

# DESIGN AND DEVELOPMENT OF FLOATING DRUG DELIVERY SYSTEM OF FAMOTIDINE

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**Abstract:** The purpose of this investigation was to prepare a floating drug delivery system of famotidine. Famotidine having poor absorption in acidic environment (upper GIT). When given orally, it shows the bioavailability near to 50%. To overcome these drawbacks, the present study was undertaken to investigate the floating dosage form of famotidine. The prepared tablets were evaluated for content uniformity, hardness, friability, buoyancy, swelling index and in-vitro dissolution studies. Further selected formulation was subjected for short term stability studies for one and two month at temperature of 25°C and 40°C respectively. 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

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. Gastroretentive systems can remain in the gastric region for several hours for significantly prolong residence time of drugs by which improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment (Shah S et al 2009). While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres (Ishwarya M et al 2017).

## MATERIALS AND METHODS

### Materials

5-Fluorouracil Ethyl Cellulose Eudragit RS 100 was purchased from Concept 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.

### Preformulation Study:

#### 1 Analysis of Drug:

##### 1.1 Organoleptic Properties

The 5- Fluorouracil was examined for its organoleptic properties like colour, odour and appearance (IP 2014).

##### 1.2 Solubility

Solubility studies of 5-Fluorouracil were carried out in 0.1N HCL and distilled water. Saturated solution was prepared in screw capped bottles by adding excess amount of drug and shaking on the shaker for 24 hr at ambient temperature. After this period the solutions were filtered, diluted and analyzed by UV Spectrophotometer and calculate the solubility of 5-Fluorouracil (IP 2014).

### 1.3 Determination of Melting Point

The melting point of drug was determined by capillary method using Thiel's tube. Precaution was taken to maintain the uniform heating tube, in which the capillary containing the drug was placed (IP 2014).

### 1.4 Infrared Spectroscopy

FT-IR absorption spectrum of 5-Fluorouracil was recorded by potassium bromide dispersion technique using JASCO 4600 FT-IR spectrophotometer where in 1-2 mg of drug sample and potassium bromide was mixed uniformly and powder blend was placed in sample holder, comprising in to disc by applying a pressure of 5 tone for 5 minutes in a hydraulic press and an IR spectrum was recorded (Rathor S et al 2011).

### 1.5 UV Method for estimation of 5-Fluorouracil:

#### 1.6 Determination of $\lambda$ max:

A UV spectrum of pure 5-fluorouracil was obtained using UV Spectrophotometer. Accurately weigh 10 mg of 5-fluorouracil was transferred into a 100ml of volumetric flask and dissolved in 0.1N HCL. The volume was made up to the mark to give a 0.1mg/ml solution (Stock-I). 10ml of stock-I solution was diluted to 100ml with 0.1N HCL (Stock-II). 1ml was withdrawn in stock-II and diluted up to 10 ml and resultant solution was scanned between 200-400 nm to determine absorption maxima.

#### 1.7 Preparation of Calibration Curve

Accurately weighed 10 mg of 5-Fluorouracil was weighed and transferred in to 100 ml of volumetric flask. The drug was dissolved in 0.1N HCL with shaking. The volume was made up to the mark to give a 0.1mg/ml solution (Stock-I). 10ml of stock-I solution was diluted to 100ml with 0.1N HCL (Stock-II). Further dilutions were made with 0.1N HCL to obtained 2 to 10  $\mu$ g/ml concentrations of 5-Fluorouracil and the absorbance was measured at 266 nm using 0.1 N HCL as a blank (Parikh SK et al 2011, Rokade PS et al 2017).

#### 1.8 Differential Scanning Colorimetry

Differential Scanning Colorimetry studies were also performed of the pure drug and selected formulation to support drug-excipient compatibility. The polymer used in formulation of 5- Fluorouracil was also assessed by carrying out the thermal analysis of pure drug (5Fluorouracil) and formulation. The differential scanning colorimetry of pure drug (Kohli KR et al 2016).

#### 1.9 Compatibility Study of Drug and Excipients:

##### a. UV Spectrum

UV Spectrum of physical mixture 1:1w/w was prepared by mixing 30mg 5-fluorouracil with 30mg of each polymer separately. At a concentration range of 0.1 mg/ml was prepared and UV scanned in the range 200-400 nm. The UV calibration model was developed with partial least square regression analysis for each polymer separately. Then test drug – polymer physical mixture containing 1:1 w/w drug polymer ratio with different set drug concentration were prepared and UV spectra were collected initially and after 3,7&14 days of storage at room temperature (Mohamed AI 2017).

