Advances in Bioresearch
Adv. Biores., Vol 14 (5) September 2023: 292-300

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.5.292300

Advances in Bioresearch

ORIGINAL ARTICLE

Enhancement of Bioavailability of 5-Fluorouracil at Colonic Site by Various Complexation Techniques

Paresh Ashok Patil[1], Mohan Lal Kori[1], Neha Jain[1*]
Vedica College of B. Pharmacy
Constituent Institute of Ram Krishna Dharmarth Foundation University, Bhopal (M.P.)
Corresponding Author's Email id: nehasniper@gmail.com

ABSTRACT
5-Fluorouracil (5-FU) has a wide assortment of anticancer activity, as well as colorectal region and is sparingly soluble in water or at the site of colonic region. It is a BCS class III drug that shows poor permeability. The proposed work permitted to develop aqueous and colonic region solubility and dissolution rate of 5-fluorouracil; thus, can be increased by a range of formulations i.e. inclusion complexation with β-cyclodextrin, by physical mixture, kneading, co-grinding and solid dispersion methods. The use of novel carriers and methodologies would be very favorable for formulation scientists to develop some solid dispersion (SDs) based formulations for their commercial use and clinical applications. This study established successful production of pH responsive 5 FU solid dispersions, by co-griding methods. The release follows Korymeyer–Peppas kinetic models and selectively delivered 5 FU to the colon which improved bioavailability at site of colonic medium
Keywords*: 5-Fluorouracil, solubility, solid dispersion, β-cyclodextrin, inclusion complex, colon cancer*

Received 21.05.2023 Revised 13.06.2023 Accepted 24.08.2023

How to cite this article:
Paresh A P, Mohan L K, Neha J. Enhancement of Bioavailability of 5-Fluorouracil at Colonic Site by Various Complexation Techniques. Adv. Biores., Vol 12 (5) September 2023: 292-300.

INTRODUCTION

Cancer of colon and rectum is one of the maximum internal malignancies. Colorectal most cancers are the second one leading purpose of cancer deaths inside the United States. Majority of human's distress with colorectal cancer are above the age of 50. Dietary factors consisting of low folate consumption are concept to increase the chance of colorectal cancer by two to five times. The prevalence of colorectal cancers could be decreased dramatically through preventive techniques including colonoscopy and detection of mutations in fecal DNA [1].

Almost all instances of colorectal cancer begin with the development of benign or noncancerous polyps. When colon cancers cells multiply outside the colon or rectum to lymph nodes, it may also spread to different lymph nodes, the liver, or other organ [2]. Structurally, the 4 essential areas of the large intestine are the ceacum, colon, rectum and anal canal [3]. The colonic mucosa is split into 3 layers: the muscularis mucosae, the lamina propria and the epithelium. The surface region of colon is lots less as compared to small intestine, for this reason not ideally fitted for absorption. The absorption potential of colon is very high which is attributed to the colon transit time and absorption is encouraged via the transport of water, electrolytes and ammonia across the mucus, and it is more in the proximal colon than the distal colon [4].

Chemotherapy is used to manage advanced colorectal cancers. Though, usual chemotherapy is not as powerful in colorectal cancers as it is effective in other cancers, as the drug does not attain the target in efficient concentrations [5-7]. The Fluorouracil (5-FU) chemotherapeutic medicines are used by alone or in combination to manage colorectal cancer, accordingly lessen the charge of recurrence and enhance possibilities of survival. Conventional drug therapies necessitate periodic doses of therapeutic medicine. These therapeutic agents are formulated to bring into being utmost stability, activity and bioavailability. For most drugs, traditional strategies of drug administration are efficient, but some drugs are unstable or toxic and have constricted therapeutic ranges. A number of drugs also own solubility problems. In such cases, a technique of continuous administration of medicine is ideal to hold fixed plasma level and

controlled release dosage forms may be capable to triumph over the problems of traditional forms. This can by lessening in medicine blood level fluctuation and through controlling the rate of medicine release, "peaks and valleys" of medicine blood levels are eliminated. Such strategies can improve patient's expediency and fulfillment with less frequency of dose administration, a patient is much less apart to overlook taking a dose.

There is as well greater patient and/or caregiver expediency with dynamic and night time medication administration. Various conventional drug delivery systems have been designed by different researchers to adapt the release a drug over an extended phase of time [8]. The rate and amount of drug absorption from conventional formulations may diverge significantly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as attendance or nonattendance of food, pH of the gastro-intestinal tract and so on [9].

