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DEVELOPMENT AND EVALUATION OF ONDANSETRON HCL MICROBALLOONS FOR TREATMENT OF EMESIS

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ABSTRACT

In present study an attempt was made to prepare microballons of ondansetron by emulsion solvent diffusion method for sustained delivery by using polymers like Eudragit RS 100 and HPMC. The extend of the drug release for about 6 hrs in to the upper GIT, this may the increase absorption and their improved bioavailability. The amount of drug release was determined by USP Dissolution test apparatus was found to range from 81.32 % to 89.34 % from all formulation. Formulation F6 containing HPMC and Eudragit polymer blend show the better release study among other formulation. Scanning electron microscopy, it was observed that, microballons were found to be spherical in shape with smooth surface texture. Among all formulations, F6 shows appropriate drug release rate 89.34 % in 6 hrs. which is considered as the best formulation.

Key words: Ondansetron HCl, HPMC, Eudragit, Microballons.

INTRODUCTION

The controlled drug delivery system represents from the major part of today's drug development technique, from this includes various scientific approaches, for individual care. The drug delivery technique having various advantages as compare to conventional dosage form, it involves improve effectiveness, lesser poisoning, embellish consumer conformity also ease. This drug delivery technique makes use of micro molecules, for caring drugs. As the relevance of forms for dosage are invented like microparticle as well as nanoparticles shown more significance.

An ideal and better oral drug delivery system is that, which precisely controls speed, time as well as specific site of release of medicament separately of normal physiological variables such as GI tract pH, digestive condition of the GI tract, peristalsis movement and circadian rhythm. Advancement of polymer science and technology outcome in pick up the pace research and developmental activity in the design of drug delivery devices. Therapeutic effectiveness of a drug particle relies upon the bioavailability and eventually solubility of drug substances. Solubility is prerequisite to accomplish desired concentration of drug in to the systemic

circulation, drug absorption and pharmacological response. When the oral route of drug administration is the simple and easiest manner of management of medication because it gives accurate affected person compliance, convenience, accurate dosing, easy manufacturing, and better stability. The hydrophilic drugs having poor dissolution rate restrictive step in the process of drug absorption (Jinuk et al., 2015; Jelvehgari et al., 2006; Iwai et al., 2004). Imminent bioavailability application is predominant with extremely hydrophobic drugs due to partial absorption from gastrointestinal tract (GIT). Bioavailability is the essential parameter of a dosage form. It is the capability of the dosage form to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form in to the systemic circulation. It is affected by a number of factors related to the drug, dosage form and patient (4-5). Dosage form related factors which can produce profound differences in the drug bioavailability include formulation and manufacturing variables such as particle size, the chemical form, solubility of the drug, the type and quantity of excipients used, the compaction pressure etc (6). It is well known that the drug bioavailability and efficacy are severely limited by its poor aqueous solubility and dissolution rate. (Jinuk et al., 2015; Majeti and Ravi Kumar, 2000; Dey et al., 2009)

MATERIALS AND METHODS:

Materials:

Ondansetron Hydrochloride was obtained as a gift sample from Torrent Pharmaceutical Pvt. Ltd, Gujarat. Resin Indion 204 was gifted by Ion Exchange (India) Ltd. Other chemicals used were of analytical grade.

Mehods:

Preparation of microsphere

The microballons were prepared by Quasi-emulsion solvent diffusion method. Desired quantity of ondensarten hydrochloride. To prepare the inner phase, Eudragit RS 100 was dissolved in 3 mL of methanol and triethylcitrate (TEC) was added at an amount of 20% of the polymer in order to facilitate the plasticity. The drug was then added to the solution and dissolved under ultra-sonication at 35°C. After that PVA dissolved in 200 mL of water in a separate container. Then the inner phase was poured into the PVA solution in 200 mL of water (outer phase). The resultant mixture was stirred for 60 min, and filtered to separate the microballons. The microballons were washed with distilled water and dried at 40°C for 24h. (D'souza and More, 2008)

Table 1: Formulation Ondansetron hydrochloride Microballons

Formulation code	F1	F2	F3	F4	F5	F6
Inner phase						
Ondensatron (g)	0.1	0.2	0.1	0.1	0.1	0.2
Eudragit RS 100 (g)	0.4	0.4	0.4	0.6	0.8	1.2
Methanol (mL)	3	3	3	3	3	3
Outer phase						
Distilled water (mL)	200	200	200	200	200	200
PVA (mg)	50	50	50	50	50	50
Drug/Polymer ratio						
	1:4	1:2	1:4	1:6	1:8	1:6

Evaluation of Microballons

Determination of Production Yield and Loading Efficiency

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microballons obtained (Kilicarslan and Baykara, 2003).

