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# FORMULATION AND DEVELOPMENT OF CAFFEINE LOADED FLOATING TABLET IN THE TREATMENT OF ORTHOSTATIC HYPOTENSION

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## ABSTRACT
The main objective of the present work was to formulate and characterize Caffeine loaded floating tablet in the treatment of orthostatic hypotension as sustain release formulation. Formulations were prepared using gas generating agent like citric acid and sodium bicarbonate. The tablets were evaluated for the hardness, thickness, friability, dissolution, weight variation, drug content, floating and swelling property. In-vitro dissolution was conducted for 16 hours in 0.1 N HCl at 37±0.5$^0$C using the USP type II (paddle type) dissolution apparatus. It was noted that the all the formulation had desired lag time and constantly float on the dissolution media for 16 hours. The observed difference between all formulation was due to the different polymers used (HPMC k-15, HPMC K-100, Carbopol) and concentration of gas generating agents.

**KEYWORDS:** Orthostatic hypotension, Floating tablet, Sustained release, Gas generating agents.

## INTRODUCTION
Over a last decades various gastro-retentive formulation has been developed for prolonging residence time for such a drug having low solubility, narrow absorption window at upper GI tract, the drug having poor stability in colon or the drug having less half-life. Gastro-retentive Drug Delivery system(GRDDS) designed to maximize the residence time and make drug available at its absorption site as well as at the site of action by keeping steady state concentration in blood plasma. It is a formulation of drug and gel forming agent or gel forming hydro-colloids meant to remain buoyant in stomach.[1,3,4]

Floating drug delivery also called hydro-dynamically balanced systems have a sufficient buoyancy to float over the gastric contents and remains buoyant in the stomach without any affection of gastric emptying rate for the prolong period of time. Rapid gastrointestinal transit results in incomplete drug release from the dosage form above the absorption zone leading to diminished efficacy of the administered dose. These considerate have led to the development of a Controlled release Drug Delivery system (CRDDS) or Sustained release Drug Delivery system (SRDDS). The main purpose for developing these systems was to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for long period of time. GRDDS is an approach to prolong gastric retention time, thereby the targeting site – specific drug release in the upper GIT for local and systemic effect. Therefore, different approaches have been proposed to retain the dosage form in the stomach like bio-adhesive systems, floating systems, swelling and expanding systems.[1,2,5]

Hydroxy propyl methyl cellulose (HPMC) is hydrophilic cellulose ether widely used as release retarding material. HPMC releases drug by diffusion mechanism.[2] Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets. Ethyl cellulose also used as the low density material and the carbopol used as gelling agent As the fluid or media penetrates the matrix tablet, the polymer swells and drug diffuses from the system at a rate determined by nature and composition of polymer. A water swellable gum from natural origin such as tragacanth prolong drug release due to its rapid hydration, good compression and gelling characteristic along with its ease of use, availability and low toxicity. So tragacanth could be used as a tablet adjuvant especially for sustained release tablets.[5,6]

Caffeine is a central nervous system (CNS) stimulant and the world's most widely consumed psychoactive drug of the methylxanthine class. Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. There are several known mechanisms of action to explain the effects of Caffeine. The most prominent is that Caffeine reversibly blocks the action of adenosine on its receptor and consequently prevents the onset of drowsiness induced

by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system (ANS).

Caffeine is a bitter, white and crystalline. It comes under BCS class II and having low half-life up to 3 to 4 hours. Due to its low half-life decided to formulate the sustained release dosage form to improve and prolong the residence time. It is a purine, methyl-xanthine alkaloid class drug, and is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

The Orthostatic hypotension (OH) is defined as a fall of blood pressure from the normal 120/80 mmHg at least systolic by 20 mmHg and diastolic blood pressure by 10 mmHg within 3 minutes of standing[9,10] It is a physical finding and not a diagnosis; so it may be symptomatic or asymptomatic fall in blood pressure.[9,10] OH is more common in the elderly, at least in part because of the frequent use of antihypertensive medications.[11] Drugs frequently associated with OH are vasodilators (e.g. nitrates, calcium channel blockers and ∝ adrenergic blockers), tricyclic antidepressant and also associated with incident coronary artery disease, stroke and heart failure.[10]

Thus, the paper explains in detail about the development of sustain release tablet formulation for Caffeine to improve and enhance the bioavailability. It also emphases on the various testing parameters for evaluation of formulation.

