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Development and *in vitro* Characterization of Gastro Retentive Raft Forming Stavudine Tablets

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ABSTRACT

The objective of the present investigation was to identify a suitable raft forming agent and to develop raft forming stavudine matrix tablets using different rate controlling natural, semi-synthetic and synthetic polymers to achieve prolonged gastric residence time, leading to an increase in drug bioavailability and patient compliance. Various raft forming agents were used in preliminary screening. Raft forming floating tablets were developed using pullulan gum as natural rate controlling polymer, and directly compressible grades of hydroxypropyl methylcellulose (Benecel K4M DC) as semi synthetic, and Carbopol 71G as synthetic rate controlling polymers respectively and optimum concentrations of sodium-bicarbonate as gas generating agent to generate optimum buoyancy by direct compression method. Raft forming tablets were evaluated for weight variation, thickness, hardness, friability, drug content, in vitro drug release, floating buoyancy and raft strength. Drug-excipients compatibility study showed no interaction between drug and excipients. Raft forming tablets showed satisfactory results when evaluated for weight variation, thickness, hardness, friability, drug content, and raft strength. The optimized formulation was selected based on physicochemical characteristics and *in vitro* drug dissolution characteristics. Further, the optimized formulation was evaluated for *in vivo* radiographic studies by incorporating $BaSO_4$ as radio opaque substance. Optimized formulation showed controlled and prolonged drug release profiles while floating and raft formation over the dissolution medium. Diffusion followed by erosion with raft forming drug release mechanism was observed for the formulation, indicating that dissolution media diffusion and polymer erosion played an essential role in drug release. *In vivo* radiographic studies revealed that the raft forming formulations remained in the stomach for 240 ± 30 min in rabbits and indicated that gastric retention time was increased by the floating and raft forming principle, which was considered and desirable for absorption window drugs.

Keywords: Raft forming floating tablets, Stavudine, Benecel K4M DC, Carbopol 71G, Floating lag time, i*n vivo* radiographic studies.

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INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received more attention and success because gastro intestinal

physiology offers more flexibility in dosage form design than other routes. [1] Oral controlled release dosage forms have been developed for the past three to four decades due to their considerable therapeutic advantages and applications. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. 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 all of the drug is released over the desired period of time. [2] Gastro retentive drug delivery offers various potential advantages for 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, low density (floating) systems, mucoadhesive systems, unfoldable, extendible, or swellable systems, superporous hydrogel systems [3], magnetic systems. [4] 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.

A raft-forming formulation requires sodium or potassium bicarbonate; in the presence of gastric acid, the bicarbonate is converted to carbon dioxide, which becomes entrapped within the gel precipitate, converting it into foam, which floats on the surface of the gastric contents. The formulation components provide a relatively pH-neutral barrier. [5-6] Calcium carbonate can be used as a raft-strengthening agent. It releases calcium ions, which react with alginate and form an insoluble gel. [7-8] Different polymers, especially various polysaccharides, have been used in different research works in the pharmaceutical research fraternity. Sodium alginates, alginic acid, and pectin are the most commonly used raft-forming agents. [9] Other polysaccharides are also being used, which include guar gum, locust bean gum, carrageenan, pectin and isapgol. [5-6, 9] Alginate rafts may be formed in liquid products by the action of gastric fluid on a soluble alginate to form an insoluble gel of alginic acid. They may also be formed by the interaction of soluble alginate with metal ions released by acid from an insoluble antacid such as calcium carbonate. The simultaneous action of gastric acid on a bicarbonate salt produces carbon dioxide, which should ideally be trapped inside the alginate gel to aid buoyancy of the raft. [10]

Acquired Immuno deficiency 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 immuno deficiency virus (HIV). Stavudine is a dideoxy nucleoside analog that inhibits reverse transcriptase and has *in vitro* activity against HIV. Stavudine is absorbed rapidly following oral administration producing peak plasma concentrations within 1hr and with a reported bioavailability of about 86%. Stavudine has a very short half-life of 1-1.5 hours, 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 raft forming tablets of stavudine to achieve prolong gastric residence time, leading to an increase in drug bioavailability and patient compliance by utilizing hydroxypropyl methylcellulose (Benecel K4M) and Carbopol 71G as directly compressible grades of synthetic polymers, pullulan gum as natural rate controlling polymers and optimum amounts of sodium-bicarbonate and calcium carbonate as gas generating and raft gel strengthening agents respectively in suitable ratios to generate optimum buoyancy.

