthesis conditions such as viscosity, rate of falling of drops, stirring rate and distance between syringe and emulsion medium, be maintained constant during the course of formation of beads. Variation in any of these parameters during the bead formation process may result in the production of non homogeneous and non uniform beads, affecting the overall results to an appreciable extent (7). All the formulated batches of MOEG buoyant beads were visually analyzed for oil leakage, shape and color.

Particle size of the prepared MOEG beads was determined using an optical microscope (Model CH-20i, Olympus Pvt. Ltd., India) fitted with the stage and an ocular micrometer. Twenty dried beads were measured for calculating the mean diameter of beads. The result is expressed as the mean diameter (mm) ± standard deviation.

Density measurements

The mean weight and diameter of MOEG beads were measured and used to mathematically calculate the densities of the spherical sodium alginate beads using the following equation:

Table 1. Composition and physiochemical properties of sodium alginate MOEG beads.

Formulation Code	Oil Concentration (% w/w)	Mean Diameter (mean ± SD) (mm)	Density (g/cm^3)	Actual Drug Content (%) (AC)	Entrapment Efficiency (%) (DEE)
FC1	10	0.92 ± 0.06	0.182	48.54 ± 0.84	92.41 ± 1.37
FC2	15	0.90 ± 0.07	0.175	49.29 ± 1.05	95.64 ± 1.88
FC3	20	0.98 ± 0.04	0.160	48.55 ± 0.72	97.11 ± 1.45
FO1	10	0.95 ± 0.03	0.177	48.92 ± 0.66	93.55 ± 1.81
FO2	15	1.02 ± 0.04	0.154	49.25 ± 0.95	96.80 ± 2.25
FO3	20	1.05 ± 0.05	0.150	49.08 ± 0.78	94.12 ± 1.75
FL1	10	0.88 ± 0.08	0.122	50.33 ± 0.84	89.64 ± 2.31
FL2	15	1.10 ± 0.05	0.101	50.14 ± 0.99	96.50 ± 1.01
FL3	20	NA	NA	47.47 ± 1.88	95.92 ± 1.54

Table 2. Some parameters studied on MOEG beads.

Formulation Code	Buoyancy %	Oil Leakage	Shape	Color of Beads
FC1	Not Floating	Yes & Highest	Spherical	Off White
FC2	40 % Floating	Yes	Spherical	Off White
FC3	35 % Floating	Yes & Highest	Spherical with tailing	Off White
FO1	Not Floating	Intermediate (Less than castor oil)	Spherical and sticky	Yellowish
FO2	30 % Floating	Intermediate	Spherical and sticky	Light Yellow
FO3	80 % Floating	Intermediate	Spherical and sticky	Light Yellow
FL1	100 % (max.) Floating	Minimum (Less than both castor oil and olive oil)	Spherical & least sticky	Yellowish
FL2	100 % (max.) Floating	Minimum	Spherical	Yellowish white
FL3	75 % Floating	Minimum	Distorted shape	Light Yellow

Table 3. Kinetic studies on MOEG beads.

Batch No.	Zero order		First order		Higuchi		Korsmeyer-Peppas		
	r^2	k_0 (h^{-1})	r^2	k_1 (h^{-1})	r^2	k_H ($h^{-/2}$)	r^2	n value	k_{KP} (h^{-n})
FC1	0.6398	0.1437	0.8561	-0.0029	0.7697	4.354	0.8664	0.5182	0.7034
FC2	0.7025	0.2928	0.9710	-0.0116	0.8566	7.6832	0.8981	0.5457	0.8373
FC3	0.6629	0.1462	0.8876	-0.0030	0.7384	3.2674	0.8348	0.4855	0.8532
FO1	0.8835	0.3278	0.8483	-0.0069	0.9754	6.5681	0.9542	0.6675	0.4531
FO2	0.7601	0.3256	0.9272	-0.0095	0.9132	8.3887	0.9364	0.6289	0.6536
FO3	0.8025	0.0376	0.9423	-0.0004	0.9139	1.3174	0.9433	0.5391	0.1635
FL1	0.9148	0.2591	0.9488	-0.0072	0.9835	6.7438	0.9619	0.5783	0.7930
FL2	0.8634	0.3843	0.9551	-0.0118	0.9764	9.3499	0.9732	0.7710	0.3067

$$D = M/V$$

where $V = 4/3\pi r^3$ (for a typical sphere), D is the density of MOEG beads, M is the weight of beads, V is the volume of beads and r is the radius of beads.

