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Research Paper

A comparative assessment of granulation methods containing effervescent granules of vitamin C.

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ABSTRACT:
Vitamin C or Ascorbic acid is one of the most widely used antioxidants that our body cannot synthesize, but it has an important role to boost our immunity. The importance of Vitamin C is unquestionable in today's post pandemic world. Effervescent granule is a type of dosage form that can be utilized to modify the release of API from the dosage form as it is formulated in such a way that supports the immediate release approach. Generally two methods are employed to formulate the effervescent granule of a drug particle i.e. by wet method and heat method.
The objective of this study was to compare the above mentioned two methods against several evaluation parameters to draw a conclusion regarding the suitability of the methods for formulating a drug into an effervescent granule.
A suitable formulation table was prepared according to which several effervescent granules are formulated using both wet method and heat method and compared by performing various evaluations such as determination of melting point, angle of repose, carr's index, hausner's ratio, effervescence time, pH measurement, amount of carbon dioxide released, drug content analysis etc.
The result of the effervescence time showed that the prepared granules disintegrated within 3 minutes which satisfies the immediate release property of a dosage form. F5, F12 formulations showed comparatively better results. It can also be seen that granules prepared by wet method gave comparatively better result than heat method. Similarly for drug content study, the percentage drug content for all the prepared effervescent granules were in the range of 76.3% to 91.1%. F5 and F12 formulations gave better data than other formulations. It was also evident that formulations of wet method showed better % drug content than formulations of heat methods.
After evaluating the effervescent granules prepared by both wet method and heat method, it can be concluded that wet method may be a better alternative than heat method. Although dry method can produce the effervescent granules of a drug, there may be an issue of stability as it requires heat for formulation of granules, which is subject to further investigation.
KEYWORDS: *Effervescent granules, Heat Method, Wet Method, Effervescent time, Drug Content*

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I. INTRODUCTION

Effervescent granules are comes under solid dosages form, intended for internal use only. It is combined form of sodium bicarbonate, tartaric acid, citric acid and sucrose or saccharine use as a sweetening agent [1]. Mainly BCS (Biopharmaceutical Classification System) class I drugs are use for effervescent granules form. High permeability and high solubility are special characteristic of this class. Diltiazem, Vitamin C etc drugs are comes under this class [2].

Certain amount of dosages form dissolves in water before administration. Acid and sodium bicarbonate react with water and release effervescence [3]. By a single dose of effervescent granule a large amount of medicament can deliver [4]. But effervescent granules shows some disadvantages like, it can cause CO_2 toxicity in children, short half life compared to other dosages form [5].

In researches has been formulated a effervescent granules which contained vitamin C(ascorbic acid) as a active agent. Vit C has high solubility in water. Vitamin C is mainly present in organic substances like fruit, vegetables. Its have immunity boosting property, anti cardiovascular property etc. [6]

II. Material and Methods

2.1 Materials

The active ingredient Ascorbic acid (Fiachlm), excipients like Sodium bi carbonateI(Merck Life Science), Citric acid (Merck Life Science), Tartaric acid(Merck Life Science) Mannitol (Merck Life Science), Flavouring agent (Sonarome).

Instruments used like Electronic Balance (NIBBIN SF-400c), Hot air oven(Indosati), UVvisible spectroscophotometer (Analytical Technologies Limited), Electric ph meter (Indosati), Heating mantle (Indosati), thermometer (Lasbworld).

2.2 Methods

For preparation of effervescent granules mainly two methods are used that's are

i.Heat Method

ii. Wet Method.

i. Dry/ heat method

In heat method active ingredient and other ingredients are well mixed and placed in a porcelain dish and dish is must be sufficiently heated by placed on the water bath. Citric acid or tartaric acid will liberate the water if we maintain the temperature. Atleast wet mass will produced by water which is liberate from crystal.

$$3NaHCO_3+C_6H_8O_7.H_2O \xrightarrow{\Delta} C_6H_5Na_3O_7+3CO_2+3H_2O$$

Sodium bicarbonate citric acid sodium citrate

$$2NaHCO_3 + C_4H_6O_6 \xrightarrow{\Delta} C_4H_4Na_2O_6+2CO_2+2H_2O$$

Sodium bicarbonate tartaric acid sodium tartrate

ii. Wet method

In wet method active ingredient and other ingredients are accurately weighed and carefully mixed. Then mixer is placed in a beaker and isopropyl alcohol mixed with mixer and produce coherent mass. Next coherent mass is passes through 22 no sieve and produce certain size of granules. Granules are dried in an oven at a temperature not exceeding 60℃.