MATERIALS AND METHODS

Materials

Stavudine and Pullulan gum were received as generous gift samples from Aurobindo Pharma Ltd, Hyderabad, India. Hydroxypropylmethylcellulose (Benecel K4M) received as generous gift sample from Ashland Inc., Carbopol 71G received as generous gift sample from Lubrizol and all other excipients were purchased from Kanwarlal Industries, India. All other chemicals used were of analytical grade.

Methods

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 raft forming 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 bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose.

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 gastro retentive floating raft forming tablets

Stavudine gastro retentive floating raft forming matrix tablets were developed by direct compression method. Accurately weighed quantities (Table 1) of stavudine, anhydrous lactose, HPMC K4M (Benecel K4M PH DC), carbopol 71G, pullulan gum, sodium bicarbonate and calcium carbonate were sifted through # 30 mesh to get uniform size particles, then they were transferred into a suitable blender (Erwika) and blended for 10 minutes at 230 rpm. Extra granular material talc was sifted through mesh # 40 and added as a glidant to the blend and blended for 5 minutes. Resulting extra-granular added blend was lubricated with magnesium stearate and compressed into tablets using a 16-station punching machine (Rimek, India).

Characterization of gastro retentive floating raft forming tablets

The prepared gastro retentive floating raft forming matrix tablets were evaluated for weight variation by sartorious balance, hardness was measured by a hardness tester (Erweka tester, Germany), thickness was measured using a verniercaliperse (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 1h. 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.

Measurement of raft thickness

The raft-forming mixture used in the formulation (1g) was added to 10 mL HCl at 37°C in a 25 mL pyrex cylinder. The raft was allowed to form for 10 min without agitation. The thickness of the raft was measured at three places around the cylinder. Three measurements were made for each raft and three rafts were studied from each formulation. Multiple repeats showed that the reproducibility was within a coefficient of variation of approximately 5%, although the uneven physical characteristics of the rafts rendered specific quantitative assessment extremely difficult.

Raft strength

Rafts were formed by dropping a gastro retentive raft forming tablet to 100 mL of 0.1M HCl, maintained at 37°C in a 250 mL glass beaker with inclusion of a wire probe. Each raft was formed around an L-shaped stainless steel wire probe held upright in the beaker throughout the whole period (around 30 min) of raft development. After 30 min of raft development, the beaker was placed on the table of a TAXT Plus Texture Analyzer (Stable Micro Systems, UK), the wire probe was hooked onto the Texture Analyzer arm and pulled vertically up through the raft at a rate of 5 mm/s. The force (g) required to pull the wire probe up through the raft, was recorded by the Texture Analyzer. [12]

Raft volume and raft weight

Rafts were formed and developed for 30 min in glass beakers, but without the inclusion of a wire probe. Each beaker used for raft formation was pre-weighed (*W*1). The position to which the top of each raft reached was marked on the outside of the beaker. The total weight of the beaker and contents was obtained after raft development (*W*2). The raft was then removed from the beaker by carefully decanting off the sub-natant liquid and tipping the raft into a pre-tared plastic weighing boat. This was left to stand for 30s, excess sub-natant liquid was drained off and the raft was weighed (*W*3).

Table 1: Stavudine unit composition of raft forming gastro retentive dosage forms

Ingredients	Formulations (mg/unit)													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Stavudine	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Anhydrous lactose	102	82	62	102	82	62	102	82	62	102	82	62	62	62
Sodium alginate	100	100	100				100	100	100				100	
Calcium carbonate	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Pectin				100	100	100				100	100	100		100
Carbopol 71G	40	60	80	40	60	80								
Benecel K4M DC							40	60	80	40	60	80		
Pullalum gum													80	80
Sodium bicarbonate	90	90	90	90	90	90	90	90	90	90	90	90	90	90
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	400	400	400	400	400	400	400	400	400	400	400	400	400	400

Table 2: Flow characterization of stavudine raft forming gastro retentive dosage forms

