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Research Article

FORMULATION AND EVALUATION OF FLOATING MICROSPHERE OF RANITIDINE HYDROCHLORIDE

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Abstract

Ranitidine HCl is H_2 receptor antagonist inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells. It competitively inhibits histamine action at all H_2 receptors but their main clinical use is as inhibition of gastric acid secretion. It inhibited histamine stimulation and gastrin stimulated acid secretion. The microspheres of each batch were subjected to various physicochemical studies i.e. particle size, bulk density, % yield, % buoyancy, drug entrapment efficiency etc. The compatibility of the drug with selected polymers was determined by FTIR spectrophotometric studies using FTIR Affinity -1. The characteristic peaks of pure drug, ethyl cellulose and chitosan were compared with that obtained with the formulation of all the nine batches. Thin layer chromatography was performed and studied comparative to the pure drug and its micro spherical formulations.

Keywords: Microsphere, Ranitidine, histamine receptor, FTIR etc.

Introduction

Ranitidine is a H_2 antihistamine drug. It is a drug used to block the action of histamine on parietal cells in the stomach decreasing acid production by these cells. It has a furan ring. It has melting point 69-70 °C. The wavelength of ranitidine is at 229 nm and 315 nm (water used as medium). The chemical name of Ranitidine HCl is N [2-[[[5-[(dimethylamino) methyl]-2furanyl] methyl] thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl.

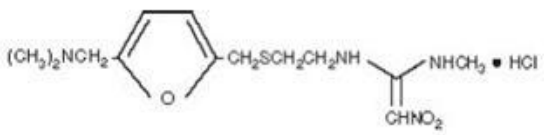

Figure 1: Structure of Ranitidine Hydrochloride

It was a white or pale yellow crystalline powder drug having melting point 136-142 °C. It is freely soluble in water, methanol and ethanol (95%), sparingly soluble in ethanol, very slightly soluble in chloroform and in dichloro methane.

The molecular formula of Ranitidine HCl is and $C_{13}H_{22}N_4O_3S$•HCl and the molecular weight is 350.87. It is preserve in well closed container, Protected from light. Ranitidine HCl is H_2 receptor antagonist inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells. It competitively inhibits histamine action at all H_2 receptors but their main clinical use is as inhibition of gastric acid secretion. It inhibited histamine stimulation and gastrin stimulated acid secretion. It decreases both basal and food stimulated acid secretion by 90% or more, but promote healing of duodenal ulcer. Specific ranitidine uses include treatment or prevention of the following conditions:

- Duodenal ulcers, Gastric ulcers (stomach ulcers), Gastroesophageal reflux disease (GERD) and Erosive esophagitis
- Pathological hypersecretory conditions (in which too much stomach acid is produced), such as Zollinger-Ellison syndrome.
- Over-the-counter ranitidine is approved for the following conditions in people 12 years

older: Heartburn, Acid indigestion and Sour stomach.

Adverse Effects

- Constipation, Diarrohoea, Headache, Stomach upset, change in the amount of urine produced; confusion, dark urine and depression
- fast, slow, or irregular heartbeat, fever, chills, or sore throat; Yellowing of the eyes or skin and Hallucination
- rash, urticaria, bronchospasm, fever, eosinophilia, angioneurotic edema, acute eosinophilic pneumonia and anaphylaxis
- to decrease mucosal perfusion in patients with acute renal or cardiac failure and increases their risk of death
- class decrease gastric intrinsic factor secretion which can significantly reduce absorption of protein-bound vitamin B_{12} in humans
- may increase the risk of pneumonia in hospitalized patients
- increase the risk of developing food allergies

Thrombocytopenia

Table 1: Pharmacokinetics of Ranitidine

Bioavailability	45-50%
Plasma Half Life	2 hrs.
Plasma Protein Binding	15- 20%
Peak Plasma Concentration (C_{max})	1- 3 hours
Excretion	Renal Excretion (65-70%) Metabolic Excretion (30-35%)
Renal Clearance	600 ml/min
Drug Interaction	It does not inhibit hepatic microsomal enzyme CYTP450 system and hence does not interact with drugs which are substrate for CYTP450 systems like Warfarin, Pheytoin, Quinidine, Caffiene etc. It does not block androgen receptors and do not cause Gynaecomastia and impotence like cimetidine.