Formulation	Vitamin C (mg)	Sodium bicarbonate (mg)	Citric acid (mg)	Tartaric acid (mg)	Mannitol (mg)	Orange flavour (mg)
F1	1000	1500	1000	0	1000	40
F2	1000	1500	0	1000	1000	40
F3	1000	1500	500	500	1000	40
F4	1000	1500	900	100	1000	40
F5	1000	1500	100	900	1000	40
F6	1000	1500	800	200	1000	40
F7	1000	1500	200	800	1000	40
F8	1000	1500	700	300	1000	40
F9	1000	1500	300	700	1000	40
F10	1000	1500	600	400	1000	40
F11	1000	1500	400	600	1000	40
F12	1000	1500	416.6	833.33	1000	40

Table 1: Several formulations of vitamin c effervescent granules

III. Evaluation Tests

3.1. Melting Point Determination

Capillary tube method is used to determine the melting point of effervescent granules. One end sealed capillary is used and sample material is put into the capillary from another end. Together a thermometer and a sample filled capillary tube was then inserted into a test tube which was filled with liquid paraffin and next heat the test tube until it reaches melting point.

3.2. Micromeritic Properties

3.2.1.Angle of Repose

The angle of Repose is determined by allowing a mass of powder to flow freely through an orifice from a certain height and form a conical heap on the horizontal surface. Equation of angle of repose is $\tan\theta = h/r$

3.2.2. Carr's Index and Hauusner's ratio

The Carr's Index is an indicator of the compressibility of a powder. It is named after the scientist J.Carr,Jr. It is determined from the bulk and tapped density.

Carr′s index= $\frac{[(TD-BD)\times 100]}{TD}$

TD- Tapped Density

BD- Bulk Density

Hausner's ratio =$\frac{\text{Tapped Density}}{\text{Bulk Density}}$

3.3. Effervescent time

One dose of each formulation (mentioned in **table 1**) of effervescent granules was placed in 200ml water in beaker. In which time completely dispersed fragments were gained and liberation of gas stopped, this time is considered as effervescent time. [7]

3.4. pH measurement

A certain dose of vitamin C effervescent granules was dissolved in a 100 ml of water. The granules are allowed to completely dissolve into the water. The pHwas measured by using digital apparatus.

3.5. Amount of CO_2

At first we have taken a 100 ml beaker and 5 ml vial. After that 7.5 g of sodium bicarbonate and 7.5 g tartaric acid were accurately weighed and placed into the beaker. 5 ml vial was filled with water and carefully placed into the beaker in such a way that the water did not fall from the vial into the beaker at the first place. After that the open portion of beaker was carefully sealed with aluminum foil. Then the initial weight of the whole system was taken. Next the beaker was gently shaken to pour the water from the vial over the sample inside the beaker. Then reaction occurs between water and chemicals and $CO_2$is produced. Again the final weight of whole system was taken. So,

Amount of CO_2 = final weight of whole system- initial weight of whole system.

And we get the standard value of CO_2 content by following the same procedure for all the formulations we calculate the CO_2 liberation from all the prepared formulations [8]

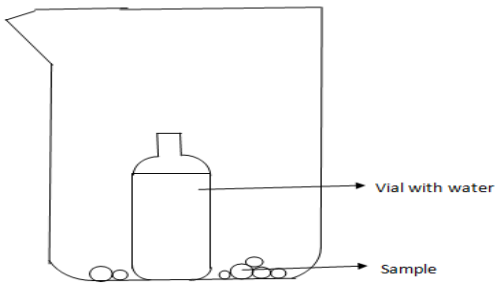

Figure 1: Test of amount of CO_2

3.6.Preparation of standard curve

Stock solution of vitamin C was prepared by accurately dissolving 500mg vitamin C in 500ml water to obtain 1000ppm of vitamin-C solution.10ml of this solution was taken from the above solution and diluted upto 100ml and obtain 100ppm concentration of solution. The above solution was subsequently diluted with 10ml water and to obtain a series of dilutions containing 10, 15, 20, 25ppm of vitamin-C solution. Then the solutions were scanned in the range of 200-350 nm by using UV-Visible spectrophotometer. And observed that at 265nm solutions show maximum absorbance.