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.54	0.62	12.9	1.15	29.4
F2	0.57	0.63	9.5	1.10	30.8
F3	0.48	0.55	12.7	1.14	31.9
F4	0.46	0.53	13.2	1.15	30.1
F5	0.49	0.56	12.5	1.14	30.2
F6	0.39	0.45	13.3	1.15	30.7
F7	0.50	0.59	15.2	1.18	31.6
F8	0.46	0.54	14.8	1.17	29.9
F9	0.41	0.50	18.0	1.22	30.3
F10	0.52	0.61	14.7	1.17	30.5
F11	0.48	0.56	14.2	1.17	31.5
F12	0.42	0.51	17.6	1.21	31.8
F13	0.39	0.49	20.4	1.26	32.6
F14	0.36	0.45	20.0	1.25	31.7

Table 3: Physio-chemical characterization of stavudine raft forming gastro retentive dosage forms

Formulation	Average Weight (mg)	Thickness(mm)	Hardness(kp)	Friability (%)	Drug content (%)
F1	399.6 ± 1.07	4.32 ± 0.14	9.1 ± 0.5	0.2	99.4 ± 0.8
F2	398.4 ± 1.21	4.29 ± 0.23	9.3 ± 0.6	0.2	100.4 ± 1.3
F3	400.5 ± 1.32	4.38 ± 0.21	9.4 ± 0.6	0.1	100.2 ±1.5
F4	399.4 ± 1.28	4.37 ± 0.23	9.4 ± 0.6	0.2	98.9 ±1.6
F5	398.6 ± 2.14	4.36 ± 0.28	9.5 ± 0.6	0.2	101.7 ±1.8
F6	399.6 ± 1.47	4.33 ± 0.20	9.8 ± 0.5	0.1	100.5 ± 1.7
F7	401.2 ± 1.25	4.39 ± 0.13	9.7 ± 0.7	0.2	99.5 ± 0.8
F8	401.6 ± 2.08	4.28 ± 0.18	9.6 ± 0.4	0.2	100.3 ± 0.6
F9	402.4 ± 2.48	4.27 ± 0.24	9.2 ± 0.5	0.1	101.1 ± 1.9
F10	399.6 ± 2.41	4.32 ± 0.25	9.5 ± 0.4	0.1	100.3 ± 1.2
F11	400.6 ± 1.35	4.31 ± 0.19	9.8 ± 0.3	0.2	100.1 ± 0.7
F12	400.7 ± 1.53	4.30 ± 0.14	9.9 ± 0.6	0.1	99.8 ± 0.6
F13	402.4 ± 2.82	4.35 ± 0.19	9.6 ± 0.7	0.3	99.3 ± 2.6
F14	402.9 ± 2.75	4.37 ± 0.23	9.2 ± 0.8	0.4	102.1 ± 2.9

Remaining liquid was removed from the inside of the beaker with a paper towel and it was then refilled with water to the marked position and weighed (*W*4).

The volume of each raft was then calculated from the following formula:

$$\text{Raft volume} = (W4 - W1) - (W2 - W1 - W3)$$

Where raft volume is measured in mL and all weights are measured in g. The formula assumes that the density of the sub-natant liquid is the same as that of water. [13]

***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 hours 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 Korsmeyer Peppas were applied to analyze the drug release mechanism and pattern. [14-16]

Tablets for *in vivo* radiographic studies

Tablets of 4.3 ± 0.2 mm thickness and of 400 ± 3% weight were prepared. To make the tablet X-ray opaque, incorporation of $BaSO_4$ was necessary. [17] For

this purpose, 40 mg of the drug was replaced with $BaSO_4$ and all other ingredients were kept constant. The tablets were characterized for hardness, floating lag time and floating duration.

