FORMULATION AND CHARACTERISATION OF FLOATING TABLETS OF 5 FLUORO URACIL WITH DIFFERENT GRADES OF HYDROXY PROPYL METHYL CELLULOSE

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ABSTRACT

Hydrodynamically balanced system (HBS) or Floating tablets has gained importance in recent days to improve absorption of drugs especially those that are absorbed from stomach and small intestine. In the present study, an attempt was made to fabricate and evaluate an HBS dosage form of 5 fluoro uracil . The different viscosity grades of Hydroxypropylmethyl cellulose (HPMC) polymer like HPMC K100, HPMC K4M, HPMC KV600 and HPMC K50 was incorporated as hydrophilic swellable polymers for preparing matrix-floating tablets. Sodium bicarbonate was incorporated as a gas-generating agent. The prepared floating tablets were evaluated for the physicochemical and biopharmaceutical parameters like thickness, hardness, friability, drug content, floating lag time, floating time, invitro dissolution studies and stability study. The mechanism of drug release was zero order kinetics, which was concluded as the major controlling factor for the drug release. The results showed that the formulation containing Drug: HPMC K 100 in the ratio of 1: 0.5 is suitable for the formulation of gastro retentive floating tablets of 5 fluoro uracil.

Keywords: 5 Fluoro Uracil, Hydroxy Propyl Methyl Cellulose, Buoyancy Lag Time, Matrix Floating Tablet, Dissolution Study, Accelerated Stability Study.

1. INTRODUCTION

HBS dosage form is an attractive gastro-retentive drug delivery system, since it permits control over time and site of drug release. This would be particularly valuable for drugs exhibiting an absorption window in the stomach and small intestine or drugs such as weak bases, which dissolve better in the acid environment of the stomach .In addition, the devices may be useful for local treatment of the stomach disorders (Moes, 1993). The system reported here is HBS dosage form of 5 fluoro uracil (5 FU), which is widely used in a variety of solid cancers, such as stomach, colon, lung, and breast cancer. It is usually given intravenously, as absorption of 5-FU from the gastrointestinal tract is erratic and unpredictable. The intravenous route of administration is associated with severe systemic side effects because of 5-FU's cytotoxic nature when it reaches unwanted sites (Dollery, 1999). HBS dosage form of the drug was formulated to overcome this problem. The system prepared was aimed at providing a sustained release of the drug (Deshpande et al., 1996; Hwang et al., 1998; Talukder. et al., 2004; Baumgartner et al., 1991). Thus, instead of entire dose reaching the absorption site of the drug, as in conventional dosage form, with a limited residence time there, only a limited fraction of the dose would be released in a controlled manner from the formulation retained in the stomach.

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2. MATERIALS

The materials used in the study, were 5 FU, Polyvinyl Pyrrolidone (PVP K-30), HPMC K-100, HPMC KV 600, HPMC K50, HPMC K4M, Iso propyl Alcohol (IPA), Polyethylene glycol (PEG 6000), Sodium bicarbonate, Magnesium Stearate, and Talc (S.D fine chemicals Pvt Ltd).

3. METHODS

Preparation of HBS Tablets

The drug 5 FU, HPMC of various grades, poly ethylene glycol 6000, Sodium bicarbonate, were passed through mesh #40 separately and blended thoroughly.

The wet mass was passed through sieve #16 and dried at 65°C for one hour to get the moisture content less than one. The blend was granulated with PVP K-30 in IPA solution. Magnesium Stearate and talc were passed through sieve #40 and blended with dried granules. The lubricated granules were compressed in to tablets on Cadmach eight punch tablet machine (Table-1).

Characterization of tablets

The compatibility study between ingredients was performed by IR spectral analysis. The granules were evaluated for its flow properties and compressibility studies by measuring the angle of repose and carr's index (Table-2). The formulated floating tablets were evaluated for the parameters like thickness, hardness, friability and drug content. The results were presented in Table 1.

Invitro floatation study

Static Volume Beaker method was used to study the floatation behavior of the prepared HBS tablet, which was placed in the 100ml beaker containing 0.1N Hcl (pH 1.2). The time required for the HBS tablet to rise to the surface of medium was termed as lag time and duration of the tablet with constant floating on the medium was termed as floatation time (Patel, 2006).

