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Design and Evaluation of Stomach-Specific Drug Delivery of Domperidone using Floating Pectin Beads

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Abstract

The objective of present study was to develop floating beads of Domperidone (DOM) in order to increase its residence time in the stomach without contact with the mucosa, improve patient compliance and obtain improved therapeutic efficacy. They are prepared by extrusion congealing technique with pectin as a polymer. Floating beads were characterized by polymer compatibility by using FT-IR. The prepared beads were evaluated for particle size, surface morphology, buoyancy, actual drug content, entrapment efficiency and in vitro drug release. Nine formulations of DOM floating beads were formulated by using different percentage of both gas forming agent and pectin. Density of the formulated beads was found to be ranging between 0.101 and 0.182 g/cm3. The particle size was distributed between 0.6 to 1.6 mm. Buoyancy percentage was 71-87% and Drug entrapment efficiency was 54.4-64.48%. The micrometric properties were found to be good and scanning electron microscopy (SEM) confirmed their hollow structure with smooth surface. The content of drug release was done by UV spectrophotometer at 284 nm. In vitro drug release of DOM, for F2 is 81.10% and for F6 is 82.6%. And the beads formulated using 0.3w/w (F2) and 0.4% w/w (F6) of pectin was more uniform in shape and exhibited maximum buoyancy. The drug content of the formulated beads was found to be satisfactory by this method. It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug. From the study it was concluded that the gastro retentive drug delivery system designed as floating beads could be suitable drug delivery system for DOM.

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Key words:
Domperidone (DOM), Gastroretentive floating beads, $NaHCO_3$, Pectin.

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INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence time (GRT) [5]. 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, 2]. 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 [7]. 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} [6]. 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]. Here we are using gas generating floating drug delivery system. In gas-generating systems, the buoyant delivery systems utilize effervescent reactions between carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime.

Pectin is a structural hetero polysaccharide contained in the primary cell walls of terrestrial plants. It is produced commercially as a white to light brown powder, mainly extracted from citrus fruits, and is used in food as a gelling agent thickening agent and stabilizer in food. Domperidone is a synthetic benzimidazole compound that acts as a D_2 receptor antagonist and is used as a prokinetic agent for treatment of upper gastro intestinal motility disorders [8]. It continues to be an attractive alternative to metoclopramide because it has fewer neurological side effects. After oral administration, domperidone rapidly absorbed from the stomach and the upper part of the gastrointestinal tract (GIT) by active transport with fewer side effects. It is a weak base with good solubility in acidic pH but significantly reduced solubility in alkaline medium [9]. The short biological half-life of the drug (7h) also favors development of stomach specific floating beads. This floating bead of Domperidone release drug over 12 hr. DOM is used mainly in treatment of migraine, gastro-esophageal reflux and chemotherapy induced nausea and vomiting. The drug loaded beads were prepared by extrusion congealing technique by using different concentrations of pectin and $NaHCO_3$. It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug [10]. It has several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered and reduction of administration frequency leading to improved patient compliances. The prepared DOM beads were evaluated for particle size, surface morphology, drug content and invitro drug release studies [17].

EXPERIMENTAL MATERIALS:

Domeperidone was received as a gift sample from richer Pharmaceuticals, India. Pectin was purchased from Qualigens Fine Chemicals, India. Calcium chloride was purchased from Loba Chemicals, India. All other chemicals were of analytical grade and were used as such.