Materials and Methods

Ranitidine was received as a gift sample from Panacea biotech, Mohali. Ethyl cellulose was received as a gift samples from Fine Chem. Labs. Mumbai. Chitosan, PVA and SLS were purchased from Signet Chemical Corporation. Tween 80 and HCl were purchased from Rankem. 99% ethanol was purchased from Jiangsu Huaxi International.

Experimental work

Formulation design of Ranitidine HCl

Microspheres containing Ranitidine HCl as a core material were prepared by emulsion solvent diffusion method. Drug and polymer were dispersed in the solvent (dichloromethane and ethanol in ratio 1:1 v/v). The slurry was slowly introduced into 200 ml of water containing (0.75% w/v) polyvinyl alcohol maintained at a constant temperature of 40 °C with continuous stirring at 300 rpm using a propeller type mechanical stirrer. The solution was stirred for 2 hrs. The finely developed floating microspheres were separated by filtration washed with water & dried at room temperature in a dessicator for 24 hrs. The formulation was divided into nine batches prepared with different ratio of suitably chosen polymers as depicted in the table below .

Evaluation of floating microspheres

Micromeritic parameters

Micromeritic parameters like bulk density, tapped density, carr's index, angle of repose and hausner's ratio for formulations (F_1-F_9) were determined and found in the range of (0.24-0.68) (0.32-0.86) (14.46-23) & (12.14-18.16) respectively.

Particle Size Determination

The particle size determination was performed for all nine batches. Results were as shown in table 4. The mean particle size was found to be in the range of 128.80 - 196.21µm.

Surface morphology

The surface morphology of microspheres was examined by scanning electron microscopy.

Table 2: Formulation design of microspheres

Ingredients	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rantidine HCl	100	100	100	100	100	100	100	100	100
Ethyl cellulose	100	150	200	-	-	-	-	-	-
Chitosan	-	-	-	100	150	200	-	-	-
Chitosan+ EC	-	-	-	-	-	-	50:150	100:100	150: 50
Dichloromethane	10	10	10	10	10	10	10	10	10
Ethanol	10	10	10	10	10	10	10	10	10
SLS (mg)	20	20	20	20	20	20	20	20	20
Tween 80	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
PVA (w/v %)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Table 3: Results of Micromeritic parameters

S. No.	Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Angle of repose (θ)
1	F1	0.3435	0.4640	22.56	12.14
2	F2	0.2408	0.3285	23.00	18.16
3	F3	0.4502	0.5688	18.50	15.67
4	F4	0.2408	0.3476	16.28	15.34
5	F5	0.3683	0.4580	18.67	14.76
6	F6	0.3566	0.4143	15.28	15.98
7	F7	0.6823	0.8653	21.00	12.32
8	F8	0.5500	0.67400	17.67	14.34
9	F9	0.4429	0.4835	14.46	16.14

Tablet 4: Particle size for batch F1 - F9

Serial no.	Formulation code	Size (µm)
1	F1	134.10
2	F2	133.44
3	F3	157.23
4	F4	139.10
5	F5	144.92
6	F6	128.80
7	F7	189.65
8	F8	196.21
9	F9	192.53

