International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 **ijppr.humanjournals.com** ISSN: 2349-7203

Formulation and Evaluation of 5-Fluorouracil Loaded Multiparticulate System for Dual Targeting to Colon

Himanshi Soni[1], Jeetendra Kushwaha[2]

[1]Assistant Professor, [2]Associate Professor

[1]Balaji Pharmacy College Chhatarpur M.P. India

[2]Shanti College of Pharmacy Nowgong M.P. India.

Received: 2024-10-05 Revised: 2024-10-15 Accepted: 2024-10-20

ABSTRACT

The conventional cancer chemotherapy does not prove much effective in case of colorectal cancer as drug molecule does not reach at target site at therapeutic concentration also an effective treatment of colon cancer by conventional therapy requires a relatively large doses to compensate drug loss during its passage through upper GIT, which may be associated with the risk of undue side effects. This can be overcome by site-specific delivery of the drug molecule to colon. Hence, it was proposed to design a multiparticulates (mixture of different microspheres) system for site-specific delivery of anticancer drug (5-FU) using pH sensitive polymer coating (Eudragit S-100 and ethyl cellulose) on microspheres of natural polysaccharides (starch) bearing 5- FU for the treatment of colon cancer.

Keywords- Microsphere, 5-FU, Eudragit S-100, Ethyl cellulose.

INTRODUCTION

The various routes of administration have been searched for the effective delivery of the drug. The oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface are a among all drug delivery system for administration of various drugs. But if we consider the conditions, where localized delivery of the drug in the regions of the gastro-intestinal tract is required, the site specific drug delivery system can be helpful which deliver the drug at particular site of gastro-intestinal tract to avoid absorption of drug and degradation by gastric fluid. Controlled Drug Delivery System (CDDS) has been developing as one of the site-specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal tract (GIT), but rapidly releases drug in the colon following oral administration.

ANATOMY AND PHYSIOLOGY OF THE COLON

The large intestine is wider and shorter than the small intestine. The lumen progressively diminishes from a maximum diameter at the caecum (about 8.5 cm) to the sigmoid segment (about 2.5 cm). It can be divided into the caecum, ascending, transverse, descending, and sigmoid colon, rectum and anus (Figure No. 1).

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

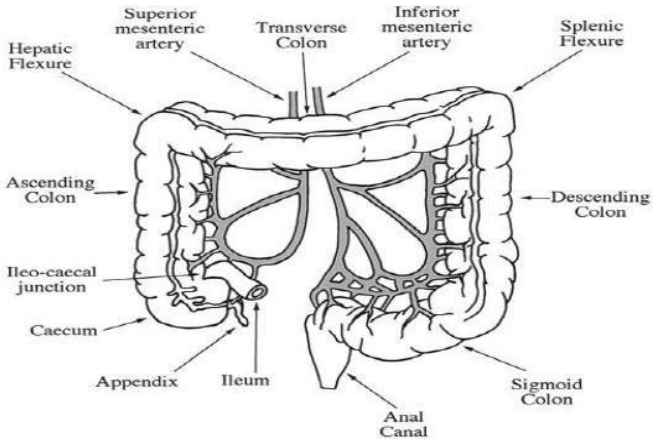


Figure 1: Anatomy and perfusion of the colon

MATERIAL METHOD-

There are following material used-

5-Fluorouracil, Eudragit S-100, Ethyl cellulose, Petroleum ether, Light liquid paraffin, Glutaraldehyde, Span 80, Hexane, Ethanol, Starch, Alpha amylase, Triethylamine citrate, Acetone, Talc, n-Octanol.

Preformulation studies- According to the Product Quality, Research division of US Food and Drug Administration (USFDA) the goal of Pre-formulation study is to investigate critical physicochemical factors which assure:

Table 1: Preformulation studies

Drug	**Test**	**Observation**
5-Fluorouracil	Chemical identification	It decolorizes bromine water.
5-Fluorouracil	General appearance	Crystalline Powder
5-Fluorouracil	Color, Odor	White, Odorless
5-Fluorouracil	Melting point	280-283°C
Solubility study		
S. No.	Solvent	Solubility
1.	Water	+++
2.	DMSO	++
3.	Methanol	+
4.	Ethanol	+
5.	Ether	-
6.	Chloroform	-
7.	Benzene	-

++++=Freelysoluble1-10parts, +++=Sparinglysoluble30-100parts,

++ = Soluble 30-100 parts,+ = Slightly soluble100-1000 parts,– = Practically insoluble>10000 parts

Solubility study in different solvents at room temperature revealed that it is soluble in distilled water and insoluble in chloroform, benzene.

Infrared Spectroscopy

FT-IR spectrum of the drug and standard are shown in FigureNo.2 and 3. The observed peaks were compared with standard reported for functional groups.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