The oral bioavailability depends on numerous factors with aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most common reason of low oral bioavailability is attributed to low solubility and low permeability. Solubility as well plays a primary function for other dosage forms like parenteral formulations. Solubility is solitary critical parameters to gain desired concentration of drug in systemic circulate for accomplish required pharmacological reaction. The drug 5-fluorouracil is soluble in water and however have sparingly or restricted solubility on colonic environment; so, drug was administered intravenously [10-11].

The drug having little bioavailability, consequently the drug was substantial limitation use for clinical purpose. When the same dose became given by way of oral ingestion to the affected person plasma level turned into underneath, and bioavailability much less, hence increased markedly if the dose was doubled. The quantity of drug concentration increases and results showed extreme toxicological harm to the gastrointestinal (GI) system, neurological, dermatological and cardiological reactions. Thus it is a crucial to enhance the solubility and dissolution rate of drug 5-FU to improve oral bioavailability to reduce the dose and the systematic side outcomes at colonic site with reduce dose strength [12-14].

Thus, it's necessary to develop promising DDSs for 5-FU to reach higher therapeutic effect with less side effects. The degree of solubility of a substance in a specific solvent is measured because the saturation concentration where adding extra solute does not increase its concentration in the solution. Solubility development strategies may be categorized in to physical change, chemical changes of the drug substance, and different techniques. The proposed investigation become capable of enhance the solubility of poorly soluble drug 5-FU at colonic site through appropriate solubility improvement method. The formulations were organized with β-cyclodextrins and methodologies of inclusion complexes and solid dispersion with different ratio on the solubility of 5-FU by using different method.

MATERIAL AND METHODS

Preparation of 5-FU complexes: Complex of 5-FU and β-cyclodextrin was prepared using a range of methods like physical mixture, inclusion complex and solid dispersion.

Preparation of neutralization complex: The neutralization complex of 5-FU was prepared by dissolving drug with β-cyclodextrin (1:1) in mixture of 0.l N NaOH and 0.l N HCl till the complex was precipitated, at pH 7.4 to 8.0. The prepared complex was filtered and dried.

Preparation of the physical mixture: The physical mixture of 5-FU was prepared by pulverized in a ceramic mortar and carefully mixed the exactly weighed amounts of drug and β-cyclodextrin (1:1). The prepared mixture was pulverized in a ceramic pestle mortar and carefully mixed.

Preparation of complex by the kneading method: The weighed amounts of 5-FU and β-cyclodextrin (1:1), dissolved in water and then ground the mixture for 1 h. The product was vacuum dried at room temperature and prepared dried complex was reduced into fine powder by using sieving method **[11]**.

Preparation of solid dispersion by physical Mixing Method: The physical mixture was prepared by mixing drug 5-FU (10 mg) and the excipients (70 mg lactose and 20 mg Microcrystalline cellulose) in a glass mortar by trituration and hand filled into 0-size hard gelatin capsules (FUSD1) **(Table 1**).

Preparation of solid dispersion by solvent Evaporation Method: A blend of lactose (240 mg) and Microcrystalline cellulose (60 mg) was mixed with the solution of drug 5-FU (100 mg) in 1 ml chloroform. The solvent was allowed to evaporate at room temperature with considerably stirring. The solid wet mass was passed through a #40 mesh sieve; upto granules were prepared and subsequently dried at 60°C using a vacuum until a constant weight was obtained for improvement of solubility at the intestinal part of GIT phosphate buffer pH 7.4. The granules were filled into 0-size hard gelatin capsules by hand manually (FUSD2) (Table 2).

Co-grinding Method: The solid dispersion (SD) was prepared by cogrinding dispersion process as mixture of solvent system was available on previous process solvent evaporation method. The influence of addition

of solubilizing agents i.e. polyvinyl Pyrollidine (PVP), Polyethylene glycol (PEG 400), or Polyglycol (PG) over drug solubility at colonic environment for enhancement of solubility at the intestinal part of GIT mainly at phosphate buffer pH 7.4 with more dissolution profile [14]. The dissolution medium solution (0.5 mL) of PVP, PEG 400, or PG was triturated with 5-FU (100 mg) until a creamy homogeneous mixture (FUSD3 – FUSD9) were obtained. The prepared 5-FU solvent polymer mixture was further triturated with excipients lactose (240 mg) and MCC (60 mg) for 10 min. The solid wet mass was passed through a #40 mesh sieve, and subsequently dried at 60°C using a vacuum until a constant weight was obtained. The granules were filled into 0-size hard gelatin capsules by hand manually. The formulations were prepared by using the variability in polymeric concentration of PEG 400, PG, and PVP K30 as independent variables. Tween 80 (20 mg) and SLS (10 mg) were dissolved in the aqueous solution of solubilizing agents. Batches of factorial design were prepared by the cogrinding method using lactose (50 mg) and MCC (50 mg) (Table 3).