##### b. Infrared Spectroscopy

FT-IR absorption spectrum of 5-Fluorouracil and excipient physical mixture was recorded by potassium bromide dispersion technique using JASCO 4600 FT-IR spectrophotometer where in 1-2 mg of physical mixture and potassium bromide was mixed uniformly and powder blend was placed in sample holder, comprising in to disc by applying a pressure of 5 tone for 5 minutes in a hydraulic press and an IR spectrum was recorded.

##### Preparation Method of Floating Microsphere

Floating microsphere was prepared by spray drying technique. For formulation of microsphere full factorial 2<sup>3</sup> 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).

a. **Evaluation of Floating Microspheres:**

1. **Particle Size Distribution Analysis**

The size of microsphere was determined by using a motic microscope and optical microscope fitted with an ocular micrometer and a stage micrometer. Accurately weighed 1mg of microspheres was added into 2ml of liquid paraffin in watch glass. From that 1 drop was transferred on glass slide, put the cover slip on it and observed under 45X objective of motic microscope. Calculated the number of area and average diameter of microspheres (Azeem A et al 2017, Hire NN et al 2014).

2. **Percentage Yield**

The prepared microsphere were collected and weighed. The actual weight of obtained microsphere divided by the total amount of material (Nair MN et al 2016, Durgapal S et al 2017, Bhardwaj P et al 2012).

$$\text{Percentage yield} = \frac{\text{Driedmicrosphere (mg)}}{\text{Totalweightofdrugandpolymer}} \times 100$$

ii. **Angle of Repose**

It is the maximum angle possible between the surface of pile of powder and horizontal plain. It is a pre-formulation parameter used for the determination of flow property of powders, represented by 'Θ'. It determined by funnel method. It done by taking the accurately weighed powder blend and allowing it flow freely through the funnel, fixed to a stand at definite height. The height (h) and diameter (d) of the powder cone are measured and angle of repose was calculated in triplicate by the following formula,

$$\tan \Theta = \frac{h}{r}$$

$$\Theta = \tan^{-1} \frac{h}{r}$$

Where, Θ = angle of repose, h= height of the cone, r= radius of the cone base (Rao SK et al 2011).

The flow property of powders determined by its standard relation with angle of repose which is given in table below.

Flowability	Angle of Repose
Excellent	<20
Good	20-30
Passable	30-34
Very poor	>40

**Table 1 : Flow Properties of Powder.**

iii. **Bulk Density**

Bulk density is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk

Density is calculated according to the formula mentioned below (Nesalin AJ et al 2016). It is expressed in g/cc and is given by:

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}}$$

iv. **Tapped and Bulk Density**

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 50 times. Then the tipping was done for 100 times and the tapped volume was noted. It is expressed in g/cc and given by (Patil C et al 2011):

$$\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Tapped volume}}$$

### v. Carr's Compressibility Index

Compressibility index (CI) or Carr's index value of was computed according to the following equation (Rao DS 2015):

$$\% \text{Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Flowability	%Compressibility
Excellent	5-15
Good	12-16
Fait to passable	18-21
Poor	23-35
Very poor	33-38
Extremely poor	>40

Table 2. : Carr's Compressibility Index.

### Formulation of Floating Microsphere of 5- Fluorouracil

Preparation Method of Floating Microsphere

#### 1. Formulation of Floating Microsphere of 5- Fluorouracil

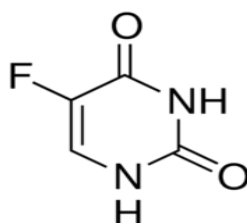
Sr. No.	Drug: Polymer ratio	Inlet Temp. (°C)	Outlet Temp. (°C)	Aspirator speed	Vacuum pressure	Air pressure kg/cm <sup>2</sup>	Feed Rate (ml/min)
1	1:1	100±1°C	42±3°C	45±2	55±5	15-20	15
2	1:1	100±3°C	42±2°C	55±3	55±5	15-20	15
3	1:1	100±5°C	42±4°C	45±5	55±5	15-20	25
4	1:1	100±2°C	45±5°C	55±4	55±5	15-20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