PREPARATION OF FLOATING DOMEPERIDONE BEADS:

Floating beads of DOM is prepared by extrusion congealing technique with pectin as a polymer. Nine formulations of DOM floating beads were formulated

by using different percentage of gas forming agent and polymer. A solution was prepared by dissolving two different concentrations (0.3% and 0.4%) of pectin in 10ml distilled water [4]. Then, gas forming agent such as $NaHCO_3$ was added to the solution with levels from 10mg to 40mg with pectin dispersion (gas-forming agent/pectin, w/w). Then to the above dispersion add 150mg of DOM. The mixture was then degassed under bath sonicator for 30 min. The resulting solution was dropped through a 23G Syringe needle into 1% (w/v) $CaCl_2$ solution containing 10% (v/v) acetic acid. The solution containing suspend beads was stirred with a magnetic stir bar for 100rpm to improve the mechanical strength of the beads and allowed to complete the reaction to produce gas. Since the carbonate salts are insoluble at neutral pH, the divalent ions were only released in the presence of acid, thereby preventing premature gelatination. The fully formed beads were collected, washed with ethanol and distilled water, and subsequently freeze dried (Fig: A) [17]. Different formulations and their polymer: gas forming agent ratios are shown in Table1.

Table1: formulation of domperidone loaded pectin beads

Batch code	Domperidone (in mg)	Polymer (Pectin) concentration	Gas forming agent($NaHCO_3$) concentration in mg
F1	150	0.3%	10
F2	150	0.3%	20
F3	150	0.3%	30
F4	150	0.3%	40
F5	150	0.4%	50
F6	150	0.4%	60
F7	150	0.4%	70
F8	150	0.4%	80
F9	150	0.4%	90

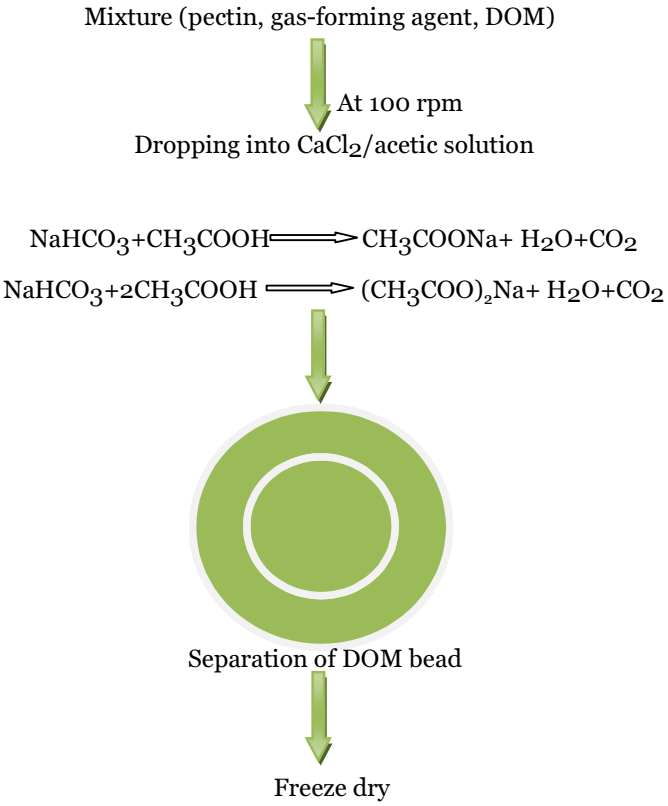

Fig: A Schematic diagram of method of preparation

EVALUATION OF FLOATING BEADS:

Morphology and particle size analysis:

All the formulated batches of pectin buoyant beads were visually analyzed for shape and color. Particle size of the prepared 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 [15].

Scanning Electron microscopy (SEM):

Morphological examination of the surface and the internal strength of the dried beads were carried out using a scanning electronic microscope (SEM-JEOL MODEL 8404; Japan at magnification of 500 xs) 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.

Yield of floating beads:

The prepared floating beads with a size range of 0.6 to 1.6 mm were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres [11].

%yield = (Actual weight of product/Total weight of excipient and drug) x 100

Determination of the beads buoyancy:

The beads (n = 20) were kept in a beaker filled with 50mL of 0.1M HCl (pH = 1.2). Temperature was maintained at 37°C. The floating ability of beads was measured by visual observation for the overall time period of 12 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. The preparation was considered to have buoyancy in the test solution only when all the beads floated in it. The integrity of the beads was also observed visually during the buoyancy test [16].

