ABSTRACT

Background: Effervescent floating tablets are used oral dosage form, to enhance the patient compliance, drug bioavailability and to increase the absorption rate. Cranberry (Vaccinium macrocarpon), widely used as a preventive agent against urinary tract infections, also suggested for Type II diabetes, myalgic encephalomyelitis, scurvy, and as a diuretic pill for being rich in nutrients and anti-oxidant properties. Objectives: The aim of the study is to formulate and evaluate the effervescent tablets of Cranberry and Vitamin C. Methodology: As per defined criteria of US FDA, effervescent tablet as per composition is formulated by citric acid and sodium bicarbonate and intended to dissolve in water before administration. Active substance and excipient compatibility studies were done by UV and FTIR, resulted absence of any interaction. Pre-formulation studies including Bulk density, tapped density, angle of repose, Hausner’s ratio, Carr’s index and water content. Results: Formulations were evaluated for weight variation, thickness, hardness, pH of solution, drug dissolution time, content uniformity as defined specification of U.S.P and BP. Stability and storage condition studies were also monitored with average results of 96% drug assay and dissolution. All the results showed excellent formulation of tablet and flow properties of granules. Conclusion: Further studies required to approach targeted and spontaneous release of active as optimized effervescence maybe helpful in delivery of actives and enhancing patient compliance.

Keywords: Effervescence, Dosage form, Tablets, Formulation, Cranberry, Effervescent Tablets
INTRODUCTION

Oral dosage forms are the most common route of drug administration despite having several disadvantages such as poor patient compliance, slow absorption etc. However, in liquid formulations problems such as stability concerns may arise and even slow onset of action. This gives an option for the use of effervescent tablets to overcome such problems (1).

Effervesce is the evolution of bubbles in response of a chemical reaction. The most common reaction being acid base reaction between citric acid and sodium bicarbonate, giving us evolution of carbon dioxide bubbles in the presence of water (2). There are several advantages of making an effervescent formulation as they are already in liquid form so they are easier to administer. They may also be flavored to increase patient compliance. Due to less gastric irritation, the effervescent liquid can be very easily tolerated in the stomach and intestine (3, 4).

The main components of the formulation include active ingredients, mixture of acids or their salts, bicarbonates or carbonates or their salts which on addition of water gives CO2. The formulation also includes fillers, sweeteners, binders, flavoring agents and lubricants. The methods of preparation of effervescent tablets include wet granulation, fluidized bed granulation, fusion method and direct compression (5). Formulation requires controlled conditions of temperature and humidity i.e., a relative humidity of RH 25% or less and moderate temperature to prevent sticking of tablets or granules to machine as a result of absorbed moisture. High moisture content may also cause pre-effervescence or moisture retaining in tablet and hence formulation problems (1, 6).

The major limitation with the use and formulation of effervescent is the inability of excipients to prevent moisture absorption. Hence the formulation scientists are focusing on exploiting different techniques such as a direct compression method (7). The bubble- or gas-generating reaction of the effervescent couple in the granule is most often the result of the reaction of an acidic agent and an alkaline agent. The reaction of these two general classes of compounds produces effervescence upon contact with water (8).

Cranberry Vaccinium macrocarponis is an anti-oxidant rich fruit. It contains more than 80% water and 10% carbohydrates. The major components are flavonoids, catechins, terpenoids and a small amount of ascorbic acid (9). Juice of cranberry and its extracts are widely used in relieving the symptoms of UTI’s as it has hippuric acid that is said to reduce the urine pH (10). Several studies have also been done from time to time to give us clinical effects of ingestion the cranberry that showed promising results for patients with bacteriuria (11) in both randomized and controlled studies (12). The strongest evidence available is of sexually active women with pervious case of STD. Cranberry is effective in prophylaxis of recurrent UTI. Therefore, the potential of cranberry products to act as a non-antibiotic alternative for preventing UTI, thereby reducing the total amount of antibiotics prescribed for UTI, is great public health significance (13, 15).
This study's goal was to develop synthesize and analyze effervescent cranberry extract pills. Tablets with cranberries in them have a shorter time to action and are more effective in treating UTIs. The merits of the formulations created for this study are that they share the same weight and flavor requirements as other effervescent tablets. Because they taste better and are more palatable, effervescent pills are more suited in children. Due to the product's appearance during effervescence, ease of administration, and utilization of enticing colors and flavors in these formulations, patients' compliance with the medication may be elevated. The rapid effervescent tablets can be produced using the suggested method in this study without the need for specialized equipment or strict atmospheric conditions, which ultimately lowers the cost of the manufactured tablets.