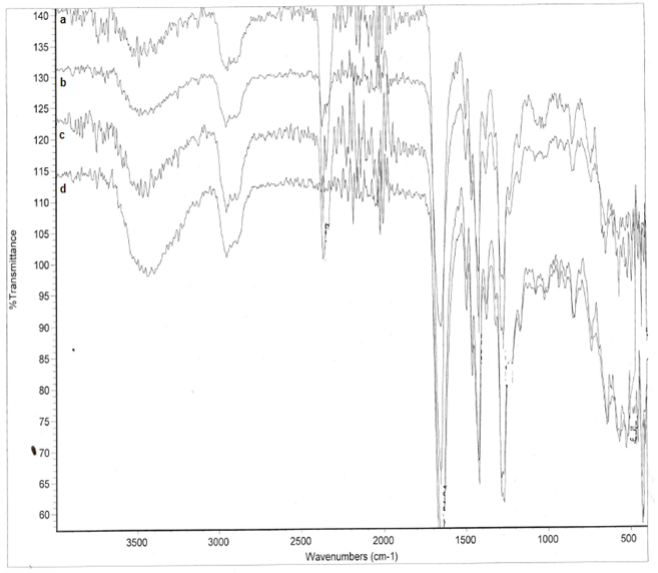

Fig. 1: a). FTIR Spectra of Stavudine, b-d). FTIR Spectra of Optimized formulations of b). F3, c). F6 and d). F12

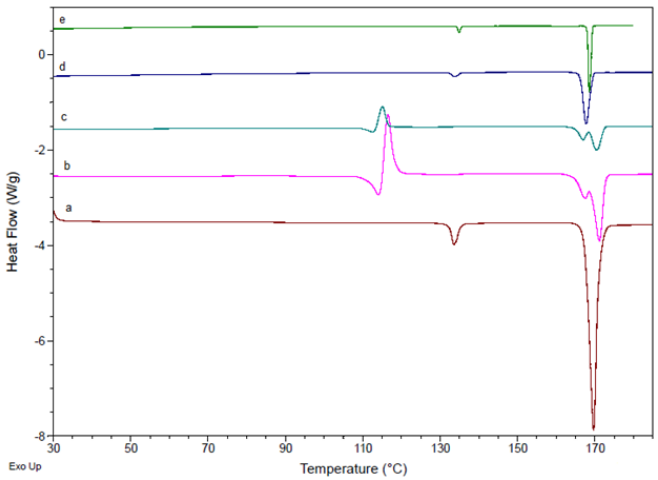

Fig. 2: a). DSC Thermograms of Stavudine, b-e). DSC Thermograms of Optimized formulations of b). F3, c). F6, d). F12 and e). F14

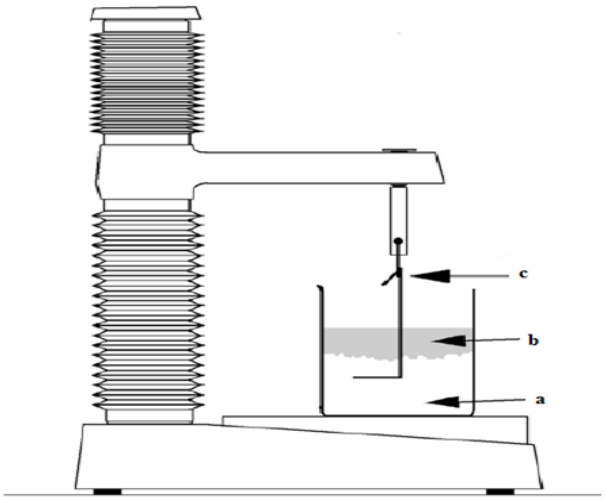

Fig. 3: Pictorial representation of Texture Analyzer for Raft strength measurement a). Media 0.1N HCl, b). Raft formation of the product c). L-shaped wire test probe

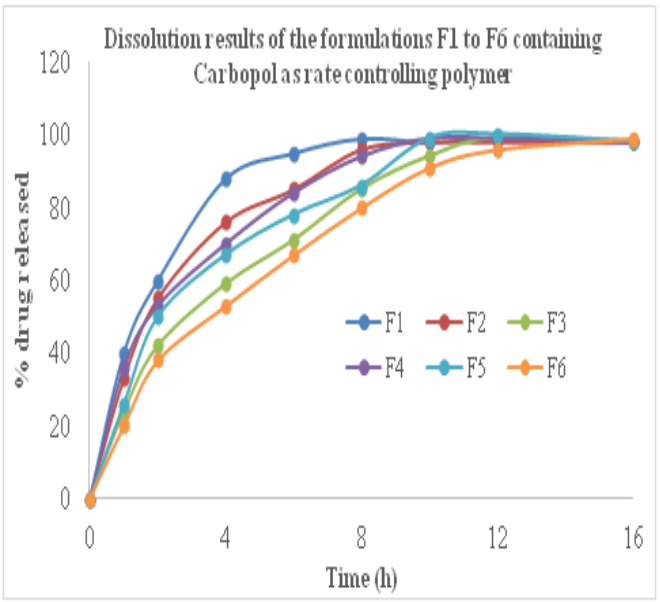

Fig. 4a: Dissolution results of the Formulations containing carbopol as a rate controlling polymer

