JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF ENTERIC COATED PELLETS OF "ROXATIDINE ACETATE

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ABSTRACT

The objective of the current research is to formulate and evaluate delayed release pellets of Roxatidine acetate. The formulations of Roxatidine acetate delayed release pellets of Roxatidine acetate were developed by enteric film coating process varying the compositions of drug loading, barrier coating and enteric coating. Eudragit L-30 D 55, Triethyl citrate, NF, Hydroxy Propyl Methyl Cellulose E5, Polyethylene Glycol – 6000 and HPMC were used as enteric polymers. The process variables were standardized and the different batches prepared were evaluated for assay/drug content, water content, acid resistance and dissolution rate. The drug dissolution profiles of Roxatidine acetate delayed release formulations developed were compared with that of innovators product. Finished products were evaluated for friability test, assay, and *In-vitro* release studies performed for 1hr in acidic media at 0.1N HCL, after that 1 hr in 6.8 pH Phosphate buffer.

Keyword: Roxatidine acetate, Delayed release pellets

1.1 Pellets

The term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of manufacturing equipment. These agglomerates includes fertilizers, animal feeds, iron ores, and pharmaceutical dosage units and thus do not only differ in composition but also

encompass different things for different industries. Although pellets have been used in the pharmaceutical industry for more than 4 decades, It is only been since the late 1970s, with the advent of controlled release technology, that the advances of pellets over single-unit dosage forms have been realized.

Pellets are described to be produced systematically, as geometrically defined agglomerate obtained from diverse starting materials using different processing conditions. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 mm to 1.5 mm and that are intended mostly

for oral administratio. Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided in to desired dose strengths without formulation or process changes and can be blended to deliver incompatible bioactive agents simultaneously and or to provide different releases profiles at the same or different sites in the gastrointestinal (GI) tract. In addition, pellets taken orally disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs, and reduce inter-intra patient variability.

2. MATERIALS AND METHODS

2.1 Preformulation Studies:

A. Solubility analysis:

Solubility is affects the dissolution and bio availability of drug. Appropriate quantity of drug was weighed and added to the suitable volume of solventlike hexane, ethanol and water.

B. Melting point:

The melting point of Roxatidine acetate was determined by capillary method, Determined the melting point and matched with standards.

C. Bulk density:

Bulk density is determined by following formula

Bulk Density = Bulk Mass / Bulk Volume

D. Tapped density :

Tapped density was determined by using Electrolab density tester, Tapped density is calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

E. Loss on drying:

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where,

W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

F.Compatibility study

Drug- excipient compatibility studies carried out by IR spectra of drug, drug and polymers and excipients were obtained by using Bruker optic GMBH FTIR spectrometer.

2.2 Formulation of roxatidine acetate pellets

Different batches of pellets (F1 to F9) were formulated using the ingredient given in the

Table no.2.1: Formula for Roxatidine acetate pellets

Batch no.		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sr.no.	**Ingredients**	**mg/unit**	**mg/ unit**	**mg/unit**	**mg/unit**	**mg/unit**	**mg/unit**	**mg/ unit**	**mg/unit**	**mg/unit**
A	**DRUG LAYERING**									
1	Sugar Spheres (600-800 micron)	100	105	110	115	120	125	130	135	140
2	Roxatidine acetate	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00
3	Di-sodium hydrogen Orthophosphate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
4	Hydroxy Propyl Methyl Cellulose	10	10	15	15	20	20	25	30	30
5	Talcum Powder	10	10	10	10	10	10	10	10	10

6	Polyethylene Glycol 6000	4	4	4	4	4	4	4	4	4
7	Sodium lauryl sulphate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
8	Purified water	qs	qs	qs	qs	Qs	qs	qs	qs	qs
	Total	202	207	217	222	232	237	247	257	262

C	**ENTERIC COATING OF ROXATIDINE ACETATE PELLETES**									
15	Eudragit L-30 D 55	75.00	70.00	65.00	60.00	55.00	50.00	45.00	40.00	35.00
16	Triethyl citrate, NF	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
17	Talc, USP	12	12	12	12	12	12	12	12	12
18	Polysorbate 80, NF	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
19	Purified water	qs	qs	qs	qs	Qs	qs	qs	qs	qs
	Total	329	334	349	354	369	374	389	404	409

