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Formulation and Evaluation of Floating matrix tablets of Stavudine using Pullulan gum

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ABSTRACT

Gastro retentive floating matrix tablets are developed to increase the gastric residence time of the drug after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma concentration and improving bioavailability. With the above objective, floating tablets containing Stavudine with out the gas generating agent was designed for the treatment of HIV and AIDS. The matrix tablets were prepared by using natural polymer such as pullulan gum. The drug release kinetics study reveals that the formulations follow first order release with diffusion mechanism. In vivo x-ray studies showed the gastric residence time of the tablet up to 8 hours. The release and floating was depends on the polymer proportion in the matrix tablets. The formulations were evaluated for in vivo floating time which shows the floating time up to 12 hours. The DSC and FTIR study shows that there is no drug polymer interaction

Key words: Floating Tablets, Stavudine, Pullulan gum, X-ray study, DSC and FTIR.

1. INTRODUCTION

Effective gastroretentive drug delivery systems (GRDDS) depend upon the factorssuch as the gastric emptying process, gastrointestinal transit time of the dosage form,drug release from the dosage form and the site of drug absorption. Rapid GI transit leadsto incomplete drug release from the dosage form in the absorption zone. This led to thedevelopment of GRDDS. Several approaches cited in the literature [1–4] include mucoadhesion,swelling or expansion, modified shape systems, floatation, gastric emptying delaying devices [5] or simultaneous administration of gastric emptying delaying drugs.

Among the various approaches, the floating drug delivery systems offer the most effective, simple and practical approach to achieve increased gastric residence time and sustained drug release compared to the other methods [4]. Based on the mechanism of buoyancy, non-effervescent and effervescent technologies have been utilized in the development of floating drug delivery systems (FDDS). Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids. Effervescent systems utilize swellable polymers and inclusion of gas generating agents, i.e., sodium bicarbonate and citric or tartaric acid [6].

Stavudine is the FDA-approved drug for clinical use for the treatment of HIV infection, AIDS and AIDS-related conditions either alone or in combination with other antiviral agents. Stavudine, a nucleoside analogue of thymidine, is phosphorylated using cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate thymidine triphosphate and by causing DNA chain termination following its incorporation into viral DNA [7].

Stavudine is typically administered orally as a capsule and an oral solution. The drug has a very short half-life (1.5 h) thus necessitating frequent administration to maintain constant therapeutic drug levels. However patients receiving stavudine develop neuropathy and lactic acidosis. The side effects of stavudine are dose-dependent and a reduction of the total administered dose reduces the severity of the toxicity. Hence one of the methods of fabricating controlled release formulations is incorporation of the drug in the floating matrix containing a hydrophilic rate controlling polymers and gas generating agent was used to formulate the stomach specific drug delivery of stavudine [8,9].

2. MARERIALS AND METHODS

2.1. Chemicals

Stavudine was obtained as a gift sample from Alkem laboratories Ltd (Mumbai, India), Pullulan gum was obtained as gift sample from Aurobindo pharma Ltd,Hyderabad. All other

chemicals and reagents used in the study were of analytical grade.

2.2. Preparation of Stavudine floating matrix tablets

Stavudine, microcrystalline cellulose was mixed manually in poly bags with pullulan gum at different concentrations. Then the above blend was pre lubricated with talc and aerosol and finally lubricated with magnesium stearate. Then mixed blend was compressed into tablets by direct compression method using 9.5 mm punches a sixteen station rotary tablet punching machine.

2.3. Evaluation of Tablets

The prepared tablets were evaluated for physiochemical parameters, in vitro dissolution, DSC and FTIR.

2.3.1. Weight Variation

For weight variation, 20 tablets of each type of formulation were weight individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight. The % Weight variation also calculated.

% deviation = (Individual weight – Average weight / Average weight) X 100

2.3.2 Thickness

The thickness of tablets was determined using digital micrometer. Ten individual tablets from each batch were used and the results averaged.

2.3.3. Friability

It is a measure of mechanical strength of tablets. Roche friabilator was used to determined the friability by following procedure. Pre-weighed tablets (10 tablets) were placed in the friabilator. This device consists of a plastic chamber that is set to revolve around 100 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. At the end of test, tablets were reweighed; loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$F\ (\%) = [1\text{-}Wo/W]X100$$

Where,

Wo is the weight of the tablets before the test and

W is the weight of the tablets after test.

2.3.4. Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage, depends on its hardness. For each formulation, the hardness was determined using Monsanto hardness tester and the average was calculated and presented with standard deviation.

2.3.5. Assay

The drug content of the prepared floating matrix tablets was determined in triplicate. For each batch, 10 tablets were taken, weighed, and finely powdered. An accurately weighed powder equivalent to 100 mg of pure drug was taken and suitably dissolved under sonication for 30 minutes (Power sonic 505, HWASHIN technology co) and shaking for 30 minutes in pH 1.2 0.025 N HCl. The above solution was filtered through 0.45 µ (Millipore) filter. The sample was analyzed after making appropriate dilutions using UV spectrophotometer (Schimadzu, UV-1700 E 23) at 250 nm against blank.

2.3.6. Buoyancy / Floating test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of floatation i.e. as long the dosage form remains buoyant is called Total Floating Time (TFT) [10].