3.7.Drug content analysis:

10 mg of each prepared formulation was accurately weighed and mix in 100 ml water. Subsequent dilution was made from the stock solution and absorbance was observed at 265 nm in the UV-Visible Spectrophotometer. Drug content was found out from the following equation. [9]

$$\text{Drug content} = \frac{(\text{Absorbance} \times \text{Dilution factor})}{\text{Slope of standard curve}}$$

$$\% \text{ Drug content} = \frac{(\text{Practical drug content})}{\text{Theoritical drug Content}} \times 100$$

IV. Result and Discussion

4.1. Melting point

The melting point of pure drug was found to be 190 °C and the formulations both in terms of wet method and heat/dry method was in the range of 148 – 171 °C (mentioned in **table 2**). So we can say that the influence of citric acid (melting point- 153 °C), tartaric acid (melting point-173.625 °C) and sodium bicarbonate (melting point- 50 °C) was evident because as the melting point of these excipients were lower than the pure drug, it influenced the decrease in melting point of all the formulations.

Formulation	Wet method (°C)	Heat / Dry method(°C)
Pure drug	190(°C)	
F1	166	168
F2	168	171
F3	155	158
F4	158	160
F5	155	158
F6	155	155
F7	165	168
F8	148	150
F9	160	165
F10	155	160
F11	152	155
F12	155	158

Table 2: Melting point of several formulation of effervescent granules

4.2. Micromeritics properties

4.2.1. Angle of repose

After performing the evaluation test of angle of repose of the prepared granules we found out that all the formulation possessed the angle of repose (mentioned in **table 3**) at a range of 24.59 – 38.75 which indicated that the prepare granules of formulations are having flow property of good to satisfactory nature especially formulation F2, F3, F4, F6, F8, F9 and F10 have good flow property which indicated that it can further be utilized for preparing effervescent tablets.

Formulation	Wet method	Heat / Dry method
F1	30.04	32.34
F2	27.47	36.02
F3	26.98	29.74
F4	25.60	28.07
F5	30.90	33.11
F6	28.63	29.24
F7	31.59	33.67
F8	27.72	30.96
F9	29.16	33.20

F10	24.59	27.34
F11	38.75	37.04
F12	31.65	32.61

Table 3: Angle of repose of several formulation of effervescent granules

4.2.2. Carr's index and Hausner's ratio

From Carr's index and Hausner's ratio data (mentioned in **table 4 and 5**) we can conclude that most of the formulations are good to fair flow properties which are an essential prerequisite for developing a suitable dosage form. These data give us a base depending upon which we can go for further processing of a dosage form. According to the data obtained for these aspects, we can conclude that these are satisfactory enough to move ahead with further processing.

Formulation	Wet method	Heat / Dry method
F1	19.23	22.03
F2	11.07	11.53
F3	21.33	22.58
F4	20.75	25
F5	15.86	23.80
F6	18.09	21.74
F7	17.74	21.42
F8	16.41	19.31
F9	19.60	21.42
F10	22	25.45
F11	32.72	33.33
F12	17.24	21.66

Table 4: Carr's index of several formulation of effervescent granules

Table 5: Hausner's ratio of several formulation of effervescent granules

4.3 Effervescent time

Formulation	Wet method	Heat / Dry method
F1	1.23	1.25
F2	1.19	1.21
F3	1.30	1.29
F4	1.21	1.23
F5	1.30	1.31
F6	1.21	1.26
F7	1.21	1.25
F8	1.25	1.31
F9	1.24	1.27
F10	1.28	1.34
F11	1.48	1.5
F12	1.20	1.26

As per the effervescent time data (mentioned in **table 6**) we can conclude that all the prepared formulations disintegrated within 3 minutes with satisfies the general criteria for any effervescent granules specially F5, F12 were showing better effervescent time. If we closely observe the data generated from both dry and wet methods we will get to see that from a formulation to formulation comparison it can be found that the granulation prepared by wet method disintegrated more quickly than dry granulation. Although the dry granules were also within the limit. Shown in **figure 2.**

Formulation	Wet method	Heat / Dry method
F1	2 min 12 sec	2 min 25 sec
F2	2 min 35 sec	2 min 45 sec
F3	2 min 40 sec	2 min 53 sec
F4	2 min 20 sec	2 min 35 sec
F5	2 min 02 sec	2 min 16 sec
F6	2 min 28 sec	2 min 40 sec
F7	2 min 30 sec	2 min 42 sec
F8	2 min 25 sec	2 min 35 sec
F9	2 min 42 sec	2 min 48 sec
F10	2 min 55 sec	2 min 15 sec
F11	2min 35 sec	2 min 50 sec
F12	1 min 50 sec	2 min 06 sec

Table 6: Effervescent time of several formulations of effervescent granules

4.4. pH measurement

The solution prepared for the disintegration time test were subjected to observing the pH value and subsequent data are given in **table 7** and as the formulations are containing several acid components like citric acid, tartaric acid and ascorbic acid. So we can find that both types of formulations contain the pH value which are less than 7 (range from 4.55- 5.35) which indicated that each formulation contained more amounts of acid than base.