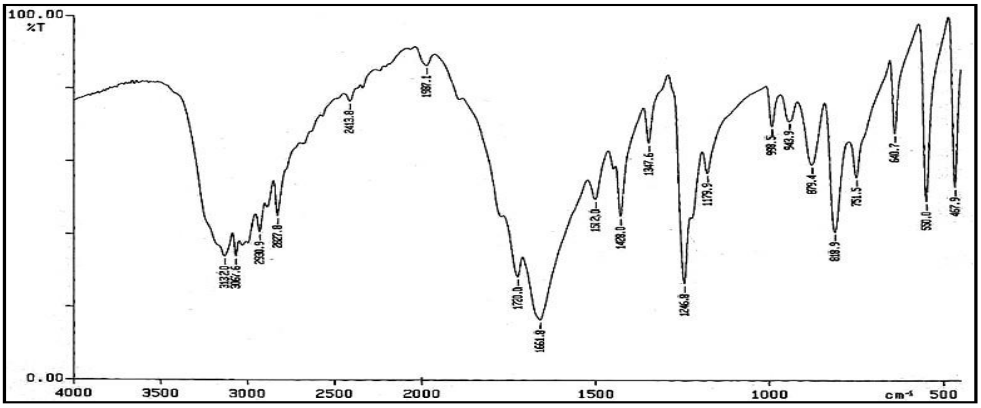


Figure 2: FT-IR spectrum of 5-fluorouracil

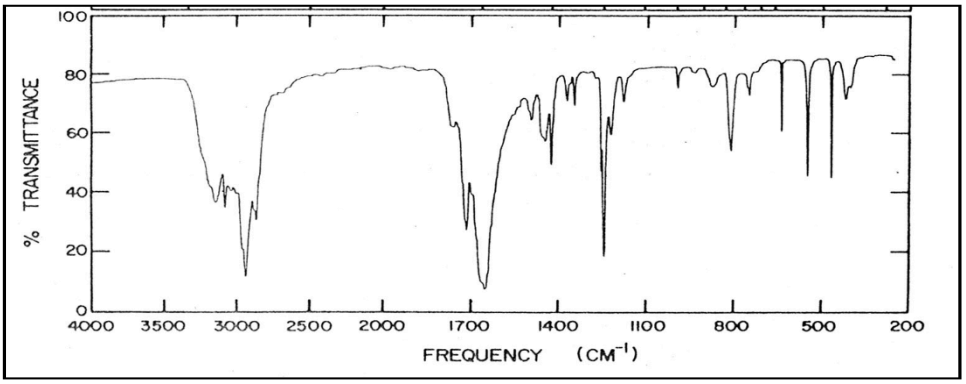


Figure 3: Reference FT-IRspectrumof5-fluorouracil

Table 2: Important band frequencies in IR spectrum of 5-FU

S. No.	Named Group	Reported Band frequency	Band frequency obtained
1.	NH stretch	3124	3132.0
2.	C=O stretch	1716and1657	1720.0&1661.8
3.	CH in plane deformation	1245	1246.8
4.	CH out of plane deformation	813	818.9
5.	C-F	1028	998.5
6.	Benzene ring	1495	1502.0

As the spectra of drug and standard shown in Figure No. 2 & 3, it was observed that there was small shift in frequency which may be due to the presence of moisture or improperly drying. According to various research papers small shift in frequency can be neglected but large shift in frequency is responsible for major change in a compound. Therefore the drug can be use for further studies.

Partition Coefficient

Partition coefficient of drug is shown in three different phases in Table no. 3.

Table 3: Partition coefficient values of 5-fluorouracil

S. No.	Solvent system	Partition Coefficient
1.	n-Octanol/Distilled water	0.1685
2.	n-Octanol/PBS(pH7.4)	0.1246
3.	n-Octanol/PBS(pH7.0)	0.1057

Partition coefficient value of 5-FU also revealed its hydrophilic nature.

Determination of Absorption Maxima (λmax)

An acidic solution of 5-FU was scanned in the U.V. range of 200-400 nm using Shimadzu 1800 UV Visible spectrophotometer. The Spectrophotometric method of analysis of 5-FU at λmax 266. 0 nm was found to be reproducible and highly sensitive.

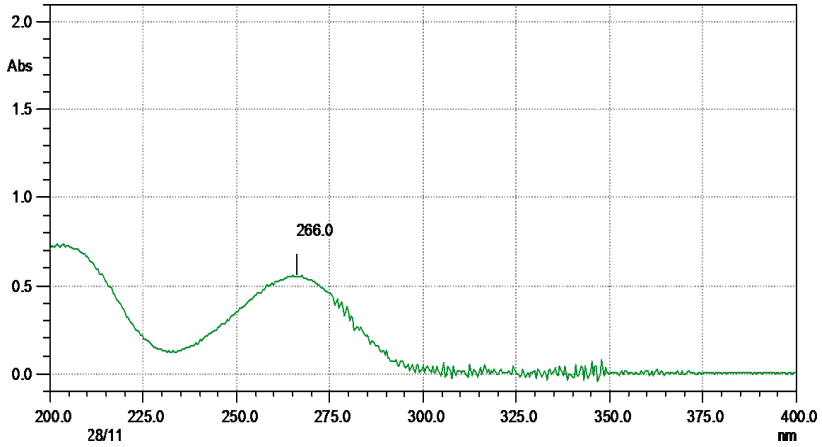


Figure 4: UV spectra of 5-fluorouracil

PREPARATION OF STANDARD CURVE OF 5-FU IN DIFFERENT SOLUTIONS

Preparation of Standard Curve of 5-FU in Water

Table 4: Standard curve of 5-FU in water at 266.0 nm

S. No.	Drug Conc. (µg/ml)	Absorbance	Regressed Absorbance	Statistical Parameters
1.	2	0.0910	0.077	
2.	4	0.1912	0.165	
3.	6	0.2834	0.252	
4.	8	0.3543	0.340	
5.	10	0.4432	0.428	
6.	12	0.5328	0.515	R2=0.9994
7.	14	0.6312	0.603	y=0.0438x+0.0104
8.	16	0.7168	0.690	
9.	18	0.8013	0.778	
10.	20	0.8810	0.866	

