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Research Article

Effervescent technique in development of floating tablets for antiviral drugs

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ABSTRACT

The purpose of this investigation was to prepare a regiospesific drug delivery system of Stavudine. Floating tablets of Stavudine were prepared by direct compression method employing different concentration of HPMC K15M by effervescent technique. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, swelling studies, in vitro buoyancy and dissolution studies. The effect of different concentration of HPMC K15M on drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for more than 12 hours. Increased in the HPMC K15M level, decreased the floating lag time but tablets floated for longer duration. The formulation with 1:1 drug: Polymer ratios were found to float for longer duration as compared with other formulations containing HPMC K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Keywords: Effervescent floating tablets, HPMC K15M, In vitro buoyancy, Non-fickian transport.

INTRODUCTION

Stavudine is thymide analogue reverse transcriptase inhibitor that is active in-vitro against HIV-1 and HIV-2. Stavudine is absorbed rapidly following oral administration producing peak plasma concentration within 1 hour with 86 % bioavailability. Elimination half life is 1 to 1.5 hours following single or multiple doses. Sustained release delivery systems for oral dosing are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration which eliminate rapidly. One of the methods of fabricating controlled release formulations is incorporation of the drug in the

floating matrix containing a hydrophilic rate controlling polymer and gas generating agent [1-5].

The hydrodynamically balanced system (HBS), also called as floating drug delivery system (FDDS) is an oral form (capsule or tablet) designed to prolong the residence time of dosage form within the GIT. It is a formulation of drug with a gel forming hydrocolloides meant to remain buoyant in the stomach content. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled condition.

Hydroxy propyl methyl cellulose (HPMC) is the polymer most widely used as the gel-forming agent in the formulation of solid, liquid, semisolid and even controlled release dosage forms. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage forms are controlled by the hydration of HPMC, which forms a gel barrier through which the drug diffuse. The adjustment of the polymer concentration and addition of gas generating agent to the HPMC matrix can modify the drug release. In this study floating matrix tablet of stavudine was prepared using HPMC K15M and evaluated for its suitability.

MATERIALS AND METHODS

Materials

Stavudine was obtained from CIPLA Ltd., (Mumbai, India). HPMC K15M (15,000 cPs, apparent viscosity as a 2% solution) were received as gift samples from Colorcon Asia Pvt. Ltd., (Goa, India). Micro-crystalline cellulose was received as gift samples from Griffon Pvt. Ltd., (Mumbai, India). Other materials Sodium Bicarbonate, Polyvinylpyrolidone, Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, (Mumbai, India).

Methods

Preparation of regiospesific floating tablets

The composition of different formulations of stavudine floating tablets is shown in Table 1. Different tablet formulations were prepared by direct compression technique. All the powders passed through 40/60 mesh sieve. The required quantity of drug and low density polymer were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed (9 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet contained 80 mg of stavudine.

Evaluation of powder blend

The flow properties of granules (before compression) were characterized in terms of angle of repose, Bulk density, Tapped density, Carr index and Hausner ratio. For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface.

Differential Scanning Calorimetry (DSC)

The DSC analysis of pure drug and a mixture of drug and HPMC K15M polymer were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºc at heating rate of 10ºc /min under nitrogen flow of 30ml/min.

Evaluation of Floating Tablets

The prepared floating tablets were evaluated for Dimension (Diameter and Thickness) using 6 tablets (vernier calipers), uniformity of weight using 20 tablets (Shimadzu BL-220H analytical balance), hardness using 6 tablets (Monsanto hardness tester), friability using 20 tablets (Roche type friabilator).

Drug content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 25 mg was added in 100ml of 0.1N hydrochloric acid followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer at 266 nm using 0.1N hydrochloric acid as blank.

In-Vitro buoyancy

The *in vitro* buoyancy was determined by floating lag time and total floating time, as per the method described by Rosa *et al.* The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablet was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1 N HCL at 37±0.5ºC.

In Vitro Release studies

The release rate of stavudine from floating tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium..

