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Formulation and evaluation of effervescent granules of Fexofenadine hydrochloride

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The present work is based on the formulation of effervescent granules of Fexofenadine hydrochloride unit dose. Eight such formulations were prepared using different acids, salts, diluents and superdisintegrants by the wet granulation method. The prepared granules were evaluated for flow property (like angle of repose, bulk density, tapped density and Hausner's ratio), particle size, moisture content, Effervescence time, *in vitro* dissolution studies and stability studies. The formulated effervescent granules exhibited excellent flow properties and bulk density suitable for a unit dose. The low moisture content of the formulations supported the stability of the formulations. All the formulations exhibited effervescence time less than 20 sec and dissolution profile was found to be more than 95% in 5 mins. The stability studies revealed that the product was stable at variable temp and humidity conditions.

Keyword: Fexofenadine hydrochloride, effervescent granules, wet granulation, effervescence time, stability study.

1. Introduction

Effervescent granules are popular delivery systems for many pharmaceutical products such as antacids, analgesics, and cough/cold formulations. They are fast dissolving, highly soluble, stable, convenient dosage forms. The granules are added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The granules are quickly dispersed by internal liberation of Carbon dioxide in water due to interaction between acid with alkali metal carbonates or bicarbonates in the presence of water. Due to liberation in Carbon dioxide gas, the dissolution of the API in water as well as taste masking effect is enhanced [1, 2]. The advantages of effervescent granules compared with other oral dosage forms includes an opportunity for the formulator to improve taste, a more gentle action on the patient's stomach and marketing aspects. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy [3]. Granules show better flow ability, more stability, more wetting, and more uniformity in particle size, thereby drug content than powders [4]. Fexofenadine hydrochloride is a non-sedating antihistamine used in the symptomatic relief of allergic conditions, including seasonal allergic rhinitis and urticaria [5]. In present work an attempt has been made to formulate a unit dose of effervescent granules containing immediate release of Fexofenadine hydrochloride using various acids and bases. In present work different acids and bases in different concentration were used to make granules. The prepared granules were evaluated for drug content, particle size, moisture content, effervescence time, *in vitro* drug release and stability studies.

2. Materials and Methods

2.1 Materials

Fexofenadine Hydrochloride was a gift sample from Aurobindo Pharmaceuticals, Hyderabad, Croscarmellose, Crospovidone, and Spray dried lactose was gifted from BAL Pharma, Bangalore, India. All the ingredients used were of Analytical grade.

2.2 Methods

Effervescent granules of Fexofenadine hydrochloride were prepared by wet granulation method [6] (F1-F8).

The granules were prepared in combination of different acids and bases with various diluents (Mannitol, Spray dried lactose) to increase the bulk, superdisintegrants (Croscarmellose, Crospovidone) to promote the bursting effect of the granules and Sodium saccharin as sweeteners. The amount of acids and bases were determined by stoichiometric calculation [7] sufficient to prepare 2 gm of powder containing 120 mg of Fexofenadine hydrochloride, with taking an excess to encounter the loss due to release of moisture and carbon dioxide during preparation as mentioned in Table 1.

Fexofenadine hydrochloride and all other excipients according to the formula were weighed accurately, passed through sieve no 20 and mixed according to geometric dilution to ensure proper distribution of drug in the powder mixture. Then sufficient binder was added to make a damp mass. This mass was passed through sieve no 10 to get granules and these granules were dried in hot air oven at 40 °C and then they were packed in airtight container.

Table 1: Composition of formulations of Fexofenadine Hydrochloride effervescent granules

Ingredients	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Fexofenadine Hydrochloride(mg)	120	120	120	120	120	120	120	120
Citric acid (%w/w)	24	40	45	46	51	45	51	45
Tartaric acid (%w/w)	18	-	-	-	-	-	-	-
Fumaric acid (%w/w)	-	11	-	-	-	-	-	-
Sodium bicarbonate (%w/w)	44		-	-	-	-	-	-
Sodium Carbonate (%w/w)	-	40	-	-	39	-	39	
Potassium Bicarbonate (%w/w)	-	-	-	43	-	-	-	-
Potassium Carbonate (%w/w)	-	-	45	-	-	45	-	45
Calcium Carbonate (%w/w)	-	-	-	-	-	-	-	-
Spray Dried Lactose (%w/w)	-	-	1.5	-	-	-	1.5	
Crospovidone (%w/w)	-	-		1.5	-	-	-	1.5
Croscarmellose (%w/w)	-	-	-	-	1.5	-	-	-
Mannitol (%w/w)	-	-	-	-	-	1.5	-	-
Sodium saccharin (%w/w)	1	1	1	1	1	1	1	1
HPMC in alcohol (%w/w) up to	5	5	5	5	5	5	5	5

3. Evaluation of granules

3.1 Particle size distribution

The size and size distribution of the granules produced was determined by agitation for 10 min with a sieve shaker fitted [8] with a progression of standard sieves. From the weight retained on each sieve, a particle size distribution graph was plotted from which the median diameter was determined.