## MATERIAL AND METHOD

### Material

Caffeine was procured from S D Fine- Chem Pvt. Ltd (SDFCL) with 99.5% potency, Low density Ethyl Cellulose, Polyvinylpyrolidone K-30 (PVP k-30) was procured from Loba Chemie Pvt. Ltd., citric acid and sodium bicarbonate procured from Merk specialties Pvt. Ltd., HPMC K-100 and HPMC K-15 was procured from Accutech research Laboratory, Mumbai, Microcrystalline cellulose 101 (MCC 101) was procured from chemified cellulose Pvt. Ltd., Magnesium stearate was procured from GRS Pharma Pvt. Ltd., Carbopol was procured from Corel pharma chem Pvt. Ltd.

## METHODOLOGY

The floating tablets of Caffeine were prepared by direct compression technique. All ingredient weighed properly except magnesium stearate and mixed separately in mortar in ascending order. PVP K90added as a binder and lubricated with magnesium stearate 0.8% w/w) and the powders were passed through #40 or #60 mesh sieve. Final blend of powder was mixed well using Octagonal blender (Mec-well pharma machinery, Model: MPM/LAB/0B5/151). Then powder mixture blend was compressed using tablet compression Machine (Model 10 STD D LABPRESS GMP, Cemach Machineries Lmt., Ahmedabad).

### Formula

The number of trials were carried out varying with the proportion of MCC 101, PVP K-30, $NaHCO_3$, HPMC K-15, HPMC K-100, Citric acid, Low density Ethyl Cellulose and Carbopol, to develop SRDDs, as mentioned table no. 1.

**Table 1: Formulation of Caffeine loaded floating tablet.**

| Sr. no. | Composition | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | Caffeine | 200 | 200 | 200 | 200 | 200 | 200 |
| 2 | HPMC K-100 | 0 | 50 | 0 | 40 | 0 | 0 |
| 3 | HPMC K-15 | 0 | 0 | 20 | 20 | 125 | 150 |
| 4 | Acrypol 934 | 100 | 50 | 100 | 100 | 50 | 50 |
| 5 | Ethyl cellulose | 15 | 0 | 0 | 15 | 110 | 50 |
| 6 | Citric acid | 50 | 50 | 25 | 50 | 20 | 25 |
| 7 | Sodium bicarbonate | 100 | 100 | 100 | 100 | 60 | 75 |
| 8 | PVP k-30 | 0 | 0 | 0 | 0 | 0 | 15 |
| 9 | MCC 101 | 100 | 115 | 120 | 40 | 0 | 0 |
| 10 | Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 |
| 11 | Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| | Total | 575 | 575 | 575 | 575 | 575 | 575 |

## EVALUATION AND CHARACTERIZATION

### A. Pre-evaluation parameter

1. **Organoleptic properties-** Color of the tablet was observed to find out the instability problems, incompatibility and mottling (uneven color distribution or mark with spots).
2. **Solubility-** Solubility of the drug measured in ppm i.e. parts per million in the different solvents like water, methanol and 0.1 N HCl. The solubility was determined by solubility chart mentioned in table no. 2.

**Table 2: Solubility chart.**

| Solubility | Parts of solvent to dissolve 1 part of solute |
|---|---|
| Very soluble | Less than 1 |
| Freely soluble | 1-10 |
| Soluble | 10-30 |
| Sparingly soluble | 30-100 |
| Slightly soluble | 100-1000 |
| Very slightly soluble | 1000-10,000 |
| Practically insoluble | More than 10,000 |

3. **Angle of repose-** The angle of repose denoted by $\theta$, was formed by the horizontal base surface of the bench and the edge of a cone-like pile of powder. Stainless steel funnel was used and the size of the orifice was 10 mm and the height from the beginning of funnel to end of orifice was 111 mm. The funnel was fixed in place, 4 cm above from the bench surface. After the cone from 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured. The angle of repose (θ) was calculated by using following formula-

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, h= Height of pile
R= Radius of pile base
$\theta$ = Angle of repose

