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RESEARCH ARTICLE

FORMULATION DEVELOPMENT OF MICROBALLOONS FOR THE MANAGEMENT OF HYPERACIDITY USING RANITIDINE HYDROCHLORIDE

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Abstract:

The aim of the present research is to develop multiple unit dosage form as microballoons of a drug meant for management of hyperacidity using ranitidine hydrochloride employing poly vinyl alcohol (PVA), and eudragit RS 100 as polymers by Quasi-emulsion solvent diffusion technique. Different batches of microballoons (F1 to F6) were prepared by varying the polymer ratios. With the increase in eudragit concentration entrapment efficiency were increased which may be due to extended release property of polymer. The formulation F6 was selected as an ideal formulation based on entrapment efficiency and in vitro drug release tests. In vitro drug release was carried out in simulated gastric fluid (50ml of 0.1N HCl) for 6h by dialysis technique. The shape of microspheres demonstrated by scanning electron microscopy and found to be spherical. The drug release from the ideal formulation (F6) followed Higuchi model than the zero order kinetic models.

Key words: Ranitidine hydrochloride, PVA, Eudragit RS 100, scanning electron microscopy.

INTRODUCTION:

Controlled drug delivery technique presents front line part of today's developed technique, in this includes many scientific approaches, serving for individual care.[1] The drug deliverance technique having abundant advantages than existing conventional type of dosage, it involves enhanced effectiveness, minimized poisoning, enhanced consumer conformity also ease.[2-3] This type of drug deliverance technique utilizes micro molecules, for caring drugs. As the varieties of forms for dosage are invented like microparticle as well as nanoparticles shown more significance.[4-6]

An ideal and advanced oral drug delivery system is that, which exactly controls speed, time as well as site of release of medicament separately of normal physiological variables such as gastrointestinal tract pH, digestive condition of the gastrointestinal tract, peristalsis movement and circadian rhythm. Advance in polymer science and technology outcome in pick up the pace research and developmental activity in the design of drug delivery devices.[7-9]

Ranitidine is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease and gastroesophageal reflux disease.[10-12]

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H2-receptors found in gastric parietal cells. This results in decreased gastric acid secretion and gastric volume, and reduced hydrogen ion concentration.[7,13]

H_2-receptor antagonists are widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration the dose of famotidine 20mg by oral twice daily for 6 to 12 weeks, where gastroesophageal reflux disease is associated with esophageal ulceration, the recommended dosage is 40mg twice daily for a similar period. For the short term symptomatic relief of heartburn or non ulcer dysopsia a dose of 10mg up to twice daily is suggested.[12-16]

The purpose of this research was to develop a controlled delivery system containing drug Ranitidine with different ratio of synthetic hydrophilic polymers. Hydrophilic polymers are widely used in the formulation of modified release oral dosage forms.[17-18] Their convenience and ease of manufacture may cut down the cost of the final product. Besides,

hydrophilic polymer matrix system offers several additional advantages over other technologies for controlled release drug delivery.[19-20]

METERIAL AND METHOD:

Ranitidine Hydrochloride obtained as gift sample from Torrent Pharmaceutical private limited, Ahmedabad.

PVA from Fisher scientific, eudragit RS 100 were purchased from Finar scientific. Methanol and other chemical was purchase from Loba Chemical Private Limited Mumbai.

Method:

Preparation of microballoons containing Ranitidine Hcl:

Inner phase

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 ultrasonication at 35°C.

Outer phase

To prepare the inner phase PVA dissolved in 200 ml of water in a seprate container.

Mixing step

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 microballoons. The microballoons were washed with distilled water and dried at 40°C for 24h.

Table 1: Composition of microballoons containing Ranitidine Hcl

	Ranitidine Microballoons					
Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
	Inner phase					
Drug (mg)	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit RS 100 (g)	0.23	0.28	0.36	0.50	0.83	2.5
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

Evaluation of Microballoons :

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 microballoonsobtained.

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

The loading efficiency (%) of the microballoons 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 microballoons was carried by using Malvern Particle Size Analyzer Hydro 2000 MU (A). Microballoons 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 microballoons were coated with platinum at room temperature so that the surface morphology of the microballoons 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 J. I., 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.

