Available online at www.ijpsdr.com

**International Journal of Pharmaceutical Sciences and Drug Research 2016; 8(3): 174-181**

Research Article

**ISSN: 0975-248X**
**CODEN (USA): IJPSPP**

# Formulation, Optimization and *in vitro* Characterization of Stavudine Gastro Retentive Floating Matrix Tablets

**Mahendar Rupavath[1*], Kranthi Kumar G[2], Chinna R Palem[2], K. S. K Rao Patnaik[1]**

[1]*University college of Technology, Osmania University, Hyderabad-500007, Telangana, India*
[2]*Vijay College of Pharmacy, Manikbandar, Nizamabad-503003, Telangana, India*

**ABSTRACT**

The aim of the present investigation was to develop floating matrix tablets of stavudine to achieve prolong gastric residence time, leading to an increase in drug bioavailability and patient compliance. Floating tablets were prepared by wet granulation technique, using hydroxypropyl methylcellulose (HPMC K15M) as synthetic, pullulan gum as natural rate controlling polymers and optimum amounts of sodium-bicarbonate and citric acid as gas generating agents in suitable ratios to generate optimum buoyancy. Developed formulations were evaluated for weight variation, thickness, hardness, friability, drug content, *in vitro* drug release, floating lag time and floating buoyancy. All the formulations exhibited acceptable physical properties and the best formulation (F3) was selected based on *in vitro* characteristics. Further, the optimized formulation was evaluated for *in vivo* radiographic studies by incorporating $BaSO_4$ as radio opaque substance. All the formulations were studied for *in vitro* drug release characteristics for 16 h. Optimized formulation showed controlled and prolonged drug release profiles while floating over the dissolution medium. Diffusion followed by erosion drug release mechanism was observed for the formulation, indicating that water diffusion and polymer erosion played an essential role in drug release. *In vivo* radiographic studies revealed that the tablets remained in the stomach for 8 ± 0.5 h in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered and desirable for absorption window drugs.

**Keywords:** Floating matrix tablets, stavudine, gastric residence time, floating lag time, *In vivo* radiographic studies.

## INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Using current technology, oral delivery for 24 h or more is possible for many drugs; however, the substance must be well absorbed throughout the gastrointestinal tract (GIT). A significant obstacle may arise if there is a narrow therapeutic window for drug absorption in the GIT, if the drug is poorly soluble in the intestine or acts locally in the stomach or a stability problem exists in gastrointestinal fluids. Thus, the real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of the drugs for more than 12 h, but to prolong the presence of the dosage forms in the stomach or somewhere in the upper part of intestine until the entire drug is released over the desired period of time. [1] Gastro retentive drug delivery offers various potential advantages for

***Corresponding author: Mr. Mahendar Rupavath,**
Department of Pharmaceutics, University College of Technology, Osmania University, Hyderabad-500007, Telangana, India; **E-mail:** pcreddy147@yahoo.co.in & mahi1.rupavath@gmail.com
**Received:** 08 May, 2016; **Accepted:** 22 May, 2016

drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [2], low density (floating) systems that causes buoyancy in gastric fluid [3-5], mucoadhesive systems that causes bioadhesion to stomach mucosa [6], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [7-8], superporous hydrogel systems [9], magnetic systems. [10] Among these, the floating dosage form has been used most commonly. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach, and for drugs that are poorly soluble or unstable in the intestinal fluid. The floating systems include single, multiple, and raft forming systems. The principle of these systems offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

Acquired Immunodeficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation, was first identified in California in 1981. AIDS is a disease in which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). Stavudine is a dideoxynucleoside analog that inhibits reverse transcriptase and has *in vitro* activity against HIV. Stavudine is absorbed rapidly following oral administration producing peak plasma concentrations within 1h and with reported bioavailability of about 86%. Stavudine has a very short half-life of 1-1.5 h, thus necessitating frequent administration to maintain constant therapeutic drug levels. [11-12] Formulation of sustained release effervescent floating tablets of stavudine improves patient compliance and minimizes the dose-related side effects. Based on the above physicochemical and biopharmaceutical properties, Stavudine was selected as a drug candidate for developing floating drug delivery systems to reduce the severity of toxicity and also to improve patient compliance.

The aim of the present investigation was to develop floating matrix tablets of stavudine to achieve prolong gastric residence time, leading to an increase in drug bioavailability and patient compliance by utilizing hydroxypropyl methylcellulose (HPMC K15) as synthetic, pullulan gum as natural rate controlling polymers and optimum amounts of sodium-bicarbonate and citric acid as gas generating agents in suitable ratios to generate optimum buoyancy.

## MATERIALS AND METHODS

Stavudine and Pullulan gum were received as generous gift samples from Aurobindo Pharma Ltd, Hyderabad, India. Hydroxypropyl methylcellulose (HPMC K15) was gifted by Dr Reddys Laboratories Hyderabad, India. Microcrystalline cellulose, Lactose, Sodium bicarbonate, Citric acid, Magnesium stearate and talc were purchased from Qualigens fine chemicals, Mumbai, India. Phosphate buffer saline, Dulbecco's was purchased from Hi Media, Mumbai, India. All other chemicals used were of analytical grade.