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

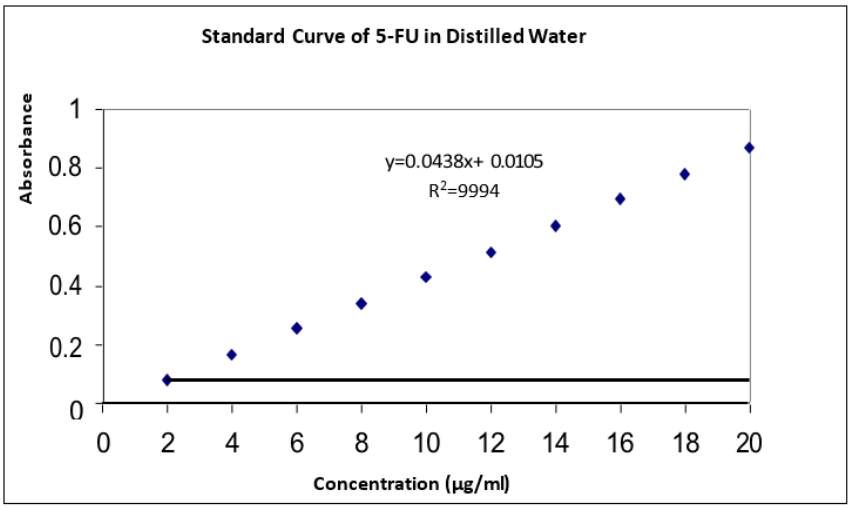


Figure 5: Linearly regressed standard curve of 5-FU in water at λmax 266. 0 nm

6.1.4.2 Standard Curve of 5-FU in Buffer Saline (pH1.2)

Table 5: Standard curve of 5-FU In buffer saline (pH1.2) at 266. 0 nm

S. No.	Drug Conc. (µg/ml)	Absorbance	Regressed Absorbance	Statistical Parameters
1.	2	0.1382	0.1223	
2.	4	0.2452	0.2451	
3.	6	0.3744	0.3679	
4.	8	0.4921	0.4907	
5.	10	0.6085	0.6135	
6.	12	0.7238	0.7363	
7.	14	0.8318	0.8591	R2=0.9971
8.	16	0.9632	0.9819	y=0.061x-0.0005
9.	18	1.0982	1.1047	
10.	20	1.2728	1.2275	

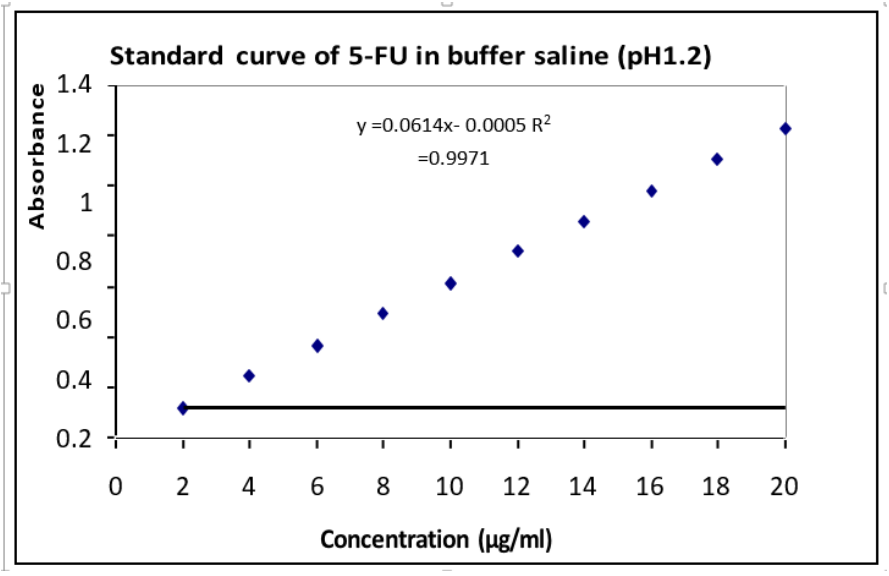


Figure 6: Linearly regressed standard curve of 5-FU in buffer saline (pH 1.2) at λmax 266.0 nm

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

6.1.4.3 Standard Curve of 5-FU in Buffer Saline (pH4.5)

Table 6: Standard curve of 5-FU in buffer saline (pH4.5) at 266. 0 nm

S. No.	Drug Conc. (µg/ml)	Absorbance	Regressed Absorbance	Statistical Parameters
1.	2	0.0874	0.0843	
2.	4	0.1208	0.1233	
3.	6	0.1678	0.1623	
4.	8	0.2056	0.2013	
5.	10	0.2438	0.2403	
6.	12	0.2721	0.2793	
7.	14	0.3049	0.3183	R2=0.993
8.	16	0.3442	0.3573	y=0.0195x+0.0453
9.	18	0.3931	0.3963	
10.	20	0.4552	0.4353	

RESULT AND DISCUSSION

OPTIMIZATION

Optimization of Formulation Variables

Various formulation variables were tried to prepare microspheres. The effect of drug concentration, starch concentration, volume of cross- linking agent and emulsifier concentration were optimized in terms of the particle size and drug entrapment efficiency.

Table 7: Optimization of drug concentration

S. No.	Formulation Code	Amount of 5-FU (mg)	Amount of starch (mg)	Average diameter (µm)	Drug entrapment
1	SMD1	50	500	184.14±6.54	68.24±1.82
2	SMD2	100	500	185.25±8.60	70.82±1.65
3	**SMD3**	**200**	**500**	**185.65±6.51**	**74.98±0.78**
4	SMD4	300	500	188.79±7.53	72.28±1.02

