Floating Drug Delivery Systems Using Metronidazole as a Model Drug Part I:
By Effervescent Method

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Abstract:
Gastric retentive dosage forms are highly useful for the delivery of many kinds of drugs. The use of floating dosage forms (FDFs) is one of the methods used to achieve prolonged gastric residence time (GRT).

Formulation of Metronidazole (MDZ) as FDF provides an opportunity for both local and systemic drug action for eradication of Helicobacter pylori which is a gram-negative bacterium that is associated with gastric inflammation, peptic ulcer, and gastric cancer.

This study was undertaken in order to formulate effervescent single-unit floating drug delivery system (FDDS) for MDZ.

In the effervescent method, a carbon dioxide generating agent, e.g. sodium bicarbonate, was incorporated in hydrophilic polymer matrix together with MDZ.

Different formulation parameters were studied and their effects on the floatation and in vitro drug release profiles were investigated.

Polyvinyl pyrrolidone (PVP) provided rapid hydration of matrix, and this influence was decreased with time.

Pectin was found to meet the requirements needed from a matrix for drug delivery applications including suitable mechanical properties to confine the gas, and to sustain MDZ release.

The optimal amount of polymer and effervescent agent, lubricant agent concentration, and compression force were also demonstrated.

The stability of the selected floating MDZ tablet formula (6) was also studied at different temperatures for three months and the calculated expiration date was found to be more than 4 years.
Introduction:

Various approaches have been pursued to increase the retention of an oral DFs in the stomach, one of which is the floating systems \[^{[1,2]}\].

Floating drug delivery system (FDDS) also called hydrodynamically balanced system (HBS); it remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.

After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations in some cases \[^{[3]}\].

Based on the mechanism of buoyancy, two distinctly different technologies, i.e. effervescent and non-effervescent systems have been utilized in the development of FDDS.

The former technology is used in this work, so it will be discussed mainly.

Effervescent FDDS is based on the formation of carbon dioxide within the device upon arrival in the stomach. When carbon dioxide is generated and entrapped within the gellified hydrocolloid, it produces an upward motion of the DFs and maintains its buoyancy \[^{[4]}\].

For the formulation of a FDF, three major conditions must be met \[^{[3]}\]:

(i) It must have sufficient structure to form a cohesive gel barrier.

(ii) It must maintain an overall specific gravity lower than that of gastric contents (reported as 1.004-1.01 g/cc).

(iii) It should dissolve slowly enough to serve as a ‘reservoir’ for the delivery system.

For In vitro evaluation of FDDS various parameters are needed to be investigated for their effects on GRT, Which can be categorized into the following different classes:

1- Galenic parameters: diameter, flexibility and density of matrices.

2- Control parameters: floating time, dissolution, specific gravity, content uniformity, hardness and friability (if tablets).

3- Geometric parameters: shape.

The major objective of the present investigation is the development of floating drug delivery systems incorporated with MDZ, which is used in gastric ulcer therapy. The method of preparation that is used in the development of such systems is the effervescent method to prepare floating tablets.

After preparation, the drug release mechanism and floating behavior were evaluated.

Drug release properties of various floating tablet formulas were evaluated in vitro by unconventional dissolution test using double layer ring-mesh modified apparatus II device.

The effect of important formulation and processing parameters on the floating and drug release behavior of this system were studied.

Furthermore, the selected floating tablet formula was subjected to stability study.

Materials and methods:
Formulation of MDZ floating tablet by effervescent method:

Different formulas of MDZ floating tablets were suggested as shown in table (1).

They were prepared using wet granulation method.

After an appropriate dry blending of previously sieved ingredients, they were granulated by gradual addition of an appropriate amount of PVP aqueous solution and then kneaded to the proper consistency.
The wet mass was then passed through a 1.25 mm sieve and dried at 40°C for 24 hours.
A known weight of the dried granules was mixed with a desired amount of magnesium stearate and compressed using 9 mm flat face punch tableting machine.