**Drug-excipients compatibility study**

**Fourier transform infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) study**

Fourier transform infrared (FT-IR) Spectroscopy was used to study the physical and chemical interaction between the drug and excipients used. FT-IR spectra of pure drug and optimized effervescent floating matrix tablet were recorded using KBr mixing method on FT-IR Spectrophotometer (FT-IR-1700, Shimadzu, Tokyo, Japan). DSC was used to study physical and chemical interaction between the drug and excipients used. DSC spectra of pure drug and drug composite mixture were recorded on differential scanning calorimeter (DSC-60, Shimadzu, Tokyo, Japan).

**Pre-compression parameters of granules**

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, and Carr's index. Angle of repose (θ) was determined by using a funnel whose tip was fixed at a constant height (h) of 2.0 cm from the horizontal surface. The granules were passed separately through the funnel until the tip of the conical pile touches the tip of the funnel. The radius of the base of the conical pile is measured as r (cm). It was calculated with the formula:

$$\theta = \tan^{-1}(h/r)$$

The previously weighed granules were collected into a graduated measuring cylinder and the initial (or bulk) volume was noted. It was placed in the tapped density tester USP (Electrolab, Mumbai, India) and subjected to constant tapping at a rate of 100 drops/min. It was recorded as the final tapped volume. Carr's index and Hausner's ratio were calculated with the following formulae:

$$\% \text{ Carr's index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

**Development of Stavudine effervescent floating matrix tablets**

Accurately weighed quantities (as specified in Table I) of stavudine, Micro crystalline cellulose, anhydrous lactose, HPMC K15, pullulan gum, sodium bicarbonate and citric acid were passed through # 30 mesh to get uniform size particles, then they were transferred into

rapid mixer granulator (Freund-Vector, GMX LAB Micro, Japan) and mixed for 10 minutes at optimum rpm. Accurately weighed quantity of purified water was slowly added to the blend at slow kneading and chopper off. The resulting wet mass was passed through 4.0 mm screen attached to the rapid mixer granulator. Screened wet granular mass was allowed to dry in rapid dryer (Retsch GmbH Retsch-Allee, Germany) at 50°C, drying was continued till to the LOD below 2% w/w. The dried granules were shifted through # 20 mesh. Extra granular material talc was sifted through mesh # 40 and added as a glidant to the sifted dried granules. Resulting final granules were lubricated with magnesium stearate and compressed into tablets using a 16-station punching machine (Rimek, India).

**Characterization of floating tablets**

The prepared floating tablets were evaluated for mass uniformity was measured by sartorius balance, hardness was measured by a hardness tester (Erweka tester, Germany), thickness was measured using a vernier caliperse (Mitutoyo Corporation, Japan) and friability was determined using a Roche friabilator (Germany).

The drug content in each formulation was determined by triturating 20 tablets and a quantity of powder equivalent to the mass of one tablet was transferred into a 100 mL volumetric flask. To this, 50 mL of 0.1N HCl was added and then the solution was subjected to sonication for about 1 h. The solution was made up to the mark with 0.1N HCl, filtered and suitable dilutions were prepared with 0.1N HCl. The drug content was estimated by recording absorbance at 266 nm by using a UV-Visible spectrophotometer (ELICO, India).

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 250 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

***In vitro* drug release studies**

Dissolution studies on each formulation were performed in a calibrated eight station dissolution testing apparatus (TDT-08T, Electrolab, India) equipped with paddles (USP apparatus type II method) employing 900 mL of 0.1N HCl as dissolution medium. The paddles were operated at 75 rpm to simulate gastric peristaltic movement and the temperature was maintained at 37 ± 2°C throughout the experiment. Samples were withdrawn at regular time intervals for 16 h and replenished with equal volume of fresh dissolution medium to maintain the constant volume and sink conditions throughout the experiment. Samples withdrawn at pre-defined time intervals were diluted appropriately and the amount of drug released was estimated by UV-Visible double beam spectrophotometer (ELICO, India) at 266 nm. To analyse the mechanism of drug release studies from the obtained dissolution data, various kinetic model calculations based on the equations of Zero-order, First order, Higuchi and Koresmeyer Peppas were applied to analyze the drug release mechanism and pattern. [13-15]

**Table 1: Formulation unit composition of stavudine gastro retentive effervescent floating matrix tablets**

| Ingredients | Formulations (mg/unit) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Stavudine | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Microcrystalline cellulose | 71.5 | 51.5 | 31.5 | 71.5 | 51.5 | 31.5 | 71.5 | 51.5 | 31.5 |
| Anhydrous lactose | 71.5 | 51.5 | 31.5 | 71.5 | 51.5 | 31.5 | 71.5 | 51.5 | 31.5 |
| HPMC K15M | 40 | 80 | 120 | | | | 20 | 40 | 60 |
| Pullalum gum | | | | 40 | 80 | 120 | 20 | 40 | 60 |
| Sodium bicarbonate | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| Citric acid | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| Magnesium stearate | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| Total weight | **300** | **300** | **300** | **300** | **300** | **300** | **300** | **300** | **300** |