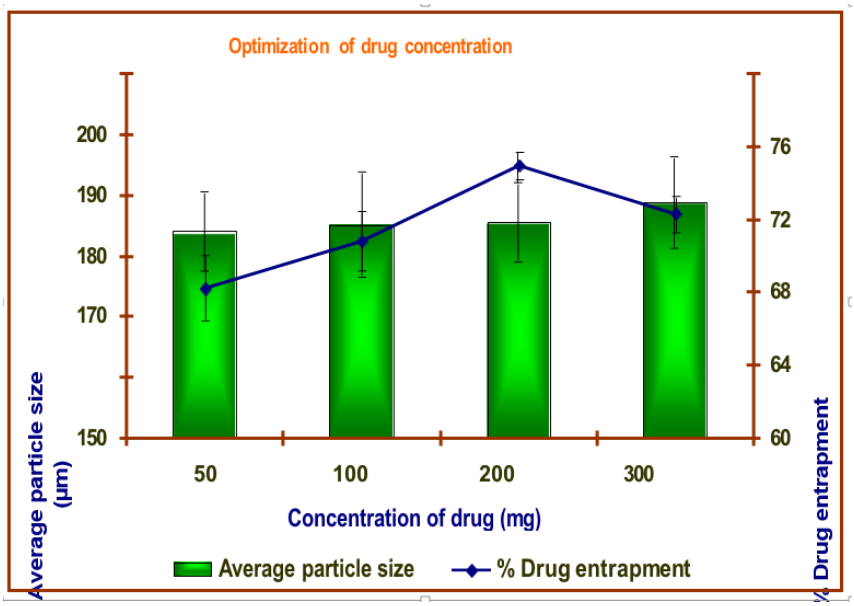


Figure 7: Optimization of drug concentration with respect to particle size and % drug entrapment efficiency

The mean diameter of starch microspheres varied from 184.14 µm to188.79µm on varying the amount of 5-FU from 50mg to 300 mg. The average particle size of starch microspheres increased with increasing 5-FU concentration and the total drug entrapment efficiency varied from 68.24% to74.98%. As the drug entrapment efficiency was highest in cased SMD3 i.e. 74.98% and the size of microspheres was 185.65µm respectively, and hence this formulation containing 200mg of 5-FU was considered optimum and selected for further study.

Optimization of Emulsifier concentration:

Table 8: Optimization of Emulsifier concentration

S. No.	Formulation Code	Emulsifier concentration (%)	Average diameter (µm)	% Drug entrapment
1	SMD3P2C2E1	0.75	189.18±7.45	70.32±0.98
2	SMD3P2C2E2	1.0	175.76±6.70	72.41±1.21
3	**SMD3P2C2E3**	**1.25**	**174.00±5.51**	**73.92±0.72**
4	SMD3P2C2E4	1.5	172.37±8.66	64.25±1.04

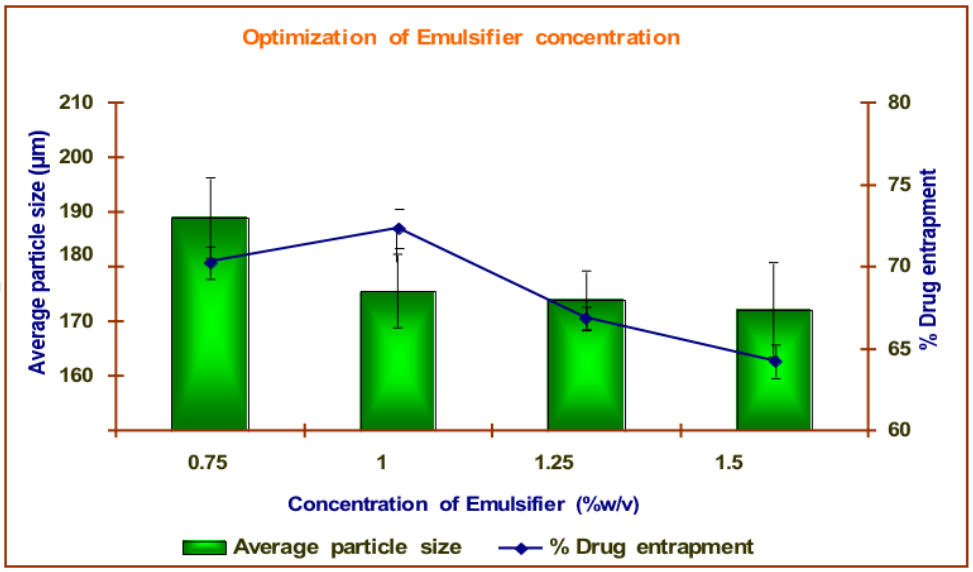


Figure 8: Optimization of Emulsifier concentration with respect to particle size and % drug entrapment efficiency

In the study of the effect of emulsifier concentration on formation of starch microspheres it was observed that on varying emulsifier concentration (Span80) from 0.75 to 1.5 ml w/v the size of microspheres was found to be 172.37 to 189.18 µm. Above 1.25 ml. emulsifier concentration, the dispersed particles were fused to produce larger microsphere (according to their reduced surface area). The total drug entrapment efficiency varied from 64.25% to 73.92% for the production of optimum formulation (SMD3P2C2E3: volume of cross-linkers0.8ml).

EUDRAGIT COATING OF STARCH MICROSPHERES

Optimization of Core: Coat Ratio

Table 9: Effect of core: coat ratio on particle size, shape and size distribution of Eudragit coated starch microspheres

Formulation Code with core: coat ratio	Average Diameter (µm)	Shape
SMD3P2C2E3R2T4-1(1:5)	254.04±12.54	Uncoated particles seen, Coating insufficient
SMD3P2C2E3R2T4-2(1:10)	**256.46±10.84**	**Spherical with uniform coating**