4. **Bulk density-** The bulk volume was measured after manually tapping the cylinder two times on a flat table top surface. The bulk density was obtained by placing a known mass of powder to a graduated cylinder. The density was calculated as mass/volume and measured in gm/ml.
5. **Tapped density-** The tapped volume was measured with the drug, powder or granules Tap Density Tester (Electrolab, model: ETD1020) after tapping in increments of 500, 750 and 1250 taps with 250 drops per minute. Tapped density was obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed. The tapping can be performed using different methods. The tapped density is calculated as mass divided by the final volume of the powder. The inter-particulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow. It was possible to gain information about interactions in a given powder by comparing the bulk and tapped densities, and such a comparison can be used to index the ability of the powder to flow. The density was calculated as mass/volume and measured in gm/ml.
6. **Percent Compressibility or Carr's Index-** Bulk and Tapped densities were used to calculate the Carr's compressibility index to provide a measure of the flow properties and compressibility of granules. Carr's Index were generally expressed in % and calculated using the following formula-

$$\text{Carr's Index}(\%) = \frac{\rho\text{tapped density} - \rho\text{bulk density}}{\rho\text{tapped density}} \times 100$$

7. **Hausner Ratio-** Bulk and Tapped densities were used to calculate the Hausner Ratio to provide a measure of the flow properties and compressibility of granules. The Hausner ratio was calculated using following formula-

$$\text{Hausner Ratio} = \frac{\rho\text{tapped density}}{\rho\text{tapped density}}$$

8. **Sieve analysis-** The Caffeine and other excipient that were weighed accurately about 500 g. Ingredient were placed over a stack of sieves into the mechanical shaker having opening sizes from lower numbers to higher numbers in ascending manner, the full set of sieves(#s 4 and 200 should always be included). The very last sieve was #200 and a pan was placed under it to collect the portion of material passing #200 sieve, stuck particles in the openings poked them out using brush. All sieved material were weighed separately. The material was poured into the stack of sieves from the top and place the cover, put the stack in the sieve shaker and clamps was fixed, were fixed adjusting time on 10 to 15 minutes and shaker put on. The sieve shaker was stopped and mass of retained material on each sieve measured and finally % retained weight of material was calculated.
9. **Loss on drying-** Loss on drying (LOD) was measured with the drug and excipient using the digital loss on drying testing apparatus (Sartorius, model: MA35M). LOD widely used test method to determine the moisture content of a sample, sometimes it may refer to the loss of other volatile matter from the sample. Loss on drying does not usually refer to molecularly bound water or water of crystallization. LOD was expressed in % and calculated using following formula-

$$\text{Loss on drying} = \frac{\text{Initial weight} - \text{final weight}}{\text{inital weight}} \times 100$$

Many times Karl Fischer test (KF- test) also used to determine amount of moisture content.

**B. Post- compression parameter**[7,8]

1. **Appearance-**. Appearance of tablet was observed and tried to keep constant for factors like size, color, shape, presence or absence of odor, taste etc.
2. **Size and shape-** Size and shape of a tablet has been determined by its thickness and thickness calculated by the sliding caliper scale also known as Vernier calipers scale. Unit used to express the thickness of tablet was Micrometer. The allowed variation for size and shape were ±5% of standard deviation.
3. **Hardness-** Horizontal position operating Schleuniger type digital tablet hardness test apparatus (Veego, model: VDIITAB-I) was used to determine the hardness of tablet. It was expressed in kg/cm$^2$. Three randomly selected tablets was tested

from each batch and hardness was determine. Then the mean and standard deviation values was determined. Table no. 3 mentions about the various hardness testers with its material/ mechanism.

**Table 3: Types of hardness tester.**

| Hardness tester | Material/ Mechanism |
|---|---|
| Monsanto | Plungers |
| Pfizer | Pliers |
| Strong-Cobb | Hydraulic pressure |
| Erweka | Operates in a vertical position |
| Schleuniger | Operates in a horizontal position |