**Table 2: Flow characterization of stavudine gastro retentive effervescent floating matrix tablets**

| Formulation | Angle of repose (θ) | Compressibility Index (%) | Hausner ratio |
|---|---|---|---|
| F1 | 27.4 | 9.6 | 1.08 |
| F2 | 28.8 | 9.8 | 1.09 |
| F3 | 30.9 | 10.1 | 1.10 |
| F4 | 30.1 | 9.9 | 1.09 |
| F5 | 31.3 | 10.2 | 1.09 |
| F6 | 32.4 | 10.4 | 1.10 |
| F7 | 28.6 | 9.8 | 1.08 |
| F8 | 29.4 | 9.9 | 1.09 |
| F9 | 29.9 | 9.9 | 1.09 |

**Swelling index**

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1N HCl at 37 ± 0.5°C. After 1, 4, and 6 h, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. [16] The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula. The swelling indexes for various selected formulations of stavudine effervescent floating matrix tablets are shown in Table 4.

$$\text{Swelling index} = \frac{\text{(Wet weight of tablet - Dry weight of tablet)}}{\text{Dry weight of tablet}}$$

**Table 3: Physio-chemical characterization of stavudine gastro retentive effervescent floating matrix tablets**

| Formulation | Average Weight (mg) | Thickness(mm) | Hardness(kp) | Friability (%) | Drug content (mg/tablet) |
|---|---|---|---|---|---|
| F1 | 299.6 ± 0.97 | 3.8 ± 0.1 | 7.1 ± 0.4 | 0.2 | 39.6 ± 0.4 |
| F2 | 298.4 ± 1.12 | 3.9 ± 0.2 | 7.3 ± 0.6 | 0.2 | 40.4 ± 0.3 |
| F3 | 300.2 ± 1.24 | 3.8 ± 0.2 | 7.4 ± 0.6 | 0.1 | 40.2 ± 0.3 |
| F4 | 299.8 ± 1.08 | 3.7 ± 0.3 | 7.4 ± 0.6 | 0.2 | 38.8 ± 0.6 |
| F5 | 298.7 ± 2.08 | 3.8 ± 0.3 | 7.5 ± 0.6 | 0.2 | 41.7 ± 0.8 |
| F6 | 299.9 ± 1.04 | 3.8 ± 0.2 | 6.8 ± 0.5 | 0.1 | 40.5 ± 0.7 |
| F7 | 301.2 ± 1.26 | 3.9 ± 0.3 | 7.7 ± 0.7 | 0.2 | 39.2 ± 0.8 |
| F8 | 301.6 ± 1.20 | 3.8 ± 0.3 | 7.6 ± 0.4 | 0.2 | 40.3 ± 0.6 |
| F9 | 302.4 ± 2.04 | 3.7 ± 0.4 | 7.2 ± 0.5 | 0.1 | 41.1 ± 0.9 |

**Tablets for *in vivo* radiographic studies**

Tablets of 3.8 ± 0.2 mm thickness and of 300 ± 3% mass were prepared. To make the tablet X-ray opaque, incorporation of $BaSO_4$ was necessary. For this purpose, 40 mg of the drug was replaced with $BaSO_4$ (40 mg $BaSO_4$ + 40 mg stavudine) and all other ingredients were kept constant. The tablets were characterized for hardness, floating lag time and floating duration.

***In vivo* radiographic studies**

The study was conducted on four healthy male volunteers, weighing between 55–75 Kg and in the age group of 25 ± 2 years. The tablets prepared for radiography were administered orally with a glass of water. During the study, the subjects were not allowed to eat but water was available *ad libitum.* After ingestion of optimized placebo floating tablets containing barium sulphate, the volunteers were exposed to X-ray photography in the abdominal region. The X-ray photographs were taken at 1, 2, 4 and 8 h after administration of the tablets. The mean gastric residence time was calculated.

**Stability Study**

To determine the stability study floating matrix tablets of stavudine were packed in 40cc Heavy weight HDPE bottle and stored at 40 ± 2°C and 75% ± 5% RH for a period of six months as per the ICH guidelines. The tablets were withdrawn at a period of 1, 3 and 6 months and evaluated for content uniformity, *in vitro* floating behavior and dissolution study. [17] The differences in parameters from floating tablets were evaluated using unpaired *t*-test. In *t*-test, a probability value of $p < 0.05$ was considered to be statistically significant.

## RESULTS AND DISCUSSION

Gastro retentive matrix tablets of stavudine were developed to increase the gastric retention time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 16 h. The floating matrix tablets were prepared using gel-forming polymers, HPMC K15M as synthetic polymer and pullulan gum as natural polymer for rate controlling drug delivery. HPMC K15M and Pullulan gum is known to be beneficial in improving the buoyancy characteristics and drug release characteristics.

When in a combination of gas generating mixture improved (sodium bicarbonate and citric acid) *in vitro* and *in vivo* buoyancy characteristics were observed. The talc and magnesium stearate were employed for their glidant and lubricant property.