Infrared Spectroscopy

FTIR spectroscopy was conducted using Perkin Elmer, Spectrum 100 FT-IR spectrometer. Spectrum was recorded in the wavelength region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample in excess of potassium bromide nearly at the ratio 1:100, mixed well, after which the mixture was kept into the sample holder for analysis.

Differential Scanning Calorimetry (DSC)

Thermal analysis is an important evaluation technique to find any possible interaction between the drug and used polymers. Any of such interaction may reduce the drug entrapment efficiency of the polymer and may also alter the efficacy of the drug. Such interaction can be identified by any change in thermogram.

***In-vitro* Release Study of Microballoons**

Accurately weighed loaded microballoons (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 spectrophotometrically at 350 nm for ranitidine. The contents of drugs were calculated at different time intervals up to 6hrs.

Results and Discussion:

- **Yield of the product**
  - **Percentage Yield**

Table 2. Percentage yield of formulated microballoons

Formulation code	Production yield (%)
F1	86.17±1.23
F2	85.74±2.28
F3	86.38±2.06
F4	84.76±1.52
F5	85.94±2.04
F6	84.42±1.24

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

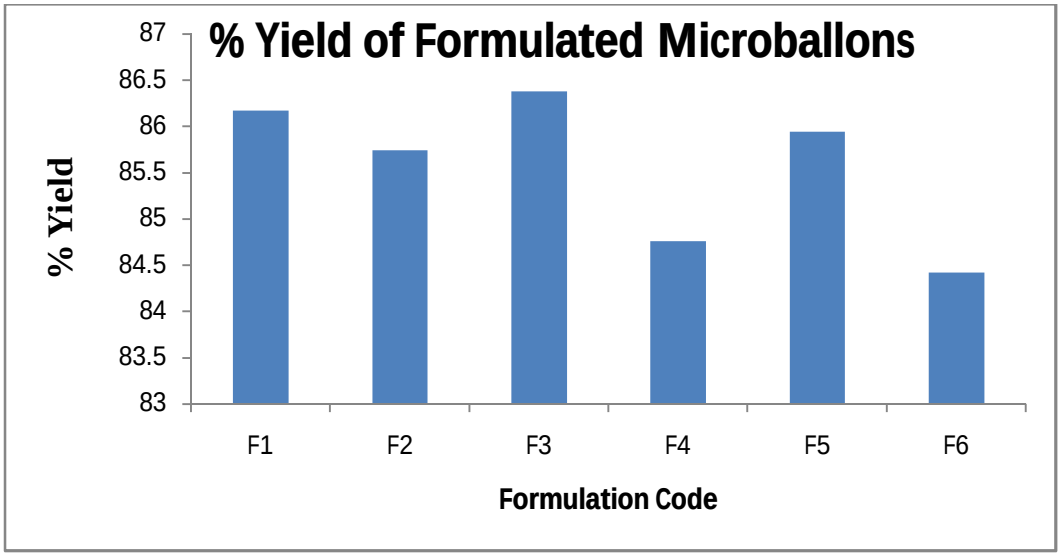

Figure 1: Percentage yield of ranitidine microballoons formulations

Production yield of Ranitidine microballoons were between 84.42 to 87.73%. In case of Eudragit RS 100 microballoons , it was revealed that, by increasing drug: polymer ratio there is increase in the production yield of the microballoons .

Drug Loading Efficiency

Table 3: Drug loading efficiency of Salicylic acid microballoons formulations

Formulation code	Drug Loading efficiency (%)
F1	86.17±1.13
F2	85.74±0.18
F3	84.38±1.24
F4	86.76±2.03
F5	87.94±1.28
F6	85.42±0.68

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

The loading efficiency was found to be high i.e. 84.38 to 88.73 % in ranitidine microballoons it was found that as drug: polymer ratio increases, drug loading efficiency also increases.

