

FORMULATION AND EVALUATION OF GASTRORETENTIVE (FLOATING) DRUG DELIVERY SYSTEM OF ANTI- METABOLITE DRUG.

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Abstract: A multiple unit oral floating drug delivery system of famotidine was developed to prolong gastric residence time, target stomach mucosa and increase drug bioavailability. Drug and polymer compatibility was studied by subjecting physical mixtures of drug and polymers to differential scanning calorimetry. DSC study decreases in sharpness and enthalpy of drug characteristic peak indicate the drug goes in to microspheres and reduces its crystalline as well as formulations goes in to amorphous state which indicates glass transition temperature.

XRD graph of pure 5-Fluorouracil drug. It is concluded that drug was crystalline in nature due to the sharpness in peak height. Sharpness in peaks was decreased in microspheres that indicated drug in the both the formulation goes to the amorphous nature which can enhance bioavailability. SEM showed that microspheres of drug with ethyl cellulose and eudragit RS 100 were smooth and porous almost spherical microspheres. The rough surface which may be due to presence of drug crystals on the surface of microspheres.

Keywords: XRD, Drug, floating drug delivery systems, gastric residence time,

INTRODUCTION

The oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. However, oral administration has only limited use for important drugs, from various pharmacological categories, that have poor oral bioavailability due to incomplete absorption or degradation in the gastrointestinal tract. Some of these drugs are characterized by narrow absorption window at the upper part of the gastrointestinal tract. This is because of proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time of a narrow absorption window the drug may significantly improve the net extent of its absorption (Kataria S et al 2011). Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Floating drug delivery systems (FDDS) is to organize the recently focus on the principal mechanism of floatation to achieve gastric retention time. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design floating systems, and their classification and formulation aspects are covered in detail. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the gastric emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

MATERIALS AND METHODS

Materials

5-Fluorouracil Ethyl Cellulose Eudragit RS 100 was purchased from Grail Pharma Aurangabad. Sodium starch glycolate (SSG) and microcrystalline cellulose was obtained as a gift sample from lab chem. India Mumbai. All other ingredients were of analytical grade.

Formulation of Floating Microsphere of 5- Fluorouracil

Preparation Method of Floating Microsphere

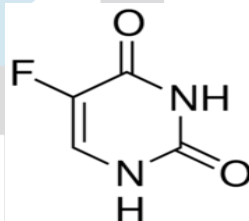
1. Formulation of Floating Microsphere of 5- Fluorouracil

Sr. No.	Drug: Polymer ratio	Inlet Temp. (°C)	Outlet Temp. (°C)	Aspirator speed	Vacuum pressure	Air pressure kg/cm ²	Feed Rate (ml/min)
1	1:1	100±1°C	42±3°C	45±2	55±5	15-20	15
2	1:1	100±3°C	42±2°C	55±3	55±5	15-20	15
3	1:1	100±5°C	42±4°C	45±5	55±5	15-20	25
4	1:1	100±2°C	45±5°C	55±4	55±5	15-20	25
5	1:2	100±4°C	45±1°C	45±6	55±5	15-20	15
6	1:2	100±3°C	45±3°C	55±9	55±5	15-20	15
7	1:2	100±6°C	45±4°C	45±1	55±5	15-20	25
8	1:2	100±5°C	45±2°C	55±7	55±5	15-20	25

Floating microsphere was prepared by spray drying technique. For formulation of microsphere full factorial 2³ design was applied. The independent factors were D: P ratio, aspirator speed and feed rate. Total 8 batches were prepared. An aqueous solution containing different ratios of the polymer table no. 16 were prepared by dissolving ethyl cellulose and eudragit rs 100 in ethanol (95%). The drug (1gm) was dissolved in 50ml distilled water, was added to the polymer solution and resulting mixture sonicated 1hr. at room temperature and solution is spray dried by spraying through the nozzle of a spray dryer observing following conditions – air flow rate, inlet temperature, outlet temperature, feed rate of solution and vacuum pressure etc. The resulting microspheres were collected from the spray dryer (Malik A et al 2014, Sapkale H et al 2013, Naik DR et al 2012, Kharwade RS et al 2017, Ishwarya M et al 2017, Aute SM et al 2015, Bansal H et al 2011).