**Drug–excipients compatibility study**

The compatibility evaluations were performed by Fourier transform infrared spectroscopy, and Differential scanning calorimetry. IR spectroscopic studies indicated that there are no drug excipients interactions in the optimized formulation. By compared FT-IR spectra of stavudine with FT-IR of optimized formulation, it was observed that there was no physical and chemical interaction between stavudine and other excipients during the formulation process, because all the principle peaks of pure drug were still there in the FT-IR spectra of the optimized formulations (Fig. 1 a & b).

The DSC thermogram of Stavudine showed sharp endothermic peak at 173.5°C (Fig. 2 a & b), while that of HPMCK15M showed broad endothermic peak at 64.6°C. The DSC thermograms of admixture of Stavudine with HPMC K15M and pollulan gum in formulations showed sharp endothermic peaks for Stavudine at the temperatures similar to that of the peak of Stavudine alone. This indicated that there were no drug excipients interactions in the formulations. So we can conclude that there is no chemical interaction between drug & excipients. Studies implied that polymers and drug were compatible with each other.

**Flow Properties of stavudine final granules**

The final lubricated granules for the formulation of stavudine floating matrix tablets were evaluated for angle of repose, Carr's index and Hausner's ratio and results were represented in Table 2. Angle of repose was in the range of 27.4° to 30.9° with granules containing HPMC K15M, 30.1° to 32.4° with granules containing Pullulan gum and 28.6° to 29.9° with granules containing HPMC K15M & Pullulan gum, Hausner's ratio was found to be between 1.08 to 1.10 with granules of different formulations. Carr'sindex was in the range of 9.6 to 10.1 with granules containing HPMC K 15M, 9.9 to 10.4 with granules containing Pullulan gum and 9.8 to 9.9 with granules containing HPMC K15M & Pullulan gum. These values indicate that the prepared granules exhibited good to excellent flow properties.

**Physico-chemical Characterization of Stavudine Effervescent Floating matrix tablets**

The stavudine floating matrix tablets were white to off-white, smooth, and round shaped in appearance. The results of physico-chemical characterizations are

represented in Table 3. All the batches of tablets were compressed under identical conditions to minimize processing variables. The compressed matrix tablets were further evaluated for physico-chemical parameters such as weight uniformity, hardness, friability and drug content. [18] These studies revealed that all the tablet formulations were found to be stable and meeting Indian Pharmacopoeia specified limits for weight variation, friability and drug content. The hardness and thickness of all the stavudine effervescent matrix tablet formulations were in the range of 6.8 ± 0.5 to 7.6 ± 0.4 kp and the 3.7 ± 0.3 mm to 3.9 ± 0.3 mm respectively. Weight uniformity of all the tablet formulations were in the range of 298.4 ± 1.12 mg to 302.4 ± 2.04 mg. Friability of the tablet formulations were negligible and were in the range of 0.1 to 0.2%. Drug content estimated for all the tablet formulations were highly uniform with less than 3% variation.

**Floating behavior of Stavudine effervescent floating matrix tablets**

All the floating matrix tablet formulations were developed by effervescent technique, in which sodium bicarbonate induces carbon dioxide generation. The *in vitro* buoyancy of floating matrix tablets was induced by sodium bicarbonate and citric acid in the appropriate concentration in presence of dissolution medium in optimized ratio without compromising the matrix integrity with the possible shortest lag time and buoyancy duration of up to 16 h. It was observed that the gas generated was trapped in the tablet and was protected within the gel formed by hydration of polymers, thus decreasing the density of the matrix tablet below 1, and the tablet became buoyant. Higher viscosity grade of hydroxypropyl methyl cellulose (HPMC K15M) in the formulations was used to obtain viscous gel to prevent the air bubble from rupture. By using this type of HPMC, stable and persistent buoyancy was achieved. All the developed formulations swelling behavior was observed radially and axially during *in vitro* buoyancy studies. The effervescent floating matrix tablets containing HPMC K15 exhibited buoyancy lag time of 50 to 75 seconds and floated up to16h, while the floating effervescent matrix tablets containing Pullulan gum exhibited buoyancy lag time of 30 to 50 seconds and floated up to 8h and the floating effervescent matrix tablets containing HPMC K15M and Pullulan gum exhibited buoyancy lag time of 40 to 55 seconds and floated up to 14h and mean values of each formulations were represented in Table 4. These results shows that the formulation containing higher amount of HPMC K15M has moderate floating lag time and more total buoyancy in comparison to the formulations containing higher amount of Pullulan Gum. It is evident from the *in vitro* release data that increase in HPMC K15M concentration decrease in the drug release and also increased in the floating duration, probably due to viscous gel formation.

***In vitro* Dissolution Study**

*In vitro* dissolution studies of effervescent floating matrix tablets of stavudine were carried out in 0.1 N HCl. The study was performed for up to 16 h, and cumulative drug release was calculated.