B	**Seal coating of Roxatidine acetate pellets**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
9	Roxatidine acetate layered pellets	202	207	217	222	232	237	247	257	262
10	Hydroxy Propyl MethylCellulose E5	10	10	15	15	20	20	25	30	30
11	Polyethylene Glycol – 6000	4	4	4	4	4	4	4	4	4
12	Talc, USP	10	10	10	10	10	10	10	10	10
13	Di-sodium hydrogen orthophosphate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
14	Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
	Total	228	233	248	253	268	273	288	303	308

2.3 Evaluation of formulated roxatidine acetate pellets:

a. FRIABILITY:

The friability was calculated as percentage weight loss according to the following equation:

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

W_1 - Initial Weight W_2 - Final Weight

b. BULK AND TAPPED DENSITY:

Bulk density:

Bulk density is defined as the mass of the powder divided by the bulk volume.

Bulk Density = Bulk Mass / Bulk Volume

Tapped density:

Tapped density was determined by using Electrolab density tester, which consists of a graduated cylinder. Tapped density was calculatedusing following formula.

Tapped density = Wt. of sample in gm / Tapped volume

Hausner's ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is the determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = v_i / v_t$$

Where

v_t = Tapped volume

v_i = untapped volume

c. ANGLE OF REPOSE:

Angle that can be obtained between the free surface of a powder heap and horizontal plane. The height of the heap was measured and then circumference of the base of heap was drawn on a graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

$$\theta = \tan^{-1}(h/r)$$

Where, θ= angle of repose

h= height of the heap

r = radius of the base of the heap

d. Particle size determination:

In order to determine the particle size distributions of the prepared pellets containing Roxatidine acetate, standard sieve method was used. Mechanical sifter with sieves between apertures 355-2000 μm were used by using all the amount of pellets prepared. The fraction collected on each of the sieves was calculated by the percentage value.

e. Gastric acid resistant test:

Weighed amount of pellets were placed in the vessel and test was carried out in 0.1N HCl for 1hr at 75 rpm. Roxatidine acetate released at 1hr in 0.1 N HCl was estimated as per method specified in USP. Minimal amount of drug release in this test is indicative of gastric acid resistance.

f. Invitro dissolution study :

The samples were analyzed spectrophotometrically at 275nm using UV-spectrophotometer.

g. Accelerated stability study

The ICH Guidelines have established that accelerated stability testing should be done at 40^0C/75%RH for 3 months.

Stability study was carried out for the optimized formulation. Tablets of optimized formulation were packed in strip and kept in stability chamber for 3 months on above mention temperature. Samples were analyzed at 1, 2, 3 months for invitro dissolution study.

ICH guidelines for stability study

Table no.2.2: ICH guidelines

Study	Storage condition	Time period
Long term*	25°c±2°c/60% RH±5% RH or 30°c±2°c/65% RH±5% RH	12 month
Intermediate**	30°c±2°c/65% RH±5% RH	6 month
Accelerated	40°c±2°c/75% RH±5% RH	6 month

3. RESULTS AND DISCUSSION

3.1 Result of Preformulation Studies:

A. Solubility:

Roxatidine acetate is soluble in organic solvents such as ethanol and DMSO. It is also soluble in water. The solubility of roxatidine acetate in ethanol, DMSO, and water is approximately 12, 78, and 77 mg/ml, respectively.

B. Melting point:

The Melting point of Roxatidine acetate was found to be 147 – 151 ^{o}C

C. Bulk and tapped density

Table no.3.1: Bulk density and tapped density of Roxatidine acetate

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
Roxatidine acetate	0.73	0.69

D. Loss on drying:

LOD of Roxatidine acetate was found to be 0.21% w/w (not more than 2 % w/w)

E. Compatibility studies:

FTIR spectrum of Roxatidine acetate and physical mixture of Roxatidine acetate and excipient were obtained according to procedure and results the IR spectroscopy it was clear that the Roxatidine acetate was compatible with the polymer used Eudragit L30 D55 and HPMC E- 5.