Table 03. Formulation of Floating Microsphere of 5- Fluorouracil

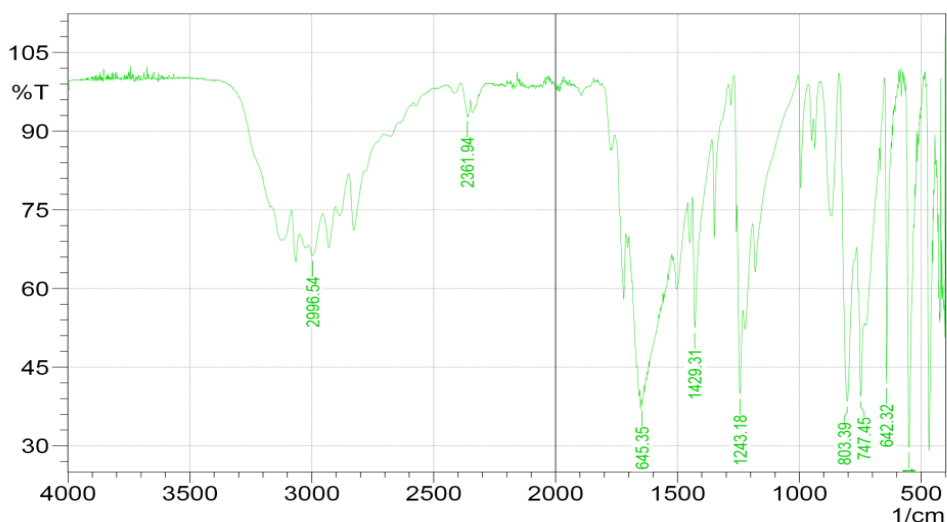
Floating microsphere was prepared by spray drying technique. For formulation of microsphere full factorial 23 design was applied. The independent factors were D: P ratio, aspirator speed and feed rate. Total 8 batches were prepared. An aqueous solution containing different ratios of the polymer table 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



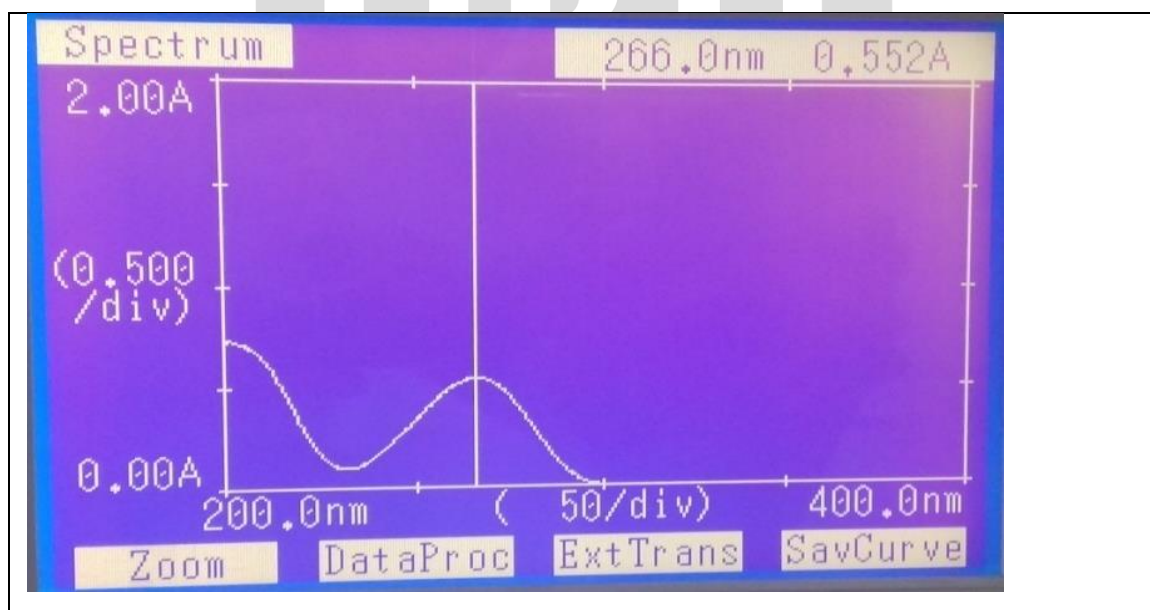
**Fig.01: FT-IR Peaks of Pure Drug 5-Fluorouracil.**

Functional group	Observed value $\text{cm}^{-1}$	Standard value $\text{cm}^{-1}$
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. :FT-IR Peaks of Pure Drug 5-Fluorouracil.**