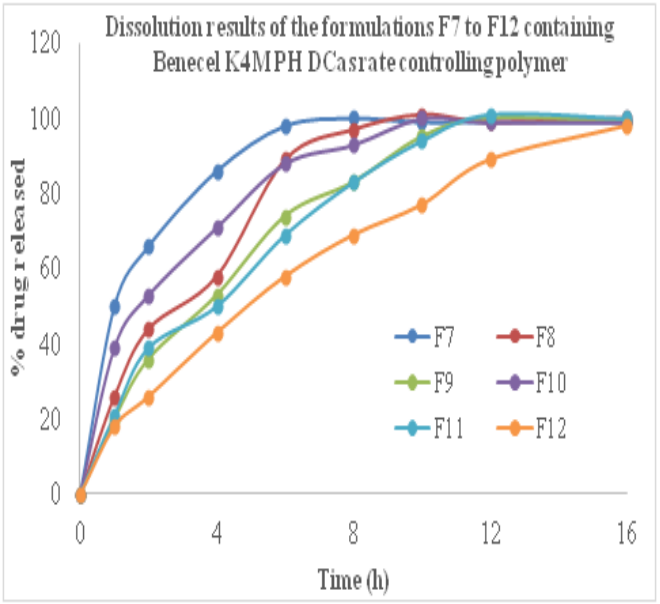

Fig. 4b: Dissolution results of the Formulations containing Benecel HPMC K4M PH DC as a rate controlling polymer

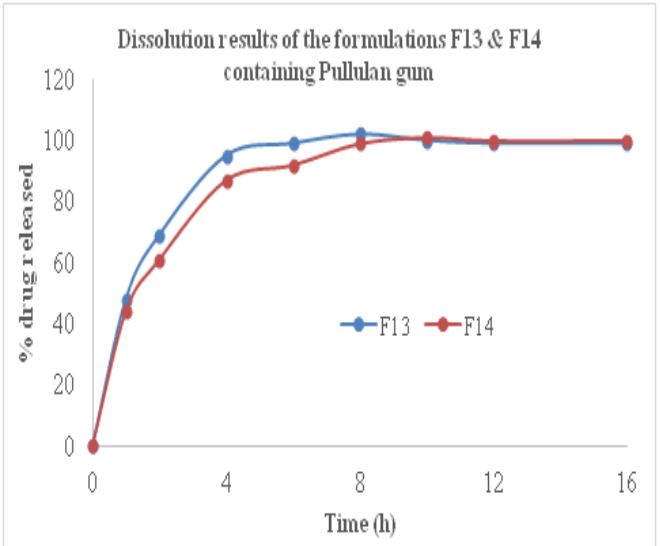

Fig. 4c: Dissolution results of the Formulations containing Pullulan gum as a rate controlling polymer

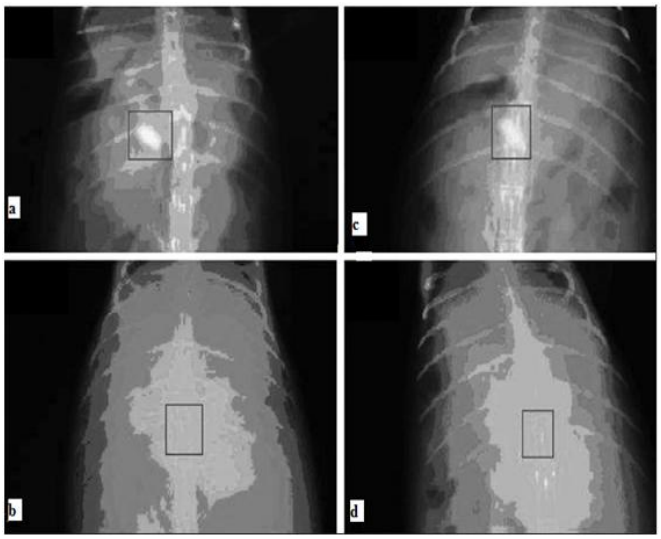

Fig. 5: X- Ray Photographs of rabbits after administration of optimized formulation without drug after (a) 1 h, (b) 2h, (c) 4h, (d) 8h