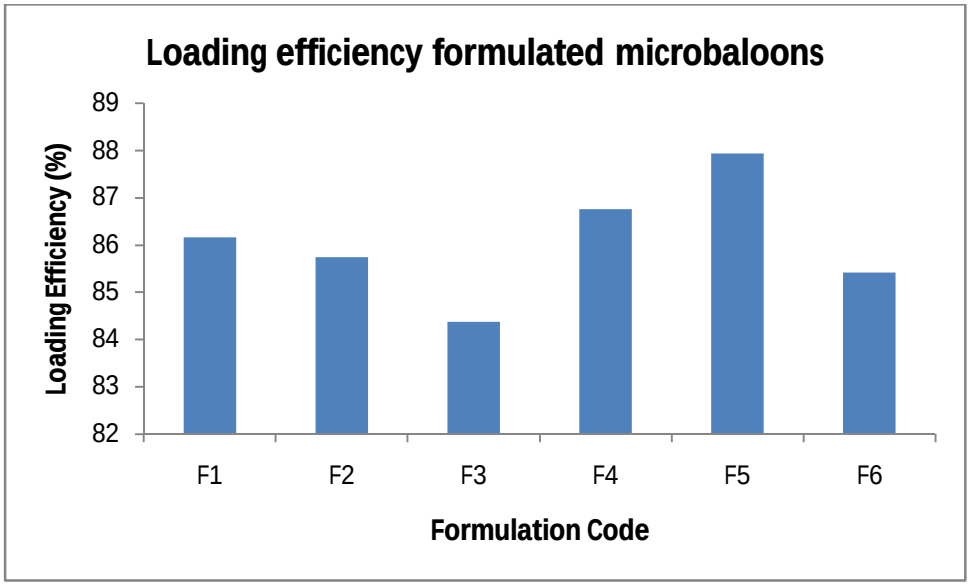

Figure 2: Loading efficiency of ranitidine microballoons formulations

Particle Size Analysis

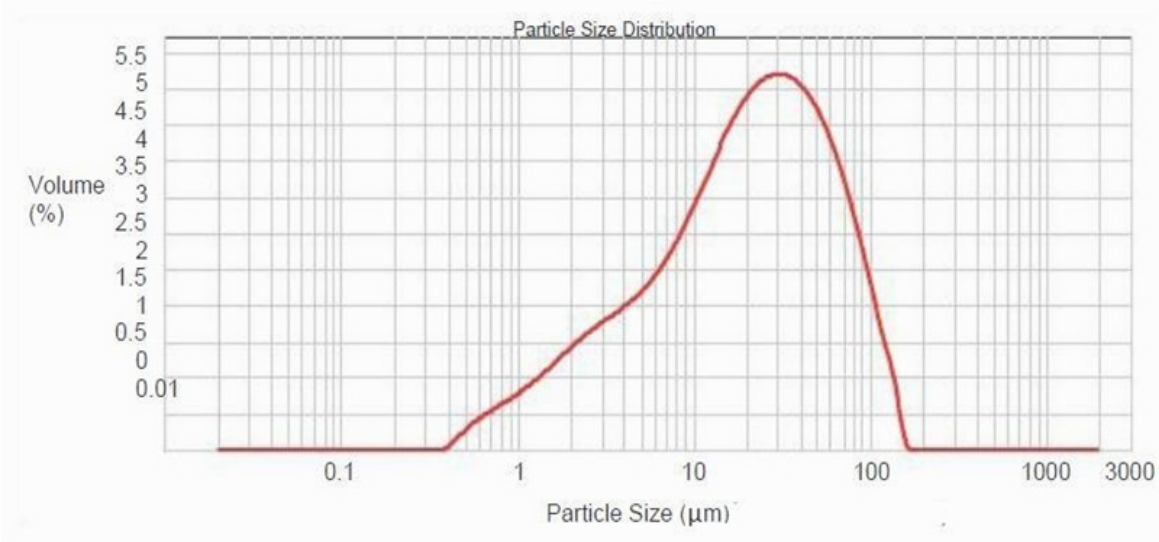

Figure 3: Particle size distribution of ranitidine microballoons (Mean particle size 39.92µm)

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 ranitidine microballoons found to be 39.92µm.

Scanning Electron Microscopy

The morphology of the microballoons prepared by entrapment method and quasi-emulsion solvent diffusion method were investigated by SEM. The representative SEM photographs of the microballoons are shown in Figure.

SEM images showed that microballoons prepared by liquid-liquid suspension polymerization method were finely spherical and uniform; no entire drug crystals were observed visually.