Density measurements:

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

D=M/V

Where $V = 4/3\pi r^3$ (for a typical sphere),

D is the density of beads,

M is the weight of beads,

V is the volume of beads and r is the radius of beads.

Determination of actual drug content and entrapment efficiency:

An accurately weighed amount of 50mg of domperidone loaded pectin beads was dissolved in 100mL of 0.1M 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 spectrophotometrically (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 pectin beads, M_{ms} is the weighed quantity of beads and M_{the} 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 [24].

Drug-polymer interaction study by FT-IR:

Drug polymer interaction was studied by taking FT-IR. Infrared spectra of DOM and pectin floating beads were carried out by using KBR pellet technique and were recorded on a shimadzu FT-IR spectrometer.

Swelling studies [19]:

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug-loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37°C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

Swelling ratio = weight of wet beads/weight of dried beads.

***In vitro* drug release studies:**

The dissolution of DOM-loaded pectin beads was studied using USP Type II dissolution apparatus containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37±0.5°C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. These samples were analyzed for the drug present in them with help of UV spectrophotometer (UV-1700, Shimadzu). Only those batches were selected for the release study, which have good drug content and drug entrapment efficiency more than 50% [21].

Statistical analysis of data:

The experimental results were expressed as the mean ± standard deviation. *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:

Morphology and particle size analysis:

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, should 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].

Particle size and morphology/uniformity of beads the mean diameters of domperidone loaded pectin beads are shown in Table 2. In fact, small values of standard deviation revealed in Table 2 confirmed high process uniformity regarding homogenization efficiency and low variability in processing conditions. The results in Table2 reveal that the mean diameter of beads ranges between 0.92± 0.06 ñ 1.10 ± 0.05. The prepared pectin beads were shown in the figure 3.

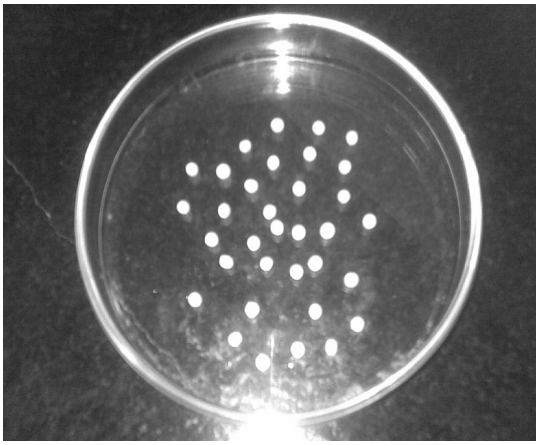

Figure 3: Optical photo micrograph of pectin beads

Scanning electron microscopy (SEM):

The scanning electron micrographs (SEM) and optical micrographs of the domperidone beads are illustrated in Fig4. Beads were found to be well rounded spheres with uniform size distribution under optical microscope. It can be revealed from SEM that the formulated pectin 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.

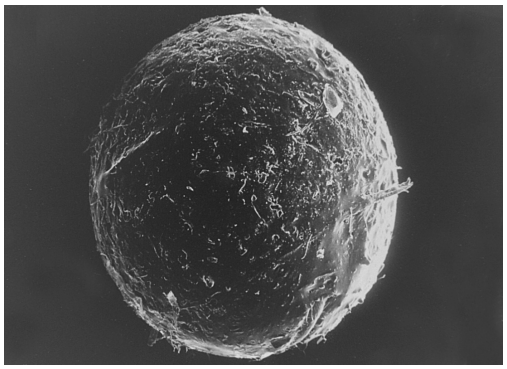

Figure 4: SEM micrograph of drug loaded pectin bead

Yield of floating beads:

The percentage yield of beads was in range of 62.40 ± 0.72 to 89.45 ± 1.50 (as shown in Table 3). To observe the effect of polymer concentration on the percentage yield of the resulting micro beads formulation were prepared using varying gas forming agent: polymer ratio of $NaHCO_3$ and pectin. The percentage yield of the microspheres was found to be increased with increasing gas forming agent: polymer concentration.

