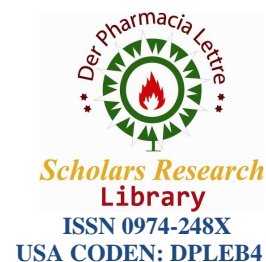




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Preparation and *in vitro* evaluation of a microballoon delivery system for domperidone

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ABSTRACT

Gastroretentive dosage forms have potential for use as controlled-release drug delivery systems. Multiple unit systems avoid the all-or-none gastric emptying nature of single-unit systems. A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of Microballoon delivery system by emulsion solvent diffusion method. The effect of various formulation and process variables on the internal and external particle morphology, micromeritic properties, in vitro floating behavior, physical state of the incorporated drug, drug loading and in vitro drug release was studied. Formulation demonstrated favorable in vitro floating and release characteristics. The drug encapsulation efficiency was high. Domperidone loaded microballoons proved desired release behavior and buoyancy. The designed system, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of Domperidone. Domperidone loaded Microballoon was found to be stable at various conditions.

Keywords: Domperidone, Microballoon, Emulsion solvent diffusion, Buoyancy, floating behavior.

INTRODUCTION

Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for longer period of time such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore, prolonged gastric retention is important in achieving control over the GRT because this helps to retain the CR system in the stomach for a longer time in a predictable manner. [1] In recent years, scientific and

technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short GRT and unpredictable gastric emptying times (GET). The gastro-intestinal residence time determines the time period available for drug release from oral controlled release delivery systems within the gastrointestinal tract [2]. Approaches to increase the GRT include: (i) bioadhesive delivery systems, which adhere to mucosal surfaces [3] (ii) swellable delivery systems, which increase in size after swelling and retard the passage through the pylorus [4]; and (iii) density-controlled delivery systems, which either float or sink in gastric fluids [5–7]. Floating drug delivery is of particular interest for drugs which (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment [2].

Floating has been achieved with the preparation of low-density dry solid systems e.g. inclusion of sponges, highly porous systems [8,9] or with systems, which decrease in density upon contact with gastric fluids based on the expansion of swelling agents [10] or CO₂ generation [11]. Unfortunately, floating devices administered in a single-unit form such as hydrodynamically balanced systems (HBS) are unreliable in prolonging the GRT owing to their 'all-or none' emptying process and, thus, they may cause high fluctuation in bioavailability and local damage due to a large amount of drug delivered at a particular site of gastrointestinal tract [12]. In contrast, multiple-unit particulate dosage forms (e.g. microballoons) have the advantages that they pass uniformly through the gastrointestinal tract to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the intersubject variability in absorption and risk of local irritation. Recently, hollow microspheres with a lower density than that of the GI fluids were adopted. The Microballoons were prepared by emulsion solvent diffusion technique using Eudragit RS 100, HPMC.

A floating drug delivery system has been patented by Muller and Anders [8] which is less dense than gastric juice due to incorporation of at least one porous structural element, such as foam or a hollow body. An object of the present investigation was to develop a multiparticulate floating delivery system consisting Monostearin acted as membrane forming agent, carvidilol as a drug and Eudragit RS 100 and HPMC as a polymers, which is capable of floating on gastric fluid and delivering the therapeutic agent over an extended period of time.

Domperidone is a synthetic benzimidazole compound that acts as a dopamine D2 receptor antagonist. Its localization outside the blood-brain barrier and antiemetic properties has made it a useful adjunct in therapy for Parkinson's disease. There has been renewed interest in antidopaminergic prokinetic agents since the withdrawal of cisapride, a 5-HT₄ agonist, from the market. Domperidone is also used as a prokinetic agent for treatment of upper gastrointestinal motility disorders. It continues to be an attractive alternative to metoclopramide because it has fewer neurological side effects. Patients receiving domperidone or other prokinetic agents for diabetic gastropathy or gastroparesis should also manage diet, lifestyle, and other medications to optimize gastric motility. It is rapidly absorbed from the stomach and the upper part of the gastrointestinal tract, after oral administration, and few side effects have been reported. It is a weak base with good solubility in acidic pH but in alkaline pH solubility is significantly reduced. Oral controlled release dosage forms containing drug, which is a weak base, when exposed to environments of increasing pH and poorly soluble freebase may be precipitated within the formulation in the intestinal fluid. Precipitated drug is no longer capable of being released from formulation. The short biological half-life of drug (7 h) also favors development of a sustained release formulation. The objective of the present investigation was to develop a gastroretentive