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

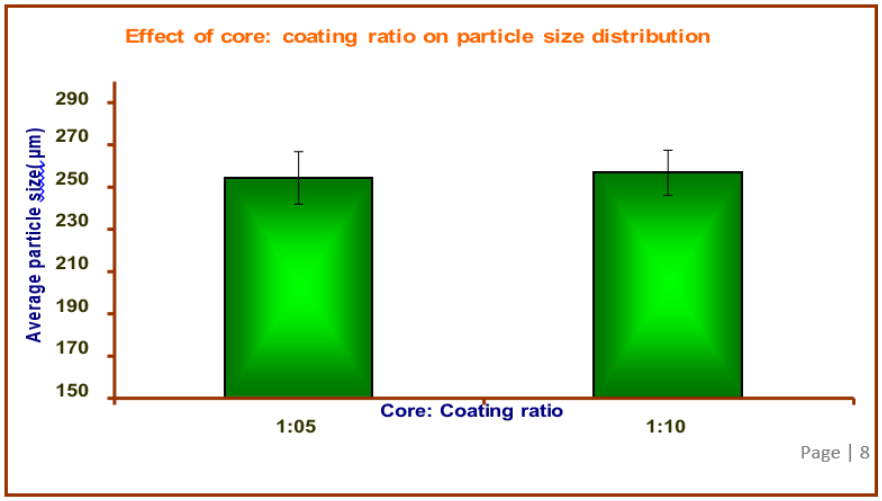


Figure 9: Effect of core: coat ratio on particle size distribution of Eudragit coated microspheres

For core: coat ratio from 1:5 to 1:10 the mean diameter of Eudragit S-100 coated microspheres varied from 254.04 to 256.46 µm. The coated microspheres were found to be of spherical shape and had sufficient coating with (1:10) core: coat ratio. Therefore, 1:10 ratio of core to coat was selected as optimal.

ETHYL CELLULOSE COATING ON STARCH MICROSPHERES

Optimization of Core: Coat Ratio

Table 10: Effect of core: coat ratio on particle size, shape and size distribution of ethyl cellulose coated starch microspheres

Formulation Code with core: coat ratio	Average Diameter(µm)	Shape
SMD3P2C2E3R2T4-1 (1: 5)	254.53±10.77	Uncoated particles seen, Coating insufficient
SMD3P2C2E3R2T4-2 (1:10)	**260.80±9.55**	**Spherical with uniform coating**

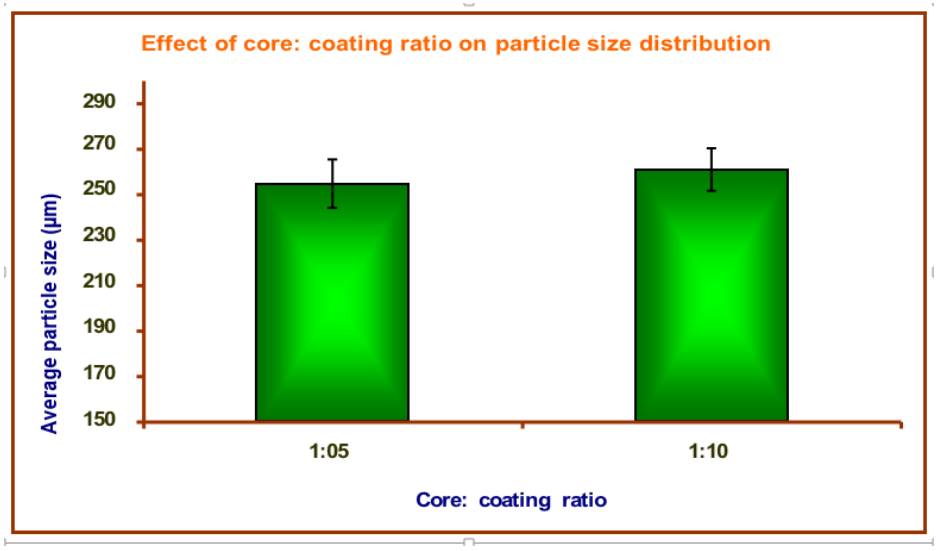


Figure 10: Effect of core: coat ratio on particle size distribution of ethyl cellulose coated microspheres

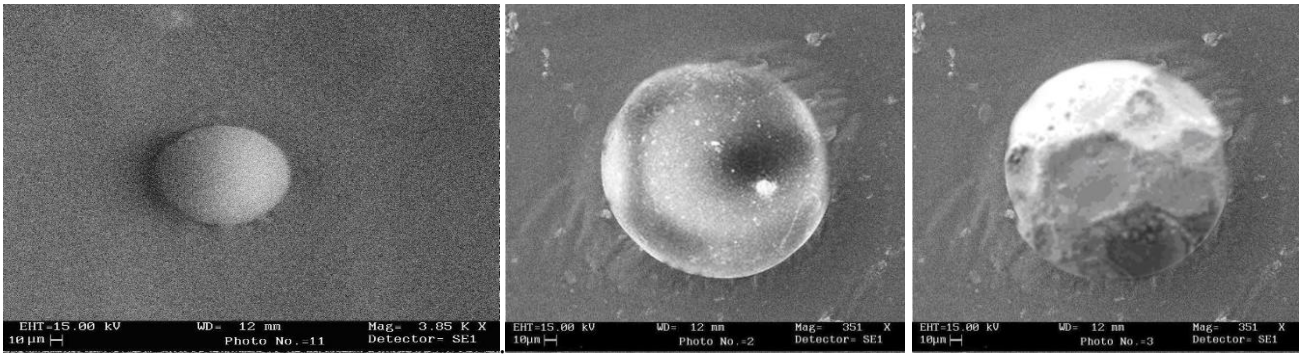
For core: coat ratio from 1:5 to 1:10 the mean diameter of ethyl cellulose coated microspheres varied from 254.53to 260.80 µm. The coated microspheres were found to be of spherical shape and had sufficient coating with (1:10) core: coat ratio. Therefore 1:10 ratio of core to coat was selected as optimum for ethyl cellulose coating.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

CHARACTERIZATION OF PREPARED MICROSPHERES

Shape and Surface Morphology

In order to examine the surface morphology, the formulations were viewed under scanning electron microscope (SEM). SEM photomicrographs of microspheres are shown in photograph 24(a) for starch microspheres and photograph 24(b) for Eudragit coated microspheres and photograph 24(c) for Ethyl cellulose coated microspheres.