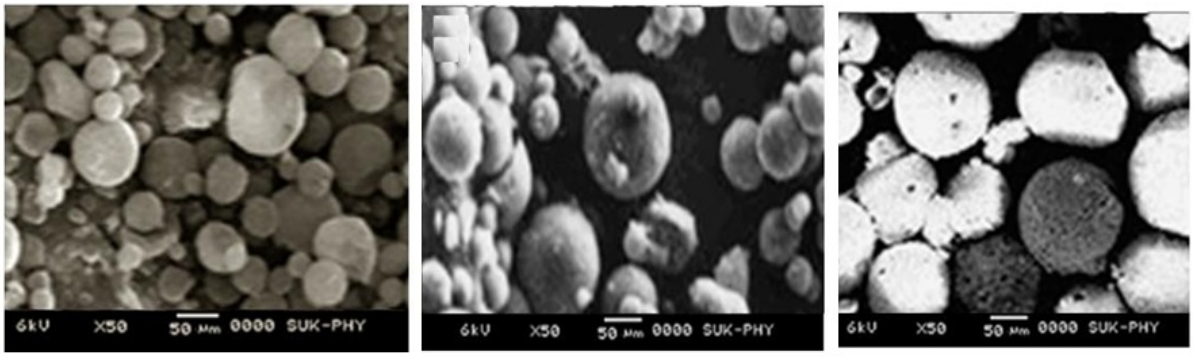

Figure 4: SEM Photographs of Ranitidine Microballoons

Infrared Spectroscopy

FTIR spectra of ranitidine microballoons

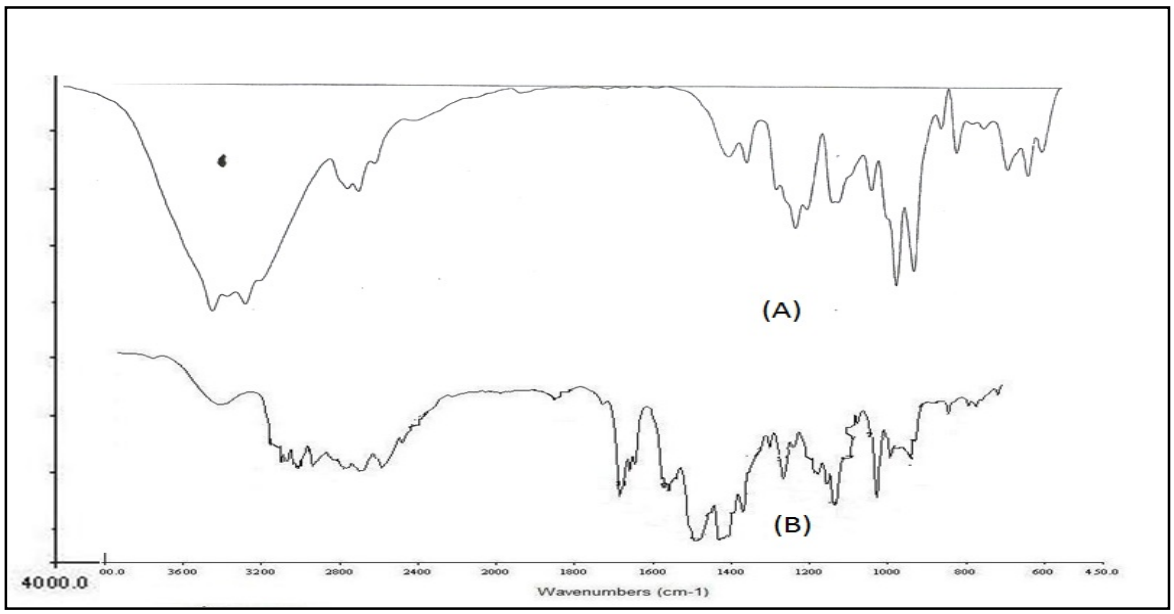

Figure 5: Overlay FTIR Spectra of: (A) Ranitidine and (B) Ranitidine microballoons formulation.

All characteristic peaks of drugs in the IR spectra of F 6 f o r m u l a t i o n were observed to be concordant with respective pure drugs.

Differential Scanning Calorimetry (DSC)

The results of DSC were observed for the integrity of the drug in microballoons formulation prepared by the entrapment process. In the DSC curve of selected F6 formulation, the endothermic melting peak concerning ranitidine. According to this data, there was no interaction between drug and Eudragit RS 100 in microballoons results showed that there was no interaction between the drugs and the polymer.