Dissolution studies were performed on all the tablet formulations by using USP paddle method (apparatus II). The drug release from the matrix tablet formulations were extended up to 16h in the formulations F2, F3 containing HPMC K15M at 26.6% w/w and 40% w/w concentrations respectively as rate controlling polymer. The formulations F4 to F6 prepared by using Pullulan gum at 13.3% w/w to 40% w/w concentration in tablet formulations as rate controlling polymer have failed to extend drug release up to 12 h. The formulations F7–F9 containing combination of HPMC K15M with Pullulan gum, showed initial rapid drug release due to presence of natural gum, while extending the drug release up to 12 h due to presence of HPMC K15M. It was found that the drug release from the matrix tablet formulations were dependent upon the concentration of the matrix polymer. As the concentration of matrix polymer in the formulation increases the extended drug release from the matrix tablets over a prolonged period of time were observed.

**Drug release kinetics**

The tablet formulation containing a polymeric matrix builds, on contact with water, a gel layer around the tablet core, which governs the drug release. It is known that the drug release from polymeric matrices is controlled for water soluble drugs by diffusion through the gel layer or, for poorly soluble drugs, by erosion of the outer polymer chains. [19-20] Hence, the kinetics of swelling is important because the gel barrier is formed with water penetration. The drug release rate kinetics was calculated for zero order, first order, Higuchi and Korsemeyer Peppas models**.** Drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but in addition to diffusion, other processes are also important. There is also relaxation of the polymer chains that influences the drug release mechanisms. This process is described as non-Fickian or anomalous diffusion. Release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery, shows anomalous diffusion as a result of the arrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of diffusion. A third class of diffusion is case II diffusion, which is a special case of non-Fickian diffusion. [15] A simple semi empirical equation can be used to analyze data of controlled release of water-soluble drugs from polymer matrices. This equation predicts the mechanism of diffusional release. [14]

$$\frac{M_t}{M_\infty} = kt^n$$

Where *M*t is the amount of the drug released at time *t*,

$M_\infty$ is the overall amount of the drug (whole drug), 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. For tablets of a known geometry (in this case a slab) $n$ = 0.5 means Fickian diffusion, 0.5 <$n$ < 1.0 non-Fickian diffusion, and $n$ = 1.0 case II diffusion. [15]

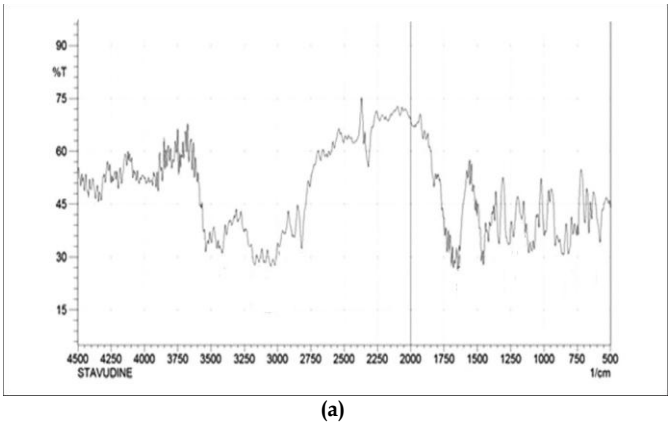
The dissolution profiles of prepared formulations are shown in Fig. 3a-c. The correlation coefficient values ($R^2$) are represented in Table 5. The drug release from the matrix tablet formulations were by diffusion process. The release exponent ($n$ values) for all the matrix tablet formulations were in the range of 0.54 to 0.72, indicated that the drug release was by non-fickian diffusion. Thus the drug release from the matrix tablet formulations was by diffusion of the drug from the polymeric matrix followed by erosion of the polymer. The mechanism of drug release from all the matrix tablet formulations was by both polymer erosion and diffusion of the drug from the matrix systems.

**Table 4: Swelling index, floating lag time and total floating time of stavudine gastro retentive effervescent floating matrix tablets**

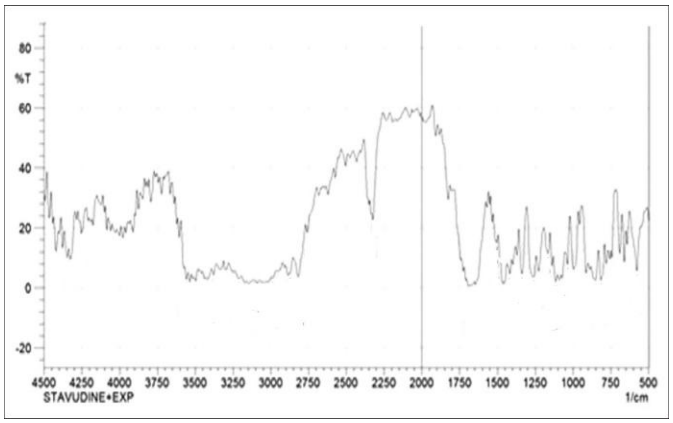
| Formulation | Swelling index (%) at 6 h | Floating lag time (sec) | Total floating time (h) |
|---|---|---|---|
| F1 | 78.6 ± 3.8 | 50 ± 5 | >14 |
| F2 | 87.4 ± 4.7 | 60 ± 4 | >15 |
| F3 | 98.2 ± 4.6 | 65 ± 7 | >16 |
| F4 | 38.9 ± 5.8 | 35 ± 5 | >04 |
| F5 | 44.6 ± 4.3 | 45 ± 4 | >06 |
| F6 | 52.3 ± 5.8 | 50 ± 5 | >07 |
| F7 | 61.8 ± 3.9 | 45 ± 5 | >11 |
| F8 | 64.2 ± 4.5 | 50 ± 3 | >12 |
| F9 | 69.8 ± 3.1 | 50 ± 5 | >12 |

