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FORMULATION AND EVALUATION OF 5 FU LOADED EUDRAGIT MICROSPHERE FOR EFFECTIVE MANAGEMENT OF COLON CANCER

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Abstract:

5-Fluorouracil (5-FU) has a wide anticancer activity versus several types of solid tumors. The activity of 5-FU can be improved and its toxicity can be diminished by enhancing the relative specific accumulation in the tumor regions. The aim of this work was to develop Eudragit RS100 based 5-FU microsponges (MS) for treatment of colon cancer. Oil in oil emulsion solvent diffusion method was used for the preparation of 5-FU sustained release Eudragit RS100 MS. MS were characterized for their encapsulation efficiency, production yield, and drug release profiles. the mean particle size for Eudragit RS 100 was found in the range of 41.9±3.387 µm to 43.8±4.405 µm. As shown in the table the entrapment was less for Eudragit RS 100 and found in the range of 28.82 to 39.82 %. Methanol was used to dissolve the drug in all formulation and was an important factor that affects the production yield. The F3 was showed sustained release of drug up to 12 hours as compared to other formulations F1 and F2. The results demonstrated that 5-FU with Eudragit RS100 was successfully formulated as sustained release manner and could be a substitution delivery method of 5-FU for oral anticancer treatment.

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INTRODUCTION:

Among the various types of cancers, colorectal cancer is a significant source of morbidity and mortality in the United States and other Western countries. The cancer is one of the most dreaded and threatening diseases in the world, causing more than 6 million deaths a year [1]. Colorectal cancer is the second leading cause of death followed by lung cancer [2]. Colon cancer is the second most cause of death after lung cancer by cancer diseases. Many different drugs or drug combinations have been tested for a successful therapy. 5-Fluorouracil (5-FU) is a commonly applied anticancer drug in the treatment of colon cancer [1]. At present, the standard regimen is an intravenous bolus injection of 5-fluorouracil (5-FU) modulated by folinic acid (leucovorin) [3, 4]. Only few approaches for an oral administration have been described in literature. Recently, enzyme dependent tablet-based systems have been proposed, which might allow an efficient treatment combined with a reduction of adverse effects [5].

However, due to variations in transit time throughout the colon, the drug release can be incomplete when the colon specific tablet matrix is not readily disintegrated and the treatment will remain insufficient. Especially, diarrhea has been observed as of one of the major adverse effects and also a toxicity limiting factor of the therapy [6–9]. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery may allow topical treatment of colorectal cancer. Treatment may be made moreeffective if drug(s) can be targeted directly to the colon leading to reduction in systemic side effects. Conventional drug delivery system for treatment of colorectal cancer are failing as the drug does not reach the site of action in appropriate concentration, due to hostile environment of upper Git, and absorption of maximum administered dose from upper GIT which produce severe toxic effect.

In the present study it will propose to prepare eudragit S-100 coated starchmicrospheres encapsulating the anticancer drug (5-fluorouracil). Natural polysaccharidesstarch is chosen for formation of microspheres because they are easily degraded by themicrobial flora/enzymes present in the colon. These microspheres will further be coatedwith pH sensitive polymers (which dissolves at or above pH 6.4). By using pH Sensitive polymers the microspheres will remain intact throughout the GI tract and release the drug specifically near the colon region. Thus preparation of colon specific microspheres of 5-fluorouracil will improve the therapeutic efficacy of the drug by local action and reduce side effects by minimizing the systemic absorption of drug.

MARTIAL AND METHODS:

The materials required for the present work were procured from diverse sources. 5 fluorouracil was obtained as a gift sample from Pharmaceutical Company and Eudragit R-100 was provided as gift sample by Evonik Pharma, Mumbai, India. Mg. Stearate were procured from Central Drug House Pvt. Ltd., Mumbai, India

All the other ingredients used were of analytical grade and were used as procured. Demineralised and double distilled water was prepared freshly and used whenever required. All other reagents and chemicals used were of analytical grade.

Preparation of Microsphere

The technique used in preparation of microsphere was 'O/O emulsion' solvent evaporation. Three preparations of Eudragit RS100 were prepared with drug 5-FU in 1:1, 1:2 and 1:3 ratios. The polymer was dissolved in acetone and drug was dissolved in 13 ml of ethanol. These above solutions were mixed, 10 mg of magnesium stearate was dispersed in the mixture which was then stirred for about 15 min using magnetic stirrer. The resultant mixture was then poured in 500 ml beaker containing external phase of (135ml liquid paraffin light and 15ml of n-paraffin) with stirring. Mechanical stirrer was used to stir at 750 rpm the solution for 4 hours until complete acetone and methanol was evaporated. After formation of microsphere the resultant product was filtered through whatman filter paper no.41. The residue was washed 4-5 times in about 25 ml n-hexane followed by 4-5 times in 50 ml of petroleum ether (40-50 degree Celsius). Finally, the prepared microspheres were dried in desiccators for 24 hours at room temperature. The microsphere was stored in desiccators [10].