(a) **(b)** **(c)**

Photographs 24: SEM Photomicrographs of (a) uncoated microspheres; (b) Eudragit S-100 coated starch microspheres; (c) Ethyl cellulose coated starch microspheres.

Size and Size Distribution

Microspheres size and size distribution was studied by microscopically and the effect of drug concentration, polymer concentration, volume of cross linking agent, emulsifier concentration, stirring rate and stirring time on the particle size, shape and size distribution were also studied on starch microspheres. The observations are recorded in the Table and graphically shown in Figure. Effect of core: coat ratio was also studied for Eudragit and Ethyl cellulose coating on starch microspheres and observations are recorded in Table, graphically represented in Figure 9 and 10 for Eudragit S-100 coated starch microspheres and Ethyl cellulose coated microspheres respectively.

Study of Degree of Swelling

Table 11: Degree of swelling of starch microspheres, EudragitS-

100 and ethyl cellulose coated starch microspheres and their combinations.

S. No.	Microspheres	Formulation Code	Degree of Swelling
1.	Starchmicrospheres	SMD3P2C2E3R2T4	2.84
2.	Eudragit S-100 coated starch microspheres	ESM D3P2C2E3R2T4	0.18
3.	Ethyl cellulose coated starch microspheres	ECSM D3P2C2E3R2T4	0.11
4.	Mixed multi particulates (1:1:1)	MM	1.12

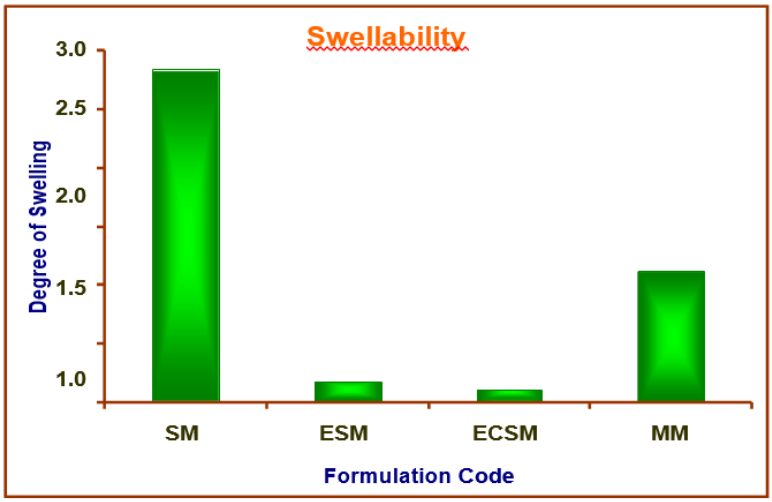


Figure 11: Degree of swelling of various microspheres formulations

Swellability of different microspheres was determined. No significant swelling was observed with the Eudragit coated microspheres, ethyl cellulose coated microspheres as compared to starch microspheres. This showed the better resistance of Eudragit S-100 and Ethyl cellulose coating on microspheres for swelling in upper GIT and subsequent drug release at the non-target site.

***IN VITRO* DRUG RELEASE STUDY IN SIMULATED GASTROINTESTINAL FLUIDS OF DIFFERENT pH**

Table 12: % Cumulative release of 5-FU from various microspheres system at different pH

Formulation Code	Cumulative% 5-FUReleasedatdifferenttimeintervals									
	(pH1.2)		(pH4.5)		PBS (pH6.8)		SCF (pH7.5)			
	1h	2h	3h	4h	5h	6h	7h	8h	9h	10h
SMP D3P2C2E3R2T4	8.52± 0.04	16.81 ±0.07	46.62 ±0.12	68.38 ±0.22	79.92 ±0.24	81.72 ±0.30	83.70 ±0.08	87.92 ±0.16	88.23 ±0.15	90.12 ±0.35
ESMP D3P2C2E3R2T4	O.34 ±0.012	0.93 ±0.010	1.26 ±0.011	2.12 ±0.031	4.62 ±0.42	16.12 ±0.12	38.32 ±0.46	69.32 ±0.36	70.12 ±0.33	72.22 ±0.18
ECSMP D3P2C2E3R2T4	0.23 ±0.015	0.28 ±0.031	0.99 ±0.036	1.76 ±0.018	8.12 ±0.025	12.24 ±0.26	40.28 ±0.53	70.92 ±0.11	75.82 ±0.18	86.98 ±0.53
MM {1:1:1}	3.16 ±0.12	5.36 ±0.16	16.12± 0.11	25.22± 0.14	30.92 ±0.36	42.92 ±0.19	67.84 ±0.25	78.42 ±0.23	83.74 ±0.11	85.98 ±0.38

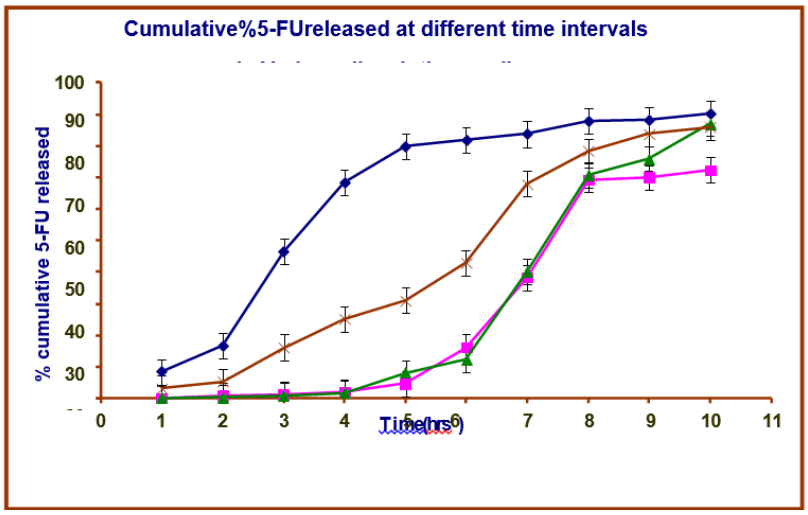


Figure 12: % Cumulative release of 5-FU from various microspheres at different pH

The *in vitro* release profile of starch microspheres, Eudragit coated and ethyl cellulose coated microspheres and mixed multiparticulates (1:1:1) was performed in phosphate buffer saline medium of different pH (Table No. 12).