Characterization of complexes and SD powder: Organoleptic properties of 5-FU complexes such as color, odor and taste were noted by sensory organs. The physical characteristics of 5-FU complexes i.e. density, particle size, flow properties, compatibility, solubility in various dissolution medias, partition coefficient and drug-excipients compatibility study were characterize.

Organoleptic properties: The organoleptic properties of 5-FU complexes such as color, odor and taste were noted by sensory organs**.**

Microscopic examination: Microscopic examination of the drug complex was done to study the texture of the powder. A pinch of drug powder was spread on a glass slide and observed under phase contrast microscope.

Physical Characteristics:

Density: The drug 5-FU complex was exactly weighed and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined.

Particle size: The average particle size (d_{avg}) of 5-FU complex was determined by using a microscope (66172/Olympus, 100 X, Olympus (India) Pvt. Ltd., New Delhi) fitted with ocular micrometer and stage micrometer.

Flow properties: The flow properties of 5-FU complex were characterized in terms of Carr's index (%), Hausner's ratio and angle of repose (ɵ). The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to previous discuss equations (Table 4).

Solubility determination: The solubility of 5-FU complex was determined in various dissolution media (Water, 0.1 N HCl, pH 7.4 phosphate buffer and pH 6.8 phosphate buffer. The solubility value of 5-FU complex in different medium was determined by UV spectrophotometric method. The samples were filtered by using Whatmann filter paper (0.45µm pore size). The solubility assessment of 5-FU complex was determined by UV spectrophotometric method. The absorbance was taken at λ_{max} 262.0 nm in 0.1 N HCl, λmax 266.0 nmin pH 7.4 phosphate buffer, λmax 266.0 nm in pH 6.8 phosphate buffer and λmax 267.0 nm simulated intestinal fluid (pH 6.8) containing 4% w/v rat caecal medium (Table 5).

Wettability study: The various formulations i.e. physical mixture complexes or solid dispersion (1 g) was placed in a sintered glass funnel (55 mm i.d.). The funnel was plunged into beaker containing water so that the surface of the water in the beaker remained at the same level as the powder in the funnel. Methylene blue powder (100 mg) was poured onto the surface of the test sample. The time required for wetting the methylene blue powder was measured. The average of three observations was calculated (Table 6).

Differential scanning calorimetry: The melting behavior of the pure drug, carrier and solid dispersions was evaluated by using DSC instrument (DSC Q10 V 9.9 Build 303). Samples were heated under nitrogen atmosphere on an aluminum pan at a rate of 10 °C/min. over the temperature range of 30 to 300 °C. The melting behavior of the pure drug carrier and solid dispersions was evaluated by using DSC instrument (DSC Q10 V 9.9 Build 303) (Figure 1).

Fourier transforms infrared spectroscopy: Infrared spectra of drug, carriers and solid dispersions were recorded using FTIR spectrometer (Thermo Nicolet 380, USA) to ascertain the presence of different functional groups. A small amount of the powdered solid (1-2 mg) was added to pure potassium bromide powder and grounded up as fine as possible. This was then placed in a small die and put under pressure mechanically to form KBr pellet. Pellet was then scanned in the range from 400 to 4000 cm-1. The Infrared spectra of pure 5-FU, carriers and solid dispersions were recorded using FTIR spectrometer and scanned in the range from 400 to 4000 cm-1 (Figure 2).

In vitro dissolution studies: Drug release studies of pure drug, carrier and solid dispersions were performed in triplicate using United State Pharmacopoeia Type II dissolution test apparatus, employing phosphate buffer (pH 6.8) as dissolution media, at a temperature of 37±0.5°C and at a speed of 75 rpm. Dissolution studies were performed of solid dispersion containing capsule (10 mg) and the different solid dispersions containing an equivalent amount of drug. Aliquots of the periodically withdrawn samples (10 ml) were

analyzed spectrophotometrically at 267 nm and were replaced with an equal volume of dissolution medium. Drug release studies were performed in triplicate using United State Pharmacopoeia Type II dissolution test apparatus, employing phosphate buffer (pH 6.8) as dissolution media and analyzed spectrophotometrically at 266 nm and were replaced with an equal volume of dissolution medium (Table 7 and Figure 3 – 6).