The following formulation parameters were studied:

Effect of type of polymer:
Four different types of polymer; methyl cellulose, carboxymethyl cellulose, sodium alginate and pectin, were used to study the effect of polymer type on the floatation and drug release properties as in formulas (1), (2), (3) and (6) respectively.

Effect of the amount of polymer:
Formulas (6), (7) and (8) were made to study the effect of polymer amount on the floatation properties and to determine the amount of polymer that is enough to sustain the release of the drug. Three different amounts of pectin 50 mg, 75 mg, and 100 mg were used in this study.

Effect of the quantity of the effervescent agent:
Formulas (4), (5) and (6) were used to study the quantitative effect of effervescent agent in an attempt to determine and optimize the floating lag time and floating duration of the delivery system. Dissolution behavior was also studied using three different quantities of sodium bicarbonate 15mg, 20mg, and 25 mg as in formulas (4), (5) and (6) respectively.

Effect of lubricant agent concentration:
Drug release studies were conducted on formulas (6), (9) and (10) containing three different concentrations of magnesium stearate 1%, 1.5%, and 2% respectively, to investigate lubricant concentration effect on floatation and dissolution behaviors.

Table-1: Schedule of different formulas of MDZ floating tablets.

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidasole (mg)</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvinyl pyrrolidone (mg)</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl cellulose (mg)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboxymethyl cellulose (mg)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium alginate (mg)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pectin (mg)</td>
<td></td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate (mg)</td>
<td>25</td>
<td>15</td>
<td>20</td>
<td></td>
<td></td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate (%)</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect of compression force:
Various compression forces 8, 10, and 12 ton/cm2 were utilized in the preparation of MDZ floating tablet using formula (6) to study its effect on the floating and dissolution behaviors.

Quality control of the prepared MDZ floating tablets:

Uniformity of weight:
From each formula prepared, 20 tablets were weighed individually and their mean weight was calculated.

Crushing strength (Hardness):
Tablets hardness was determined by mean of Erweka hardness tester, which was
expressed as force in kilogram required to crush the tablet \(^5\).

**Determination of floatation lag time and floating duration:**

Floatation properties were determined using USP dissolution apparatus in 900 ml 0.1 M HCl solution as dissolution media and the paddle rotation speed was adjusted to 50 rpm.

As soon as tablet float the time was recorded as floating lag time and the time spend for the tablet floating was recorded as floating duration.

**Dissolution test:**

The *in vitro* release studies of each formula were conducted in accordance with double layer ring-mesh modified apparatus II device \(^6\) at 37°C in 900 ml 0.1 M HCl solution using Erweka Apparatus, Type DT6.

The paddle speed was 50 rpm. Samples were withdrawn at different time intervals, filtered and the U.V. absorbance at 277 nm was measured and MDZ concentration was deduced by means of calibration curve of the drug in the same medium.

Analysis of drug release kinetics:

The release data of all formulas have been further substantiated by fitting the fraction release data, \(M_t/M_\infty\) to an empirical equation proposed by Peppas in order to establish the release rate constant \((k)\) and kinetic mechanism associated with drug release\(^8\).

\[
F = \frac{M_t}{M_\infty} = kt^n
\]

Where \(F\) is the fractional release of a drug, \(M_t\) is the amount of released drug at time \(t\), \(M_\infty\) is the overall amount of the drug (whole dose), \(k\) is the constant incorporating structural and geometric characteristics of the controlled release device, and \(n\) is the release exponent indicative of the drug release mechanism.

When \(n= 0\), \(tn=1\) and the release process is of zero order; if \(n= 0.5\), Fick’s law holds and the release represented by a square root equation.

The results were compared with Medazole® 200 mg tablet from SDI and Flagyl® 250 mg tablet from Aventis.

**Assay for MDZ content:**

Ten tablets from formula (6) were accurately weighed, well powdered and a weight of 250 mg of the powdered tablet (which is equivalent to 128.58 mg MDZ) was extracted using 100 ml of 5% HCL solution, and then filtered.

A sample of 2 ml was taken and diluted to 250 ml with 5 % HCL solution. The absorbance was determined spectrophotometrically at 277 nm.