Formulation	Wet method	Heat / Dry method
F1	4.80	4.72
F2	4.65	4.55
F3	4.72	4.59
F4	4.85	4.70
F5	4.74	4.68
F6	5.04	4.95
F7	5.35	5.31
F8	5.29	5.25
F9	4.85	4.80
F10	4.79	4.74
F11	4.75	4.62
F12	4.82	4.67

Table 7: pH of several formulation of effervescent granules

4.5. Amount of CO_2

After performing the CO_2 liberation processes for all the formulation designed according to the literature mentioned above, the amount of CO_2 was calculated for all the formulations and the data is given below. As per the data we can observe that the amount of CO_2 liberated from the formulation was similar to that of the mixture given in the literature. We can also observe that for most of the formulations prepared by wet method liberated more amount of CO_2 than the formulations prepared by heat or dry method when compared on a formulation to formulation basis (mentioned in **table 8**).

Formulation	Wet method	Heat / Dry method
Tartaric acid + Sodium bicarbonate	0.245 g	
F1	0.226 g	0.218 g
F2	0.236 g	0.228 g
F3	0.238 g	0.231 g
F4	0.248 g	0.243 g
F5	0.245 g	0.238 g
F6	0.252 g	0.246 g
F7	0.253 g	0.256 g
F8	0.246 g	0.242 g
F9	0.229 g	0.231 g
F10	0.262 g	0.258 g
F11	0.226 g	0.221 g
F12	0.272 g	O.269 g

Table 8: Amount of CO_2 of several formulations of effervescent granules

4.6. Standard curve

From this standard curve which is prepared against various concentrations of samples of pure drug by checking the absorbance in the UV-visible spectrophotometer, we can observe an overall linearity without any significance deviation. The R^2 value was found to be 0.994 (mentioned in **figure 2**) which was close to 1 and justified the property of linearity. Also we have obtained the equation of straight line from the graph which can be further used for correlation of various formulations.

Serial No.	Concentration	Absorbance
1.	10	0.7131
2.	15	1.0376
3.	20	1.301
4.	25	1.5378

Table 9: Concentration vs absorbance table

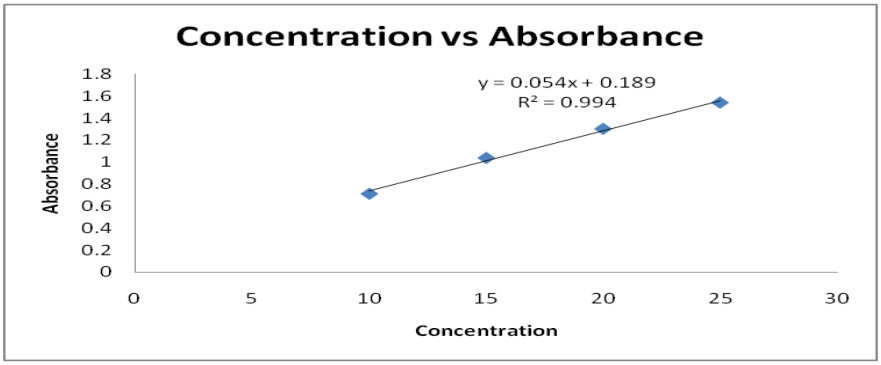

Figure 2: Standard curve of vitamin C

4.7. Percentage of drug content

The overall drug content of all the prepared formulation was in the range 76.3%- 91.1% (mentioned in **table 10**)out of which F5, F12 formulation were showing relatively higher percentage drug content and also from the data we can see that the formulations prepared by wet method gave better drug content compare to dry method.

Formulation	Wet method (%)	Heat / Dry method (%)
F1	78.2	76.8
F2	79.5	77.7
F3	80.3	79.4
F4	88.7	84.10
F5	91.1	87.9
F6	89.6	83.8
F7	77.9	76.3
F8	88.10	82.4
F9	80.5	79.8
F10	89.2	87.8
F11	78.7	76.7
F12	90.1	88.9

Table 10: Percentage of drug content

V. Conclusion

After performing all the evaluation test we conclude that the test results indicated the fact that our prepared effervescent granules passed various evaluation parameters and granules prepared by wet method showing better results than granules prepared by heat method and we also concluded in terms of effervescent time, drug contain study, formulation F5 and F12 gave better result also contain lesser risk of degradation.

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