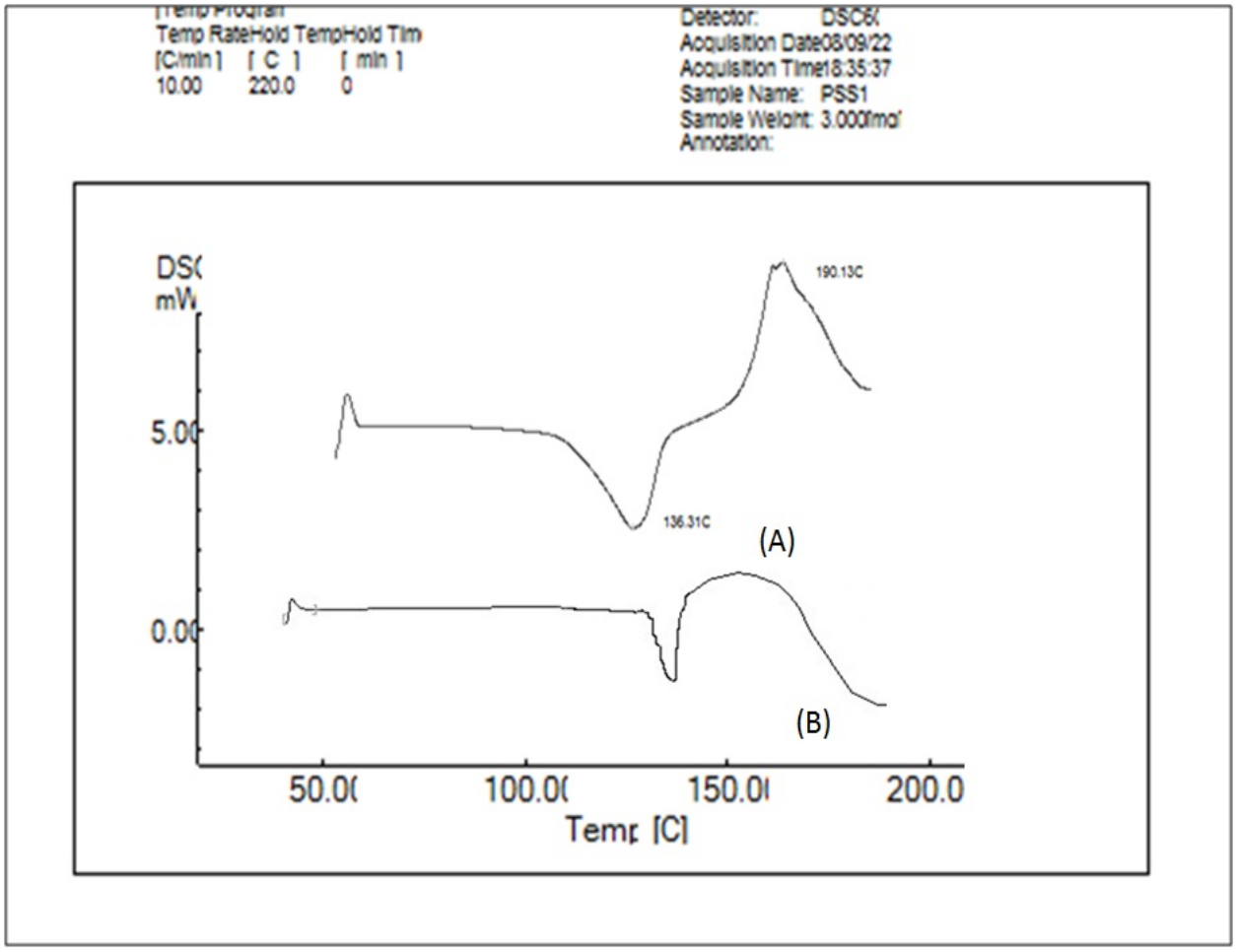

Figure 6: DSC Thermograms of A: Pure Drug, B: drug loaded microballoons formulation