EVALUATION OF PREPARED FLOATING MICROSPHERE OF 5- FLUOROURACIL

1. Infrared Spectroscopy



Structure of 5-Fluorouracil

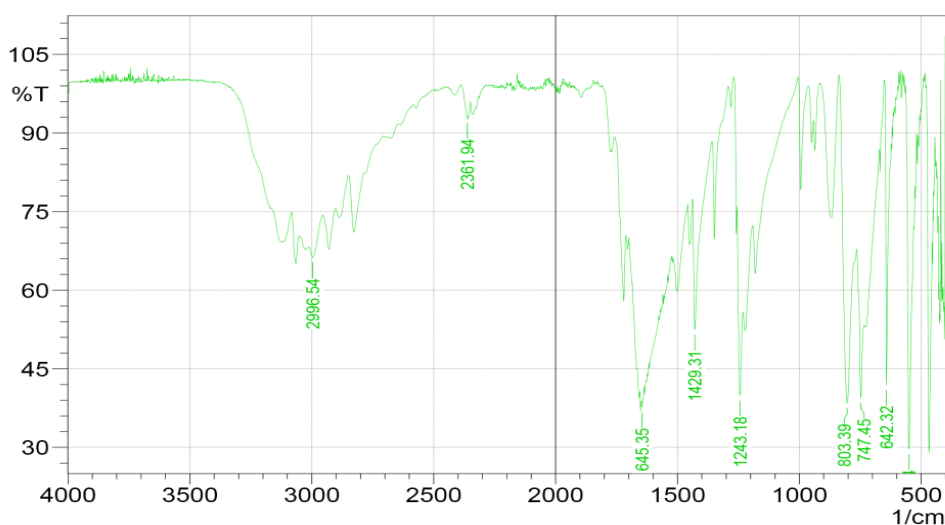


Fig.01: FT-IR Peaks of Pure Drug 5-Fluorouracil.

Functional group	Observed value cm^{-1}	Standard value cm^{-1}
N-H Stretching (1* & 2*)	3150	3400-3150
C-H Stretching	2996.54	3000-2850
C=O Stretching	1645.35	1780-1670
C-C Stretching	1429.31	1500-1400
C-N Stretching	1243.18, 1170	1250-1020
F	1243.18	1400-1000

Table No. 01: FT-IR Peaks of Pure Drug 5-Fluorouracil.