***In vivo* radiographic studies**

The study was conducted on rabbits, weighing between 2.5–3.5 kg. The tablets prepared for radiography were administered orally. During the study, rabbits were not allowed to eat but water was available *ad libitum.* After ingestion of optimized placebo floating tablets containing barium sulphate, the rabbits were exposed to X-ray photography in the abdominal region. The X-ray photographs were taken at 1.0, 2.0, 4.0, and 8.0 h after administration of the tablets. The mean gastric residence time was calculated.

Stability Study

To determine the stability study of the gastro retentive raft forming floating matrix tablets of stavudine were packed in 40 cc 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 and dissolution study. [18] 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 raft forming floating 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 20 h. The raft forming floating matrix tablets were prepared using directly compressible cellulose derivative HPMC K4M (Benecel K4M PH DC), and polycarbophil derivative Carbopol 71G and Pullulan gum as natural polymer for rate controlling drug delivery. Benecel K4M PH DC, Carbopol 71G and Pullulan gum is known to be beneficial in improving the buoyancy characteristics and drug release characteristics. When in a combination of gas generating agent (sodium bicarbonate) and raft gel strengthening agent (calcium carbonate) improved *in vitro* and *in vivo* buoyancy characteristics were observed. The talc and magnesium stearate were employed for their glidant and lubricant property. Raft forming preparation includes raft forming agent which forms floating raft on contact with gastric fluid, and gas generating agent like sodium bicarbonate. Here calcium carbonate also used for raft strengthening agent.

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 (Figure 1a-d).

The DSC thermogram of Stavudine showed sharp endothermic peak at 170.1°C (Figure 2a). The DSC thermograms of optimized formulations of Stavudine with Benecel K4M PH DC, Carbopol 71G and Pollulan gum in formulations showed sharp endothermic peaks for Stavudine at the temperatures similar to that of the peak of Stavudine alone (Figure 2b-e). This indicated that there were no drug excipient interactions in the formulations. So we can conclude that there is no chemical interaction between drug & excipients. Studies implied that the selected polymers and drug were compatible with each other.

Flow Properties of stavudine gastro retentive raft forming final granules

The lubricated granules for the formulation of stavudine gastro retentive raft forming 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 29.9^{o} to 31.8^{o} with granules containing Benecel K4M PH DC, 29.4^{o} to 31.9^{o} with granules containing Carbopol 71G and 31.7^{o} to 32.6^{o} with granules containing Pullulan gum, Hausner's ratio was found to be between 1.10 to 1.26 with granules of entire formulations. Carr's index was in the range of 14.2 to 18.0 with granules containing Benecel K4M PH DC, 9.5 to 13.3 with granules containing Carbopol 71G and 20.0 to 20.4 with granules containing Pullulan gum. These values indicate that the prepared granules exhibited good flow properties; this may be due to directly compressible grades of the rate controlling polymers and excipients.

Physico-chemical Characterization of stavudine gastro retentive raft forming floating matrix tablets

The stavudine gastro retentive raft forming 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 variation, thickness, hardness, friability and drug content. [19] 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 the entire stavudine gastro retentive raft forming floating matrix tablet formulations were in the range of 9.1 ± 0.5 to 9.9 ± 0.6 kp and the 4.27 ± 0.24 to 4.38 ± 0.21 mm respectively. Weight uniformity of all the tablet formulations were in the range of 398.4 ± 1.21 to 402.9 ± 2.75 mg. Friability of the tablet formulations were negligible and were in the range of 0.1 to 0.4%. Drug content estimated for all the tablet formulations were highly uniform with less than 3% variation.