4. **Uniformity of thickness-** Randomly selected 20 tablets from all batch was tested and measured its thickness independently. Thickness was measured using Sliding caliper scale i.e. Vernier calipers scale. Thickness of the tablet was tried to keep within limit.
5. **Friability-** Roche friabilator (Electrolab, Model: EF2) was used for the determination of friability and was expressed in percentage. The initial weight of 20 the tablets ($W_1$) measured and tablets was placed in a plastic chamber which revolves at 25 rpm and subjected to fall from a height of 6 inches in the friabilator for about 100 revolutions as mentioned in table no. 4. Acceptance criteria- Weight loss should be NLT 1%. Then the weight of the tablets ($W_2$) was measured and weight difference before tablet and after the test was observed. Percentage of friability was calculated using following formula-

$$F = \frac{(W1) - (W2)}{(W1)} \times 100$$

**Table 4: Parameters for friabilator apparatus.**

| Name of the apparatus | Roche friabilator |
|---|---|
| Revolutions | 25 rpm |
| Total revolutions | 100 |
| Time required | 4 minutes |
| Distance of dropping the tablets | 6 inches |

6. **Drug content uniformity-** Initial weight of the tablet was noted and then tablet were powdered. Then powdered tablet was transferred into a 100 ml volumetric flask, 0.1 N HCl was added and volume was made up to the mark. Then the solution was filtered. 10 ml of was pipetted out into a 50 ml volumetric flask and make up the volume using 0.1 N HCl then the resulted solution was analyzed spectrophotometrically at 273 nm. The concentration of the drug content (µg/ml) was calculated by using the standard calibration curve.
7. **Weight variation test** – Randomly 20 tablets were selected from each batch and weight of the each tablet was noted down and weight variation was observed. According to USP/ IP limit variation in the weight of tablets was observed. According to USP and IP Standard limits for weight variation mentioned in table no.-5.

**Table 5: Parameters for weight variation test.**

| Average weight of tablets (mg) USP | Average weight of tablets (mg) IP | Maximum percentage difference allowed (IP) |
|---|---|---|
| 130 or less | 80 or less | 10 |
| 130-324 | 80-250 | 7.5 |
| More than 324 | More than 250 | 5 |

8. **Wetting time-** The wetting time of a tablet was tested using a piece of tissue paper which was double folded and kept in a petridish containing 6 ml of water and place the tablet on the tissue paper. The time taken for complete wetting of the tablet was noted down. The procedure was repeated three times for each batch and standard deviation was also calculated from the obtained results.

9. **Swelling index-** The tablets were weighed individually ($W_0$) and placed separately in petri dish containing 5 mL of 0.1 N HCl solution and incubated at 37∘ C ± 1 ∘ C. At every second hour the tablets were removed from petri dish, and the excess surface liquid was removed carefully using the tissue paper until 12 h.[2] The swollen floating tablets were then reweighed ($W_t$) and % swelling index (SI) was calculated using the formula-

$$\text{Swelling index} = \frac{\text{Initial weight}(W_0) - \text{Final weight}(W_t)}{\text{Initial weight}\ (W_0)} \times 100$$

## RESULT AND DISCUSSION

All trials was performed by varying the concentration of the gas generating agents and polymers. The HPMC used as a matrix forming agent to retard and control over a drug release. Upon the gas generation the air entrapped in the gel layer formed by the Carbopol over a tablet that reduces the density of tablet and helps to buoyant the tablet over a simulated gastric fluid. Synergistic effect with low density Ethyl cellulose and Carbopol increased in floating time and reduction in floating lag time.

The in-vitro buoyancy study was studied, floating lag time and floating time was determined simply by placing the tablet in 500ml of 0.1 N HCl. Observed floating lag time for 6 formulation was found between 5 to 15 seconds and floating duration more than 16 hours.

The results for solubility parameters for the Caffeine in the different solvent were studied and their results mentioned in table no. 6.

The results for tablet characterization mentioned in table no. 7. Weight variation data of prepared tablet indicated no significant difference from average value in the weight of tablet from every batch. Hardness of prepared tablet was observed within range 5.5±0.32 kg/cm$^2$ to 5.5±0.93 kg/cm$^2$. Thickness of prepared tablet was observed within range 5.80±0.15 to 5.88±0.30mm. Friability of all tablets was found below 1%. The drug content in the all batch was found with in the range of 97.25% to 101.12%. Swelling Index of formulation F1, F3 and F4 more than F2, F5 and F6 due to presence of more amount of carbopol.

The calibration curve for the Caffeine was taken, its graph was plotted concentration vs absorbance (figure no.1). The linear graph was observed. The In-vitro dissolution study was carried out for the Caffeine loaded floating tablet for 16 hours with 2 hour interval, about 88.10 % of drug release observed during the dissolution study, its graph was plotted time in hours vs % cumulative drug release (Figure no. 2).