The result indicated that cumulative percent drug release of 5- FU from starch microspheres in (pH1.2), (pH4.5) and PBS (pH6.8) after 6 hrs was found to be 8.52 to 81.72 % respectively, Eudragit S-100 coated starch microspheres after 6 hrs was found to be 16.12% (Table No. 12) and from ethyl cellulose coated starch microspheres after 6hrs it was found to be to 12.24% (Table No. 12) and from mixed starch multiparticulate after 6 hrs, it was found to be 42.92% (Table No. 12).

In Phosphate buffer solution containing α-Amylase (pH7.5) after 10 hrs study, the drug release in 7 to 10 hrs was found to be 83.70 to 90.12 % from plain starch microspheres, 38.32 to 72.22% from Eudragit S-100 coated starch microspheres, 40.28 to 86.98 %. From ethyl cellulose coated starch microspheres and 67.84 to 85.98 for mixed multiparticulates formulation.

The maximum release of 5- FU from microspheres in Phosphate buffer solution containing α- Amylase (pH7.5) may be due to colonic pH which is around (pH6.8- 7.5) and presence of α-Amylase which is responsible for starch digestion.

The study also suggested that the in vitro release of drug in initial 6 hrs from Eudragit S-100 coated and ethyl cellulose coated microspheres was less than that from uncoated starch microspheres.

SUMMARY AND CONCLUSION

Colorectal cancer is the second leading cause of cancer deaths. The conventional cancer chemotherapy does not prove much effective in case of colorectal cancer as drug molecule does not reach at target site at therapeutic concentration also an effective treatment of colon cancer by conventional therapy requires a relatively large doses to compensate drug loss during its passage through upper GIT, which may beassociated with the risk of undue side effects. This can be overcome by site-specific delivery of the drug molecule to colon. Hence, it was proposed to design a multiparticulates (mixture of different microspheres) system for site-specific delivery of anticancer drug (5-FU) using pH sensitive polymer coating (Eudragit S-100 and ethyl cellulose) on microspheres of natural polysaccharides (starch) bearing 5- FU for the treatment of colon cancer.

In the present study, natural polymer (starch) is used as it is resistant to the digestive action of gastrointestinal enzymes and enteric polymers (Eudragit S-100 and ethyl cellulose) as protective coating on the microspheres. These enteric polymers helps microspheres to release the drug at particular pH of colonic fluid. Hence a combined mechanism of release is followed to protect the drug loss in upper GIT due to inherent property of polysaccharide and deliver the loaded drug in the colon only.

The drug 5-FU (from Biochem pharmaceutical Industries Ltd. Daman) is a white crystalline, odourless, hygroscopic powder. Its melting point was found to be 280-283°C.The results indicated that the drug was pure. The solubility and partition coefficient studies revealed that drug (5-FU) is highly polar and hydrophilic in nature.

On scanning the aqueous drug solution on UV visible spectrophotometer between 200 to 400 nm the λmax was observed at 266.0nm. Standard curve of 5-FU were prepared using Shimadzu 1800 UV Visible spectrophotometer in distilled water, buffer saline (pH1.2), (pH4.5) PBS (PH6.8), PBS (pH7.4) and PBS (pH7.5) at λmax 266.0 nm.

The Beer-Lambert's law was followed at the concentration range of 2-20 µg/ml at λmax 266.0 nm.

Drug-excipients compatibility study was carried out and it was observed that starch, Eudragit S-100 and ethyl cellulose had good compatibility with 5-FU.

The starch microspheres were formulated by modified emulsion cross linking method with slight modification .Results suggested that formulation variables and process variables influenced the average diameter and entrapment efficiency.

Then the prepared starch microspheres were characterized for its shape and surface morphology, size and size distribution, swellability, entrapment efficiency and *in vitro* drug release.

Shape and surface morphology of starch microspheres were observed microscopically using scanning electron microscope and was found to be spherical in shape with smooth surface.

The average diameter of dried microspheres was determined by using calibrated ocular eyepiece. It was observed that the average diameter of microspheres increased with increasing concentration of polymer and volume of cross linking agent. The size of

microspheres, decreased with increasing rate of stirring, time of stirring and emulsifier concentration. The average diameter of optimized uncoated starch microspheres was found to be 177.83±5.80 µm.

Eudragit S-100 and ethyl cellulose coating of starch microspheres was done by solvent dip coating method. The different core: coat ratios 1:5 and 1:10 were optimized to get spherical microspheres with smooth surface in 1:10 core: coat ratio.

The shape and surface morphology of Eudragit S-100 and ethyl cellulose coated microspheres were observed microscopically using scanning electron microscope and microspheres were found to be spherical in shape with smooth surface.

In vitro drug release was carried out in buffer saline of different pH 1.2, 4.5, PBS 6.8, and in PBS containing α-Amylase pH 7.5. It was observed that drug released in PBS 1.2 and PBS 6.8 from mixed multiparticulates. A loss of drug was found in PBS 1.2 + PBS 6.8 up to 42.92±0.19. This may be due to the swelling of starch in the medium. The drug release 85.98±0.38 in PBS 7.5, it may be due to the intestinal pH which is around pH 6.8-7.5 and α-Amylase which is responsible for starch digestion.