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Therotical Mass (polymer + drug)}} \times 100$$

The loading efficiency (%) of the microballons can be calculated according to the following equation:

$$\text{Loading Efficiency} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Therotical drug Content}} \times 100$$

Particle Size Analysis

Particle size analysis of prepared microballons was carried by using Malvern Particle Size Analyzer Hydro 2000 MU (A). Microballons were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument's sensitivity range.

During the measurement, particles are passed through a focused laser beam. These particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors. The map of scattering intensity versus angle is the primary source of information used to calculate the particle size. The scattering of particles is accurately predicted by the Mie scattering model. The Mastersizer 2000 software, allows accurate sizing across the widest possible dynamic range.

Scanning Electron Microscopy

For morphology and surface topography, prepared microballons were coated with platinum at room temperature so that the surface morphology of the microballons could be studied by SEM. The SEM, a member of the same family of imaging is the most widely used of all electron beam tools. (Goldstein, 2003) The SEM employs a focused beam of electrons, with energies typically in the range from a few hundred eV to about 30 keV, which is across the surface of a sample in a rectangular scan pattern. Signals emitted under this electron irradiation are collected, amplified, and then used to modulate the brightness of a suitable display device which is being scanned in synchronism with probe beam.

***In-vitro* Release Study of Microballons**

Accurately weighed loaded microballons (5 mg) were placed in 50 ml of ethanol/methanol in 100 ml glass bottles. The later were horizontally shaken at 37°C at predetermined time intervals. Aliquot samples were withdrawn (replaced with fresh medium) and analysed UV spectrophotometer at 310 nm for Ondansetron hydrochloride. The contents of drugs were calculated at different time intervals up to 6hrs.

Stability Profile of Microballons Formulation

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light (Tripathi et al., 2011).

Stability profile of the active component is the major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Optimized formulation sealed in aluminium packaging coated inside with polyethylene, and various replicates were kept in the humidity chamber maintained at 40±2°C and 75±5% RH for 6 months. The samples were analyzed for the physical changes and *in-vitro* release profile at an interval of 1 month for 6 months.

RESULT AND DISCUSSION:

Production yield of Ondansetron hydrochloride microballons were between 84.42 to 86.17%. In

case of Eudragit RS 100 microballons, it was revealed that, by increasing drug: polymer ratio there is increase in the production yield of the microballons.

Table 2. Percentage yield of formulated microballons

Formulation code	Production yield (%)	Drug Loading efficiency (%)
F1	83.03±0.58	87.33±1.83
F2	79.81±0.27	84.33±1.53
F3	81.38±0.85	82.11±1.76
F4	76.33±0.39	85.33±1.83
F5	82.33±0.73	86.57±1.53
F6	77.33±0.32	83.22±1.29

*****Each value is average of three separate determinations ±SD

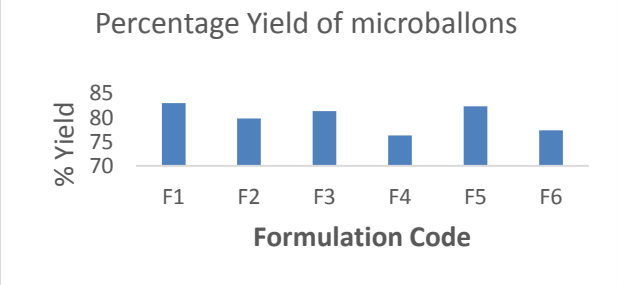

Figure 1: Percentage yield of Ondansetron hydrochloride microballons formulations

The loading efficiency was found to be high i.e. 84.38 to 87.94 % in Ondansetron hydrochloride microballons it was found that as drug: polymer ratio increases, drug loading efficiency also increases.

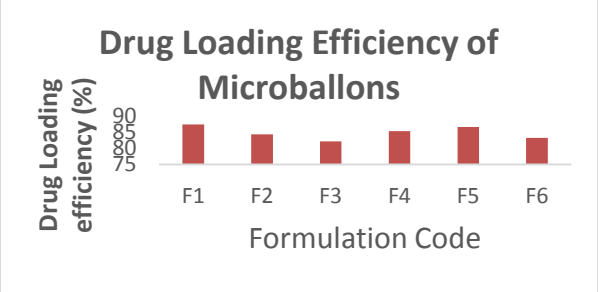

Figure 2: Loading efficiency of Ondansetron hydrochloride microballons formulations

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during both the polymerization methods. The mean particle size of Ondansetron hydrochloride microballons found to be 41.62µm.