In-vitro Release Study of Microballoons

Table 4: *In-vitro* release study of ranitidine microballoons

Time (Min)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	15.62±0.12	20.34±1.11	28.21±1.32	13.41±1.54	15.83±1.99	16.82±0.86
30	25.35±0.45	34.45±0.41	34.1±0.19	23.19±1.52	25.72±2.03	27.05±1.38
45	44.81±0.37	49.32±1.14	38.32±1.13	38.86±1.93	39.42±1.96	36.31±1.96
60	55.67±0.16	54.92±0.53	44.41±1.17	52.68±1.57	56.81±2.31	44.52±1.56
120	64.58±0.42	60.12±0.17	60.73±0.16	61.21±1.05	65.21±2.08	52.14±0.87
180	74.73±0.76	66.34±1.47	68.84±0.14	70.35±1.48	72.47±1.00	61.32±1.37
240	80.98±1.18	76.81±0.25	76.72±1.81	75.54±1.55	78.52±0.99	70.54±1.23
300	85.97±0.87	82.16±0.48	80.22±1.04	81.14±1.56	82.85±1.52	76.25±0.85
360	89.34±1.02	87.84±0.72	88.41±0.18	84.85±1.52	83.69±1.02	83.62±0.74

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

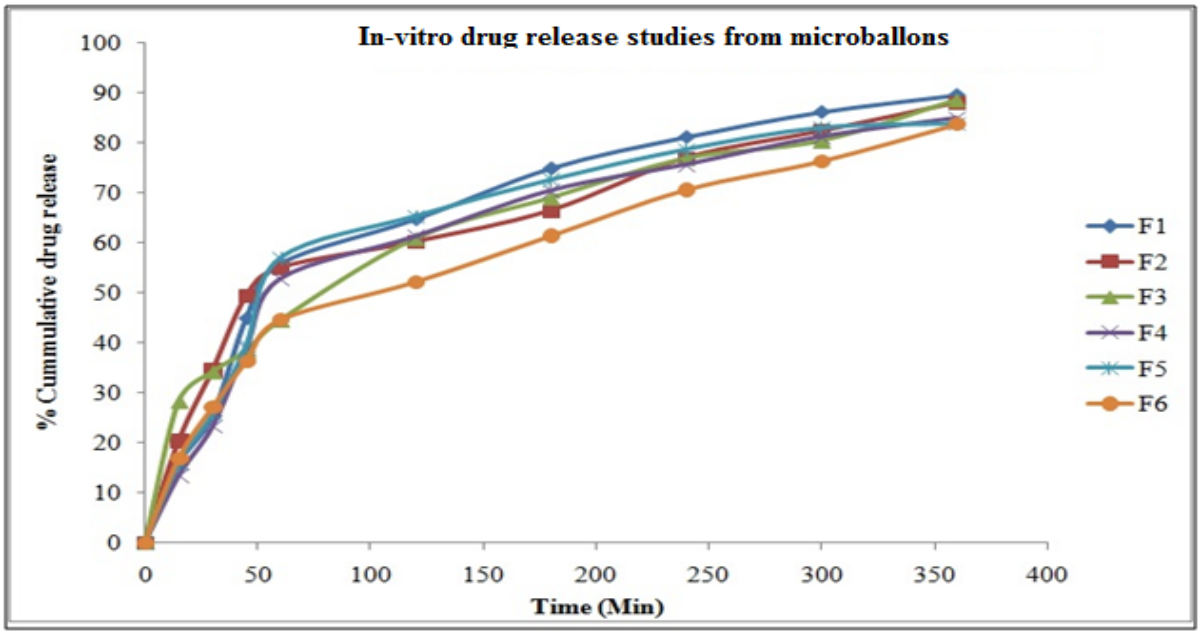

Figure 7: *In-vitro* drug release profiles of ranitidine microballoons formulations

The drug release profiles of the ranitidine microballoons formulations are illustrated in Table and Figure. Drug release from ranitidine microballoons 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 microballoons and second, well known porous nature of microballoons , the pores providing a channel for release of the drug (Mandal T. K., 2001).

The microballoons 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 microballoons having a more porous internal structure, exhibited a faster drug release rate than that of rigid microspheres (Kawashima Y., 1992). Release from F6 formulation has Higuchi release pattern followed zero order reaction kinetics (R^2= 0.948, 0.965 and 0.983).