drug delivery system containing domperidone using simplex lattice design as an optimization technique. [9]

MATERIALS AND METHODS

Materials

Carvidilol was procured as a gift sample from CIPLA, Goa, India. EUDRAGIT® RS 100 and HPMC was obtained as a gift sample from Ranbaxy Pharmaceuticals, Dewas, India. Ethanol, dichloromethane and other solvents were purchased from Himedia Chemical, India. All other chemicals were of analytical reagent grade and were used as received.

Preparation of Domperidone loaded microballoons

Microballoons with an internal hollow structure were prepared by emulsion solvent diffusion method with slight modification in the method established by Kawashima et al (1992). 0.9 gm of Eudragit RS 100, 0.1 gm of HPMC, Domperidone (100 mg), monostearin (0.5 gm) was dissolved in mixture of ethanol and dichloromethane (2:1). The polymer solution was slowly introduced into 200 ml of 0.25% PVA (polyvinylalcohol) aqueous solution at 40°C; forming an oil-in-water (o/w) type emulsion. The resultant emulsion was stirred. The finely dispersed droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent. After agitating the system for 30 min, the resulting polymeric particulate systems were dried overnight at 40°C to produce microballoons.

Characterization of microballoons

Micromeritic properties

The microballoons were characterized by their micromeritic properties, such as particle size, true density, tapped density, compressibility index and flow properties. The size was measured using Zeta sizer (Malvern Zetasizer U.K.)

The tapping method was used to determine the tapped density and percent compressibility index as [14] follows:

Tapped density = Mass of microspheres/Volume of microballoons after tapping %

Compressibility index = $[1 - V/V_0] \times 100$

Here V and V₀ are the volumes of the sample after and before the standard tapping, respectively. True density was determined using a benzene displacement method. Porosity [14] was calculated using the equation: $\epsilon = (1 - P/P_t) \times 100$

where P_t and P_p are the true density and tapped density, respectively. Angle of repose h of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method [14] and calculated as $\tan \theta = 2H/D$

where 2H/D is the surface area of the free standing height of the heap that is formed on a graph paper after making the microballoons flow from the glass funnel.

Morphology

The morphology of the Microballoons was studied by scanning electron microscopy (SEM). The samples for SEM were pre-pared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300 Å

under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope (HEG Bhopal)

Drug content

50-mg of dried microballoons containing a drug were dissolved in 10 ml of ethanol followed by agitation with a magnetic stirrer for 12 hours to dissolve the polymer and extract the drug. The dissolved drug amount was measured spectrophotometrically with UV (UV-1700, Shimadzu). Drug content of microballoons was calculated according to following equation

$$\text{Drug content} = \frac{\text{Weight of drug in microballoons}}{\text{Weight of microballoons recovered}} \times 100$$

Buoyancy

Microballoons (100 mg) were dispersed in solution composed of HCl and NaCl (300 ml, pH 1.2, 37 °C) containing Tween 20 (0.02 w/v %) to simulate gastric fluid. The mixture was stirred with a paddle at 100 rpm. After 12 h, the layer of buoyant particles was pipetted and the floating particles were separated by filtration. Particles in the sinking particulate layer were separated by filtration. Both particles types were dried at 40°C overnight. Each weight was measured and buoyancy was determined by the weight ratio of the floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy (\%)} = \frac{Q_f}{Q_f + Q_s} \times 100$$

Here Q_f and Q_s are the masses of the floating and settled hollow microspheres, respectively.