3.2 Bulk density

15 g granules blend introduced into a dry 100 ml cylinder, without compacting. The granules was carefully levelled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the following formula [9].

ρbulk= M / Vo……..(1)

Where, ρbulk = Apparent bulk density, M = Weight of the sample, Vo = Apparent volume of powder.

3.3 Tapped density

A suitable amount of granules was placed in a 100 ml measuring cylinder. After absorbing its initial volume, the sample was tapped 500 times initially followed by an additional taps of 750 times until the difference between succeeding measurement is less than 2% and then tapped volume, was measured, to the nearest graduated unit. Tapped density was calculated using equation [9].

ρtab = M / V_f ……....(2)

Where, ρtab = Tapped Density, M = Weight of the sample, V_f= Tapped volume of powder

3.4 Hausner's ratio

Hausner's ratio is the ratio of tapped to bulk density and was calculated by using the following equation.

Hausner's Ratio = ρtab/ρbulk……(3)

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.6 showing moderate flow properties, cohesive powder and more than 1.5 poor flow [9].

3.5 Angle of repose

The angle of repose was determined by allowing granules to flow through a funnel and fall freely onto a graph paper on a horizontal surface. The height and diameter of the resulting cone were measured and the angle of repose is calculated from this equation:

tan Ø = h / r…….(4)

Where, h is the height of the powder cone and r is the radius of the powder cone.

Values for angle of repose ≤ 30° usually indicate a free flowing material and angles ≥ 40° suggest a poorly flowing material, 25- 30 show excellent flow properties, 31-35 show good flow properties, 36-40 show fair flow properties and 41-45 showing passable flow properties [9].

3.6 Moisture content

Titration method was used to determine the water content. With the Karl Fischer (KF) titration both free and bound water can be determined [10]. Around 50 ml of methanol was taken in the titration vessel of Karl Fischer titrator and titrated with the Karl Fischer reagent to end point. In a dry mortar the granules were ground to fine powder. Weighed accurately about 0.5 g of the sample and transferred quickly to the titration vessel, stirred to dissolve and titrated with the Karl Fischer reagent to end point.

Moisture content = V * F * 100/Weight of sample (mg)……..(5)

Where, F= factor of Karl Fischer reagent, V=volume in ml of Karl Fischer reagent consumed for sample titration.

3.7 Drug content

A dose of the effervescent granules was accurately weighed and mixed in 100 ml phosphate buffer pH 6.8 in a volumetric flask. Subsequent dilution was made from the stock solution and the concentration of the dilution was measured at λ max i.e. 259 nm in Spectrophotometer ((UV-1601), (UV-2550) Shimadzu-Corporation, Japan). Drug Content was found out from the following equation.

Drug content = (Absorption x Dilution Factor) /Slope…….(6)

3.8 Effervescence time

In vitro effervescence time was measured by pouring the one dose of granules in a beaker containing 50 ml of Water [11]. Granules from each batch were randomly selected and in vitro effervescence time was measured.

3.8.1 Statistical analysis
The difference in the release data for the different formulation was done by one way analysis of variance of means (ANOVA)at the 5% significance level using Microsoft 2007 excel package. *In vitro* disintegration time was taken as the parameter for ANOVA analysis.

3.9 Dissolution studies
The *in vitro* dissolution studies were carried out in the USP dissolution test apparatus (Electro lab TDT – 08 L Dissolution testers USP) type 2 (paddle) [12]. A 900 ml of the dissolution medium (phosphate buffer pH 6.8) was taken in a covered vessel and the temperature was maintained at 37± 0.5 ºC. The speed of the paddle was set at 50 rpm. Sampling was done at every one minute interval. For each sample one ml of the dissolution medium was withdrawn and the same amount of dissolution medium at 37±0.5 ºC was replenished to the dissolution medium. The sample withdrawn was filtered with Whatman filter paper and diluted with phosphate buffer to analyze in the UV spectrophotometer. The absorbance was noted; the cumulative % release was calculated.