2. UV Method for Estimation of 5-Fluorouracil

Determination of λ_{max}

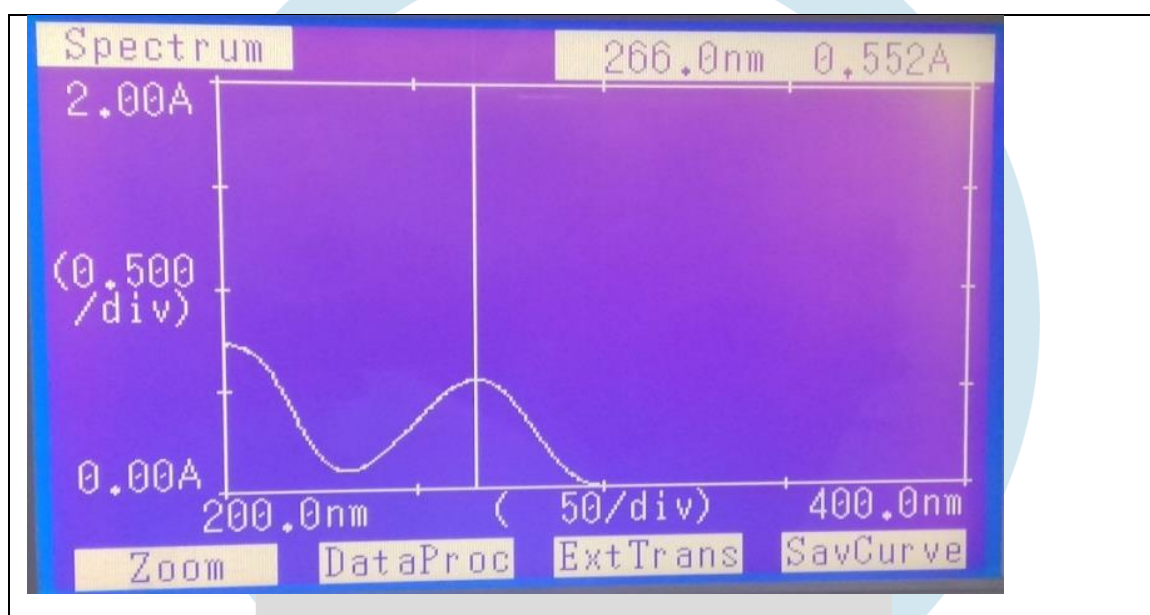


Fig. 2: UV Spectrum of 5-Fluorouracil.

The UV absorption spectrum was determined in the 0.1N HCL as shown in Fig. 2. The maximum absorbance of 5-Fluorouracil at 266nm.

3. Particle Size Distribution Analysis

Sr. No.	Batch No.	No. of Particle	Avg. Diameter
1	B1	5447	0.3278±0.150
2	B2	4614	0.2530±0.004
3	B3	156	0.3945±0.150
4	B4	710	0.3825±0.078
5	B5	156	0.5625±0.056
6	B6	188	0.5686±0.035
7	B7	154	0.8125±0.155
8	B8	123	0.7723±0.217

Table No.2: Particle Size Distribution.

Particle size as shown in table no. 17 average diameter of microspheres was in the range of 0.2530 to 0.8125. During spray drying process, liquid feed is sprayed in a heating environment through nozzle where the feed comes in contact with drying air. Feed pump speed, aspiration rate, size of nozzle are the main parameters affecting particle size. As feed

pump speed increases which leads to the increase in particle size. Concentration of drug-polymer and feed rate increases to the microsphere size also get increased (Mane R et al 2013).

i. Percentage Yield

Sr. No.	Batch No.	Total Weight (mg)	Actual Weight (mg)	% Yield
1	B1	2000	520	26
2	B2	2000	403	20.15
3	B3	2000	693	34.65
4	B4	2000	673	33.65
5	B5	3000	1170	39
6	B6	3000	1238	42.26
7	B7	3000	1236	41.20
8	B8	3000	1379	45.96

Table No. 3: Percentage yield.

Percentage yield was found in the range between 20.15-45.96% table no.18 for microspheres. These relatively low values may be due to loss of material in a spray drying system by the design of the cyclone separator, which cannot trap particles of diameter 2 μm , but less than pass through into the outlet air and inadequate process conditions of the spray dryer. Concentration drug-polymer and feed rate increases to the percentage yield will be increased. Hence percentage yield below 50% is being considered as a standard yield of lab scale spray drier (Belgamwar VS et al 2011, Elkordy AA et al 2010).

ii. Micromeritic properties

Formulation code	Angle of repose (Degree) n=3	Bulk density (gm/ml) n=3	Tapped density (gm/ml) n=3	Carr's index (%) n=3	Hausner's ratio n=3
B1	21.67 \pm 0.222	0.173 \pm 0.01	0.198 \pm 0.04	12.62 \pm 0.663	1.144 \pm 0.02
B2	20.23 \pm 0.867	0.134 \pm 0.02	0.151 \pm 0.12	11.25 \pm 0.543	1.126 \pm 0.03
B3	23.13 \pm 0.532	0.231 \pm 0.12	0.264 \pm 0.10	12.50 \pm 0.250	1.142 \pm 0.02
B4	22.67 \pm 0.325	0.201 \pm 0.16	0.231 \pm 0.15	12.98 \pm 0.310	1.149 \pm 0.04
B5	27.03 \pm 0.543	0.280 \pm 0.05	0.305 \pm 0.08	8.19 \pm 0.125	1.089 \pm 0.03
B6	25.27 \pm 0.420	0.274 \pm 0.14	0.295 \pm 0.05	7.11 \pm 0.255	1.076 \pm 0.06
B7	24.54 \pm 0.320	0.260 \pm 0.02	0.285 \pm 0.09	8.77 \pm 0.321	1.096 \pm 0.02
B8	25.92 \pm 0.244	0.275 \pm 0.06	0.298 \pm 0.04	7.71 \pm 0.254	1.083 \pm 0.05