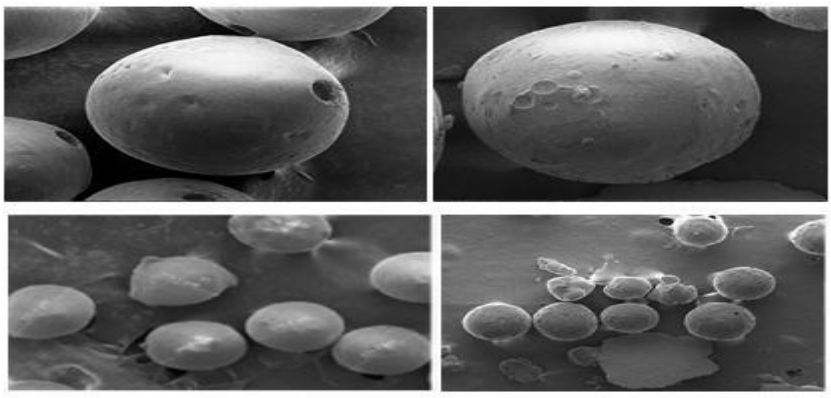

Figure 2: SEM photomicrographs of micro spherical particles

It revealed rough texture of microspheres with minute dents on the surface.

Percentage Buoyancy

The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The particles were spread over the surface of a simulated gastric fluid and the fraction of microspheres settled down as a function of time was quantities. The fraction of microspheres reduced up to 12 hrs suggested that the absorption of the drug in vivo pertaining to sustained release would be linear with time.

Buoyancy of Formulations F3, F8, F9 were found to be 65.39%, 65.45% and 65.41% respectively thus indicating that microspheres were still floatable even after 12 hrs.

Drug Entrapment Efficiency

The microspheres of batch F3, F6 and F7 formulations showed entrapment of 69.77%, 77.57%, 80.42% respectively while formulations F1 and F4 particles were least entrapped. It attributed to the permeation characteristics of each polymer.

Percentage Yield

The maximum % yield was found to be 79.60% with batch F7 and minimum of 66.92% with F6 batch.

In vitro dissolution study

Correlation coefficient (R^2) and diffusion exponent (n) after fitting of dissolution data (simulated gastric fluid) into various releases kinetic models:

All the release data were fitted into various kinetic models like, zero order, First order, Higuchi and Korsmeyer-peppas in order to find out the mechanism of drug release from polymeric microspheres. The correlation & diffusion coefficients were calculated as summarized in table.

Analysis of the release data as per zero order kinetic model best suited to describe the release rate of drug from the microspheres. When the release data was analyzed as per peppas equation, the release exponent 'n' was in the range of (0.531-0.742) with all the microspheres indicating non-fickian diffusion. Higuchi's plots resulted in linearity (r^2> 0.932) indicating non-fickian diffusion mechanism.

Table 5: Percentage buoyancy for batch F1 - F9

Sr. No.	Formulation Code	% Buoyancy
1	F1	56.91
2	F2	63.60
3	F3	65.39
4	F4	52.72
5	F5	53.59
6	F6	55.57
7	F7	60.52
8	F8	65.45
9	F9	65.41