2.3.7. In Vitro Drug Release Studies

The in vitro dissolution studies were performed for the prepared micro capsules using dissolution apparatus (LABINDIA, DISSO-2000, Mumbai, India). The microcapsules were filled in a capsule shell and then kept in the basket of the dissolution medium. The dissolution medium consisted of 0.1 N HCl (1000 mL), 50 rpm speed, maintained at 37 ±0.5 °C. The microcapsules of the highest sieve fraction ie 660 µm were taken for the dissolution studies. The microcapsules were weighed based on the drug content estimated and filled in the empty hard gelatin capsules subjected for the dissolution study. The solution was filtered through 0.45 µm membrane filter (MILLIPORE). Drug content was determined by UV- visible spectrophotometer (Schimadzu, UV-1700 E 23) at 250 nm. The release studies were conducted in triplicate [11].

2.3.8. DSC and FTIR studies

Thermal properties of pure drug and the formulation were evaluated by Differential scanning colorimetry (DSC) using a diamod (DSC) (Mettler star sw8.10). The analysis was performed

at a rate 50c min-1 to 2000C temperature range under nitrogen flow of 25 ml min-1.

The FT-IR spectrum of pure drug and formulation were determined. A FT-IR (Thermo nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - 400cm-1 and 4cm-1 resolutions. A quality equivalent to 2mg of pure drug was used for the study.

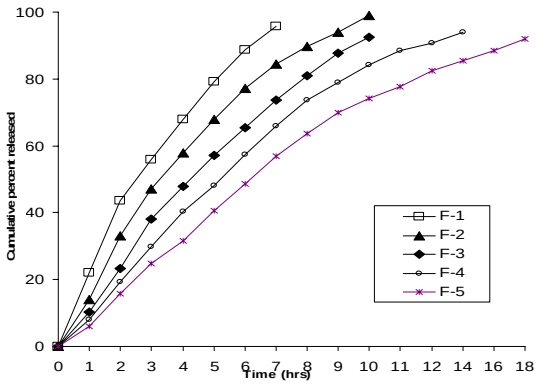
Table – 1: Formulation data of stavudine floating tablets

Ingredients	F1	F2	F3	F4	F-5
	mg/tablet				
Stavudine	100	100	100	100	100
Pullulan gum	100	125	150	175	200
MCC- PH 200	150	125	100	75	50
Talc	2.0	2.0	2.0	2.0	2.0
Aerosil	1.5	1.5	1.5	1.5	1.5
Mg. sterate	1.5	1.5	1.5	1.5	1.5
Total weight	355	355	355	355	355

3. RESULTS AND DISCUSSION

Prepared tablets were evaluated to weight variation study. The results of weight variation test are shown in the table and the values are with in the pharmacopoeial limits. The tablets thickness of the various formulations was observed to be in the range of 5.52mm to 5.57 mm. The hardness of all the tablets was found to be in the range of 6 to 7 kg/cm^2. The friability of the prepared tablets was below 1% clearly indicates the good mechanical strength of the tablets.. The drug content ranged from 99.13±0.87 in formulation to 100.28±0.66 in formulation clearly indicating good content uniformity. The formulations were summarized in Table 1. In vitro buoyancy study in 100 ml of the 0.1 N HCl shows that the prepared matrix tablets were rapidly floated to the surface of the medium with in 15sec. The total floating time of the prepared formulations was 16 hours and more. The in vitro dissolution study showed that the drug release was extended up to 18 hours. The release kinetics form the dissolution data was followed first order release with diffusion mechanism.

Figure-1: Cumulative percent drug release vs time plot of Stavudine floating tablets



Differential scanning calorimetry (DSC) study of pure Stavudine showed a sharp endothermic peak at 172° C. The thermograms of stavudine matrix tablets showed similar endothermic peak at 171° C. This further confirms that there is no drug to polymer interaction. This was further conformed by FTIR

Figurep- 2: DSC thermogram of (A) pure Stavudine (B) Stavudine floating tablets

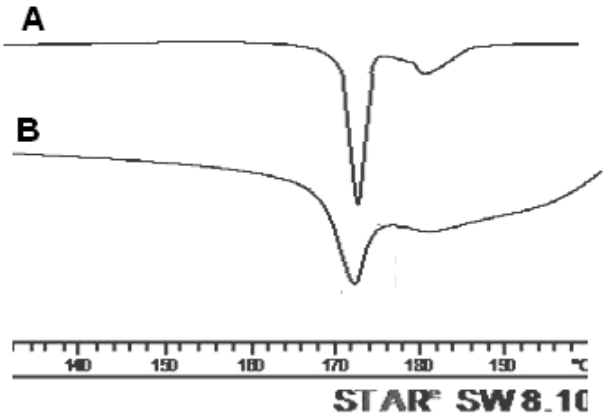
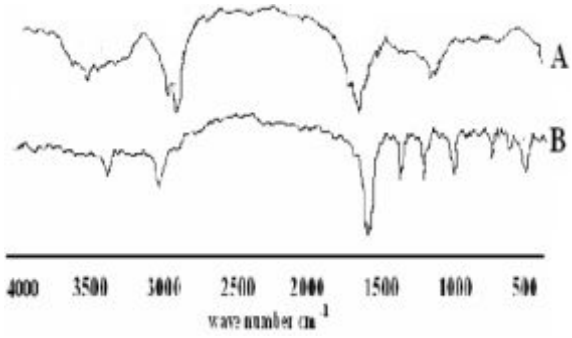


Figure – 3: FTIR spectrum of (A) pure Stavudine(B) Stavudine floating tablets



4. CONCLUSION

Floating tablets of stavudine were prepared by direct compression method. Good

floating property was observed with the pullulan gum used in the present study. DSC and FTIR study shows no drug polymer interaction. The prepared formulations have good industrial applications.

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