Differential Scanning Calorimetry

To evaluate the possible interaction between the drug and polymers, thermal analysis was performed by differential scanning calorimetry (Perkin Elmer). The instrument was calibrated using indium (156 °C), Tin (232 °C) and Zinc (419.5 °C) as internal standards. Samples of 2–10 mg were placed in aluminum pans (Al-Crucibles, 40 µl) and sealed. Samples were placed in aluminium pans and heated at a scanning rate of 10°C/min. four samples i.e. pure Domperidone, and physical mixture of Domperidone, HPMC , Eudragit RS 100 were analysed. (SAIL/DSC/M0020901)

In vitro release studies

The different formulations prepared by changing the process variables were subjected to *in vitro* drug release studies. The release of Domperidone from the microballoons was determined as a function of time in Phosphate buffer (pH=6.8) using egg membrane bag.

The drug release was determined by using the treated biological membrane, mounted on the one end of open tube, containing 50 mg of microballoons. The dialysis tube was suspended in 100 ml beaker, containing 100 ml phosphate buffer (pH=6.8). The solution was stirred at 100 rpm with the help of magnetic stirrer at 37°C. Perfect sink conditions were maintained during the *in-vitro* drug release. The samples were withdrawn at suitable time interval up to 12 hr. The dissolution medium was replaced with same amount of fresh PBS saline (pH=6.8) solution to maintain the volume up to 100 ml throughout the experiment. The drug content was estimated by UV spectrophotometer.

RESULTS AND DISCUSSION

1. Formation of microballoons

The microballoons, with intragastric floating properties were formulated by the emulsion solvent evaporation method using polymers Eudragit RS 100 and hydroxypropylmethyl cellulose (HPMC). They exhibited good flow properties. The organic solvents employed were ethanol and dichloromethane. Monostearin acted as membrane forming agent. Microballoons were evaluated for particle size, drug entrapment, buoyancy percentage differential scanning calorimetry and *in vitro* drug release.

Optimization of Process variables

Effect of solvent composition

Solvent composition was found to be a vital factor in the formulation process governing the yield of microballoons. When the amount of dichloromethane was increased the production yield and drug content of microballoons decreased as some polymer aggregated on the shaft. Such result was attributed to the fact that as ethanol diffused into the aqueous phase, dichloromethane became major constituent of the internal organic phase. The polymer being insoluble at the dichloromethane and aqueous interface, started to solidify because of rapid evaporation of dichloromethane polymer aggregated on the shaft.

Best results were obtained when the ratio of ethanol: dichloromethane was 2:1. With increasing the ethanol volume, it took more time for ethanol to diffuse in the external aqueous phase, forming stable emulsion droplets and preventing the aggregation of embryonic microsphere droplets. Thus increasing the yield of microballoons.(table1)

2. Effect of temperature

The temperature of the dispersing medium was an important factor in the formation of microspheres, because it controls the evaporation rate of the solvents. Floating properties of microballoons were also affected with variation in temperature. At lower temperatures (20°C), prepared microballoons had low yield. At higher temperature, faster evaporation of dichloromethane lead to the formation of porous structure immediately after diffusion of ethanol resulting in good floating percentage. The optimum temperature to form good microspheres was in the range of 35-40°C. Microballoons prepared at 40°C were hollow and buoyancy percentage was high. In contrast, microballoons prepared at 50°C had poor buoyancy because higher temperature resulted in settling of particles.(table1)

3. Effect of different grades of Eudragit polymer

The effect of Eudragit S100 and Eudragit RS100 was studied in the preparation of microballoons. When Eudragit S100 was used some fraction of Eudragit S100 was aggregated around the shaft, and the resultant yield of microballoons was relatively low. Some of the polymer solution aggregated in a fibre-like structure, as it solidified prior to forming droplets or the transient droplets were broken before the solidification was complete. As ethanol quickly diffused out of the organic phase (polymer solution) into the aqueous phase Eudragit S100 dissolved in ethanol solidified in fibre-like aggregates. No fibres were observed when Eudragit RS100 was used and good incorporation efficiency was observed. (table1)