4. Stability studies
To assess the drug and formulation stability, stability studies were done according to ICH guidelines. All the formulations were tested for Short term testing for a period of 1st month at 25±2 °C/ 60±5% RH and Accelerated testing for a period of 2nd month at 40±2 °C/ 75±5% RH, for their moisture content, drug content and effervescence time [13].

5. Results and discussion
5.1 Particle size analysis
The particle size analysis showed maximum retention was in the size range 355-500 µm for all the formulations as shown in Fig 1. The mean diameter of the granules was found to be 0.4 mm approximately.

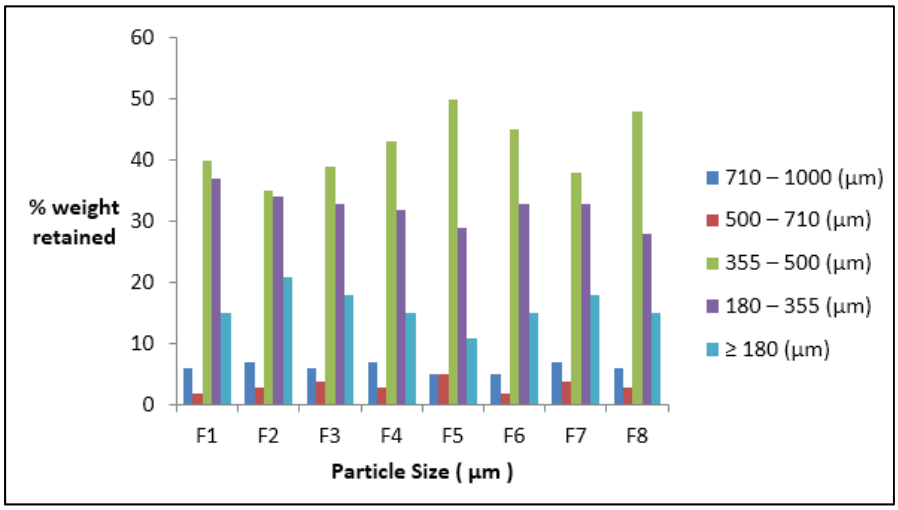

Fig 1: Particle size analysis

5.2 Flow property of granules
The values obtained for bulk density, tapped density, Hausner's ratio, angle of repose are tabulated in Table 2. All the formulations showed good flow properties. The bulk density was varied from a minimum of 0.54±0.01 gm/ml to a maximum of 0.66±0.01 g/ml, indicating an average of 1.5-2 ml of bulk volume per gram of granules and suitability for a unit dosage packaging. Hausner's ratio ≤ 1.19 and angle of repose < 35^0, indicates a good flow property of the granules.

Table 2: Flow properties of the granules

Formula	Bulk Density (g/ml) ± SD	Tapped Density (g/ml) ± SD	Hausner's ratio	Angle of repose ± SD
F1	0.6 ± 0.01	0.85 ± 0.01	1.19	27.3 ± 0.41
F2	0.55 ± 0.01	0.86 ± 0.01	1.13	29.1 ± 0.34
F3	0.61 ± 0.02	0.77 ± 0.01	1.22	30.73 ± 0.23
F4	0.66 ± 0.01	0.74 ± 0.01	1.11	31.4 ± 0.30
F5	0.54 ± 0.01	0.63 ± 0.01	1.16	27.3 ± 0.32
F6	0.66 ± 0.01	0.86 ± 0.01	1.3	33.69 ± 0.19
F7	0.61 ± 0.01	0.64 ± 0.02	1.06	26.67 ± 0.59
F8	054 ± 0.01	0.74 ± 0.04	1.16	30.46 ± 0.50

SD=Standard deviation and no of replicates (n) = 3

5.3 Moisture content

The moisture content of the samples is shown in Table 3. The moisture content was found to be within the range of a minimum of 0.01±0.01 and maximum of 0.06±0.01. This low moisture content indicates the ability of the granules to retain effervescence quality, free flow ability. Formulations containing Crospovidone (F4, F8) showed comparatively more moisture content than others. Formulations with only effervescent mixtures and Mannitol as diluents showed the least moisture content. This is attributed to the non-hygroscopic nature of the excipients [14].

5.4 Drug Content

The drug content was in the range of 96.81±0.01 -99.44±0.01 for all the eight formulations as in Table 3. So it qualified the IP specifications for assay of drug content which should not be less than 90% and should not be more than 110%.