A stock solution of MDZ was prepared (as a standard) by dissolving accurately weighed 128.58 mg of pure drug in 100 ml 5 % HCL solution.

A sample of 2 ml was then taken and diluted to 250 ml with 5 %HCL solution. The absorbance was determined spectrophotometrically at 277 nm.

The quantity of MDZ per tablet was calculated according to the following equation assuming homogenous distribution of the active ingredient \(^7\).
Value of $n$ greater than 0.5 indicate anomalous diffusion, due generally to the swelling of the system in the solvent before the release takes place in addition to polymer relaxation\[^9\].

The rate constant $k$ and the diffusional exponent $n$ can be obtained from the intercept and the slope of a plot of $\ln F$ versus $\ln t$ respectively.

Since the rate constant $k$ is expressed as percent, the fraction release, $F$, is also expressed in the percentage unit in the equation:

$$\ln F (\%) = \ln k + n \ln t$$

This makes an available model for computing fractional released in percent per unit time, and the time at which 100% of the drug is released\[^9\].

**Kinetic study:**

The effect of temperature on the degradation rate of a selected floating tablet formula (6) was studied.

The study was done by storing the tablets in ovens of different temperatures (40, 50, and 60 °C) for three months.

Samples were taken at different time intervals and analyzed for MDZ content spectrophotometrically.

**Results and Discussion:**

**Technological optimization of the floating matrix tablets:**

The contribution of polyvinyl pyrrolidone (PVP) for hydrating the polymer matrix in which it is present was considerable initially and its influence on polymer hydration decreased with time.

This result is consistent with the fact that PVP alone absorbed water rapidly, and did not form a gel because PVP dissolve in water\[^10\].

**Effect of polymer type:**

Different dissolution, diffusion and swelling behaviors were observed for several polymers.

Methyl cellulose, carboxymethyl cellulose, and sodium alginate formed inconsistent gel layer that was unable to entrap carbon dioxide in the matrix and this leads to gas liberation, and inability to sustain release of the drug.

This resulted in late floating time (18, 20 and 30 min), and short floating duration (1.5, 1.5 and 1.25 hr) for methyl cellulose, carboxymethyl cellulose, and sodium alginate polymer matrices respectively.

Rapid release of the drug was also observed as shown in Table-3. On the other hand, pectin meets the requirements needed from a matrix for drug delivery applications including suitable mechanical properties to confine the gas, and to sustain the release of the drug as shown in Figure-1.

**Effect of polymer amount:**

Figure-2 shows that increasing pectin amount from 50 mg (F8), to 75 mg (F7), and then to 100 mg (F6) in the systems decreased MDZ release rate. This could be attributed to the formation of a denser gel and slower erosion at the higher pectin content\[^11\], as shown in Table-3.

**Effect of the amount of effervescent agent:**

To determine and optimize the floating lag time and buoyancy duration of the delivery system, three different amount of sodium bicarbonate were used.

As would be expected slower floating and longer buoyancy duration were achieved by formulas containing small amount of effervescent agent as could be seen in formula (4) and (5) which contain 15 mg and 20 mg sodium bicarbonate.
respectively, this could be due to less gases evolved and less matrix expansion.

A faster release was shown for formula containing higher effervescent agent (F6), as shown in Figure-3, the reason would be that with the evolution of gas, the matrix would become more relaxed allowing water penetration and the drug diffusion might be easier, as shown in table-3.

Effect of lubricant agent concentration:
Floating lag time was found to increase with increasing magnesium stearate concentration, as shown in table-3, and this may be due to reduction in water uptake caused by hydrophobic nature of magnesium stearate [12].

The effect of magnesium stearate on drug release is shown in Figure-4, which revealed that drug release was retarded with increasing magnesium stearate concentration ($ln k$ values were 0.682, 0.5407 and 0.5135 for tablet matrices prepared with 1 %, 1.5 % and 2 % magnesium stearate concentration respectively).

