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Formulation and Evaluation of Micro Balloons of Domperidone

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ABSTRACT

The present study on the manufacturing of Microballons of Domperidone elaborates various steps taken during the development and manufacturing of microballoons keeping in constant knowledge of quality by design guidelines. The importance of target product profile and critical quality attributes which results in the finalization of product design have been demonstrated in the present work. Every steps were taken after due consideration of risk evolved by virtue of prior technical knowledge and experimentation. In the product design space the product characterization involved critical quality attributes which ultimately leads to critical process parameters that are design space. Control strategies for continuous monitoring process and product have also been recommended. Critical process parameters were also validated to achieve and monitor the quality of final product. The CPP has direct impact on critical quality attributes hence these parameters were develop with proper tolerances. The QbD principle demonstrated in present research will play an important role in the understanding and creating opportunities for investigation and control strategy in formulation and process development.

Keywords: Microballoons QbD; CPP, Risk Assessment.

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INTRODUCTION

Conventional oral dosage forms such as tablets, capsules provide a specific drug concentration in systemic circulation which do not release at the constant rate for prolonged period of time. Controlled release drug delivery system (CRDDS) provides drug release at a precontrolled, predictable rate either systematically or locally for intended duration of time and optimizes the therapeutic effect of a drug by controlling its release into the body with lower and less frequent dosing[1]

Gastroretentive drug delivery systems (GRDDS)

Dosage forms that can be retained in stomach for longer periods of time are called gastroretentive drug delivery systems (GRDDS).

GRDDS are suitable and beneficial for such drugs by improving their absolute bioavailability, therapeutics efficiency, increase gastric residence time (GRT), possible reduction of the dose, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

Floating drug delivery system

Many floating systems have been generated based on granules, powders, capsules, tablets, laminated films, beads and hollow microspheres[2,3].

It can be classified into two systems:[4,5]

Effervescent System

Volatile liquid containing systems (Intragastric floating GRDDS) Gas-generating Systems (Intra gastric single layer and bilayered floating tablets, Multiple unit type floating pills)

Non-Effervescent Systems

Hydro colloidal gel barrier systems

Micro porous compartment system

Alginate and pectin beads

Hollow microsphere (Microballoons)

Microballoons are gastro retentive drug-delivery systems with non-effervescent approach. Microballoons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer[6].

Microballoons are considered as one of the most favourable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The slow release of drug at desired rate and better floating properties

mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polylactic acid, Eudragit® S and hydroxy propyl methyl cellulose cellulose acetate are used in the formulation of hollow microspheres, and the release of drug can be modulated by optimizing polymer concentration and the polymer -plasticizer ratio[7].

Hollow microspheres / microballoons loaded with drug in their outer polymer shell are prepared by a novel methods such as solvent evaporation or solvent diffusion/evaporation to create a hollow inner core. The drug and an enteric acrylic polymer mixture is dissolved in ethanol/dichloromethane solution and it is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40 ºC. After the formation of stable emulsion, the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring[8]. The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drug. The microballoon is continuously float over the surface of an acidic dissolution media containing surfactant for more than 12 hours[9,10].

MATERIALS AND METHODS

Table No. 1: Name of Materials

Sr. No.	Name of Materials	Supplied By/Gifted By
1	Domperidone	Research Lab. Fine Chem Industries Mumbai
2	Ethanol	Sahyadri Scientific Research Islampur
3	Dichloro methane	Sahyadri Scientific Research Islampur
4	HPMC	Sahyadri Scientific Research Islampur
5	Eudragit	Sahyadri Scientific Research Islampur
6	PVA	Sahyadri Scientific Research Islampur

Inactive ingredient profile

Table No. 2 Inactive Ingedient Guide limit

Sr. No.	Name of Inactive Ingredients	Quantity Taken Per Tablet	Maximum quantity as per IIG for Immediate Release Tablet
1.	Eudragit RS	9 mg	15mg
2.	HPMC	1mg	4 mg
3.	Ethanol	5ml	12ml
4.	Dichloromethane	10ml	16ml
5.	Polyvinyl alcohol	1g	4g

Preparation of Domperidone loaded microballoons

Step 1: 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).