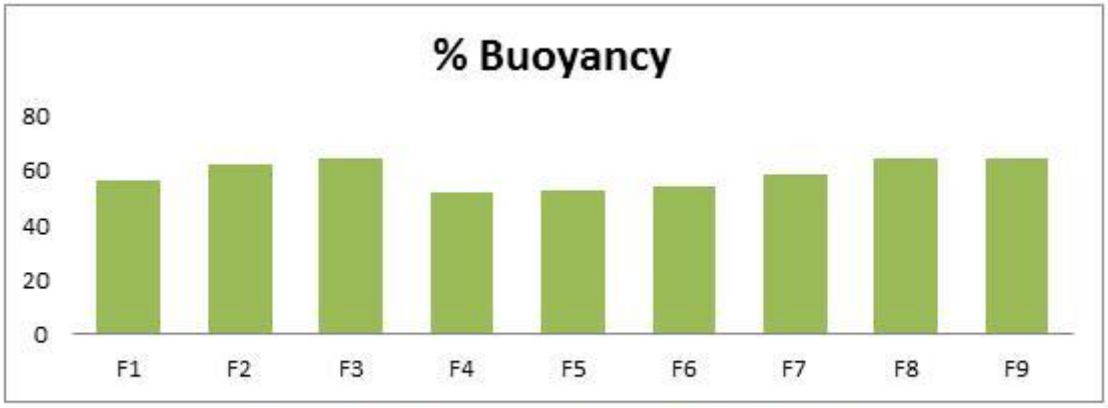

Figure 3 % Buoyancy of Formulation F1-F9

Table 6: Percentage Entrapment for batch F1 - F9

Formulation Code	% Entrapment
F1	51.91
F2	64.60
F3	69.77
F4	56.24
F5	69.51
F6	77.57
F7	80.42
F8	60.87
F9	62.99

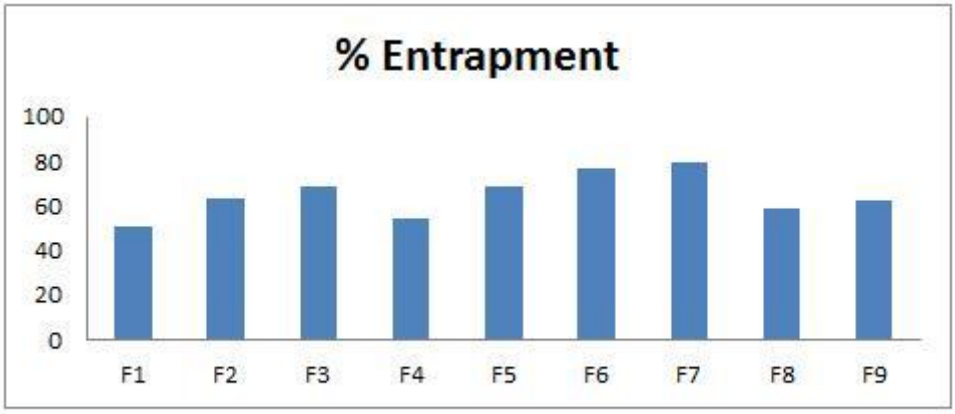

Figure 4: % Entrapment of Formulation F1-F9

Table 7: Percentage Yield for batch F1 - F9

Formulation	Percentage Yield (%)
F1	78.20
F2	76.80
F3	72.60
F4	75.60
F5	70.10
F6	66.92
F7	79.60
F8	77.14
F9	72.90