3.1 Effect of HPMC

In order to modulate the drug release rate from the Microballoons they were prepared by mixing HPMC (Hydroxypropylmethylcellulose), hydrophilic polymer with Eudragit RS100. Percentage entrapment decreased on increasing the ratio of HPMC. The amount of Domperidone released

from floating microballoons with Eudragit RS 100 alone was suitable (73.74%) and increased on increasing the HPMC ratio but the buoyancy decreased on increasing the HPMC ratio. The buoyancy decreased with increasing the HPMC ratio because HPMC considerably gelled in the solution. (table1)

3.2 Effect of PVA Concentration

The type and concentration of emulsifier has a key role to play in the preparation of microballons .Without the addition of emulsifier it is impossible to form microballoons (MB-1). When the concentration of emulsifier was decreased, the production yield, and drug content increased. The emulsifier employed was non-ionic and molecules can associate away from the oil-water interface at higher concentrations. Such alternative hydrophobic region can dissolve some portions of drug resulting in a reduction in drug content and production yield within the microsphere formulations. (Table1)

3.3 Micromeritic properties

The mean particle sizes were found 5.914 μm for the optimized batch. Tapped density and compressibility index of final batch was following 0.44 g/cm^3 and 25.3 % respectively. All formulations showed excellent flowability as expressed in terms of angle of repose (< 40) for optimized batch 25.3 %. The better flow property indicates that the floating microballoons produced are non-aggregated.

3.4 Morphology

Microballoons were predominantly spherical in appearance, however some were found to be elongated. Spherical shapes of the microballoons are evident from their SEM photomicrographs at different magnifications e.g 1000, 1500, 10000, and microscopic photomicrographs. (fig.1,2,3,4)

3.5 Entrapment Efficiency and Percentage buoyancy

Entrapment efficiency of formulated microballoons was the function of process variables as well as physiochemical properties of drug. It was observed that variation in polymer concentration influenced the entrapment efficiency. Increase in Eudragit RS100 concentration resulted in increase in entrapment efficiency and it was found highest for MB-II e.g. 84.28. Drug entrapment efficiency was found to be decreased with increasing HPMC concentration, because of hydrophilic nature of HPMC. Solubility of drug in the organic solvents played an important role in determining the drug entrapment within micoballoons. Selected drug Domperidone was freely soluble in dichloromethane and sparingly soluble in ethanol and because of lipophilic nature of Domperidone its leaching into PVA aqueous phase was minimum and drug entrapment was high.

The floating test was carried out to investigate the floatability of the prepared microballoons. Results of buoyancy study were that all the formulations showed good floating ability. MB-II formulation shows 76.2% of the particles kept floating for at least 12 h. (table 2)

Differential Scanning Calorimetry

The DSC curves of the pure Domperidone showed a single endothermic peak at 117.55 $^{\circ}\text{C}$ (Fig No.5 c) corresponding to the melting of the drug. In the DSC thermograms of pure HPMC (Fig No.5 b) and Eudragit RS100 (Fig No. 5 a) broad endothermic peak ranging from about 30 to 100 $^{\circ}\text{C}$ was observed. In the physical mixture of drug and polymer endothermic peak for drug was still observed at 116.85 $^{\circ}\text{C}$ (Fig No.5d). The analysis of thermograms revealed no physical interaction between the polymer and the drug.

Stability Studies

The results obtained in the stability test showed that the content and release rate of Domperidone from gastroretentive microballoons 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 microballoons. The results indicate that microballoons are more stable at 25-30°C. Increase in temperature and humidity adversely affect microballoons formulation.