Determination of the beads buoyancy

The MOEG beads (n = 20) were kept in a beaker filled with 50 mL of 0.1 M HCl (pH = 1.2). The floating ability of beads was measured by visual observation for the overall time period of 6 h (after 2 h each). The beads that floated on the surface of the medium and those that settled down at the bottom were recovered separately and the floating percentage (% buoyancy) was estimated (8). The integrity of the beads was also observed visually during the buoyancy test.

Determination of actual drug content and entrapment efficiency

An accurately weighed amount of 50 mg of domperidone loaded MOEG beads was dissolved in 100 mL of 0.1 M HCl solution. It was stirred for 6 h using magnetic stirrer (MICROSIL, MLH-1, India). The resulting solution was then filtered and the filtrate was suitably diluted. Domperidone content was determined spectrophotometically (Systronics 2202 Spectrophotometer, India) at 284 nm. Actual drug content (AC) and entrapment efficiency (EE) were calculated according to the following equations:

$$AC\ (\%) = M_{act} / M_{ms} \times 100$$

$$EE\ (\%) = M_{act} / M_{the} \times 100$$

where M_{act} is the actual drug content in MOEG beads, M_{ms} is the weighed quantity of beads and M_{the}

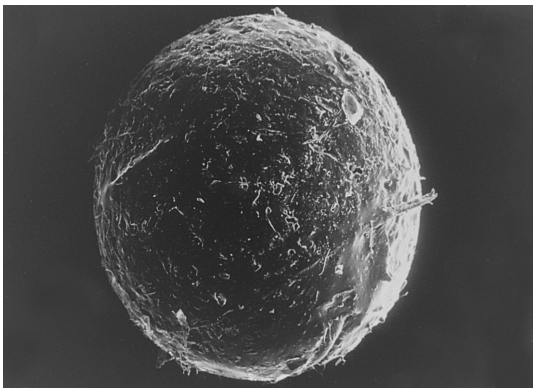

Figure 1. SEM micrograph of drug loaded MOEG bead

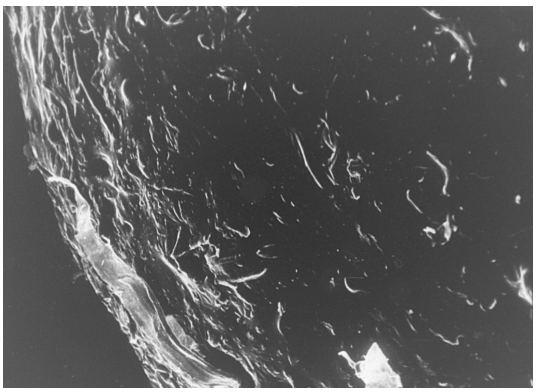

Figure 2. SEM micrograph of the surface of MOEG bead

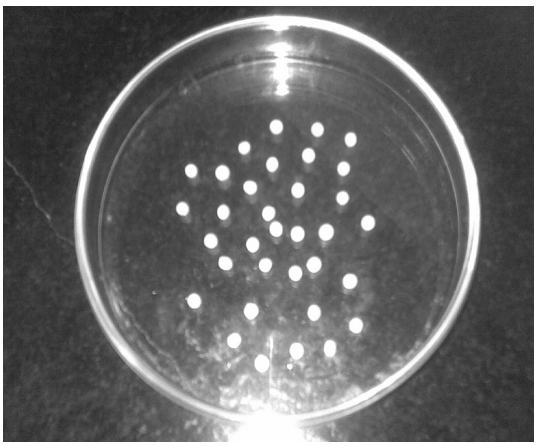

Figure 3. Optical photo micrograph of MOEG beads

is the theoretical amount of the drug in the beads calculated from the quantity added in the process. All analyses were carried out in triplicate.

Scanning electron microscopy (SEM)

Morphological examination of the surface and the internal strength of the dried MOEG beads were carried out using a scanning electronic microscope (SEM- JEOL MODEL 8404; Japan at magnification of 500×) equipped with secondary electron at an accelerating voltage of 10 kV. The sample beads were mounted on metal grids using double sided tape coated with gold to a thickness of about 30 mm in vacuum evaporator.