RESULT AND DISCUSSION

The organoleptic properties of Neutralization complex (FNC) was yellowish in color and odorless, physical mixture (FPM) was pale yellow color and odorless, for kneading method (FKM) mixture was white yellow color and odorless and Solid dispersion (FUSD3-FUSD9) were White to pale Yellow in color and having justify odor. The observation of photographs of mixtures and solid dispersions showed that it was crystalline in nature with a camera at the required magnification**.** The tapped density was determined by tapping up-to 100 times. Bulk and tapped densities of drug complexes was found from 0.292 gm/cm^3 to 0.311 gm/ cm^3, for FNC, FPM and FKM. The result of bulk and tapped densities of SD were found 0.327 gm/cm^3 to 0.386 gm/cm^3 for FUSD1 to FUSD9. The particle size of drug complex powder was 112 µm, 101 µm and 106 µm, respectively for FNC, FPM and FKM. The particle size of SD was found 33 µm to 43 µm for FUSD1 to FUSD9. The drug complex with kneading method FKM exhibited excellent flow, whereas FNC and FPM exhibited good flow characteristics (Table 4). The formulation SD i.e. FUSD6 showing excellent flow due to having good particle size The solubility studies of drug β-CD systems in water at 25°C revealed that the solubility of drug increased linearly for the preparation of complexes by kneading method. Solid inclusion complexes of drug were prepared by kneading method appeared that the solubility behavior of the material was modified by altering its surrounding environment. The solubility of physical mixtures and solid complexes prepared with a number of methods increased due to the surface tension lowering effect of the β-cyclodextrin, resulting in wetting of hydrophobic drug surface. The increase in solubility was also due to the formation of water-soluble inclusion complexes with the β-cyclodextrin. It was also observed that the β-cyclodextrin complexes may exhibit higher dissolution rate than the pure drug and their corresponding physical mixtures. The solubility of drug was determined in 0.1 N Hcl, pH 7.4 phosphate buffer, in pH 6.8 phosphate buffer and simulated intestinal fluid (pH 6.8) containing 4% w/v rat caecal medium **(Table 5)**. The wetting time of solid dispersion of 5-FU by co-grinding method were evaluated and was in the range between 5.15 sec to 6.54 sec, it was found that the solid dispersion able to wet within a limited set of seconds in predetermined time for enhancement of solubility at pH 6.8 phosphate buffer **(Table 6)**.

Table 1: Composition of solid dispersion by physical method

Formulation code	Drug (mg)	Lactose (mg)	Microcrystalline cellulose (mg)
FUSD1	100	50	50

Table 2: Composition of solid dispersion by physical method

Formulation code	Drug (mg)	Lactose (mg)	Microcrystalline cellulose (mg)	Solvent (ml) Chloroform
FUSD2	100	50	50	1

Table 3: Various composition of solid dispersion by co-grinding method

S.No.	Formulation code	Polyethylene glycol (PEG) 400 (mg)	Propylene glycol (PG) (mg)	Polyvinylpyrrolidone (PVP) K30 (mg)
1	FUSD3	20	20	20
2	FUSD4	20	10	30
3	FUSD5	20	30	10
4	FUSD6	10	20	30
5	FUSD7	30	20	10
6	FUSD8	10	30	20
7	FUSD9	30	10	20

Table 4: Flow properties of drug complex and Solid dispersion

Type of powder	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
FNC	13.11±0.011	1.01±0.01	22.1±0.013
FPM	12.91±0.012	1.11±0.02	23.2±0.011
FKM	12.15±0.013	1.17±0.01	21.12±0.12
FUSD1	12.11±0.011	1.12±0.01	22.18±0.008
FUSD2	12.21±0.013	1.15±0.02	23.16±0.009
FUSD3	12.08±0.008	1.08±0.01	21.17±0.012
FUSD4	12.14±0.009	1.06±0.02	22.08±0.008
FUSD5	12.11±0.007	1.07±0.02	22.11±0.013
FUSD6	12.22±0.011	1.18±0.01	23.19±0.007
FUSD7	12.17±0.008	1.12±0.01	22.16±0.009
FUSD8	12.18±0.013	1.16±0.01	21.22±0.012
FUSD9	12.08±0.09	1.07±0.02	22.27±0.013