Table No.4: Micromeritics Properties of 5-Fluorouracil Microspheres.

a. Angle of repose

The results of angle of repose were found in the range of 20.23 0 \pm 0.867 to 27.03 0 \pm 0.543 indicated good flow properties of the microspheres.

b. Bulk density

Bulk densities of microspheres of various formulations were found to be in the range of 0.134 \pm 0.02 gm/ml to 0.280 \pm 0.05 gm/ml.

c. Tapped density

Tapped densities of microspheres of various formulations were found to be in the range of 0.151 \pm 0.12 gm/ml to 0.298 \pm 0.04 gm/ml.

d. Carr's index

From density data % compressibility was calculated. It was further supported by excellent Carr's index value in the range of $7.11 \pm 0.255\%$ to $12.98 \pm 0.310\%$ were determined to predict flowability (Tanwar YS et al 2007).

e. Hausner's ratio

Hausner's ratio of the prepared drug – excipients microspheres fall in the range of 1.083 ± 0.05 to 1.149 ± 0.04 which is less than 1.25. From the result it was concluded that the microspheres had excellent flow properties.

iii. Drug Content Uniformity Test

Sr. No.	Batch No.	Absorbance	Drug Content (mg)	% Drug Content
1	B1	0.278	4.820	96.40 ± 0.003
2	B2	0.273	4.720	94.4 ± 0.002
3	B3	0.275	4.76	95.20 ± 0.004
4	B4	0.283	4.92	98.02 ± 0.005
5	B5	0.199	3.24	97.29 ± 0.002
6	B6	0.203	3.32	99.69 ± 0.001
7	B7	0.201	3.28	98.49 ± 0.004
8	B8	0.200	3.26	97.89 ± 0.001

Table No. 5: % Drug Content of 5-Fluorouracil microspheres.

Drug content was found in the range between 94.4 - 99.69% for spray dried microspheres table no.20. Various co-solvents such as ethanol and water used for microsphere preparation since they can help to dissolved drug in major solvent and probably achieved higher drug content. Drug content depends on drug solubility in the solvent system used for physicochemical properties of drug. As 5-Fluorouracil has solubility in water, it was dissolved in water and homogeneous solution of drug and polymer obtained for processing and hence drug content was upto its maximum level (Patil JS et al 2015).

iv. Buoyancy Test

Sr. No.	Batch No	Total Wt. of Microsphere (mg)	Wt. of Floating Microsphere (mg)	% Buoyancy
1	B1	50	38	76
2	B2	50	36	72
3	B3	50	38	76
4	B4	50	37	74
5	B5	50	44	88
6	B6	50	46	92
7	B7	50	45	90
8	B8	50	41	82

Table No. 6: % Buoyancy for 5-Fluorouracil microspheres.

Percent Buoyancy for all batches was almost above 70%, which was studied for 8hr. Average buoyancy in percentage was found in the range between 72-92% for spray dried microspheres table no.21. In general with increase in the amount of polymer, there was an increase in the buoyancy percentage (Aute SM et al 2015).

v. In - Vitro Drug Release Study

Zero order release for 5-fluorouracil formulations.