MATERIAL & METHODS

Chemicals
Cranberry extract was obtained from Novamed Pharmaceuticals Pvt Ltd. Vitamin C, Sodium bicarbonate, Citric acid, Xylitol, Sucralose, Aspartame, Magnesium stearate, PVPK 30, Sodium benzoate, Falsa color and flavor were obtained from Sigma Aldrich. All excipients were of analytical grade.

METHODS

FTIR Compatibility Study of Drug-Excipient
Using an FTIR spectrophotometer, the IR spectra of the sample (the drug and the excipient) was recorded.

Figure 1. Cranberry extract FTIR result

Figure 2. Cranberry extract comparison using FTIR of formulation shows no drug excipient compatibility issues.

Pre-formulation
The formulations were formulated in the various stoichiometric ratios from sodium bicarbonate and citric acid. According to Table 1, materials of each formulation were weighed and then make granules with sodium bicarbonate in rapid mixer granulator. Mix citric acid with xylitol, sucralose, PVPK 30, flavor, dried Cranberry extract and vitamin C in octagonal blender. High speed blender mixed granules with second mixture. Lubricate the mixed material by adding magnesium stearate in lubrication blender. Compressed the final blend in tablet compression machine (KILIAN & CO, Germany) under controlled attributes (humidity, temperature), and packed with foil packing machine. Formulations with
better stoichiometric ratios were chosen with respect to three factors: pH, solubility and effervescence time.

Table 1. Formulation study data

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>F1(mg)</th>
<th>F2(mg)</th>
<th>F3(mg)</th>
<th>F4(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranberry Extract</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Sucralose</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>155</td>
<td>155</td>
<td>220</td>
<td>180</td>
</tr>
<tr>
<td>Citric acid</td>
<td>45</td>
<td>45</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Xylitol</td>
<td>100</td>
<td>175</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PVP K30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>175</td>
<td>100</td>
<td>105</td>
<td>125</td>
</tr>
<tr>
<td>Aspartame</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flavor</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>1100m</td>
<td>1100m</td>
<td>1100m</td>
<td>1100m</td>
</tr>
</tbody>
</table>

PRECOMPRESSION TESTS

Particle Size Analysis
Sieve analysis method was used to determine the average size of the granules. 100 grams of powder mixture is poured over the upper sieve of Ewerka shaking apparatus and shaken over series of sieves for 10 minutes. The percentage of amount remaining on every sieve was calculated as shown in Table 2. The flow properties were measured as follows.

Flow ability
Flow properties can be determined by angle of repose, compressibility index and Hauser’s ratio.

Angle of Repose (θ)
Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The granules were passed from the funnel. Equation number 2 was used for determining the Angle of repose.

\[
tan \theta = \frac{H}{R} \quad \text{equ.1}
\]

\[
\theta = tan^{-1} \left(\frac{H}{R}\right) \quad \text{equ.2}
\]

Where,

\[\theta = \text{Angle of repose}\]
\[H = \text{Height of pile}\]

Hausner’s Ratio and Compressibility Index
Using a glass funnel, 100 g of the mixture was added to the graduated cylinder (250 ml) to measure the bulk density. The volume of the mixture was then recorded. As long as there are no more volume changes, tapping the cylinder containing the powder produced readings that could be used to calculate the tapped density (16, 17). The following equation 3 yields the tapped density and results can be seen in Table 2.

\[
D_o = \frac{M}{V_p} \quad \text{equ.3}
\]