Table 5: The solubility of 5-FU and β-cyclodextrin complex at different solvents

Formulation code	Solubility (mg/ml)			
	0.1 N HcL	Phosphate buffer pH 6.8	Phosphate buffer pH 7.4	Simulated intestinal fluid (pH 6.8) containing 4% w/v rat caecal medium
Neutralization complex (FNC)	17.781±1.21	3.142±0.91	2.011±1.31	2.726±1.71
Physical mixture (FPM)	18.211±1.11	2.982±1.01	2.801±1.08	2.803±1.21
Kneading method (FKM)	17.231±1.01	3.041±1.11	2.521±1.14	2.911±1.41
FUSD1	17.101±1.21	2.982±1.01	2.711±1.18	3.111±1.12
FUSD2	18.103±1.11	2.123±1.11	2.722±1.21	3.213±1.11
FUSD3	18.102±1.12	2.211±1.21	2.732±1.23	3.161±1.02
FUSD4	18.111±1.14	2.112±1.21	2.341±1.22	3.321±1.11
FUSD5	18.113±1.11	2.311±1.13	2.261±1.21	3.241±1.01
FUSD6	21.119±1.01	2.999±1.31	2.981±1.21	3.321±1.03
FUSD7	17.116±1.21	2.622±1.23	2.671±1.12	3.211±1.23
FUSD8	18.118±1.11	2.712±1.31	2.761±1.23	3.111±1.09
FUSD9	17.117±1.04	2.342±1.31	2.799±1.21	3.241±1.16

Table 6: Wetting time of solid dispersion of 5-FU

Formulation code	Wetting time (Min.)
FNC	5.19
FPM	5.22
FKM	5.29
FUSD1	5.43
FUSD2	6.21
FUSD3	5.12
FUSD4	6.54
FUSD5	6.45
FUSD6	5.15
FUSD7	6.54
FUSD8	6.32
FUSD9	5.71

Table 7: In vitro drug release study of different formulations (FUSD1– FUSD9)

Time (Min.)	FUSD1	FUSD2	FUSD3	FUSD4	FUSD5	FUSD6	FUSD7	FUSD8	FUSD9
0	0	0	0	0	0	0	0	0	0
5	27.11	29.35	35.11	39.11	36.11	49.15	40.32	43.98	38.17
10	41.31	48.01	45.31	51.31	43.17	59.21	53.22	54.15	45.62
15	55.47	56.16	53.21	61.11	54.35	71.01	63.45	65.14	54.32
20	71.21	74.55	64.21	76.41	65.37	79.32	75.23	78.23	69.32
25	86.34	87.23	76.45	89.35	79.22	94.43	89.34	90.32	81.23
30	96.36	95.42	92.43	97.54	92.34	99.82	96.31	96.19	94.54

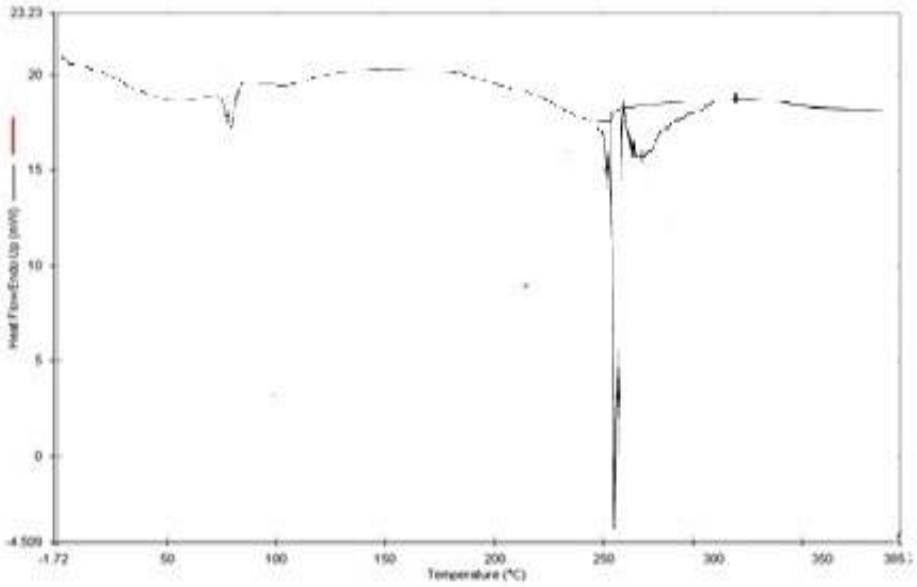

Figure 1: Differential scanning calorimeter of solid dispersion (FUSD6)