Table No.3.1: Drug - Excipient Compatibility Studies

Sr. No.	Name of ingredient	Category	Remarks
1	HPMC E- 5	Film former	Compatible
2	Eudragit L30 D55	Enteric coating agent	Compatible

3.2 Result of evaluation of formulated roxatidine acetate pellets:

A. Friability test:

Results for friability test were given in the table

Table No. 3.3: percent friability of formulations F1 to F9

Sr.NO.	FORMULATION	FRIABILITY%
1	F1	0.69±0.04
2	F2	0.74±0.08
3	F3	0.59±0.01
4	F4	0.64±0.03
5	F5	0.71±0.05
6	F6	0.61±0.02
7	F7	0.53±0.03
8	F8	0.65±0.01
9	F9	0.79±0.07

All values represent mean ± standard deviation (SD) n=3.

B. Bulk and tapped density

Table no. 3.4: Bulk and tapped density of formulation of F1 toF9

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner Ratio	Carr's Index
F1	0.956±0.01	0.978±0.05	1.03±0.05	4.97±0.02
F2	0.931±0.03	1.0054±0.04	1.04±0.02	5.31±0.05

F3	0.929±0.04	0.991±0.07	1.02±0.07	4.73±0.08
F4	0.941±0.02	0.987±0.03	1.07±0.03	5.04±0.03
F5	0.921±0.4	0.961±0.01	1.03±0.02	5.01±0.01
F6	0.949±0.01	1.031±0.05	1.05±0.04	5.39±0.05
F7	0.952±0.05	0.971±0.03	1.09±0.01	5.19±0.02
F8	0.923±0.03	0.952±0.01	1.02±0.03	5.22±0.06
F9	0.943±0.02	0.977±0.5	1.06±0.05	4.91±007

All values represent mean ± standard deviation (SD) n=3.

C. Angle of repose:

Results for angle of repose given in table no.

Table No.3.5: Angle of repose of formulations

Formulation code	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F 9
Angle of repose (degree)	29.32	27.83	30.12	29.27	29.90	28.76	29.87	28.15	29.93

All values represent mean (n) =3.

The angle of repose of formulations from F1 to F9 found between 27.83 to 30.12, so angle of repose of all formulation were below 30, therefore it was indicates that pellets were having good flow property.

D. Particle size determination:

Results for particle size determination were given in the table.

Table No.3.6: Results for particle size determination

Formulation Code	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F 9
Particle size (µm)	1159.47	1132.56	1189.34	1058.23	1129.51	1087.57	1061.25	1151.78	1191.45

E. Gastric acid resistance test:

Results for the acid resistant test were given in table no.

Table No. 3.7: Percent gastric resistant of formulation F1 to F9

Formulation	% Acid resistance
F1	91.71±0.02
F2	88.19±0.07
F3	96.72±0.04
F4	84.92±0.01
F5	89.29±0.05
F6	91.55±0.01
F7	93.48±0.03
F8	95.87±0.05
F9	92.81±0.02

All values represent mean ± standard deviation (SD) n=3.

F. Invitro dissolution studies

Table No.3.8: Cumulative percentage of Roxatidine acetate release in 0.1N HCL and phosphateBuffer pH 6.8