Time (min)	B1	B2	B3	B4	B5	B6	B7	B8
0	00	00	00	00	00	00	00	00
30	31.38	38.88	30.96	37.44	17.34	19.51	18.45	17.34
60	38.19	52.60	37.47	43.96	21.70	22.79	23.87	22.79
120	44.68	59.81	42.52	52.80	26.04	32.55	30.38	31.47
180	50.44	65.58	49.00	60.53	34.72	40.15	36.90	39.07

240	54.05	72.90	54.77	69.90	41.24	47.75	49.92	48.83
300	63.42	76.40	61.26	79.27	47.75	57.52	56.44	57.52
360	73.52	82.16	70.62	82.88	60.77	69.99	62.95	66.20
420	79.28	87.93	80.71	87.92	75.97	81.65	76.13	78.14
480	83.60	92.25	86.48	90.31	84.66	90.12	87.91	89.17
540	90.81	90.60	94.40	98.12	97.67	99.85	96.60	97.67
R ²	0.905	0.804	0.923	0.857	0.977	0.985	0.982	0.986
K	0.135	0.135	0.141	0.143	0.161	0.168	0.161	0.165

Table No. 7: Zero Order Release profile for F1-F8 formulations.

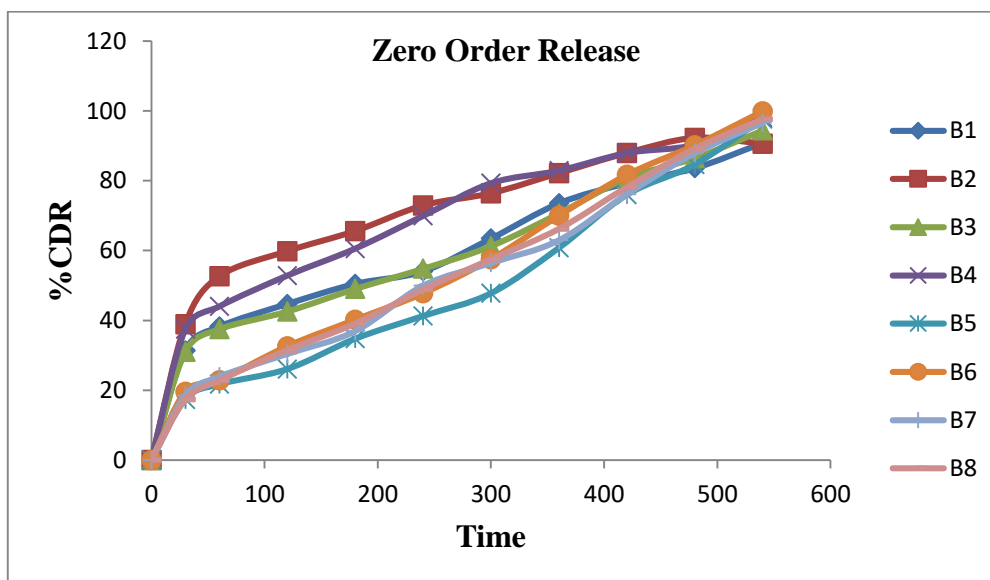


Fig.35: Zero Order Release profile for F1-F8 formulations.

CONCLUSION

Floating microspheres of 5- Fluorouracil were prepared by varying concentration of ethyl cellulose and eudragit RS 100. Microspheres were prepared by spray drying technique. Preformulation study on drug and polymer revealed that there was no interaction between drug and polymer. Calibration curve of 5- Fluorouracil linearity in 0.1N HCL solution with concentration range is 2 to 10 µg/ml and λ max of 5- Fluorouracil at 266nm. All prepared floating microspheres of 5- Fluorouracil float on the 0.1N HCL which shows their ability to float in acidic environment of stomach. From in vitro dissolution studies of microspheres were showed the drug release by Higuchi, Zero and Peppas order model. Based on preformulation, formulation and characterization studies B6 was selected as optimized batch as it float for longer duration and have 99.85% in 9 hours. Characterization of drug and formulations performed by using FTIR, DSC, XRD and SEM analysis.

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