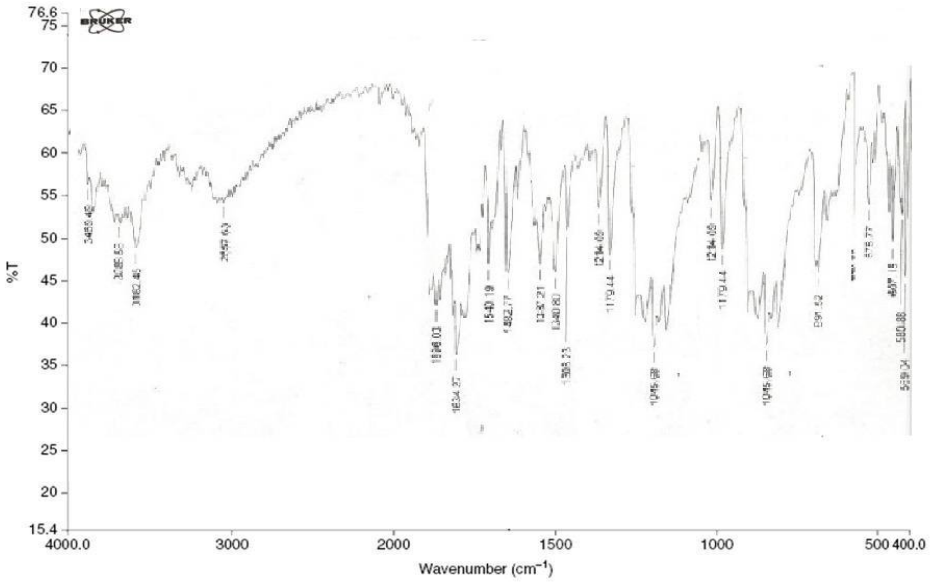

Figure 2: Fourier transforms infrared spectroscopy of solid dispersion (FUSD6)

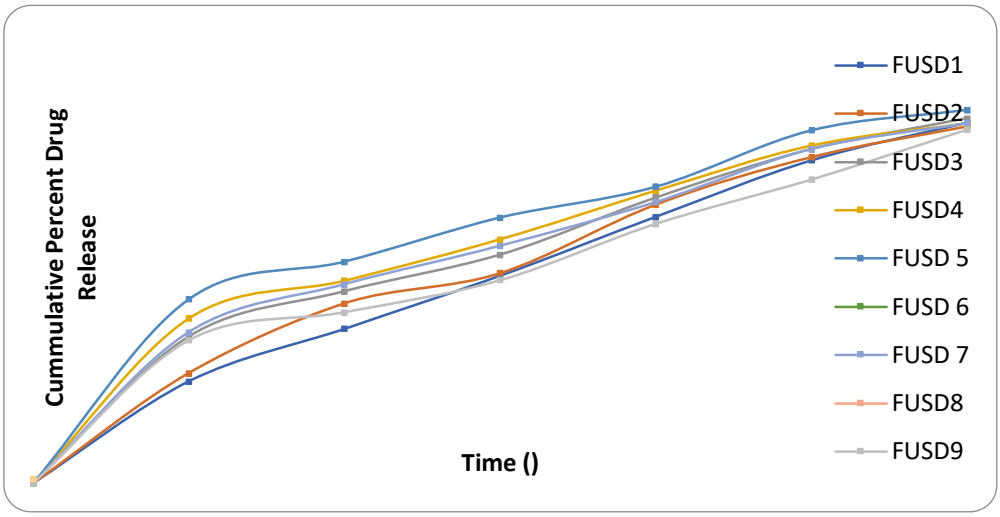

Figure 3: Zero order in-vitro drug release study of various batches (FUSD1–FUSD9)