In Vitro Release of Domperidone from Microballoons

The optimization study revealed that MB-II formulation followed the Higuchi diffusion Kinetics with cumulative release profile till 12hrs. The control release was obtained mixing hydroxypropylmethylcellulose (HPMC) with Eudragit RS100. Drug release rate from microballoons formulated with Eudragit as polymer was not optimum. The initial burst was not observed and moreover little Domperidone was released from the microballoons. Drug release rate of microballoons prepared by coformulating with HPMC was relatively improved, due to gelation of HPMC in solution. The solution can readily penetrate into microballoons due to increased dissolution of HPMC in the solution. The amount of Domperidone released from microballoons increased with increasing HPMC ratio. This behavior was explained due to increased contact area of particles with the medium due to poor buoyancy associated with increased HPMC ratio. The cumulative % drug release at particular time interval was calculated which found 66.74%.

Drug release data of Domperidone were fitted to models representing Higuchi's, zero order and first order kinetics to know the release mechanisms. The data was processed for regression analysis and interpretation of data was based on the value of resulting correlation coefficients. Higher values of correlation coefficients were obtained in case of Higuchi square root of kinetic treatment. It can be concluded that diffusion was the predominant mechanism of drug release supported by higher correlation coefficient values in the case of Higuchi's model.

Table 1 Drug content and production yield within the microsphere formulations

Formulation Code	PVA conc. (%)	solvent ratio ethanol: DCM	polymer ratio Eudragit : HPMC	Tem. (°C)	Monostearin (grms)
MB-I	0	2:1	0.9 : 0.1	40°C	0.5
MB-II	0.25	2:1	0.9 : 0.1	40°C	0.5
MB-III	0.5	2:1	0.9 : 0.1	40°C	0.5
MB-IV	0.75	2:1	0.9 : 0.1	40°C	0.5
MB-V	0.25	1:2	0.9 : 0.1	40°C	0.5
MB-VI	0.25	1:1	0.9 : 0.1	40°C	0.5
MB-VII	0.25	2:1	1.0 : 0	40°C	0.5
MB-VIII	0.25	2:1	0.8 : 0.2	40°C	0.5
MB-IX	0.25	2:1	0.7 : 0.3	40°C	0.5
MB-X	0.25	2:1	0.5 : 0.5	40°C	0.5
MB-XI	0.25	2:1	0.9 : 0.1	20°C	0.5
MB-XII	0.25	2:1	0.9 : 0.1	30°C	0.5
MB-XIII	0.25	2:1	0.9 : 0.1	50°C	0.5

Table 2 Results of buoyancy study

Formulation code	% Recovery	incorporation efficiency	% Buoyancy
MB-I	-	-	-
MB-II	80.20	84.28	76.2
MB-III	76.3	74.14	69.19
MB-IV	69.4	69.49	70.06
MB-V	65.16	71.40	55.71
MB-VI	75.43	79.06	68.4
MB-VII	78.24	86.9	71.4
MB-VIII	77.06	73.6	63.6
MB-IX	73.5	70.25	47.71
MB-X	76.39	61.67	45.24
MB-XI	65.46	74.9	54.16
MB-XII	77.41	75.37	58.2
MB-XIII	73.59	75.10	29.0