**Table 5: Fit of various kinetics models for floating matrix tablets of stavudine, correlation coefficient ($R^2$) and release exponent (N) values for different kinetic models**

| Formulation | Zero-order | First-order | Higuchi | Korsemeyer Peppas | n value |
|---|---|---|---|---|---|
| F1 | 0.9865 | 0.9245 | 0.9562 | 0.8031 | 0.684 |
| F2 | 0.9834 | 0.9783 | 0.9512 | 0.7978 | 0.712 |
| F3 | 0.9486 | 0.9513 | 0.9611 | 0.7434 | 0.608 |
| F4 | 0.9751 | 0.9811 | 0.9613 | 0.7845 | 0.619 |
| F5 | 0.9837 | 0.9910 | 0.9725 | 0.6958 | 0.597 |
| F6 | 0.9769 | 0.9832 | 0.9813 | 0.6487 | 0.578 |
| F7 | 0.9766 | 0.9048 | 0.9714 | 0.5456 | 0.541 |
| F8 | 0.9568 | 0.9438 | 0.9912 | 0.5794 | 0.598 |
| F9 | 0.9811 | 0.9676 | 0.9813 | 0.6348 | 0.567 |

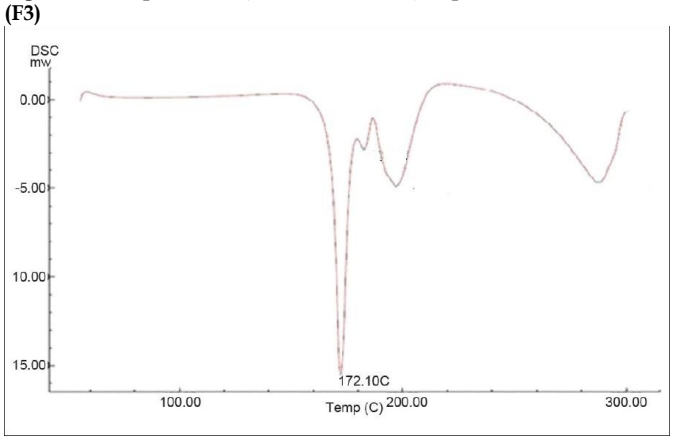



(a)

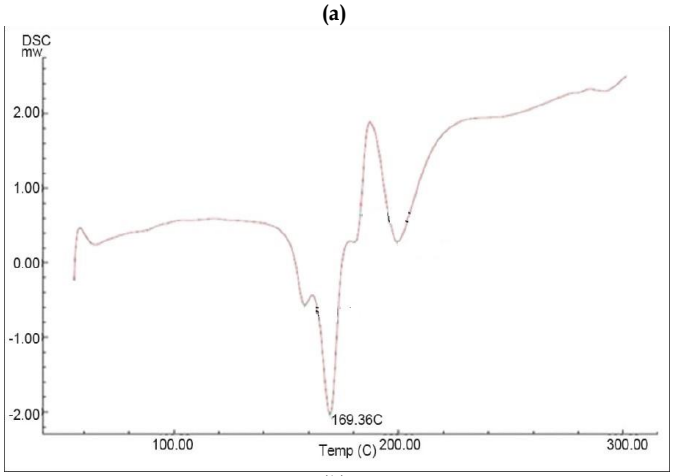



(b)

**Fig. 1: FTIR Spectra of a). Stavudine & b). Optimized formulation (F3)**

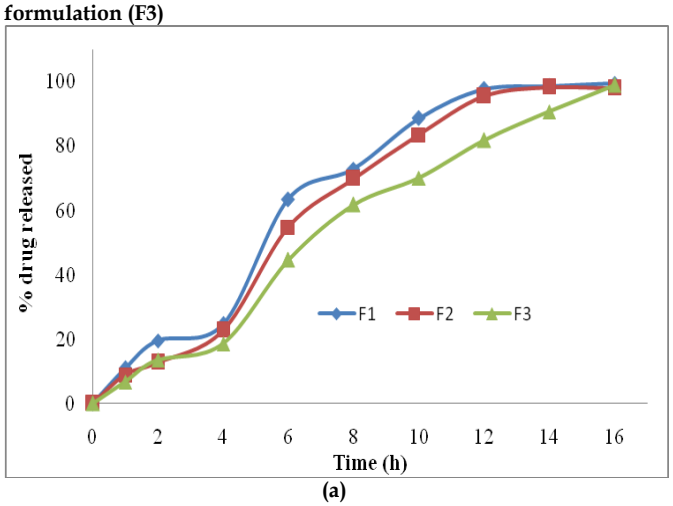



(a)