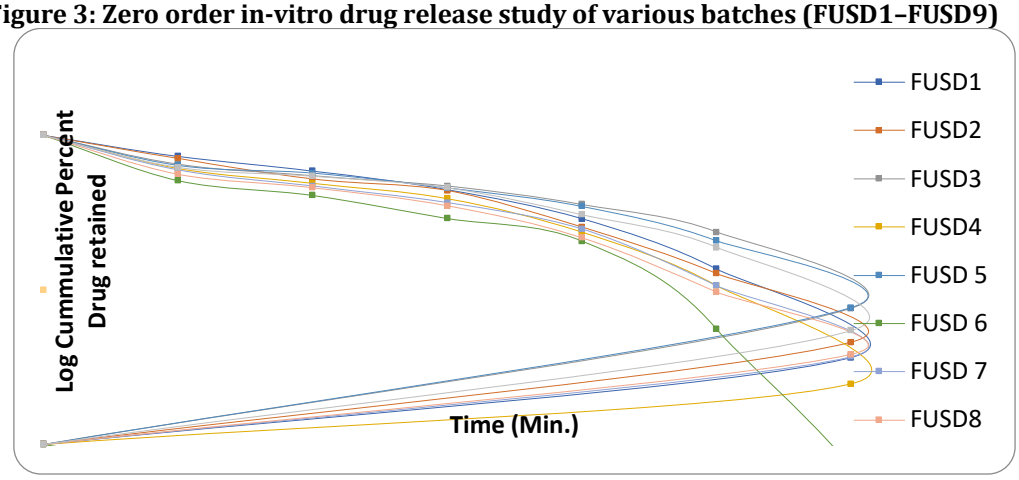

Figure 4: First order in-vitro drug release study of various batches (FUSD1–FUSD9)

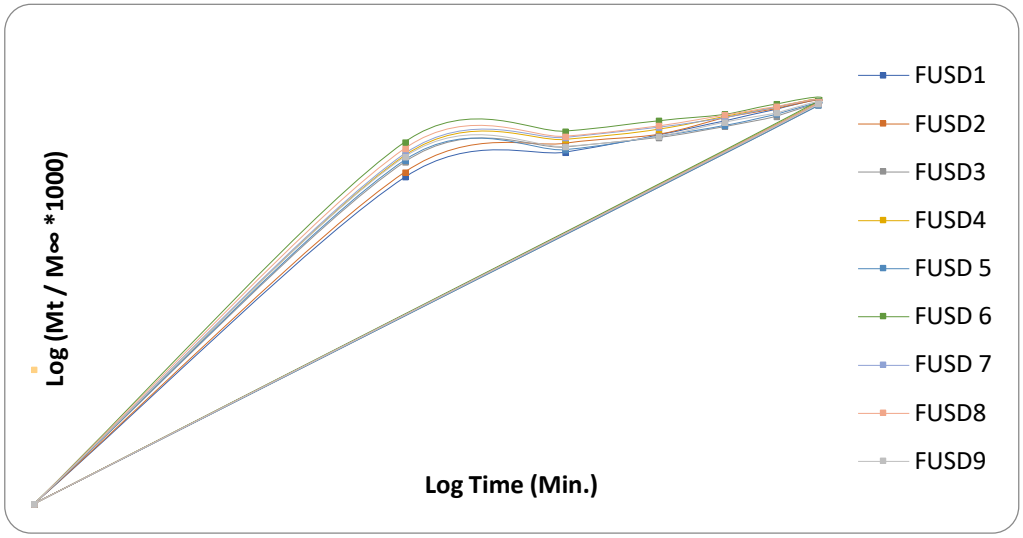

Figure 5: Korsmeyer-peppas in-vitro drug release study of various batches (FUSD1–FUSD9)

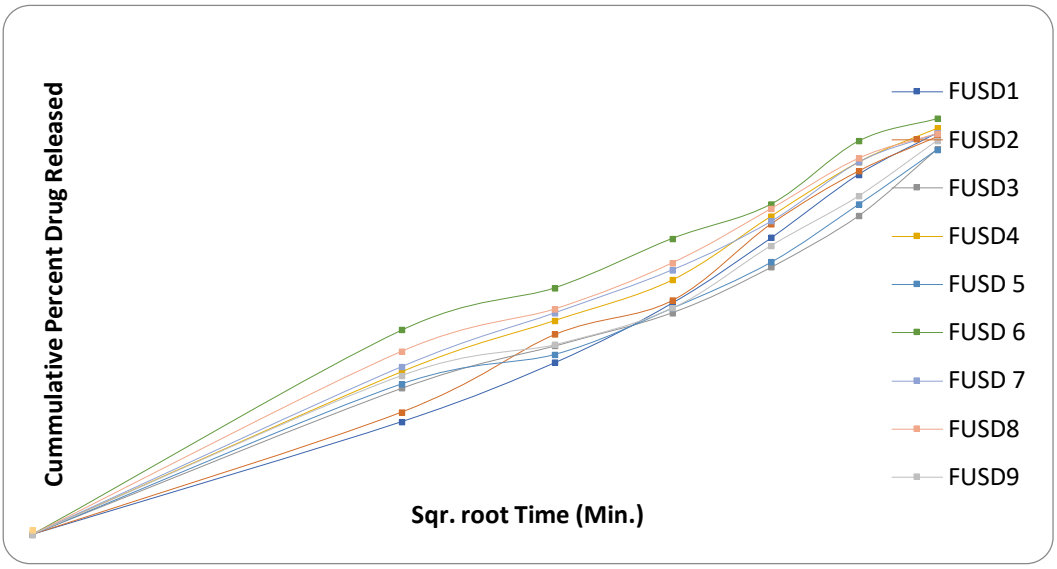

Figure 6: Higuchi plot in-vitro drug release study of various batches (FUSD1–FUSD9)