Batch code	% yield	Actual drug content (%)	Drug entrapment efficiency (%)
F1	63.4%	46.3±0.46	57.1±1.87
F2	77.6%	47.1±0.63	54.3±1.13
F3	82.1%	47.8±1.21	60.2±1.58
F4	86.7%	49.2±0.36	63.5±2.10
F5	65.1%	47.8±0.79	56.1±2.17
F6	75.7%	48.4±1.23	55.0±1.47
F7	79.5%	48.8±0.23	58.6±1.98
F8	83.1%	49.2±0.47	61.4±2.47
F9	86.1%	50.1±1.11	59.6±1.47

Table 3: Evaluation of DOM beads

Determination of the beads buoyancy:

The bead buoyancy data show in Table 2. Instantaneous *in vitro* floating behavior was observed for drug loaded pectin beads and lasted for at least 12h except for F1 batch which was not floating. Overall, F1 and F5 showed lesser buoyancy compared with other batches. This might be due to lesser symmetry in shape and probably amount of the gas forming agent in the formulation leading to unequal forces of released medium (0.1 M HCl) on their surfaces. The beads with higher concentration of gas forming agent were more floatable than those with lower concentrations. And as the gas forming agent is increases the drug release efficiency of the bead was decreases. So the optimum quantity of the both polymer and gas forming should be considered. The buoyancy percentage for all batches (except F1) was almost above 70%, which was studied for 12hr. The highest percentage was obtained with formulation F2 and F6. Average buoyancy in percentage was found to be 71% to 87%. In general with increase in the amount of polymers, there was an increase in the buoyancy percentage. The increase in the buoyancy percentage may be attributed to air and gel forming nature of pectin polymer. The floating behavior of the pectin beads were is shown in figure 1 and 2.

Fig1: Pectin beads floating in simulated gastric fluid without pepsin in a beaker (top view).

Fig 2: pectin beads floating in simulated gastric fluid without pepsin in a beaker (side view).

The results of the floating ability shows that 100% of floating was observed in F2 and F6 formulations of DOM floating beads with simulated

gastric fluid with pH 1.2 and Phosphate buffer pH 7.4 (Table 2).

Density measurements:

Density values of the pectin beads ranged from 0.182 to 0.160g/cm^3. Table2 shows that calculated densities of all the pectin beads were less than the density of 0.1 M HCl (i.e., 1.004 g/cm^3) imparting their flotation.

Table 2: Evaluation of DOM beads

Batch code	Shape	Colour of the beads	Density((g/cm^3))	Buoyancy %	Mean Diameter (mean ± SD) (mm)
F1	Spherical	Off White	0.122	68.3±1.02	0.62±0.05
F2	Spherical	Off White	0.142	85.6±1.89	0.79±0.03
F3	Spherical with tailing	Light Yellow	0.150	79.6±1.25	0.91±0.03
F4	Spherical and sticky	Yellowish	0.177	75.2±2.03	1.2±0.06
F5	Spherical and sticky	Off White	0.101	71.5±1.09	0.78±0.05
F6	Spherical	Light Yellow	0.149	86.8±2.36	0.82±0.07
F7	Spherical and sticky	Yellowish	0.159	83.4±1.36	0.93±0.03
F8	Spherical with less sticky	Yellowish white	0.168	79.1±203	1.35±0.04
F9	Distorted shape	Light Yellow	0.176	76.1±1.89	1.51±0.06

Determination of actual drug content and entrapment efficiency:

Drug entrapment ranged from 89.64to 98.92% depending upon the composition of the nine batches of pectin beads of domperidone. 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 nine batches prepared under identical conditions. All these results demonstrated the suitability of the method for the preparation of the beads, using pectin, with appropriate size and high encapsulation efficiency. (Table 3)

Drug-polymer interaction study by FT-IR:

Drug-polymer interaction studies play a vital role with respect to release of drug from the formulation amongst others. FT-IR techniques have been used here to study the physical and chemical interaction between drug and polymer used. In the present study, it has been observed that there is no chemical interaction between DOM and the polymers used. Drug has given peaks due to furan ring, secondary diamine, alkene and two peaks due to nitro functional groups. Form the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The FT-IR graphs are shown in figures 5 and 6.

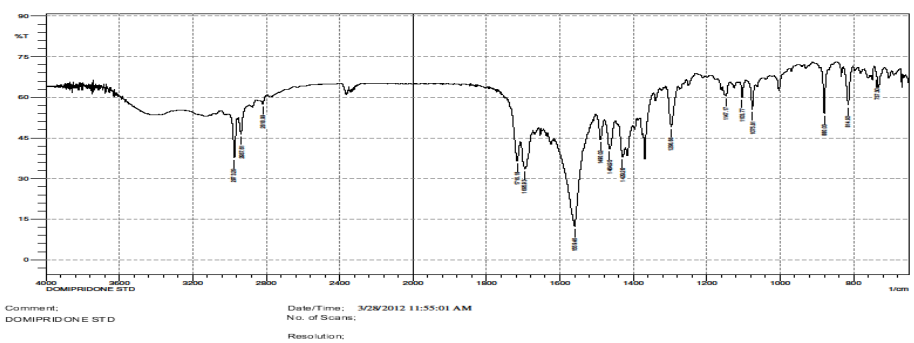

Fig 5: FT-IR graph of the pure DOMPERIDONE drug

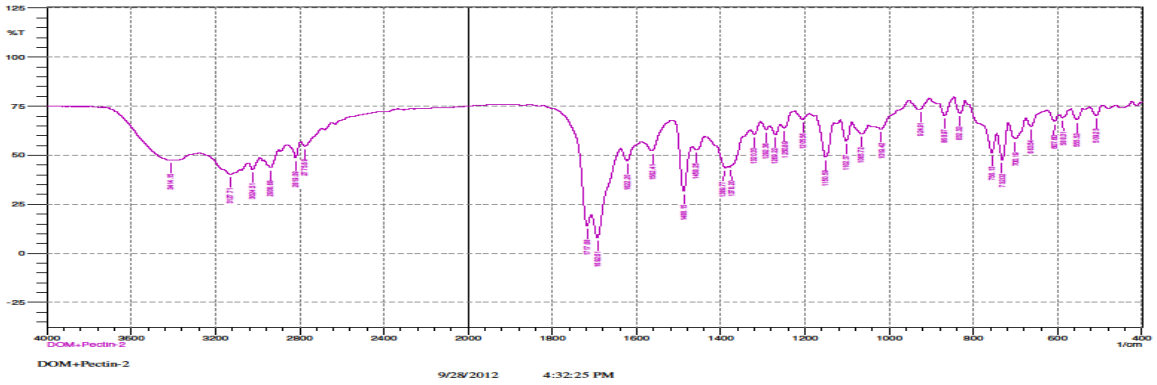

Fig 6: FT-IR graph of the DOMPERIDONE and pectin polymer

***In vitro* drug release studies:**

Nine formulation of DOM floating beads were formulated by Extrusion congealing technique using different percentage of gas forming agent and Pectin. Beads were subjected to invitro release using USP dissolution apparatus Type II in 900 ml of simulated gastric pH medium. Beads obtained in all the formulations were used for dissolution studies. With all of the formulations, there was initial intermittent burst release. But the release seems to be somewhat sustained with increase in the amount of polymer. The release rate was found to be decreased in accordance with the increase in ratio of polymer used. The formulations from Fl to F4 were prepared with 0.3% pectin solution. The formulations from F5 to F9 were prepared with 0.4% pectin solution (4%, w/v). Beads formulated with the ratio of 0.3% pectin and 20 mg of $NaHCO_3$ (F2) and beads formulated with the ratio of 0.4% pectin and 50 mg $NaHCO_3$ (F6) shown highest percentage of drug release at the end of 480 min in phosphate buffered saline (pH 7.4) and simulated gastric fluid (pH 1.2) and beads formulated without the addition of gas forming agent shown the least amount of drug release (Table 4). The percentage release of DOM from the formulation F1 was found to be 38.07% as the less gas forming agent was added to the formulation. The percentage release of DOM from the F2 was found to be 80.12% as it contains 0.3% pectin and 20mg $NaHCO_3$ gas forming agent. The percentage release of DOM from the formulation F6 was found to be 82.6% (Table: 4 and fig7).