Do = bulk density
M = weight of samples in grams
Vp = final volumes of granules in cm³
Hausner’s and Compressibility Index obtained by calculating the average of three consecutive measurements from $\rho_{tapped}$ and $\rho_{bulk}$ are given in table 2.

$$\rho_{bulk} = \frac{M}{V} \quad \text{equ.4}$$

$M$= Weight of sample in grams
$V$= Volume of sample in cm$^3$

$$\rho_{tapped} = \frac{M}{V} \quad \text{equ.5}$$

$M$= weight of tapped sample in grams
$V$= Volume of tapped sample in cm$^3$

$$\% \text{ Compressibility} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{bulk}} \times 100 \quad \text{equ.6}$$

Hausner’s ratio = $\frac{\rho_{tapped}}{\rho_{bulk}} \quad \text{equ.7}$

Post Compression Tests

Tablet Thickness Measurement
Calibrated Vernier calipers was used to measure the thickness of the tablets for each formulation. Average thickness variations should not vary by more than 5% from their limits (18).

Friability of Tablets
Take 20 tablets at random from each formulation, weigh them, and then set them in a friabilator for 4 minutes at a speed of 25 rpm, for a total of 100 rpm. Friability is unsatisfactory if it exceeds 1% (19).

Assessment of Weight Variation
20 tablets from every formulation should be taken and weighed separately. The average weight was calculated (19, 20). Variation in the weights of tablet is given in table 3 below.

Measurement of Effervescence Time
Place one tablet in beaker of 200ml of distilled water at 20 °C ± 1 °C. The time was noted when a clear solution without any floating particles was obtained (21). The values are given in table 4.

Determination of Effervescent Solution pH
pH of the solution was determined by taking a single tablet in 200ml of distilled water at $20 \pm 1 \, ^{\circ}C$ by using pH meter immediately after completing the dissolution time. Repeat this 3 times for each formulation. See table 4 (22, 23).

CO$_2$ Content Measurement
Measure any weight changes that occur after the dissolution of one effervescent tablet in 100 ml of 1N sulfuric acid solution. The weight difference revealed the quantity (mg) of CO$_2$ in each tablet. Table 4 shows the reported CO$_2$ content, which is the average of three determinations (20).

Measurement of Water Content
10 tablets from each formulation were dried for 4 hours in a desiccator with activated silica gel. As shown in table 4, water content of 0.5% or less is acceptable (24).

Quantitative Determination of Proanthocyanidin in cranberry extract
Zero the UV Visible background with blank and read the sample absorbance at peak maximum 550nm with 1cm cell.

$$\% \text{ Proanthocyanidins} = 2.618 \left( \frac{A}{W} \right)$$

$A$= Absorbance of sample at 550nm
$W$= Weight of sample

The assay of Vitamin C was done by titration method.

Study of Content Uniformity
For the purpose of determining the amount of the active component, 10 tablets from each formulation were randomly chosen. When measuring content homogeneity, the range of specified quantities in the formula (90–110%) should not be exceeded, and the
coefficient of variation (CV) should not be greater than 6. 20 more tablets must be tested if only one was outside the prior range but within the 80–120% range. Each of these 20 tablets should fall within the range of 90 to 110 percent (18).

**Dissolution test**
The tablets had a good release profile of all of four formulation within 5 minutes and the % release drug of all of the formulations are given in table 3 below (20).

**Stability Testing**
The stability studies were performed at real time and accelerated time conditions. The values for real time and accelerated stability studies are displayed in table 5 (20, 25).

**Evaluation of Taste**
Latin Square panel tests were used to assess the flavor. Each of the formulations received a score from the volunteers. The results are seen in table 4 (26).