Table 3: Evaluation of Granules

Formulation	% Moisture content ± SD	% Drug Content ± SD	Effervescence time(sec) ± SD	% Drug release at 5 mins ± SD
F1	0.01 ± 0.01	99.8 ± 0.01	8 ± 0.57	99.7±1.3
F2	0.02 ± 0.01	99.8 ± 0.01	10 ± 0.57	99.4±1.1
F3	0.02 ± 0.01	99.12 ± 0.03	11 ±0. 1	98.6±0.6
F4	0.04 ± 0.02	96.81 ± 0.01	15 ± 0.57	97.37±0.1
F5	0.02 ± 0.01	99.44 ± 0.01	9 ± 0.57	99.8±0.6
F6	0.02 ± 0.01	97.2 ± 0.04	12 ± 0.1	97.8±0.7
F7	0.03 ± 0.01	98.1 ± 0.01	13 ± 0.57	98.1±1.3
F8	0.06 ± 0.01	97.8 ± 0.01	18 ± 0.57	96.7±0.7

SD=Standard deviation and no of replicates (n) =3.

5.5 Effervescence Time

The effervescence time was less than 20 sec as shown in Table 3. Among all the formulations F1 showed the least effervescence time (8±0.57 sec) due to its less moisture content. Formulations F4 and F7 showed more effervescence time compared to others due to its high moisture content.

5.6 Statistical analysis

The differences in the effervescence time of the formulations were done by one way analysis of variance of means (ANOVA) at the 5% significance level using Microsoft 2007 excel package. Effervescence time was taken as the parameter for ANOVA analysis. The P-value was determined and the result is shown in the Table 4. One way ANOVA at the 5% significance level

and disintegration time as parameter yielded a P-value 1.34E-10, so it can be concluded all the formulations were found to be different (P-value <0.001).

Table 4: ANOVA: Single Factor

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	588.892	2	294.446	81.0069	1.34E-10	3.4668
Within Groups	76.33135	21	3.634826			
Total	665.2234	23				

5.7 Dissolution studies

All the formulation showed more than 95% release within 5 mins as shown in Table 3.The bursting of the granules into minute particles was facilitated by the production of effervescence. All the formulations showed good bursting effect due to its low moisture entrapment and hence promoted rapid dissolution.

5.8 Stability study

The stability studies of formulated granules were carried out at Short term testing for a period of 1st month at 25±2 °C/ 60±5% RH and Accelerated testing for a period of 2nd month at 40±2 °C/ 75±5% RH. The effects of temperature and humidity on the moisture content, drug content and effervescence time of the granules were evaluated for assessing the stability of the prepared formulations. There was minimal change in formulation F1, F2 and F5 in moisture content, effervescence time and drug content. Drug content of all the formulations showed minimal changes during the stability period as in Fig 4. The formulation containing Crospovidone showed increase moisture content and delayed dispersion a time as shown in Fig 2 and Fig 3. This was attributed to its hygroscopic nature which resulted in comparatively high moisture content, thereby effervescence time when exposed to humidity.