Floating behavior of stavudine gastro retentive raft forming floating matrix tablets

Raft forming preparation includes raft forming agent (sodium alginate) which forms floating Raft on contact with gastric fluid or acidic environment in presence of gas generating agent like sodium bicarbonate. In the formulation calcium carbonate is used as raft strengthening agent. The entire gastro retentive raft forming floating matrix tablet formulations were developed by direct compression method, sodium bicarbonate helps to inducing carbon dioxide generation to float. The *in vitro* buoyancy of gastro retentive raft forming floating matrix tablets was induced by sodium bicarbonate and calcium carbonate in the appropriate concentration in the presence of dissolution medium in optimized ratio without compromising the raft strength with the possible shortest lag time and buoyancy duration of up to 14h. The results of floating lag time and total floating time were represented in Table 4.

Raft thickness

The results of raft thicknesses (Table 5) of the formulations prepared with sodium alginate in combination with calcium carbonate and sodium bicarbonate as raft forming agent were showed less thickness in comparison with the formulations prepared with pectin in combination with calcium carbonate and sodium bicarbonate as raft forming agent. Raft thickness ranged from 15.4 ± 2.9 mm to 18.8 ± 2.6 mm with the formulations prepared with alginic acid, whereas the raft thickness was ranged from 25.6 ± 2.5 mm to 30.1 ± 3.7 mm with the formulations prepared with pectin. The higher the thickness was observed with the formulations prepared with pectin, this may be due to slow raft formation, partial floatation and good coherence capacity of the pectin, whereas alginic acid formulations showed less thickness due to faster raft formation, partial floatation and poor coherence capacity of alginic acid.

Raft strength, volume and raft weight

Formulations were tested at least six times for raft strength, weight, and volume as described in the methods section. Observations of the speed and character of raft formation in the beaker were made and noted. The speed of formation was assessed as immediate if a floating raft was formed within a few seconds of addition of product to the selected acid media, and slow if not. Flotation was assessed as complete if all insoluble material rose to the liquid surface. Some formulations formed very few insoluble materials which sank to the bottom of the beaker and remained there for 30 min raft development time. This was assessed as partial flotation. In one of the two formulations most of the insoluble material remained on the bottom of the beaker and this was assessed as very low flotation. The coherence of rafts was observed when removed from the beaker for weighing. Coherence was assessed as good if the rafts held together in substantially one mass during removal, but poor if they broke up into small particles. Texture analyzer measures the force in gram required to pull the L probe up through the raft (Figure 3). The results of raft strength, weight, and volume were represented in the Table-5. Formulations containing pectin showed higher raft strength, weight and volume, in comparison to that of formulations containing sodium alginate, this may be due to slow raft formation, partial floatation and good coherence capacity of the pectin.

Table 4: Floating lag time and total floating time of stavudine gastro retentive raft forming tablets

Formulation	Floating lag time (sec.)	Total floating time (h)
F1	150 ± 15	>12
F2	160 ± 14	>12
F3	165 ± 17	>12
F4	135 ± 15	>12
F5	145 ± 14	>12
F6	150 ± 15	>12
F7	145 ± 15	>12
F8	150 ± 13	>12
F9	150 ± 15	>12
F10	165 ± 15	>12
F11	135 ± 13	>12
F12	120 ± 15	>12
F13	115 ± 13	>06
F14	110 ± 15	>06

Table 5: Raft thickness, Raft strength, Raft volume and Raft weight of stavudine gastro retentive raft forming tablets

Formulation	Raft thickness (mm)	Raft strength (g)	Raft volume (mL)	Raft weight (g)
F1	18.5 ± 2.5	1.93 ± 0.25	7.45 ± 1.30	5.65 ± 1.10
F2	16.4 ± 3.4	1.76 ± 0.34	8.96 ± 1.12	6.36 ± 1.24
F3	18.8 ± 2.6	1.85 ± 0.26	8.63 ± 1.20	7.13 ± 1.28
F4	28.2 ± 3.5	12.2 ± 0.35	32.8 ± 5.32	23.6 ± 3.24
F5	26.7 ± 3.8	12.7 ± 0.38	28.6 ± 6.53	24.1 ± 3.43
F6	30.1 ± 3.7	13.1 ± 0.73	29.2 ± 7.46	21.9 ± 2.96
F7	17.5 ± 3.0	1.77 ± 0.31	8.37 ± 1.40	6.17 ± 1.02
F8	15.4 ± 2.9	1.64 ± 0.29	8.48 ± 1.31	7.28 ± 1.12
F9	15.8 ± 2.3	1.48 ± 0.27	9.33 ± 1.80	7.33 ± 1.08
F10	27.4 ± 3.3	12.4 ± 0.53	33.4 ± 6.35	23.9 ± 3.35
F11	25.9 ± 3.1	15.1 ± 0.71	32.6 ± 7.26	22.6 ± 3.26
F12	28.6 ± 3.2	16.0 ± 0.83	30.2 ± 6.43	20.9 ± 3.43
F13	15.8 ± 2.3	1.89 ± 0.36	9.14 ± 1.80	5.14 ± 1.01
F14	25.6 ± 2.5	15.3 ± 0.53	30.6 ± 7.27	20.6 ± 3.27