**RESULTS**
The samples of vitamin C and cranberry were characterized by their melting points for organoleptic qualities, identification by FTIR, and UV analysis proved the drug quality, as well as the lack of any chemical interactions between the drug and excipients as shown in figure 1 and 2. The formulations were made according to table 1. Four formulations were made with varying degrees of excipient concentration to obtain optimum results. The results of the flowability investigations in table 2 show that the powder mixture has good to exceptional flow characteristics.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Angle of repose</th>
<th>Carr's index</th>
<th>Hausner's ratio</th>
<th>% Compressibility</th>
<th>Flow property</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.58</td>
<td>0.68</td>
<td>25.45</td>
<td>18.75</td>
<td>1.17</td>
<td>14.70</td>
<td>Good</td>
</tr>
<tr>
<td>F2</td>
<td>0.50</td>
<td>0.57</td>
<td>23.50</td>
<td>17.74</td>
<td>1.14</td>
<td>12.23</td>
<td>Good</td>
</tr>
<tr>
<td>F3</td>
<td>0.56</td>
<td>0.67</td>
<td>25.68</td>
<td>15.67</td>
<td>1.19</td>
<td>16.45</td>
<td>Fair</td>
</tr>
<tr>
<td>F4</td>
<td>0.60</td>
<td>0.73</td>
<td>31.45</td>
<td>19.45</td>
<td>1.23</td>
<td>19.20</td>
<td>Excellent</td>
</tr>
</tbody>
</table>
The homogeneous tablet thickness was achieved through uniform die filling, adequate flow characteristics, optimum pressure, and punch movement. Each formulation is within the weight variation limit (1100 ± 15mg) as seen in Table 3. Friability was determined to be less than 1% for all formulations. A hardness tester was used to evaluate the tablets' hardness. The range of the values was 40 to 80 (N). The tablets' thickness ranged from 3 to 6 mm.

Table 3. Evaluation of Friability, Thickness, DT, Dissolution and Weight Variation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness (cm)</th>
<th>Friability</th>
<th>Weight Variation</th>
<th>Disintegration time(sec)</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.79±0.018</td>
<td>0.511</td>
<td>1105±7.8</td>
<td>45.6±2.42</td>
<td>95.81%</td>
</tr>
<tr>
<td>F2</td>
<td>3.82±0.019</td>
<td>0.767</td>
<td>1075±10</td>
<td>42.4±2.46</td>
<td>96.32%</td>
</tr>
<tr>
<td>F3</td>
<td>3.81±0.014</td>
<td>0.536</td>
<td>1113±6.6</td>
<td>48.4±2.12</td>
<td>95.74%</td>
</tr>
<tr>
<td>F4</td>
<td>3.78±0.016</td>
<td>0.570</td>
<td>1098±5.4</td>
<td>36.6±1.25</td>
<td>98.16%</td>
</tr>
</tbody>
</table>

Table 4. Evaluation of pH, effervescence time, % water content, taste and CO₂ content

<table>
<thead>
<tr>
<th>Formulation</th>
<th>CO₂ Content</th>
<th>pH</th>
<th>% Water content (w/w)</th>
<th>Effervescence time (sec)</th>
<th>Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>244±0.56</td>
<td>4.32±0.04</td>
<td>0.20±0.019</td>
<td>74±3.55</td>
<td>A bit bitter</td>
</tr>
<tr>
<td>F2</td>
<td>253±0.67</td>
<td>4.85±0.02</td>
<td>0.18±0.011</td>
<td>83±4.12</td>
<td>Too Sweet</td>
</tr>
<tr>
<td>F3</td>
<td>276±0.14</td>
<td>5.32±0.01</td>
<td>0.14±0.006</td>
<td>84±3.61</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>F4</td>
<td>250±9.47</td>
<td>5.38±0.04</td>
<td>0.14±0.012</td>
<td>67±2.45</td>
<td>Excellent</td>
</tr>
</tbody>
</table>
In-vivo taste evaluation by analysis reveals that formulation F4 in table 1 is more popular and has a better taste than other formulations of varied effervescent compositions due to variations in the pH of the solutions. The dosage form's uniformity was confirmed by the content uniformity measured in accordance with USP standards. According to the stability research findings, even after 9 months of storage at varied temperatures and humidity levels, there was no discernible change in the physiochemical attributes. It can be assumed that the formulation was unchanged and did not degrade all the results of zero-month study showed good percentage release within USP range and were mostly around 90-110%.