## 2. UV Method for Estimation of 5-Fluorouracil

### Determination of $\lambda_{\text{max}}$



**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.04 : 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. 05 : 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  $\mu\text{m}$ , 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±0.222	0.173±0.01	0.198±0.04	12.62±0.663	1.144±0.02
B2	20.23±0.867	0.134±0.02	0.151±0.12	11.25±0.543	1.126±0.03
B3	23.13±0.532	0.231±0.12	0.264±0.10	12.50±0.250	1.142±0.02
B4	22.67±0.325	0.201±0.16	0.231±0.15	12.98±0.310	1.149±0.04
B5	27.03±0.543	0.280±0.05	0.305±0.08	8.19±0.125	1.089±0.03
B6	25.27±0.420	0.274±0.14	0.295±0.05	7.11±0.255	1.076±0.06
B7	24.54±0.320	0.260±0.02	0.285±0.09	8.77±0.321	1.096±0.02
B8	25.92±0.244	0.275±0.06	0.298±0.04	7.71±0.254	1.083±0.05

**Table No.06 : Micromeritics Properties of 5-Fluorouracil Microspheres.****a. Angle of repose**

The results of angle of repose were found in the range of  $20.23^{\circ} \pm 0.867$  to  $27.03^{\circ} \pm 0.543$  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  $1.083 \pm 0.05$  to  $1.149 \pm 0.04$  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	$96.40 \pm 0.003$
2	B2	0.273	4.720	$94.4 \pm 0.002$
3	B3	0.275	4.76	$95.20 \pm 0.004$
4	B4	0.283	4.92	$98.02 \pm 0.005$
5	B5	0.199	3.24	$97.29 \pm 0.002$
6	B6	0.203	3.32	$99.69 \pm 0.001$
7	B7	0.201	3.28	$98.49 \pm 0.004$
8	B8	0.200	3.26	$97.89 \pm 0.001$

**Table No. 07. : % Drug Content of 5-Fluorouracil microspheres.**

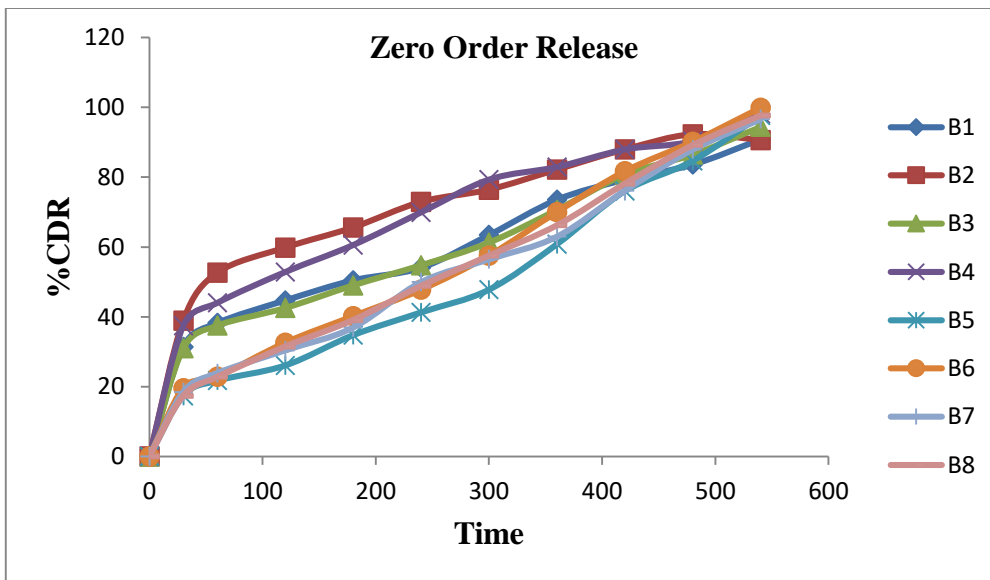
Drug content was found in the range between 94.4 - 99.69% for spray dried microspheres table no.20. Various co-solvents such as ethanol and water used for microsphere preparation since they can help to dissolved drug in major solvent and probably achieved higher drug content. Drug content depends on 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).