![Figure 1: Effect of polymer type on the release of MDZ from floating tablets](image1)

F1: Methyl cellulose polymer matrix  
F2: Caboxy methylcellulose poly matrix  
F3: Sodium alginate polymer matrix  
F6: Pectin polymer matrix

![Figure 2: Effect of polymer (pectin) amount on the release of MDZ from floating tablets.](image2)

F6: formula contain 100 mg pectin  
F7: formula contain 75 mg pectin  
F8: formula contain 50 mg pectin
Figure-3: Effect of the amount of sodium bicarbonate on the release of MDZ from floating tablets
F4: formula contain 15 mg sodium bicarbonate
F5: formula contain 20 mg sodium bicarbonate
F6: formula contain 25 mg sodium bicarbonate

Figure-4: Effect of lubricant agent concentration on the release of MDZ from floating tablets
F6: formula contains 1% of magnesium stearate
F9: formula contain 1.5% of magnesium stearate
F10: formula contains 2.0% of magnesium stearate

Effect of compression force:
Reduced floating lag time could be achieved by reducing the compression forces, which results in an increase in tablet porosities. Compression force did affect floating performance (table-2).

Rapid release of MDZ was seen in tablets prepared with lesser compression force as shown in Figure-5.
Table-2: Different floatation parameters of formula 6 Prepared with different compression forces.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Compression Force used (ton/cm²)</th>
<th>Floating lag time (min)</th>
<th>Floating duration (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6a</td>
<td>8</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>F6b</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>F6c</td>
<td>12</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure-5: Effect of compression forces on the release of MDZ from floating tablets in formula 6.
F6a: tablet prepared with compression force of 8 ton/seq.cm
F6b: tablet prepared with compression force of 10 ton/seq.cm
F6c: tablet prepared with compression force of 12 ton/seq.cm

Quality control of the prepared MDZ floating tablets:
Determination of floatation lag time and floating duration:
Due to the gradual and continuous generation of gas in the matrix, it gradually floats [14].

Due to the gradual and continuous generation of gas in the matrix, it gradually floats [14].
The floating lag time and the duration of floating were determined in the USP dissolution apparatus II in an acid environment.
The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium which was taken as buoyancy lag time and the duration of system buoy were observed visually.
The floating lag time and duration for the formulas under test are presented in table-3.

Drug release and dissolution study:
By comparing commercial MDZ plane tablets Medazole® and Flagyl® with the prepared floating MDZ tablet in formula (6b), it was noticed that 100 % of the dose was released in former two within the first 30 min of the dissolution test; while with the prepared floating tablet the release was extended to about 8 hours in vitro as could be seen in Figure-6.

Double layer ring-mesh device was used to study the drug release and it is a simple modification of an existing technique.
Empirical correlations of the release data:

The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion.

But other processes in addition to diffusion are important. These are: Release from initially dry, hydrophilic glassy polymers that swell when added to dissolution media and builds a gel layer around the tablet core which governs drug release.

There is also a relaxation of the polymer chains, which influences the drug release mechanism.

These processes are described as non-Fickian or anomalous diffusion as a result of the rearrangement of macro-molecular chains [15].

Water soluble drugs appear to undergo a diffusion-controlled release through the gel layer whereas insoluble drugs are released from the perimeter of the gel by surface erosion [16, 17].

A simple empirical equation can be used to analyze the data of controlled release of drugs from polymer matrices (Peppas equation as mentioned above).

This equation predicts the mechanism of diffusional release and drug release rate constant [9,15,18].

The rate constant \( k \) and the diffusional exponent \( n \) can be obtained from the intercept and the slope of a plot of \( \ln F \) versus \( \ln t \) respectively as shown in Fig. (7). In this study the value of \( n \) was calculated for the time interval from the 30 minutes to the end of the release process, because in the first minutes the burst effect was recognized (the drug was released from the surface of the tablet before gel layer formation) [10,19].

The results for all formulas revealed that the calculated value of \( n \) of greater than 0.5 is characteristic for the non-Fickian type of drug diffusion, which means that the drug release process was regulated through both mechanisms of diffusion and polymer relaxation [20].