Invitro dissolution study

Dissolution studies were carried out in USP dissolution apparatus –II using 900ml of Simulated Gastric Fluid (SGF) as dissolution medium. The samples were withdrawn periodically over a period of 24 hours. 10ml samples were withdrawn and were replaced with fresh dissolution medium. The amount of drug released after every hour was analyzed at 266 nm using UV spectrophotometer.

The best formulation was chosen on the basis of buoyancy lag time, floating time and dissolution profile (Whitehead et al., 1998; Mohammad et al., 2006; Desai, 1993; Baumgartner et al., 2001; Daves et al., 2004)**.** The selected formulation was subjected to stability study at 75% RH and 40°c for a period of two months.

4. RESULTS AND DISCUSSION

5 FU passed all the tests for identification and percentage purity was found to be 99.13%. The physical compatibility test between drug and other tablets was carried out at 25-30ºC and 75% R.H for two months. The mixture does not show any visible change thus inferring that drug and other components do not have any physical incompatibility. The FTIR and UV scan of the HBS of 5 FU tablets exhibited similar peaks to that of the pure drug. No interactions were detected, hence confirming the suitability of excipients used in the formulation.

The bulk density and tapped density ranged from 0.494 to 0.519 and 0.521 to 0.676 respectively. The percentage compressibility index was below 30, indicating good flow properties. All the granules (F-I to F-XII) were found to be free flowing and their angles of repose were below 30.

The physical properties of 5 FU GRS tablets (F-I to F-XII) such as tablet size, hardness, friability and weight variation were determined (Table 2) and results are found to be within the limits specified in Pharmacopoeia.

The best formula should posses the minimum lag time (within few minutes) as well as maximum floatation time (more than 12h). Buoyancy lag time and duration of floating were determined using USP dissolution test apparatus and the results of buoyancy lag time were represented in Fig 1. Buoyancy lag time of tablet F-IX was 24 seconds i.e. less than one minute which is the least value as compared to other tablets . The floating time of F-IX was found to be 24 hours.

The comparison of the drug released from the tablets (F-I to F-XII) was represented in Fig 2. The percentage drug release of the formulation F-II, F-V, F-VIII, F-XI was below 50%., where as for formulations F-I, F-IV, F-VII, and F-X was below 70%. This shows that there is a linear relation ship between the drug and the polymer ratio. The formulation F-IX showed a constant release of 89.65% in a sustained manner as similar to zero order kinetics (Fig- 3)

Suitability of HPMC grades is in the order of HPMC K100 > HPMC KV600> HPMC K4M > HPMC K50, as it was concluded from the dissolution profiles.

The optimized 5 FU HBS, F-IX was subjected to stability studies at 40ºC under relative humidity

condition of 75% for a period of two months. Samples were analyzed for color change, appearance, drug content and release characteristics. From the results it was observed that there was no significant change in physiochemical properties as well as in drug release profile.

5. CONCLUSION

It can be concluded that HBS (or) floating tablets of 5 fluoro uracil (F-IX) with HPMC K 100 in the ratio of 1:0.5 shows desirable characteristics of invitro floatability of 24 hours and invitro release of 89.65% over a period of 24 hours, with zero order release kinetics and was stable. Hence F-IX was chosen as the best formulation.

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Table 1.General Formulae for 5 fluoro uracil floating tablet

S.No	Ingredients	Amount/ Tablet (mg)
1	Poly Ethylene Glycol 6000	25
2	Sodium Bicarbonate	75
3	PVP K-30	75
4	Lactose	25
5	Magnesium Stearate	4
6	Talc	4

5 FU -100 mg, HPMC of various grades used with drug in the ratios (Drug: Polymer, (1:1, 1:1.5, 1:0.5). F1 – F3 is with HPMC K4M, F4 – F6 is with HPMC K50, F7 – F9 is with HPMC K100, F10 – F12 is with HPMC KV 600.