**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

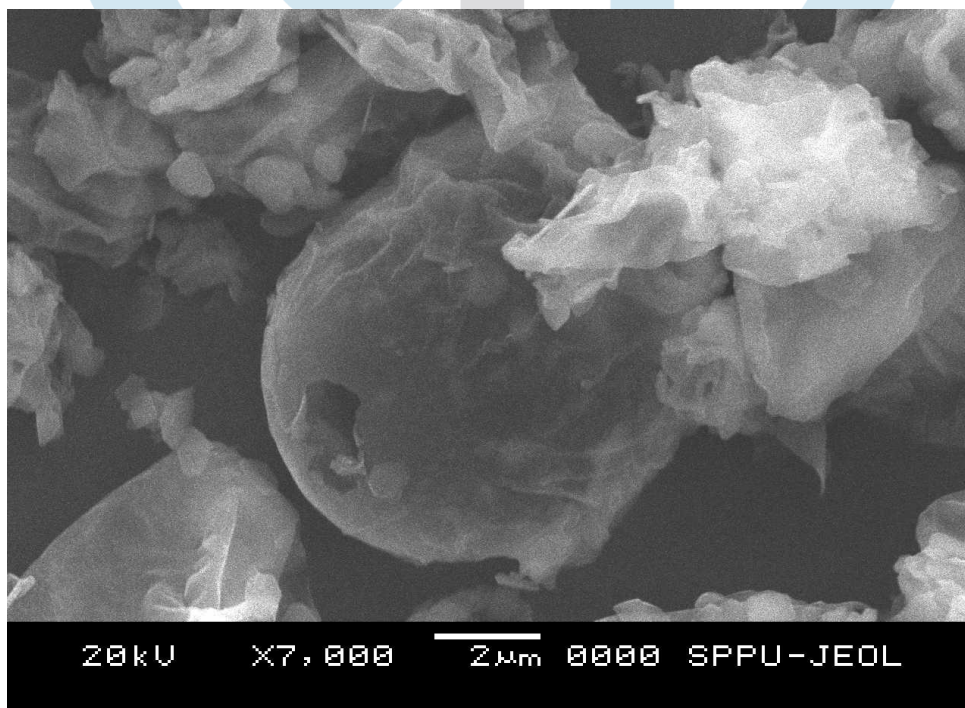
480	83.60	92.25	86.48	90.31	84.66	90.12	87.91	89.17
540	90.81	90.60	94.40	98.12	97.67	99.85	96.60	97.67
R <sup>2</sup>	0.905	0.804	0.923	0.857	0.977	0.985	0.982	0.986
K	0.135	0.135	0.141	0.143	0.161	0.168	0.161	0.165