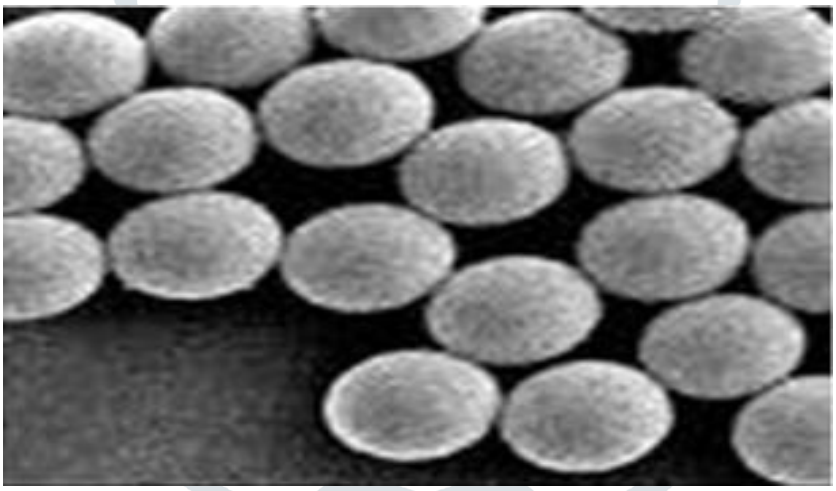
	Cumulative Percent drug release in 0.1 N HCL								
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
15	0.62	0.63	0.65	0.71	0.61	0.56	0.55	0.53	0.51
30	0.72	0.69	0.65	0.72	0.66	0.63	0.59	0.57	0.55
45	0.85	0.83	0.93	0.80	0.76	0.72	0.68	0.65	0.63
60	0.91	0.87	0.89	0.83	0.94	0.80	0.77	0.74	0.70
Cumulative Percent drug release in phosphate buffer pH 6.8									
75	57.73	59.63	61.93	63.11	66.37	65.22	68.33	70.05	72.25
90	63.11	66.29	66.25	68.41	69.79	71.18	75.13	76.92	78.10
105	65.29	74.38	69.51	73.07	72.63	77.24	80.06	81.98	86.09
120	69.82	78.56	73.59	80.13	83.67	87.56	92.20	95.15	98.87

All values represent mean (n) =3.

From the results it was observed that the formulation F9 has better cumulative percent drug release as compared to other formulations. Because it may be in formulation F9 Eudragit L30 D55 was used in low concentration, therefore the drug release from pellets occurs fastly in phosphate buffer pH 6.8. While keeping in 6.8 pH buffer, 72.25 cumulative percent drug release occur at 75 minutes, After 120 minutes 98.87cumulative percent drug release was attained, when compared to other formulation F9 showed better release, so F9 was selected as optimized formulation.

G. Scanning electron microscopy:

The scanning electron microscopy of formulation F9 showed that prepared pellets have good coating and film former and it is helpful in controlling the release of drug in acidic medium.



H. Result of Accelerated stability study

Stability profile of Formulation F9

Table No. 3.9: Dissolution data of stability

1) IN 0.1 N HCL					
S.No.	**Time (min)**	**Cumulative % drug release**			
		Initial	**1 month**	**2 months**	**3 months**
1	0	0	0	0	0
2	15	0.51	0.48	0.45	0.41

3	30	0.58	0.58	0.56	0.5
4	45	0.67	0.65	0.57	0.52
5	60	0.73	0.72	0.65	0.55
2) **IN PHOSPHATE BUFFER 6.8**					
6	75	69.25	68.91	68.15	68.85
7	90	76.10	76.87	75.10	77.68
8	105	86.09	84.06	82.70	84.51
9	120	97.82	97.69	97.55	97.49

All values represent mean ± standard deviation (SD) n=3.

After comparison of dissolution data of stability at 0, 1, 2, 3 months there was no changesobserved, and clearly showing that the formulated product was stable.

CONCLUSION

The study was undertaken with an aim to develop an optimized formulation of Roxatidine acetate Enteric Coated Pellets drug delivery system by using Eudragit L-30D-55, HPMC K5 as retarding agents. The active pharmaceutical ingredient, Roxatidine acetate was selected and formulated as Enteric Coated Pellets comparable to the innovators product. Finished products were evaluated for friability test, assay, and *In-vitro* release studies performed for 1hr in acidic media at 0.1N HCL, after that 1 hr in 6.8 pH Phosphate buffer. From the evaluation it was concluded that percent friability and percent assay for all formulations from F1 to F9 were found within the limit. *Invitro* dissolution study showed that Formulation F9 having the better resistance in 0.1 N HCL and good release in phosphate buffer pH 6.8.

From the above results and discussion it might be concluded that the formulation F9 of enteric coated pellets of Roxatidine acetate was found to be stable in acidic medium and shows better drug release in basic medium. Therefore it was an ideal and optimized formulation of enteric coated pellets.Then the optimized formulation F9 was compared with marketed product by an *invitro* study, it shows that the formulation F9 was good as compared with marketed one. The stability study was carried out for formulation F9 at 1, 2, 3 month for *invitro* dissolution study and from this it was observed that there were no changes and clearly showing that the optimized formulation F9 was stable.

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