Table 1: Formulations of 5 FU loaded microspheres

Formulation	5-FU (mg)	Eudragit RS100 (mg)	Mg. Stearate (mg)
F1	100	100	10
F2	100	200	10
F3	100	300	10

Evaluation of prepared microspheres

Production yield

The yield was calculated by dividing the weight of collected microsphere by the weight of all non-volatile substance used for microsphere preparation [11].

$$\textbf{Yield \%} = \frac{\textbf{The amount of microsphere collected}}{\textbf{Theoretical amount}} \boldsymbol{X100}$$

Particle size distribution

Formulation was analyzed by optical microscopy for particle size. The instrument was calibrated and found that the size of 1 unit was found to be 7.0 micrometer. Approximately 300 microsphere sizes were calculated at 10 X magnification [12].

Drug entrapment efficiency

10 mg of 5- FU loaded microsphere were dissolved in100 ml PBS pH 7.4 by shaking with magnetic stirrer for 24 hr. This solution was filtered through whatman filter paper no 41. Aliquotes were analyzed in UV spectrophotometer Shimadzu 1800 for 5-FU at 266 nm [13].

Drug entrapment efficiency was determined by using the following relationship:

$$\% \text{ entrapment} = \frac{\textbf{Actual content}}{\textbf{Theoretical content}} \boldsymbol{X100}$$

In vitro drug release

The dissolution rate of 5-FU was from microspheres were studied using phosphate buffer solution pH 7.4 by paddle method. Accurately weighed microspheres were taken, equivalent to 10 mg of 5 FU for studies. The medium temperature was maintained at 37±0.5 °C. The sample Aliquote were withdrawn after a predetermined time period and analyzed for drug release at 266 nm. The volume withdrawn each time was replaced with new fresh medium [14].

RESULTS AND DISCUSSION:

The effect of parameter like type and concentration of polymers on the production yield, entrapment efficiency, particle size distribution, In vitro drug release, Drug polymer interaction were studied. In the formulation the methanol was used to dissolve drug, and the mean particle size for Eudragit RS 100 was found in the range of 41.9±3.387 µm to 43.8±4.405 µm. As shown in the table the entrapment was less for Eudragit RS 100 and found in the range of 28.82 to 39.82 %. Methanol was used to dissolve the drug in all formulation and was an important factor that affects the production yield. The polymer was sticking to the vessel and the stirring while evaporation of the methanol, resulted in less production yield.

The drug release studies were performed in PBS pH 7.4 at 37.5°C foundinitial high release of drug which may be due to dissolution of crystal of drug present at the surface of the microspheres. All formulations of Eudragit RS 100 showed complete release of drug in 9, 10 and 12 hours. This data shows the sustained release of drug up to 12 hours. This study also revealed that as an as concentration of polymer increases the amount of drug release is decreases.

Table 2: Results of percentage Yield, percentage entrapment and mean particle size of prepared microspheres

Formulation	Yield (%)	Entrapment (%)	Mean particle size (µm)
F1	8.40	28.82	41.5
F2	14.50	33.10	42.5
F3	21.54	39.80	43.3

Table 3:Results of % drug release of different formulations

Time (Hrs.)	Percentage drug release		
	F1	F2	F3
2	70	65	60
4	75	70	65
6	80	90	70
8	100	100	80
10	00	00	98
12	00	00	100