**Table No. 08 : Zero Order Release profile for F1-F8 formulations.**

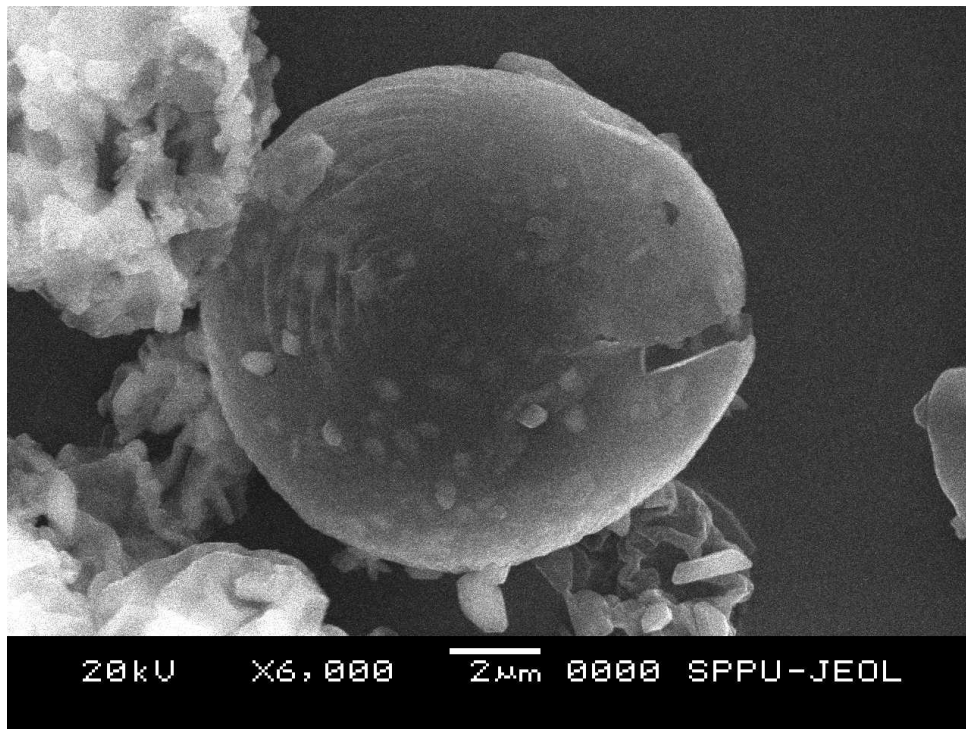


**Fig.3.: Zero Order Release profile for F1-F8 formulations.**

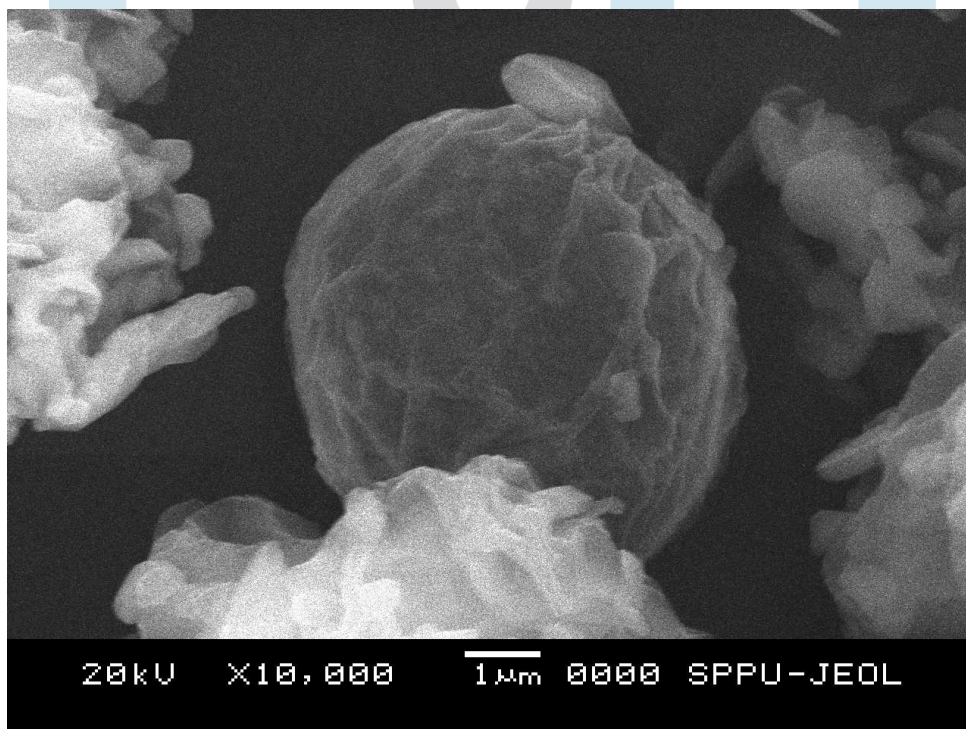
4. **Scanning Electron Microscopy of Formulations**



**Fig. 4.: SEM Formulation B4.**



**Fig. 5. : SEM Formulation B5.**



**Fig. 6: SEM Formulation B6.**

Morphology of prepared microspheres by Spray Drying method was discovered by SEM analysis. The representative SEM images of the prepared Microspheres are shown fig.66 to 68. SEM results indicated that Microspheres formed by Spray Drying Method are spherical in shape and having size 5 µm. Because, by Spray Drying method counter diffusion of organic solvents does not takes place which leads to the formation of pores. 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 (Pagar PS et al 2017, Shendge RS et al 2013).

## Accelerated Stability Study

Batch	Physical appearance	% Drug content	% Buoyancy
B1	No change	96.40	90
B2	No change	94.4	74
B3	No change	95.20	72
B4	No change	98.02	76
B5	No change	97.29	88
B6	No change	99.69	92
B7	No change	98.49	76
B8	No change	97.89	82

**Table No. 9. : Stability study of 5-fluorouracil formulations.**

The 5- fluorouracil microspheres were subjected to stability studies at elevated temperature 40°C and 75% RH for 30 days on the all formulations. Microspheres were observed for any change in physical appearance, % drug content and % buoyancy. The microspheres did not show any significant change in colour, % drug content and % buoyancy at the end of 30 days shown in table no.30. The stability result was indicated that all the formulations were stable for 30 days.

## CONCLUSION

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  $\lambda$  max of 5- Fluorouracil at 266nm. All prepared floating microsphere 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. 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.

Stability studies were carried out for the 5- fluorouracil microspheres at elevated temperature 40 and 75% RH for 30 days on the all formulations. The formulations did not show any significant change in colour, % drug content and % buoyancy at the end of 30 days. The stability result was indicated that all the formulations were stable for 30 days. Hence it can be concluded that 5- fluorouracil floating microsphere were successfully prepared and evaluated using ethyl cellulose and eudragit RS 100.

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