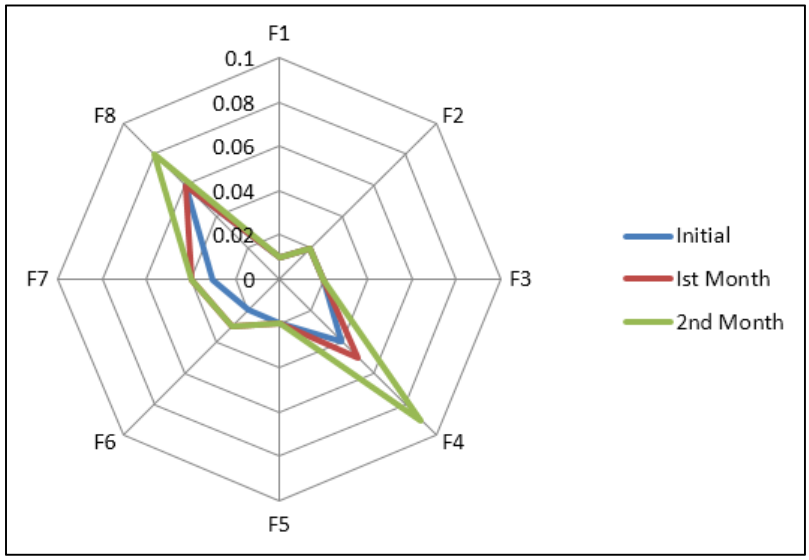

Fig 2: % Moisture content of all formulations after stability study

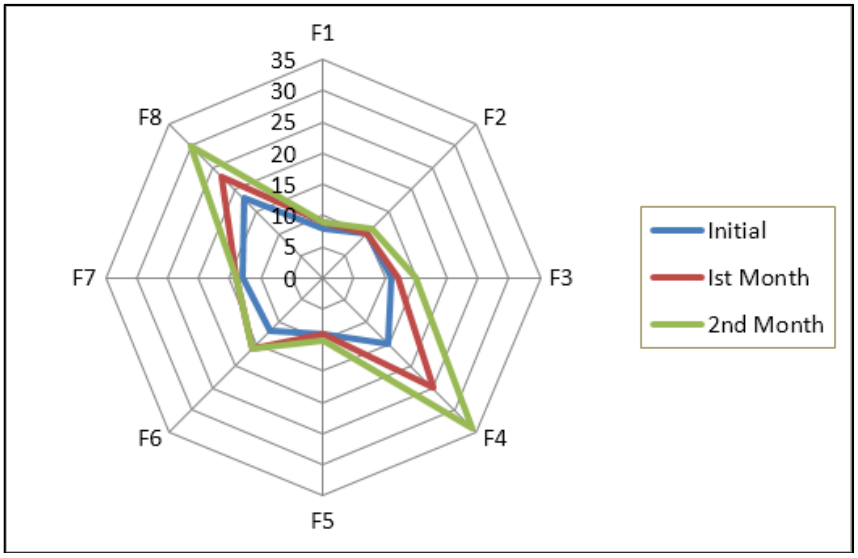

Fig 3: Effervescence time of all formulations after stability study

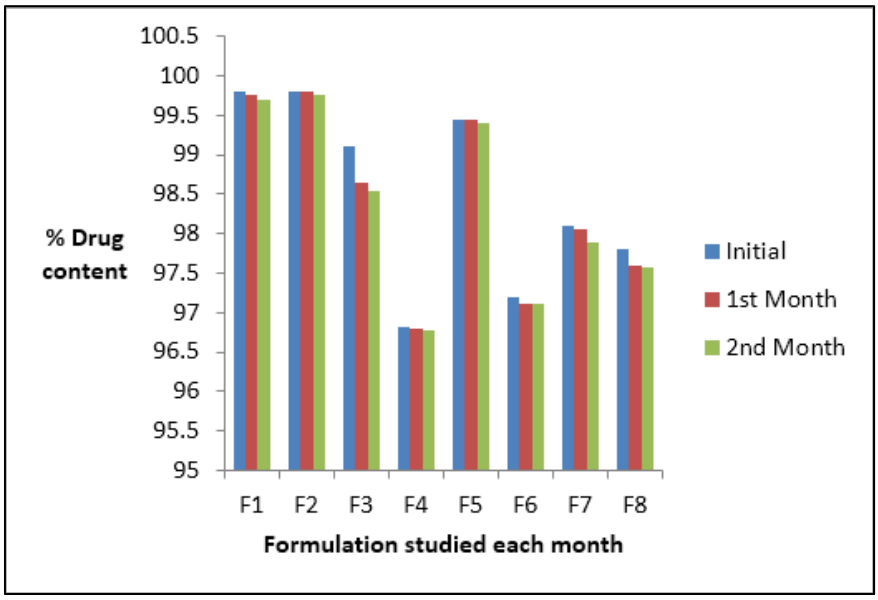

Fig 4: Drug content analysis after stability study for all formulations

6. Conclusion

The Granules were prepared by the wet granulation technique that contains Citric acid, Fumaric acid, Tartaric acid as acid components, Sodium carbonate, Sodium bicarbonate, Calcium carbonate, Potassium carbonate, Potassium bicarbonate as salts, Spray dried lactose and Mannitol as diluents, Crospovidone, Croscaramellose as Super disintegrants, Hydroxy propyl methyl cellulose as a binder and alcohol as solvent. The various formulation trials were conducted using different ratios of acid components and salts which were calculated by stoichiometric calculations. Formulated granules had given satisfactory results for various physicochemical properties i.e., bulk density, tapped density, Hausner's ratio and angle of repose and drug content. Uniform granule size, good effervescence time, release of drug and stability studies qualified the suitability of unit

dosing of Fexofenadine hydrochloride as effervescent granules in the management of Allergy.

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