***In vitro* domperidone release studies**

In vitro release studies were carried out on drug loaded MOEG buoyant beads using USP 24 dissolution test apparatus I. The weighed quantity of beads equivalent to 100 mg of domperidone were introduced into dissolution basket and the basket was placed in 900 mL simulated gastric fluid (pH 1.2) maintained at 37 ± 0.5^{o}C and 50 rpm. Aliquots of 5 mL solution were withdrawn at predetermined time intervals and replaced by fresh dissolution mediums. The withdrawn samples were analyzed for domperidone content spectrophotometrically (Double beam spectrophotometer, Systronics 2202, India) at 284 nm.

Statistical analysis of data

The experimental results were expressed as the mean ± standard deviation. Student's *t*-test was applied to determine the level of significance. The analysis of variance (ANOVA) was also applied to check significance difference in the drug release from different formulations. Difference was considered statistically significant when $p < 0.05$.

RESULTS AND DISCUSSION

Particle size and morphology/uniformity of beads

The mean diameters of domperidone loaded Na alginate MOEG beads are shown in Table 1. In fact, small values of standard deviation revealed in Table 1 confirmed high process uniformity regarding homogenization efficiency and low variability in processing conditions. The results in Table 1 reveals that the mean diameter of beads range between 0.92 ± 0.06 – 1.10 ± 0.05. Moreover, beads size was found to increase with an increase in oil concentration, irrespective of the type of oil used. This might be due to an increase in the droplet viscosity caused by higher oil content. Increased viscosity along with involvement of gravitational forces may lead to an increase in emulsion droplet size leading to larger bead formation. The scanning electron micrographs (SEM) and optical micrographs of the domperidone loaded MOEG beads are illustrated in Figs. 1–3, respectively. Beads were found to be well rounded spheres with uniform size distribution under optical

microscope. It can be revealed from SEM that the formulated MOEG beads were discrete and spherical in shape with rough outer surface along with pores or channels that might form passage to help the drug release from the inner part of the beads. Some domperidone crystals were also seen on the surface of the beads which might be present because of leaching out of the drug to the surface during drying and subsequent shrinkage. Beads prepared using castor oil and olive oil in different concentration were less acceptable in terms of shape and stickiness. Amongst the formulated batches of the MOEG beads linseed oil in 15 % concentration was found to be the best in terms of shape and stickiness. Moreover, oil leakage and color change were also found to be minimal in the batches formulated with linseed oil (FL1, FL2, and FL3).

Density measurements

Density values of the MOEG beads formulated using castor oil, olive oil and linseed oil ranged from 0.182 to 0.160, 0.177 to 0.150 and 0.122 to 0.101 g/cm^3, respectively. Table 1 shows that calculated densities of all the MOEG beads were less than the density of 0.1 M HCl (i.e., 1.004 g/cm^3) imparting their flotation. Results of lower densities obtained in the presence of higher oil concentrations are in line with results reported by Elmowafy et al. (8).

Determination of the beads buoyancy

The bead buoyancy data shown in Table 2 indicated the dependence of floating ability of the beads on the oil concentration. Instantaneous *in vitro* floating behavior was observed for drug loaded MOEG beads and lasted for at least 6 h except for FC1 batch which was not floating. Overall, FC and FO showed lesser buoyancy compared with FLI and FL2 batches. This might be due to lesser symmetry in shape and probably oil leakage from the formulation leading to unequal forces of released medium (0.1 M HCl) on their surfaces. The beads with higher concentration of oil were more flotable than those with lower concentrations of the oil. This may be attributed to a decrease in density of the beads with an increase in oil concentration.

Determination of actual drug content and drug entrapment efficiency

The effect of changing oil type and oil concentration on the drug loaded MOEG beads is shown in Table 1. Drug entrapment ranged from 89.64 to 98.92% depending upon the composition of the nine batches of MOEG beads of domperidone. A higher proportion of oil in the beads increased the drug

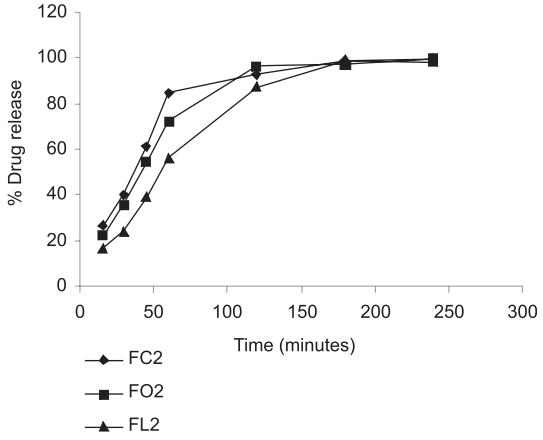

Figure 4. Release profile of domperidone from MOEG beads in 0.1 M HCl (pH 1.2)