Batch code	Cumulative % drug release at the end of 480 min
F1	40.12%
F2	80.12%
F3	71.42%
F4	69.12%
F5	58.12%
F6	82.61%
F7	79.38%
F8	71.22%
F9	68.12%

Table 4: In-vitro studies

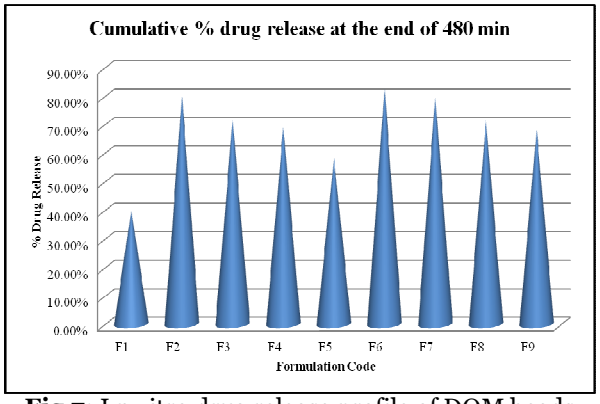

Fig 7: I n vitro drug release profile of DOM beads

The above 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 diffusion barrier by the incorporated polymer beads might be playing a collective role in retarding the release of the drug from the beads.

Stability studies:

The results obtained in the stability test showed that the content and release rate of Domperidone from floating beads stored at a temperature of 25° C and a 60%RH, 30°C and 65% RH was unchanged

during one month study. Decrease in drug content was observed in formulation stored at 40°C and 75% RH. % of drug release at the end of 12 hrs was found to be less as compared with that of freshly prepared floating beads. The results indicate that floating beads are more stable at 25-30^{O}C. Increase in temperature and humidity adversely affect formulation.

CONCLUSION:

Gastro retentive dosage form is being popular to retain the drug in the stomach for a longer period. Formulating into a gastroretentive dosage form will benefit to drugs, which are having narrow absorption window. DOM is a D2 receptor antagonist having a narrow absorption window. The present formulation study of Domperidone was performed in an attempt to prepare floating drug delivery system consisting of floating multiple unit system with pectin appears to be a promising vehicle for delivering Domperidone. So domperidone loaded pectin buoyant beads offers flexible, easily controllable and consistent process for achieving the good buoyancy homogeneity uniformity of beads formation and in vitro drug release. Hence in the present study DOM floating beads were formulated by extrusion congealing technique. The performance of these formulations was evaluated and the effect of various formulation variables was studied. The percentage drug entrapment and drug content of the formulated beads were found to be satisfactory by this method. Major advantages of the system include: ease of preparation, high encapsulation efficiency, and sustained drug release over several 12 hours. From the study it was concluded that the gastro retentive drug delivery system designed as floating beads could be suitable drug delivery system for DOM. This result suggests that beads formulated with the decrease in the concentration of the gas forming agent and increase in the polymer ratio results in the sustained release of the drug. Thus, the prepared floating beads may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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