Table 2.Physical parameters of HBS 5 FU HBS Tablets

Batch Code	Thickness (mm)	Hardness (kg/cm^2)	Floatation Time (hours)	Percentage Weigh loss	% Drug Content* Mean ±S.D
F-I	3.94	3.8	24	0.037	100.6 ± 2.71
F-II	3.40	4.1	24	0.043	100.3 ± 3.11
F-III	4.04	3.1	24	0.081	99 ± 1.69
F-IV	3.34	3.4	24	0.088	99.7 ± 3.19
F-V	3.63	4.2	24	0.049	99.6 ± 2.26
F-VI	3.98	3.2	24	0.550	101.9 ± 4.05
F-VII	3.69	3.9	24	0.063	98.6 ± 2.38
F-VIII	4.07	4.1	24	0.030	99.61 ± 1.22
F-IX	3.99	3.5	24	0.029	99.56 ± 1.04
F-X	4.10	4.1	24	0.012	100.1 ± 3.06
F-XI	3.93	4.2	24	0.079	98.4 ± 8.23
F-XII	4.14	3.8	24	0.010	97.4 ± 2.79

*n = 6

Figure: 1. Buoyancy lag time of Fabricated 5 FU GRS Tablets (FI-FXII)

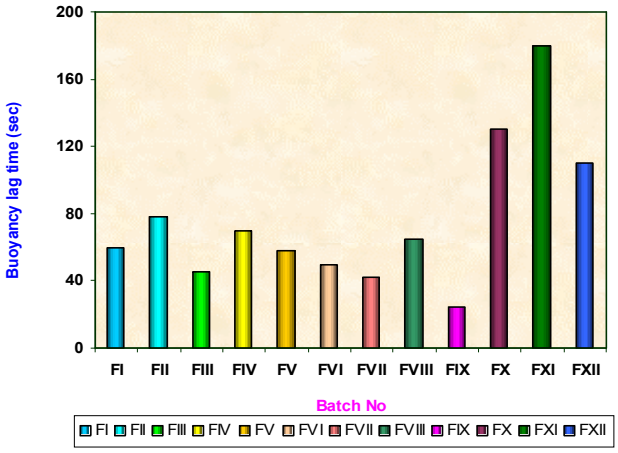


Figure 2. Comparative Invitro release profile of 5 FU HBS Tablets (FI - FXII)

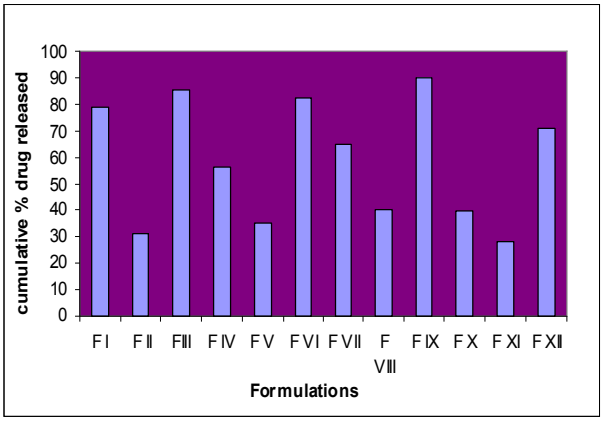
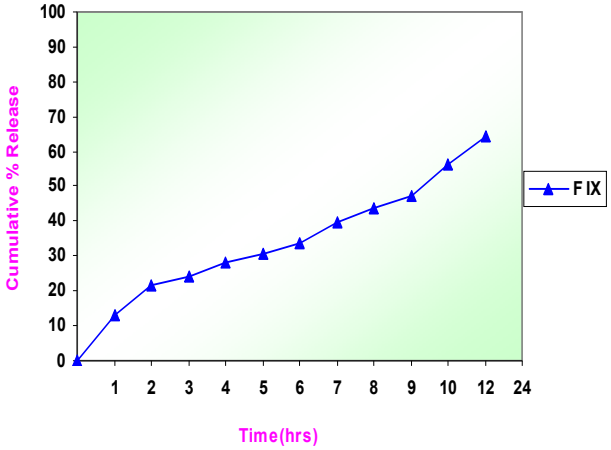


Figure: 3 Zero order release Kinetics of Best Formulation F-IX



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