**Table 6: Solubility of Caffeine.**

| Sr. No. | Solvent | Solubility Parameter |
|---|---|---|
| 1 | Water | Soluble |
| 2 | Hot Water | Freely soluble |
| 3 | Methanol | Sparingly soluble |
| 4 | 0.1 N HCl | Soluble |

**Table 7: Evaluation parameters for formulation (FLT= Floating Lag Time; FT= Floating Time; DR= Drug Release).**

| Formulation code | Weight Variation (mg) | Hardness (kg/cm$^2$) | Thickness (mm) | Drug content (%) | FLT (S) | FT (H) | DR (%) |
|---|---|---|---|---|---|---|---|
| **F1** | 575±1.68 | 5.5±0.69 | 5.83±0.20 | 97.25 | 10 | 10 | 81.47 |
| **F2** | 575±1.698 | 5.5±0.93 | 5.86±0.15 | 98.20 | 5 | 5 | 82.30 |
| **F3** | 575±1.38 | 5.5±0.66 | 5.82±0.25 | 99.32 | 20 | 15 | 82.64 |
| **F4** | 575±1.69 | 5.5±0.52 | 5.81±0.10 | 101.12 | 10 | 8 | 81.36 |
| **F5** | 575±1.88 | 5.5±0.32 | 5.88±0.30 | 100.2 | 10 | 10 | 81.19 |
| **F6** | 575±1.35 | 5.5±0.48 | 5.80±0.15 | 99.86 | 15 | 16 | 88.10 |

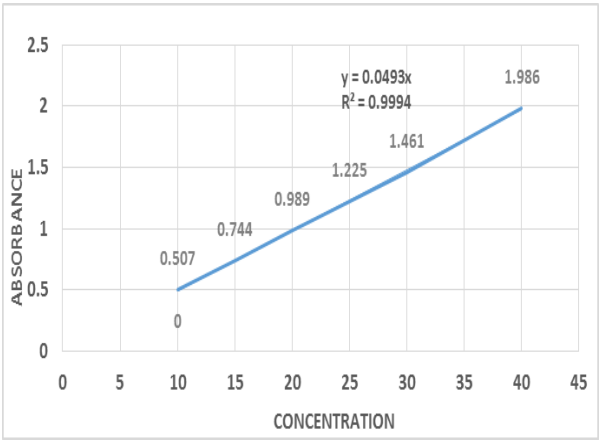


**Figure 1: Calibration curve of Caffeine**.

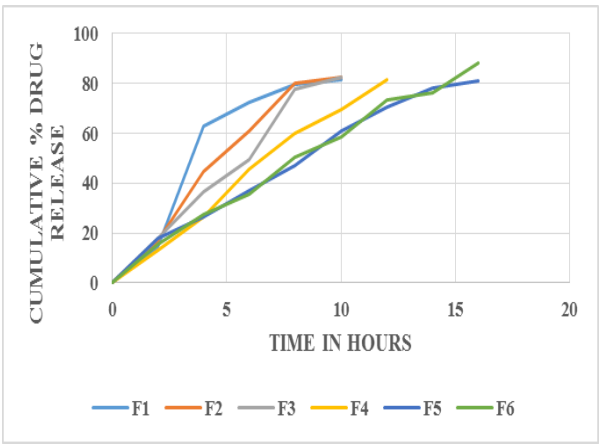


**Figure 2: In-vitro cumulative percent drug release of Caffeine loaded floating tablet.**

## CONCLUSION

Floating drug delivery system provides a potential approach for increasing gastric retention, so that the formulation float on the gastric media for more than 16 hours i.e. controlled release. The effervescent-based floating drug delivery was a promising approach to achieve in-vitro buoyancy. All batches of tablets were formulated using gas generating material i.e. sodium bicarbonate and citric acid, as decrease in the citric acid level increased the floating lag time and tablets were found to float for longer duration. Viscosity was a major factor that affected the release and floating properties. The floating lag time and floating time gets decreases at maximum thickness and increase at minimum thickness and from in-vitro dissolution data that increase in the concentration of citric acid and sodium bicarbonate there was increased in the % Cumulative drug release rate. Therefore the study concludes that the floating time and floating lag time affected by concentration of gas generating agent and polymers, resulting in efficacious formulation of SRDDS for Caffeine drug.

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