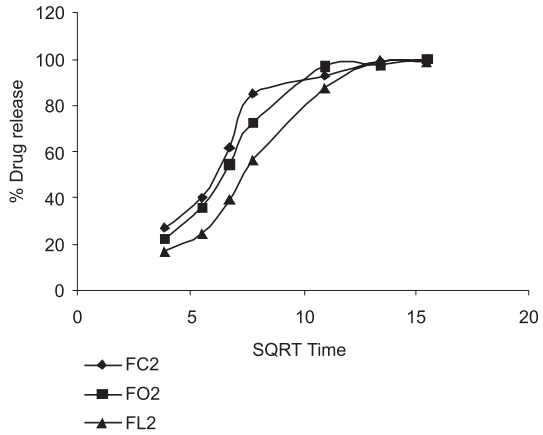

Figure 5. Higuchi release model for domperidone release from MOEG beads

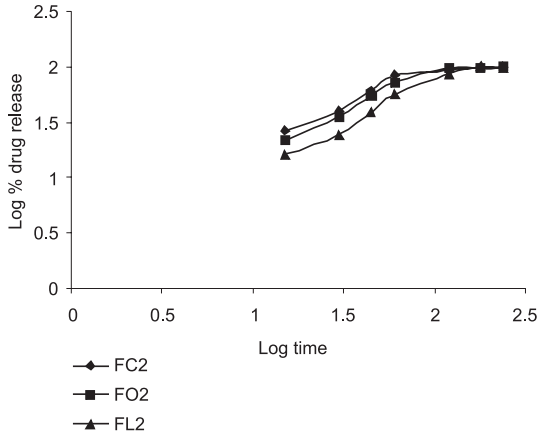

Figure 6. Korsmeyer-Peppas model for mechanism of drug release from MOEG beads

entrapment efficiency in different batches, which could be attributed to partitioning of the drug in the oil phase. A direct correlation was also seen to exist between particle size and corresponding drug entrapment efficiency. Actual drug content was found to be ranging from 47.47 to 50.33 %. Preparation method showed good reproducibility, as indicated by analyses of actual drug content and encapsulation efficiency carried out on each group of three batches prepared under identical conditions. All these results demonstrated the suitability of the method for the preparation of the beads, using suitable mineral, with appropriate size and high encapsulation efficiency.

***In vitro* domperidone release studies**

In vitro drug release profile of MOEG beads is shown in Figure 4, rate and extent of drug release from the was found to be of the order FC2 > FO2 > FL2. The drug release was found to be slower in formulations with higher oil concentration. The slow release of the drug from the MOEG beads may be due to the formation of drug-oil dispersion system in the oil pockets of the beads. The drug has to firstly diffuse from the oil pockets into the polymer matrix followed by transportation out of the polymeric matrix into the dissolution medium (9). Hence, transportation of the drug from the MOEG beads could be attributed as a two step process, which may be responsible for the slow drug release from the MOEG buoyant beads of alginate. In order to investigate the mechanism of drug release, the data were fitted to models representing zero-order, first order, Higuchi's square root of time model and Korsmeyer-Peppas model. The diffusion exponent (n) value, as calculated from Korsmeyer-Peppas model, for MOEG beads formulated using castor oil ranged from 0.4855 to 0.5457, for olive oil 0.5391to 0.6675 and for linseed oil 0.5783 to 0.7710, respectively, indicating anomalous drug release behavior from the beads involving a combination of swelling, diffusion and/or erosion of matrices. Hence polymer swelling and erosion along with formation of hydrophobic diffusional barrier by the incorporated oil in the MOEG beads might be playing a collective role in retarding the release of the drug from the beads. Higuchi model for domperidone release and Korsmeyer-Peppas model for mechanism of drug release from MOEG beads are shown in Figures 5 and 6, respectively (10, 11).

CONCLUSION

In conclusion, the emulsion gelation method for the preparation of domperidone loaded MOEG buoyant beads of alginate polymer offers flexible, easily controllable and consistent process for achieving the homogeneity and uniformity of beads formation. The results demonstrated the superiority of linseed oil over castor oil and olive oil in terms of bead buoyancy, particle size uniformity/integrity and drug release.

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