RESULT AND DISCUSSION

Regiospesific floating 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 12 h. The regiospesific floating tablets were made using gel-forming polymers such as HPMC K15M. It was known to be beneficial in improving the buoyancy characteristics and drug release characteristics. The combination of gel forming polymer and gas generating agent shows the less floating lag time and longer total floating duration. The talc and magnesium stearate were employed for their glidant and lubricant property. The composition of floating tablets of stavudine is shown in Table 1. The prepared floating tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling index, in vitro buoyancy studies and in vitro drug dissolution studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Evaluation of powder blend

The granules prepared for compression of floating tablets were evaluated for their flow properties, the results were shown to be within the limits.

Differential Scanning Calorimetry (DSC)

Any possible drug polymer interaction can be studied by thermal analysis. Stavudine exhibits a sharp endothermic peak at 175.05 °C shown in figure 2, which corresponds to its melting point. The stavudine+HPMC K15M exhibits a sharp endothermic peak at 173.87ºC shown in figure 2. Hence DSC study shows that there is no any drug polymer interaction.

Physicochemical Characterization of Floating Tablets

The floating stavudine tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown within the limits. The percentage of drug content for F1 to F5 was found to be in between 98.24±0.6 to 99.81±1.4 of stavudine, it complies with official specifications.

Floating characteristic

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. The results of floating study were shown in table 3. The floating lag time ranged from 132 to 193 s. As the concentration of HPMC K15M increased (50%, 75%, 100%, 125% and 150% w/w of drug), the floating lag time decreased. The total floating time ranged from >12 to >24 hours, the total floating time for all formulated batches was found to be more than 12 hours.

Swelling index

Swelling study was performed on all the batches (F1 to f5) for 12 hours. The result of swelling index were shown in table 4, figure 3 shows the plot of swelling index as a function of time for different formulation. The tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water.

In Vitro Release study

The release data obtained for formulations F1 to F5 were tabulated in Table 4, figure 4 shows the plot of percent drug released as a function of time for different formulations. From the in vitro dissolution data it was found that formulation F1 and F2 released more than 90% of drug before 12 hours of the study indicating that the polymer amount is not sufficient to control the drug release. While F4 to F5 released less than 90% of drug within 12 hours. It concluded that F3 had better controlled release than the other formulation.

Table: In vitro release and swelling index data (F1 to F5)

Time (h)	% Drug release (%)*					Swelling index*				
	F1	F2	F3	F4	F5	F1	F2	F3	F4	F5
0	0	0	0	0	0	0	0	0	0	0
1	36.20	34.71	30.75	28.93	26.41	0.76	0.87	0.97	1.09	1.21
2	53.49	48.92	43.07	39.94	36.20	0.92	1.05	1.21	1.28	1.49
3	62.83	59.90	53.93	50.09	43.20	1.02	1.16	1.34	1.43	1.76
4	71.19	66.52	58.61	55.67	50.57	1.26	1.47	1.63	1.59	1.89
5	79.59	73.55	68.71	64.60	57.70	1.42	1.65	1.7	1.82	2.02
6	84.96	79.64	77.71	70.59	62.34	1.66	1.86	1.95	2.14	2.17
7	89.01	86.45	85.87	77.87	69.53	2.04	2.09	2.18	2.38	2.45
8	92.94	89.95	91.13	82.06	76.24	2.1	2.31	2.4	2.45	2.56
9	96.75	94.21	93.44	85.72	82.20	1.95	2.19	2.74	2.62	2.93
10	99.79	97.51	95.53	88.05	84.23	1.83	2.08	2.58	2.79	2.82
11		99.76	97.44	90.48	86.50	1.62	2.03	2.27	2.55	2.69
12			99.68	92.73	89.24	1.54	1.8	2.03	2.27	2.46

*All the values are expressed as mean± SE, n=3.

Kinetic modeling of drug release

The data obtained from *in vitro* dissolution studies were fitted in different models viz. zero order, first order, Higuchi and Korsemeyer- Peppas equation, the results were shown in Table **5**. The first order plots were found to be fairly linear as indicated by their high regression values (r^2 = 0.8348 to 0.9947). This means that water diffusion and also the polymer relaxation had an essential role in drug release. When n takes the value of 0.5, it indicates diffusion controlled drug release. The value of n in case of optimized formulation (F3) is close to 0.5 indicating a diffusion-controlled drug release mechanism.

CONCLUSION

The effervescent-based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer HPMC K15M and gas-generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Formulation F3 showed controlled drug release and adequate floating properties. The kinetics of drug release was best explained by Korsemeyer-Peppas equation. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

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