Table 6: Fit of various kinetics models for raft forming 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	0.8065	0.8425	0.7562	0.6031	0.643
F2	0.8534	0.8738	0.8512	0.6978	0.612
F3	0.9612	0.8513	0.9011	0.5434	0.668
F4	0.8751	0.8811	0.8613	0.5845	0.694
F5	0.8873	0.8960	0.8715	0.6518	0.579
F6	0.9649	0.7832	0.8813	0.6187	0.638
F7	0.8153	0.8295	0.7612	0.6341	0.632
F8	0.9034	0.8698	0.8823	0.6718	0.626
F9	0.9724	0.8437	0.9161	0.5324	0.638
F10	0.8914	0.8932	0.8832	0.5925	0.697
F11	0.9373	0.8260	0.8715	0.6518	0.529
F12	0.9649	0.7832	0.8813	0.6187	0.638
F13	0.9083	0.8022	0.9215	0.7158	0.704
F14	0.9429	0.8032	0.9613	0.7287	0.713

***In vitro* Dissolution study**

In vitro dissolution studies of stavudine raft forming floating matrix tablets were carried out in release media (0.1 N HCl, pH 1.2). The dissolution release study was performed for up to 16h, and cumulative drug release was calculated. Dissolution studies were performed on all the developed formulations by using USP paddle method (apparatus II). Formulations F1 to F6 were developed using Carbopol 71G as directly compressible rate controlling polymer. In the same formulations studied the role of raft forming agents i.e. sodium alginate & pectin in combination of raft strengthening agent (calcium carbonate) and gas generating agent (sodium bicarbonate). The drug release from the formulations F1 to F3 slightly faster in comparison to that of the formulations F4 to F6 and results are represented in Figure 4a, these differences in dissolution results may be higher raft strength, volume and raft weight of the formulations. The drug release from the formulations F7 to F9 significantly high in comparison to that of the formulations F10 to F12 was observed and are represented in Figure 4b, these difference in dissolution results may be due to higher raft strength, raft volume and raft weight of the formulations. Dissolution results of the formulations containing Pullalum gum as a rate controlling natural polymer showed faster release in comparison to the formulations developed with synthetic polymers Carbopol 71G and Benecel K4M DC and the dissolution results represented in Figure 4c. Over all it was found that the drug release from the developed raft forming floating matrix tablet formulations was dependent upon the concentration of the rate controlling matrix polymer. As the concentration of rate controlling matrix polymer in the formulation increases the extended drug release from the 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. [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 Korsmeyer 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 penetrate 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. [18] 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 [16]

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

Where *M*t is the amount of the drug released at time *t*, M_∞ 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. [17]

The dissolution profiles of the developed formulations are shown in Figure 4a-c. The correlation coefficient values (R^2) are represented in table 6. The drug release from the raft forming floating matrix tablet formulations were diffusion immediately followed by erosion process. The release exponent (*n* values) for all the tablet formulations were in the range of 0.529 to 0.713, indicated that the drug release was by non-fickian diffusion. Thus the drug release from the raft forming floating tablet formulations was by diffusion of the drug from the polymeric matrix followed by immediate erosion of the polymer. The mechanism of drug release from all the tablet formulations was by polymer erosion, raft formation and diffusion of the drug from the raft systems.

Intra-gastric behavior of floating tablets

The $BaSO_4$-containing floating tablets showed a floating lag time of 145 ± 5 s, hardness of 8.16 ± 0.02 kp and thickness of 4.3 ± 0.2 mm. The tablets were clearly seen in the GIT at different positions during the study (Figure 5). The average residence time was found to be 4 ± 0.5 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.

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