Step 2:0.9 gm of Eudragit RS 100, 0.1 gm of HPMC, Domperidone (100 mg)was dissolved in mixture of ethanol and dichloromethane (2:1).

Step 3: The polymer solution was slowly introduced into 200 ml of 0.25% PVA (polyvinylalcohol) aqueous solution at 40oC; forming an oil-in-water (o/w) type emulsion.

Step 4: The resultant emulsion was stirred.

Step 5: The finely disperseddroplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent.

Step 6: After agitating the system for 30 min, the resulting polymeric particulate systems were dried overnight at 40oC to produce microballoons.

Table No. 3: Formula for different batches for formulation of Domperidone Micro balloons

Sr.No.	Ingredients name(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Domperidone	20	20	20	20	20	20	20	20	20
2	Ethanol	5	5	5	5	5	5	5	5	5
3.	Dichloromethane	10	10	10	10	10	10	10	10	10
4.	HPMC	1.5	1	0.5	1.5	1	0.5	1.5	1	0.5
5.	Eudragit RS	1.5	1.5	1.5	1	1	1	0.5	0.5	0.5
6.	Polyvinyl alcohol(%)	25	25	25	25	25	25	25	25	25

EVALUATION OF MICRO BALLOONS:

In vitro Dissolution

The release rate of hollow microspheres are determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus.

A weighed amount of hollow microspheres (filled into a hard gelatin capsule) equivalent to dose of drug and place in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid is maintained at 37 ± 1 °C and rotation speed at a specific rpm. Perfect sink conditions carry out during the drug release study. Few ml (5 ml) of samples are withdrawn at each time interval and analyzes using Liquid chromatography / Mass spectroscopy method to determine the concentration of microballoons present in the dissolution medium. The initial volume of the dissolution fluid is maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments are run in triplicate[11].

Acceptance criteria- In acidic stage 10 % drug release and phosphate buffer stage drug release NLT 70%

Dissolution at acid medium-

Media: 0.1N HCl
Apparatus: USP II apparatus (paddle)
RPM: 75 RPM
Amount of media: 1000ml
Temperature: 37°C
Time: up to 2 hr
Temperature: 37°C
Time: up to 8 hr

Buoyancy

Microballoons (100 mg) were dispersed in solution composed of HCl and NaCl (300 ml, pH 1.2, 37^{0}C) containing Tween 20 (0.02 w/v %) to simulate gastric fluid.

The mixture was stirred witha 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 40oC 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.

$$\text{Buoyancy (\%)} = \frac{Qf \quad x \quad 100}{Qf + Qs}$$

Here Qf and Qs are the masses of the floating and settled hollow microspheres, respectively.

Acceptance criteria 95-110%

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.

Acceptance criteria- 98-110%

RESULT AND DISCUSSION

Table No. 4: Results of Domperidone for Entrapment Efficiency, Drug content and Buoyancy study in percent.

Batch code	EE%	DC%	Buoyancy%
F1	16.26	2.81	56
F2	55.53	7.3	89
F3	68.35	8.31	63
F4	78.05	8.82	86
F5	47.01	5.89	61
F6	81.38	9.42	91
F7	30.96	4.27	82
F8	77.57	8.66	84
F9	47.18	6.82	79

CONCLUSION

In the present research work systematic evaluation were carried out and control strategies were identified in manufacturing of micro balloons of Domperidone capsule using modern concept of development i.e. Quality by design successfully. Important quality control parameters such as buoyancy, entrapment efficiency and drug content in finished product before and after stability testing were remarkably within specified limits of specification.

Hence, the product manufactured was stable and information generated with respect to its manufactured will add up to knowledge of micro balloon formulation development.

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