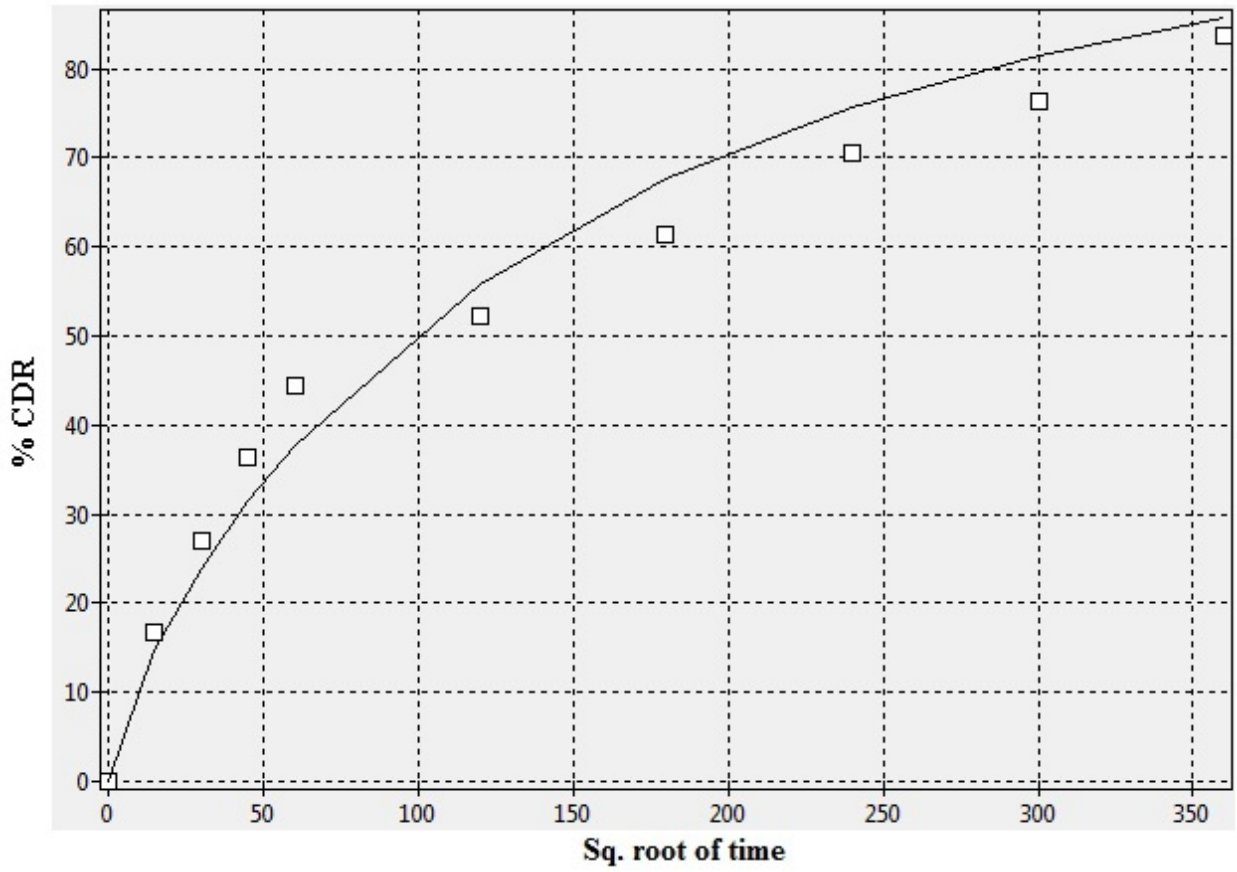

Figure 8: Higuchi Release Plot

Conclusion:

From the overall investigation, one can conclude that the optimized microballoons of ranitidine using both polymers can meet ideal requirements for microballoons. The relatively high percentage yield and loading efficiency of microballoons indicated that the method is suitable for preparing the microballon formulations. Quasi-emulsion solvent diffusion method is simple, less time consuming and involves use of safer ingredients than free radical polymerization and hence more preferred.

The microballoons differ from regular microspheres with their highly porous surface. This characteristic gives property to release the drug at a faster rate through the pores. Due to smaller pore diameter, the Eudragit Rs 100 microballoons showed less and slower drug release in the *in-vitro* release studies. Release from all the microballoons followed zero order reaction kinetics.

In future, the formulations can used as controlled release dosage form for better bioavailability and improved patient compliance.

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