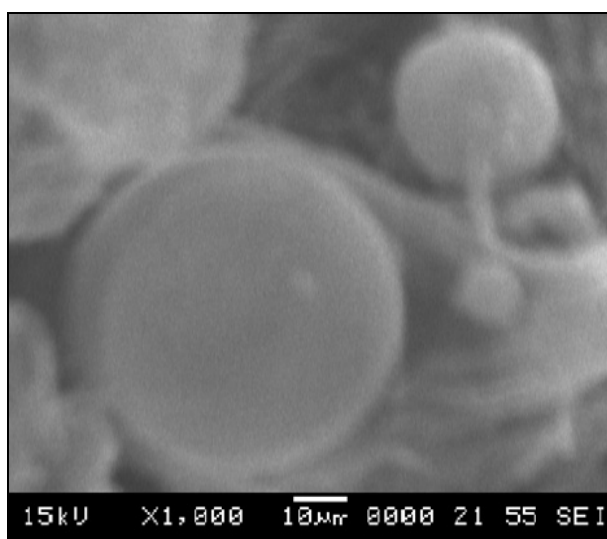
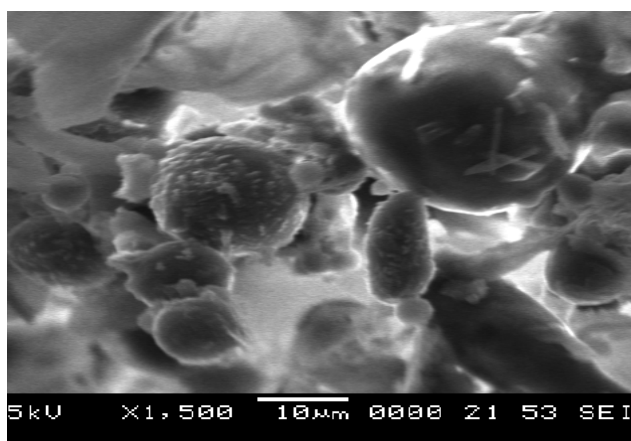
Figure1 scanning electron photomicrographs of (SEM) microballoons at 1,000**Figure 2 Scanning electron photomicrographs of (SEM) microballoons 1,500**