CONCLUSION

Colon specific drug delivery systems are designed to obtain targeted drug delivery to the large intestine (colon). They provide local delivery for the treatment of colonic diseases and colon cancer, where it is necessary to attain high concentration of the drug. Subsequent unfavorable effects owing to toxicity of conventional drugs are a challenging problem associated with chemotherapy. There is noticeable concern toward site-specific/targeted delivery of chemotherapeutic drugs specifically to the affected site of the colon in a predictable and reproducible manner. The objective of present work is to enhance solubility of drug 5-fluorouracil at colonic pH that improve the therapeutic efficacy of the drug by local action and reduce side effects by minimizing the systemic absorption of drug. Targeted delivery of 5FU is achieved through SD formulations development by co-grinding method showed drug to polymer blend significantly affect the cumulative amount of drug going into solution. The improved cumulative drug released obtained in FUSD6 significantly invariably contributed to its highest cytotoxic activities with more soluble and more bioavailable of drug to the site of action.

REFERENCES

1. Traverso G. Jr., Shuber A. Jr., Levin B. Jr., Johnson C. Jr., Olsson L. Jr., Schoetz D.J. Jr., (2002) Detection of APC mutations in fecal DNA from patients with colorectal tumors, N Engl J Med. 346, 311-320.
2. Chaurasia M., Chaurasia M.K., Jain N.K., Soni V., Gupta Y., Jain S.K., (2006) Cross linked guar gum microspheres: a viable approach for improved delivery of anticancer drug for the treatment of colorectal cancer, AAPS Pharma Sci Tech.7(3) 74-74.
3. Tortora, G.J. and Grabowski, S.R., (2000) "Principles of Anatomy and Physiology" 9th edition. 857-858.
4. Albanes D., Malila N., Taylor P.R., (2000) Effects of supplemental a-tocopherol and ß-carotene on colorectal cancer: results from a controlled trial (Finland), Cancer Causes Control. 11(3), 197-205.
5. Michor F., Iwasa Y., Lengauer C., Nowak N.A., (2005) Dynamics of colorectal cancer, Semin Cancer Biol. 15, 484-493.
6. Krishnaiah Y.S.R., Satyanarayan S., (2001) Colon-specific drug delivery systems, In: Jain NK, ed. Advances in Controlled and Novel Drug Delivery New Delhi, India: CBS Publishers and Distributors; 89, 119.
7. Jain N, Kori ML,, Jain UK, Jain AK, Natural biodegradable ciprofloxacin microspheres: optimization study by factorial design, Indian drugs, 2022, 59 (04), 24-33.
8. Madhu MN, Kumar DS, "Osmotic Drug Delivery System: A Review", Pharmakine., 2009, 2, 5-14.
9. Prescott, L.F. In The need for improved drug delivery in clinical practice, Prescott LF, Nimmo WS, Novel Drug Delivery and Its Therapeutic Application, John Wiley, UK, 1989, pp. 1–11.
10. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330.
11. Sun X, Liu C, Omer A, et al. (2019). pH-sensitive ZnO/carboxymethyl cellulose/chitosan bio-nanocomposite beads for colon-specific release of 5-fluorouracil. Int J Biol Macromol. 128:468–479.
12. Singh P, Wu L, Ren X, Zhang W, Tang Y, Chen Y, Carrier A, Zhang X, Zhang J, (2020). Hyaluronic-acid-based β-cyclodextrin grafted copolymers as biocompatible supramolecular hosts to enhance the water solubility of tocopherol, International Journal of Pharmaceutics, 586.
13. Jain N, Kori ML, (2018). Enhancement of solubility profile of plumbagin containing tablet at different colonic region

for colon targeting drug delivery system" Indian Drugs, 55 (12), 78-82, 0019462X
14. Jain N, Kori ML, Jain AK, (2018). Pectin and Its Combination with Different Polymers for Colon-Targeted Drug Delivery: A Review, Inventi Rapid: NDDS Vol. Issue 1, 1-8.