After three months Real time and accelerated showed about the same results as average 97.8% and 97.53% respectively. Same behavior was seen until the 9-month stability studies. In real time stability data, the percentage on average was 95.67% and for accelerated study data results were 95.35% on average for all the formulations. The compiled results can be seen in Table 5.

Table 5. Evaluation of stability studies

<table>
<thead>
<tr>
<th>Formulation</th>
<th>0 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Real time</td>
<td>Acc study</td>
<td>Real time</td>
<td>Acc study</td>
</tr>
<tr>
<td>F1</td>
<td>96.78%</td>
<td>96.41%</td>
<td>96.31%</td>
<td>95.97%</td>
</tr>
<tr>
<td>F2</td>
<td>98.32%</td>
<td>98.01%</td>
<td>98.46%</td>
<td>97.86%</td>
</tr>
<tr>
<td>F3</td>
<td>98.67%</td>
<td>98.45%</td>
<td>98.51%</td>
<td>98.62%</td>
</tr>
<tr>
<td>F4</td>
<td>97.49%</td>
<td>97.44%</td>
<td>97.47%</td>
<td>97.45%</td>
</tr>
</tbody>
</table>
DISCUSSION

As the development of dosage forms for easier approach to patients and enhancing patient compatibility is enforcing, some newer formulations and even formulation methods are coming forth. The most common type of dosage form and most widely prescribed by physicians is oral or by mouth dosage forms. Among which effervescent tablets are favored over tablets and capsules as they are easily dispersed and show effervescence. Effervescence is reaction between bicarbonate and acid resulting in release of carbon dioxide gas, the active ingredient gets easily dispersed in water.

Many effervescent tablets are previously made such as vitamins and minerals (27-29) effervescent tablets, ranitidine (16, 22), paracetamol (22), risperidone (30) and many more (24, 31-33). They are either in market or in development procedure. Many have shown to be excellent in rapid drug delivery (25, 34, 35). Several methods are utilized in formulation of effervescent tablets such as dry granulation, wet granulation, direct compression, fluidized air bed method (3, 23, 36). Each method has its own advantages and draw backs. Such as over effervescence, moisture absorbance, fragility etc. (36). Cranberry is widely used for the treat on UTIs in adults especially females (37). Its effervescent granules are available but its tablets are not marketed due to the fact that cranberry extract shows over effervescence as it is not properly controlled. The main objective of the study was to control the effervescence and enhance the patient compatibility and also making it compact and travel friendly (38). For this purpose several trials were made and all of them failed due to over effervescence (39). Finally, the stoichiometric ratio of carbonate and acid was developed that gave us the four formulations F1, F2, F3 and F4. Out of these, F4 was widely accepted as it was excellent with respect of all other previous formulations made. Aspartame was added in F1 but it gave a bitter after taste so it was removed in further formulations similarly the amount of xylitol was also controlled so as to make it not too sugary. The flow property of granules were satisfactory and the stability studies on the formulation also gave results in between the give USP monograph rage 90-100% (20). Hardness testing and friability testing of the all tablets were also within range and the moisture content was also studied during the stability periods.

CONCLUSION

The effervescent tablet of Cranberry with Vitamin C is a new pharmaceutical formulation for oral dose intake providing advantages such as avoiding gastrointestinal disorders. Another aspect of this formulation is absorption of actives readily and in comparison, to other related dosage forms it showed significantly better results for the treatment of UTIs in adults and especially in menopausal women. These Effervescent tablets will facilitate the consumption of Cranberry and Vitamin C and increase patient acceptance among those suffering from UTI and urate kidney stones. It will be helpful especially for women whom are more prone to Urinary Tract Disease and
help balance vaginal pH. This formulation has a significant commercial potential, therefore by extending current research, many new therapies can be developed that are similar to it and will have higher patient compliance.

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None

DECLARATIONS
Authors’ Contribution
HA, MK and SU conceptualized the, designed, reviewed and approved the final version. ST, SS and AM collected and assembled data. Editing and formatting was completed by HA. MK and MK interpreted and wrote the data. SU gave statistical expertise.

Ethical Approval
Not applicable

Conflict of Interest
The author declared no conflict of interest among them.

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