Figure 3 Scanning electron photomicrographs of (SEM) microballoons at 10,000

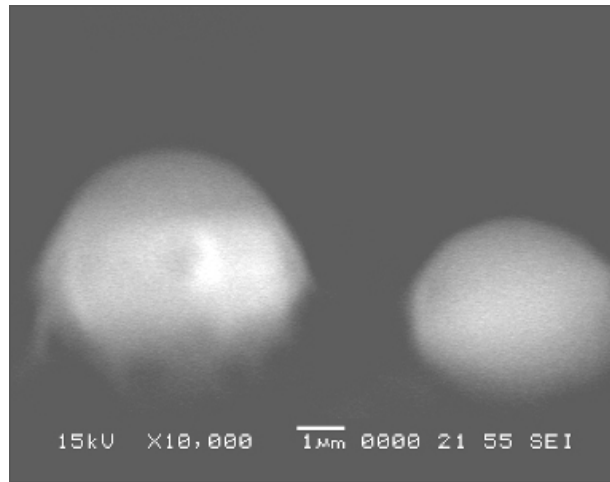


Figure 4 Photomicrograph showing Microballoons

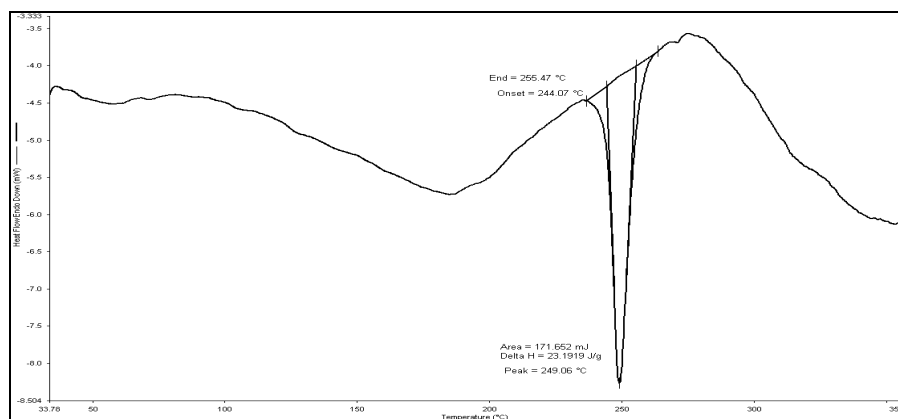


Figure 5-(A) DSC thermogram for physical mixture

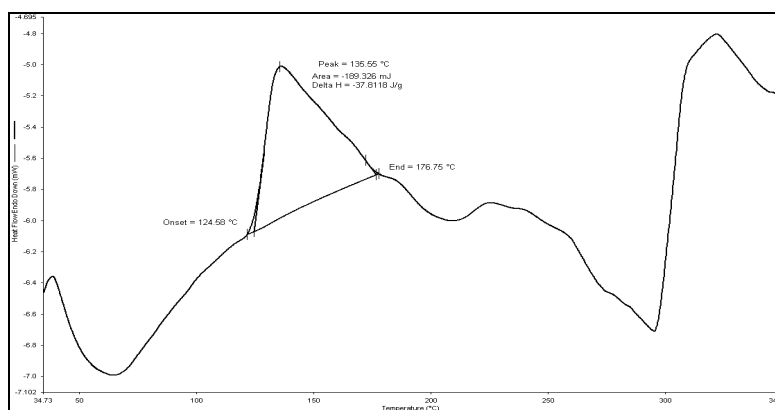


Figure5(B) Dummy microballoons

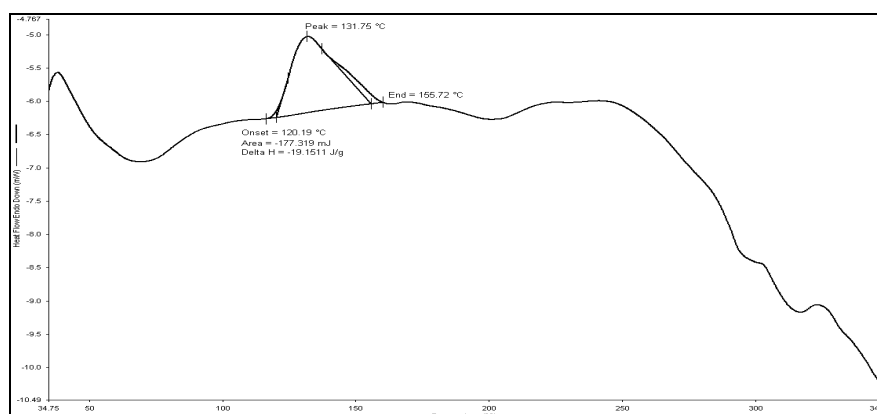


Figure 5(C) Drug loaded microballoons

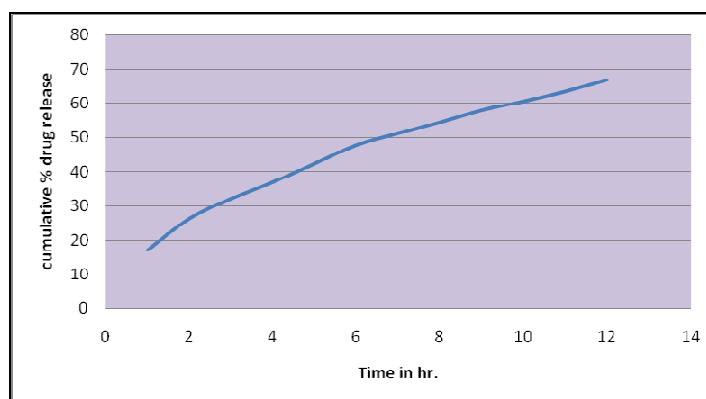


Figure-6 Cumulative % drug Release of optimized batch

CONCLUSION

The present formulation study of Domperidone was performed in an attempt to prepare floating drug delivery system consisting of floating multiple unit system. The performance of these formulations was evaluated and the effect of various formulation variables was studied. The designed system, combining excellent buoyant ability and suitable drug release pattern (Higuchi's Diffusion), could possibly be advantageous in terms of increased bioavailability of Domperidone. Major advantages of the system include: ease of preparation, good buoyancy, high encapsulation efficiency, and sustained drug release over several 12 hours. Thus, the prepared

floating microballoons may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition. The microballoons could be compressed into tablets, filled into capsules, or formulated into oral suspensions for reconstitution.

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