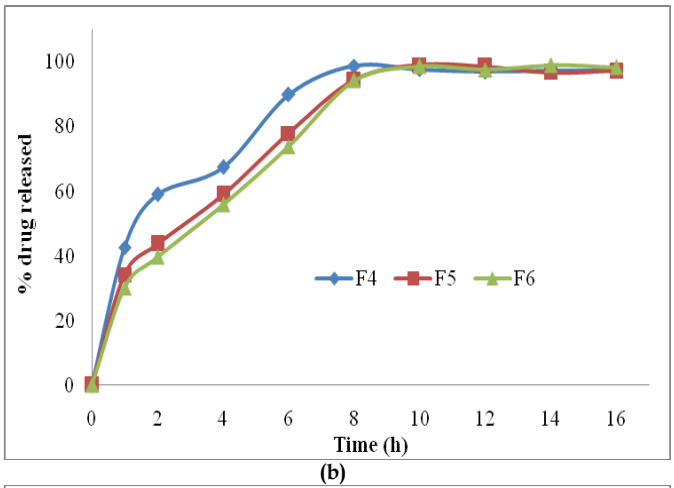



(b)

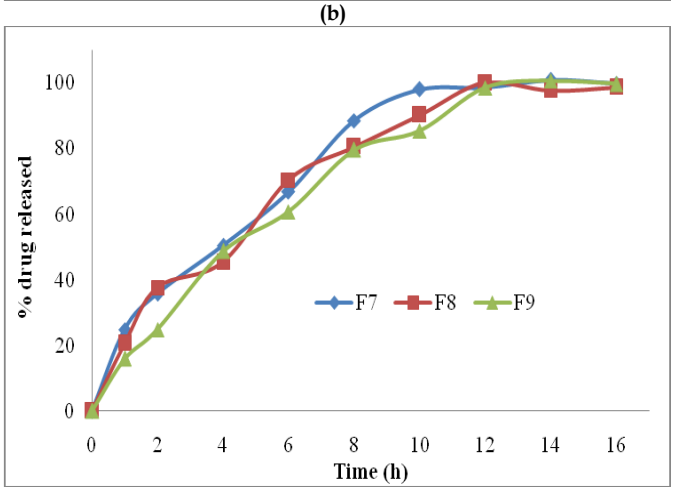
**Fig. 2: DSC Thermograms of a). Stavudine & optimized formulation (F3)**




(a)




(b)




(c)

**Fig. 3: *In vitro* dissolution profiles of stavudine effervescent floating matrix tablets a). HPMC K15M b). Pullulam gum c) Both HPMC K15M & Pullulam gum based formulations**

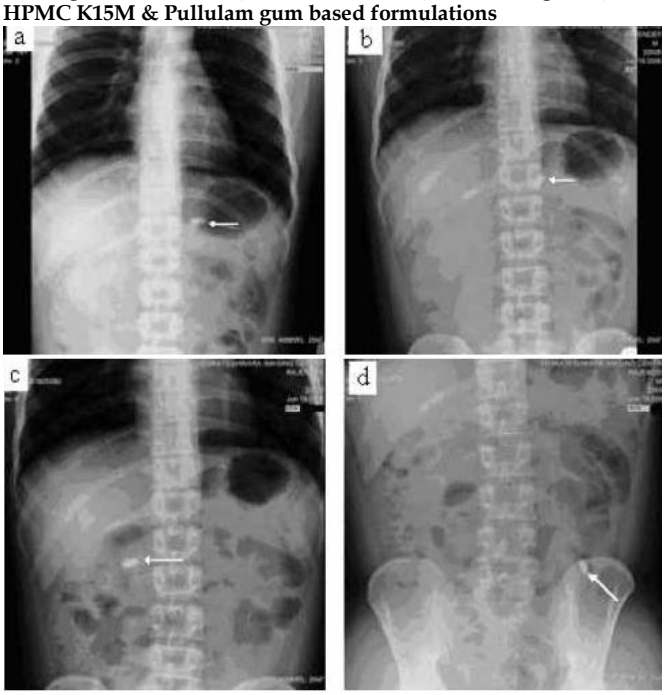



**Fig. 4: Radiographic images of $BaSO_4$-loaded effervescent floating matrix tablet in the stomach at different time periods. a) 1 h, b) 2 h, c) 4 h, and d) 8 h, after administration of tablets.**

**Swelling index**

Swelling index characteristics were performed on selected floating matrix tablet formulations. The floating matrix tablet formulation F1 to F3 containing HPMC K15M as polymer tends to swell at a rapid rate and gel surrounded by the matrix formulation, resulting slow erosion pattern observed. Formulations F4 to F6 containing Pullulan gum at 13.3%w/w to 40%w/w concentration in tablet formulations as rate controlling polymer have shown slow swelling and fast erosion, failed to extend drug release, so further trials initiated combination of Pullulan gum and HPMC K15M as rate controlling polymers. The formulations F7–F9 containing combination of HPMC K15M with Pullulan gum, showed similar swelling and erosion pattern. Formulation containing HPMC K15M showed swelling behavior predominates erosion in comparison to formulation containing Pullulan gum and combination of HPMC K15M with Pullulan gum. The swelling indexes at 6h for various selected formulations of matrix tablets are shown in Table 4.