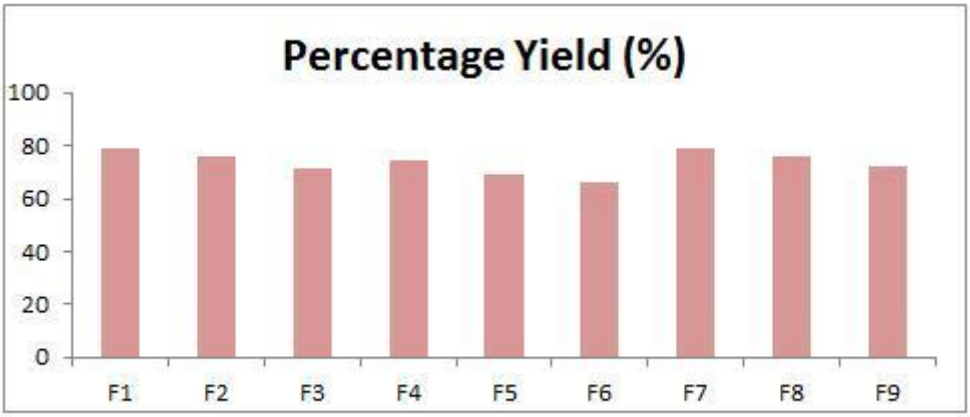

Figure 5: % Yield of Formulation F1-F9

Table 8: Kinetic values of batch F1- F9 in simulated gastric fluid

Formulation code	Zero order equation		First order equation		`Higuchi's equation		Korsmeyer's equation	
	(n)	(R^2)	(n)	(R^2)	(n)	(R^2)	(n)	(R^2)
F1	0.056	0.849	0.00	0.703	1.924	0.919	0.289	0.915
F2	0.067	0.877	0.00	0.754	2.089	0.948	0.312	0.963
F3	0.053	0.843	0.00	0.706	1.869	0.916	0.335	0.915
F4	0.091	0.932	0.00	0.805	3.178	0.984	0.521	0.985
F5	0.087	0.876	0.00	0.734	3.07	0.952	0.491	0.968
F6	0.084	0.936	0.00	0.863	2.895	0.979	0.469	0.986
F7	1.065	0.989	0.001	0.630	2.236	0.970	0.679	0.889
F8	0.057	0.913	0.00	0.783	1.889	0.982	0.425	0.818
F9	0.059	0.885	0.001	0.686	2.069	0.964	0.742	0.948

The comparative studies conducted with F2 F6 & F7 (best representatives from each class of formulation design) revealed F_7 as the overall optimized batch which was further subjected to accelerated stability studies and content uniformity test.

Summary

Three batches (F1, F2 & F3) of microspheres using the drug: ethyl cellulose (polymer) ratio of 1:1, 1:2 &1:3 respectively, three batches (F4, F5 & F6) comprising drug: chitosan (polymer) ratio of 1:1, 1:2 & 1:3 respectively and three batches (F7, F8, & F9) comprising drug: chitosan: ethyl cellulose in the ratio of 1:0.5:1.5, 1:1:1 & 1:0.5:2.5 respectively were produced by Emulsion solvent diffusion method.

The microspheres of each batch were subjected to various physicochemical studies i.e. particle size, bulk density, % yield, % buoyancy, drug entrapment efficiency etc. The compatibility of the drug with selected polymers was determined by FTIR spectrophotometric studies using FTIR Affinity -1. The characteristic peaks of pure drug, ethyl cellulose and chitosan were compared with that obtained with the formulation of all the nine batches. Thin layer chromatography was performed and studied comparative to the pure drug and its micro spherical formulations.

The particles size was determined by scanning electron microscopy and bulk density was reckoned by hand trapping method. Other parameters such as % yield, buoyancy %, drug entrapment efficiency etc. were determined by traditional methods available so far. The in-vitro dissolution studies were carried out on dissolution apparatus (Electrolab, TDT 06L, 6 basket) in pH 1.2 HCl buffer and simulated gastric fluid.

Conclusion

The microspheres of Ranitidine HCl were prepared with two polymers i.e. ethyl cellulose and chitosan. The particle size determination by SEM techniques revealed that the mean particle diameter was in the range of 128.80 - 196.21µm. The mean particle size were in the order of F2<F1 < F6 < F4 < F5 < F3 < F7 < F9< F8. The other physicochemical parameters determined with the microspheres were bulk density (0.24-0.68g/ml), particle size distribution (128.80-196.21µm), % yield (66.92%-79.60%), buoyancy % in pH 1.2 HCl buffer (52.72%- 65.45%), tapped density (0.32-0.86g/ml) and drug entrapment efficiency (51.91%-80.42%). The in vitro drug release in pH 1.2 HCl buffer ranged from 84.54%-55.10% while in simulated gastric fluid it ranged from 84.82%-56.76%. The overall determinations suggested F7 batch as the best formulation. Conclusively % yield was maximum with F7 and minimum with F6 batch. The drug entrapment efficiency was found to be of the order F1 < F7 < F4 < F8 < F2 < F9 < F5 < F3 < F6.The overall determinations suggested F7 as the best formulation. The in-vitro release of formulation F7 in pH1.2 HCl buffer and in simulated gastric fluid (SGF) were 60.52% and 59.62% respectively which showed sustained release over a period of 12 hrs. All above data satisfactorily complied with the characteristics requirements of the formulation as gastroretentive microspheres.

The present worker tended to provide impetus for future researchers to design such novel drug delivery systems which can supersede conventional dosage forms with significant pharmacokinetic and pharmacodynamic properties.

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