Table-3 summarizes the floatation and drug release characters of different formulas for MDZ floating tablets.
Figure-7: Plot of \( \ln (F) \) vs. \( \ln (t) \) of different formulation of MDZ floating tablets

Table-3: Different floatation and release parameters for different formulas of MDZ floating tablets.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Floating Lag time (min)</th>
<th>Floating duration (hr)</th>
<th>( \pi )</th>
<th>( \ln K % (min) *)</th>
<th>Regression coefficient with 95% confidence limit (( r^2 ))</th>
<th>Mechanism of release process</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>18</td>
<td>1.5</td>
<td>0.6248</td>
<td>1.6429</td>
<td>0.97785</td>
<td>Anamolous diffusion</td>
</tr>
<tr>
<td>F2</td>
<td>20</td>
<td>1.5</td>
<td>0.6791</td>
<td>1.3704</td>
<td>0.99552</td>
<td>=</td>
</tr>
<tr>
<td>F3</td>
<td>30</td>
<td>1.25</td>
<td>0.7312</td>
<td>1.2906</td>
<td>0.99318</td>
<td>=</td>
</tr>
<tr>
<td>F4</td>
<td>10</td>
<td>14</td>
<td>0.6535</td>
<td>0.5036</td>
<td>0.97013</td>
<td>=</td>
</tr>
<tr>
<td>F5</td>
<td>9</td>
<td>12</td>
<td>0.6429</td>
<td>0.6214</td>
<td>0.98428</td>
<td>=</td>
</tr>
<tr>
<td>F6 b</td>
<td>5</td>
<td>10</td>
<td>0.6477</td>
<td>0.6820</td>
<td>0.99422</td>
<td>=</td>
</tr>
<tr>
<td>F7</td>
<td>8</td>
<td>5</td>
<td>0.7061</td>
<td>0.6556</td>
<td>0.98801</td>
<td>=</td>
</tr>
<tr>
<td>F8</td>
<td>10</td>
<td>4</td>
<td>0.7528</td>
<td>0.6125</td>
<td>0.99838</td>
<td>=</td>
</tr>
<tr>
<td>F9</td>
<td>10</td>
<td>12</td>
<td>0.6544</td>
<td>0.5407</td>
<td>0.99621</td>
<td>=</td>
</tr>
<tr>
<td>F10</td>
<td>12</td>
<td>14</td>
<td>0.6332</td>
<td>0.5135</td>
<td>0.99536</td>
<td>=</td>
</tr>
</tbody>
</table>

Assay for MDZ in formula (6):

The amount of MDZ in the floating tablet prepared in formula (6) was found to be 127.32 mg, and the content uniformity for tablets was found to be 99.02%.

The floating MDZ tablet formula (6) was selected because it offers the optimum floating and release performance so this formula is subjected to stability study at different temperatures.

Kinetic study on the tablets in formula(6)

The stability of MDZ floating tablets in formula (6) was studied at different exaggerated temperatures (40, 50, and 60°C) for 3 months.

The effect of temperature on degradation rate is given by Arrhenius equation \([9]\).
In which \( k \) is the specific reaction rate constant, \( A \) is a constant known as the Arrhenius factor, \( E_a \) is the energy of activation, \( R \) is the gas constant (1.987 calories/deg mole), and \( T \) is the absolute temperature.

Plotting of log percent remaining of MDZ versus time at different temperatures was linear, indicating that MDZ degradation follows first order kinetics. The slopes of these lines were determined, and the rate constants (\( k \)) were calculated. Then Arrhenius plot was constructed by plotting log \( k \) versus 1/\( T \), and the rate constant at room temperature, was obtained from this plot and it was equal to 0.00006546 per day.

Since the degradation of the drug follows first order kinetics, the expiration date (t10%) at 25°C could be calculated using the following equation:

\[
\text{t}_{10\%} = \frac{0.105}{K_{25^\circ C}}
\]

The expiration date for floating MDZ tablet prepared in formula (6) is equal to 4.394 years.

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**References:**