Result of *in vitro* drug release studies suggested that the drug release from mixed multiparticulates was influenced by polymer and emulsifier concentrations. The initial burst release of 5-FU resulted from the dissolution of drug molecules adsorbed on the surface of mixed multiparticulates. The percent cumulative drug release was found decreased with increasing polymer concentration. This may be due to the increased matrix density and decreased pore size, which limits access of dissolution medium to the entrapped drug.

REFERENCES

1. Mashal A R, Ozturk K,Calıs S, “Preparation and *in vitro* evaluation of 5- fluorouracil-loaded PCL nanoparticles for colon cancer treatment” Journal of Applied Pharmaceutical Science, 2017; 22: 635-641.
2. Rao YueFeng, Yao Wendong, Gao Jianqing “pH-Responsive carriers for oraldrug delivery: challenges and opportunities of current platforms”. Drug delivery, (2017); 24: 569-581.
3. Patil Pallavi, P. Srinivasa Babu, G. Kishore Babu “Development and Validation of Analytical Method for Estimation of 5-Fluorouracil in Bulk and Marketed Formulation by UV-Spectrophotometer”. Int. J. Pharm. Sci. Rev. Res., 2017; 42: 8-11.
4. Nirwane Aboli, Magdum C.S, Mohite S. K, Dhughgaonkar T.D, Hommane P. P, Kore P. S, “Development And Evaluation of Multiparticulate Colon Targeted Drug Delivery System”. Sci. Revs. Chem. Commun. 2016; 6(2): 27-35.
5. Nandgude Tanaji Dilip, R. Sundara Ganapathy, “Formulation and Development of Colon Specific Multiparticulate System of Capecitabine”. Asian Journal of Pharmaceutics, 2016; 10:S402-S407.
6. P Arulraj,V Gopal, G Jeyabalan, C S Kandasamy, R Venkatanarayanan, “Studies on formulation development and in vitro evaluation of celecoxib matrix tablet containing combination of equal ratio of natural gums guargum and cyclodextrin, amylose and pectin for colon specific drug delivery”. IJPSR, 2015; 6: 5273-5278.
7. Rao Anka A , Rao Narasimha V, K. Anil, V. Vasu Naik and A. Rajesh, “Oral Controlled Release Drug Delivery System: An Overview”. International Journal of Pharma and Chemical Research, (2015); 1: 6-15.
8. Amidon Seth,Brown E. Jack, Dave S. Vivek, “Colon-Targeted Oral Drug Delivery Systems: Design Trends and Approaches”. AAPS PharmSciTech. (2015); 16(4): 731–741.
9. Mohanty Sangeeta, Panigrahi Kumar Amit, “Multiparticulate drug delivery system for colon targeting”. International journal of pharmacy andpharmaceutical sciences, (2015); 7:0975-1491.
10. Patil V. G, Sayyad F. J,“Optimization of polymer coating level for colon targeted sustain release metoprolol succinate pellets using 32 factorial design”. IJPSR, (2015); 6: 1680-1692.
11. M. Prathap, Gulshan MD, RaoN. Rama,**“**Colon: targeted drug delivery system – a review”. International Journal of Research in Pharmaceutical and Nano Sciences, 2014; 5:429 - 437.
12. Chin Fun Suk, Siti Nur Akmar Mohd Yazid, Suh Cem Pang Cem Suh, “Preparation and Characterization of Starch Nano particles for Controlled Release of Curcumin”. International Journal of Polymer Science, (2014).
13. Sharma Ankush, Singh Amritpa, Pooja, Anju, “Novel approaches for colon targeted drug delivery system” international journal of research and development in pharmacy and life sciences, (2014); 3: 877-886.
14. Danda Sreelatha, Brahma Kumar Chandan, “Colon targeted drug delivery – a review on primary and novel approaches”. Journal of Global Trends in Pharmaceutical Sciences, (2013); 4:1174-1183.
15. Mishra Sharadendu, “Formulation and evaluation of pH sensitive nanoparticles for colon targeted drug delivery system”. Pharmaceut Anal Acta, (2013); 4: 169- 175.
16. Kankana Bardhan,Liu Kebin, “Epigenetics and Colorectal CancerPathogenesis”. Cancers, (2013); 5: 676-713.
17. R. Jayaprakash, V.V Prasanth, Mathew Sam, “Colon Specific Drug Delivery Systems: A review on Various Pharmaceutical Approaches” Journal of Applied Pharmaceutical Science, 2012; 02: 163-169.
18. Ruchita V. Kumar, Sinha Ranjan Vivek “Tailoring of drug delivery of 5- fluorouracil to the colon via a mixed film coated unit system”. Acta Pharm. 61 (2011) 343–351.

19. Naidu RAS, R. Gopinath "Pharmaceutical preformulation studies. Current review". International Journel of Pharmaceutical Biological Archieves. (2011); 2(5):1391 -1400.
20. British Pharmacopoeia, Published by the stationary office on behalf of the medicine and healthcare product regulatory agency. (2011); 1: 936.
21. Indian Pharmacopoeia, Govt.of India, Ministry of Health and Family Welfare, Published by India, (2010); 3(6): 334-1367.
22. Philip Anil K, Philip Betty, "Colon Targeted Drug Delivery Systems: A review on primary and novel approaches". Oman Med J, 2010; 25(2): 79–87.

How to cite this article:
Himanshi Soni et al. Ijppr.Human, 2024; Vol. 30 (10): 151-163.

Conflict of Interest Statement: All authors have nothing else to disclose.