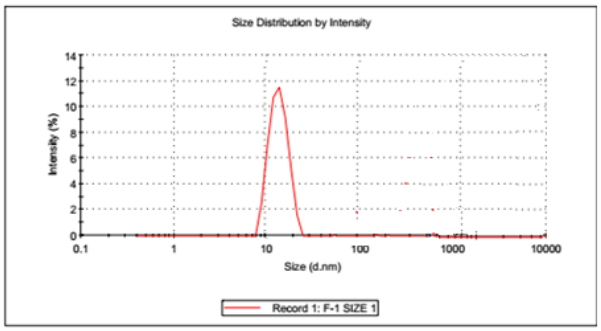

Figure 3. Particle size distribution of Ondansetron hydrochloride microballons (Mean particle size 41.62µm)

The drug release profiles of the Ondansetron hydrochloride microballons formulations are illustrated in Table and Figure. Drug release from Ondansetron hydrochloride microballons was found to range from 81.32 % to 89.34 % from all formulations.

From the results it was found that, as concentration of polymer increases, percentage of drug released decreases. The initial high drug release could be due to two reasons: first, the drug near or on the surface of the microballons and second, well known porous nature of microballons, the pores providing a channel for release of the drug.

The microballons differ from regular microspheres with their highly porous surface. This characteristic gives property to release the drug at a faster rate through the pores. Kawashima reported that microballons having a more porous internal structure, exhibited a faster drug release rate than that of rigid microspheres. (Kawashima et al., 2003) Release from F6 formulation has Higuchi release pattern followed zero order reaction kinetics (r2= 0.948, 0.965 and 0.983).

Table 3: *In-vitro* release study of Ondansetron hydrochloride microballons

Time (Min)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	18.53±0.33	22.48±0.68	20.82±1.53	15.82±1.78	17.27±0.62	15.33±0.60
30	23.04±0.69	32.69±0.59	33.17±0.83	27.68±1.36	27.33±0.74	29.19±0.33
45	47.68±0.92	46.37±0.73	38.32±1.33	36.72±1.93	38.33±0.59	33.83±0.85
60	53.83±0.38	56.83±0.82	46.39±0.38	54.38±1.53	53.46±0.92	49.71±1.03
120	61.33±0.29	61.83±0.29	58.73±0.35	58.63±1.33	61.23±0.73	56.03±0.79
180	78.18±0.45	68.72±0.49	66.53±0.47	68.46±1.33	71.20±0.62	63.11±0.92
240	84.59±0.72	78.35±0.11	73.11±0.82	72.37±1.26	75.03±0.30	72.16±0.61
300	86.04±0.39	84.82±0.36	82.47±1.25	83.58±1.71	82.85±0.73	79.45±0.82
360	91.58±0.83	89.79±0.44	86.38±0.18	85.49±1.28	86.74±0.11	84.55±0.49

*****Each value is average of three separate determinations ±SD

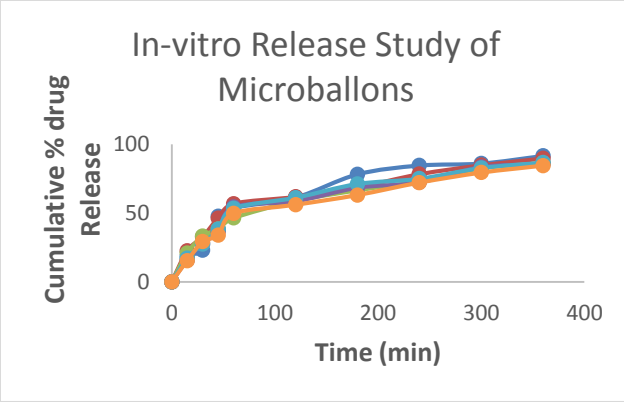

Figure 5: In-vitro drug release profiles of Ondansetron hydrochloride microballons

Conclusion:

Suspension polymerization reaction conditions used conventionally to prepare microballons were observed to be compatible with Ondansetron hydrochloride. Eudragit RS100 microballons containing Ondansetron hydrochloride were successfully prepared by this method as the drug were found incompatible with reaction conditions of liquid-liquid suspension polymerization. For Eudragit based microballons, the mean particle size was found to increase with the decrease in the polymer amount. The microballons showed homogenous particle size distribution with three blade centrifugal stirrer. Stirring speed and time has profound effect on particle size and size distribution of microballons. The relatively high percentage yield and loading efficiency of microballons indicated that the method is suitable for preparing the microballon formulations. Due to smaller pore diameter, the Eudragit Rs 100 microballons showed less and slower drug release in the *in-vitro* release studies. Release from all the microballons followed zero order reaction kinetics.

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