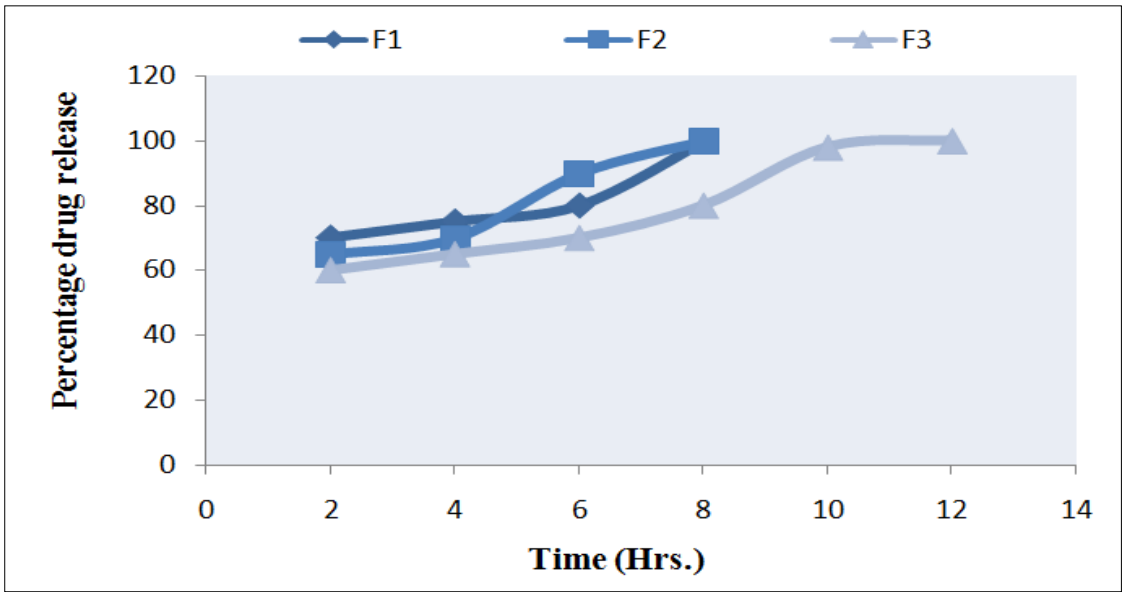

Figure 2: Graph of percentage drug release

CONCLUSION:

5-FU microspheres were prepared easily and successfully using the solvent evaporation technique. The yield and entrapment efficiency were found to be very less for all the formulations prepared. Particle size obtained for the microspheres was less for all the formulations. Particle size, entrapment efficiency and production yield were found to be highly influenced by the type of polymer and polymer concentration. It was found that the release of drug from the formulations followed diffusion mechanism. The F3 was showed sustained release of drug up to 12 hours as compared to other formulations F1 and F2.

REFERENCES:

1. C. Dhawale, A.S. Bankar, M.N. Patro, Formulation and evaluation porous microspheres of 5-fluorouracil for colon targeting, Int. J. Pharm. Tech. Res., 2 (2010), pp. 1112-1118
2. Ramesh K. Ramanathan, Jeffery W. Clark, *et al.* Safety and toxicity analysis of oxaliplatin combined with fluorouracil or as a single agent in patients with previously treated advanced colorectal cancer Am. Soc. Clin. Oncol. (2003), pp. 2904-2911
3. Labianca R, Pessi MA, Zamparelli G, Treatment of colorectal cancer. Current guidelines and future prospects for drug therapy, Drugs 53 (1997) 593–607.
4. 2. Van Cutsem E, Peeters M, Verslype C, The medical treatment of colorectal cancer: actual status and new developments, Hepatogastroenterology., 1999, 46, 709–716.
5. 3. Labianca RF, Beretta GD, Pessi MA, Disease management considerations: disease management considerations, Drugs., 2001, 61, 1751–1764.
6. 4. Krishnaiah YS, Satyanarayana V, Dinesh Kumar B, Karthikeyan RS, In vitro drug release studies on guar gum-based colon targeted oral drug delivery systems of 5-fluorouracil, Eur. J. Pharm. Sci., 2002, 16, 185–192.
7. 5. Madajewicz S, Petrelli N, Rustum YM, Phase I– II trial of high-dose calcium leucovorin and 5-fluorouracil in advanced colorectal cancer, Cancer Res., 1984, 44, 4667–4669.
8. 6. Cortesi E, Aschelter AM, Gioacchini N, Pellegrini A, Frati L, Ficorella C, Mazzei N,

Marchetti P, Efficacy and toxicity of 5-fluorouracil and folates in advanced colon cancer, J. Chemother. 1990, 2, 47–50.

9. 7. O'Connell MJ, Mailliard JA, Kahn MJ, Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer, J. Clin. Oncol. 1997, 15, 246–250.
10. Mosmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 65: 55-63.
11. Ismail IA, Kang KS, Lee HA, Kim JW, Sohn YK (2007) Genistein-induced neuronal apoptosis and G2/M cell cycle arrest is associated with MDC1 upregulation and PLK1 down-regulation. Eur J Pharmacol 575: 12-20.
12. Sandor M, Enscore D, Weston P, Mathiowitz E (2001) Effect of protein molecular weight on release from micron-sized PLGA microspheres. J Control Release 76: 297-311.
13. Goto S, Kawata M, Nakamura M, Aoyama T (1985) Effect of magnesium stearate in preparation of eudragit RS-microcapsules containing drugs. Yakugaku zasshi: J Pharm Soci Japan 105: 1087-1095.
14. Arshady R (1991) Preparation of biodegradable microspheres and microcapsules: 2 Polyactides and related polyesters. J Control Release 17: 1-21.