**Intra-gastric behavior of floating matrix tablets**

The $BaSO_4$ containing floating tablets showed a floating lag time of 125 ± 5 seconds, hardness of 7.16 ± 0.02 kp and thickness of 3.8 ± 0.2 mm. The prepared tablets were clearly seen in the GIT at different positions during the study and X-ray photographs were represented in Fig. 4. The average residence time was found to be 8 ± 0.5 h. Results of intra gastric behavior of the developed optimized effervescent floating matrix tablets revealed that the formulations float more than 8 h.

**Stability Study**

The prepared floating tablets were subjected to stability study. The tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for a period of 6 months. The results do not show any significant change ($p$ > 0.05) in physical appearance, hardness, friability, content uniformity, buoyancy and dissolution behaviour of floating tablets in comparison with initial values. Thus, it was found that the floating tablets of stavudine tablets were stable under these storage conditions.

Systematic studies were conducted using natural and synthetic polymers either alone or in combination in different concentrations to prepare stavudine effervescent floating matrix tablets. Optimized formulation with HPMC floated with a lag time of less than 2 minute and continued to float for 16 h and also showed extended in vitro drug release for a prolonged period of time with zero order release profile. The drug release from the tablets depends upon the nature of gel matrix. It was observed that polymer swelling play an important role in drug release from the floating tablets. Hence it can be concluded that the effervescent based floating drug delivery is a promising approach to achieve buoyancy. *In vivo* radiographic studies revealed that the placebo tablets remained in the stomach for 8 ± 0.5 h, which indicated that gastric residence time was increased by the floating principle and was considered desirable for improving bioavailability of the absorption window drugs.

**ACKNOWLEDGMENTS**

The author acknowledges Aurobindo Pharma Ltd, and Dr Reddys Laboratories Ltd., Hyderabad, India for providing generous gift samples for this project.

**REFERENCES**

1. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm. 2000; 195:125-135.
2. Rouge N, Allemann E, Gex-Fabry M, Balant L, Cole ET, Buri P, Doelker E. Comparative pharmacokinetic studies of a floating multiple-unit capsule, a high density multiple unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm ActaHelbetiae. 1998; 73:81-87.
3. Streubel A, Siepmann J, Bodmeier R. Multiple unit Gastroretentive drug delivery: a new preparation method for low density microparticles. J Microencapsul. 2003; 20:329-347.
4. Goole J, Vanderbist F, Aruighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm. 2007; 334:35-41.
5. Sharma S, Pawar A. Low density multiparticulate systemfor pulsatile release of meloxicam. Int J Pharm. 2006; 313:150-158.
6. Santus G, Lazzarini G, Bottoni G, Sandefer EP, Page RC, Doll WJ, Ryo UY, Digenis GA. An *in vitro- in vivo* investigation of oral bioadhesive controlled release furosemide formulations. Eur J Pharm Biopharm. 1997; 44:39-52.
7. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Rel. 2003; 90:143-162.
8. Deshpande AA, Shah N, Rhodes CT, Malik W. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997; 14:815-819.
9. Park K. Enzyme-digestible swelling as platforms for long term oral drug delivery: synthesis and characterization. Biomaterials. 1988; 9:435-439.
10. Fujimori J, Machida Y, Nagai T. Preparation of amagnetically-responsive tablet and configuration of its gastric residence in beagle dogs. STP Pharma Sci. 1994; 4:425-430.
11. Davis SS, Stockwell AF, Taylor MJ, John GH, David RW, Wilson CG. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm Res. 1986; 3:208-213.
12. Arrora S, Ali J, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS Pharm Sci Tech. 2005; 6:372-390.
13. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspensions. J. Pharm. Sci. 1961; 50:874–875.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15:25–35.
15. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. ActaHelv. 1985; 60:110–111.
16. Chavanpatil DM, Jain P, Choudhari S, Shear R, Vavia RP. Novel sustained release, swellable and bioadhesive gastro retentive drug delivery system for Ofloxacin. Int J Pharm. 2006; 316:86-92.
17. Patel MP, Patel MM, Patel DH, Patel KN. Formulation Development, Optimization and Evaluation of Famotidine Floating Matrix Tablets. Int. J. Pharm. Sci. Drug Res. 2009; 1(2): 85-90.
18. The Indian Pharmacopoeia. Indian Pharmacopoeia Commission, Govt. of India, Vol III. 2010.
19. Mitchell K, Ford JL, Armstrong DJ. The influence of concentration on the release of drugs from gels and matrices containing Methocel. Int. J. Pharm. 1993; 100:155–163.
20. Kamanashis D, Md. Yasin, Ishrak J, Tahira A, Saiful I, Md. Sagir Mia. Gastroretentive Drug Delivery System of Levo-Salbutamol Sulphate: Formulation and *in vitro* Evaluation. Int. J. Pharm. Sci. Drug Res. 2016; 8(2):87-90.

**Source of Support: Nil, Conflict of Interest: None declared.**