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Research Article

FORMULATION AND EVALUATION OF PULSED DRUG DELIVERY OF 5- FLUOROURACIL IN TREATING COLO-RECTAL CANCER

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ABSTRACT

The proposed work aimed to develop a time dependent programmable pulsatile drug delivery system of 5-Fluorouracil, intended for chronotherapy in colorectal cancer. Various batches of tablets were prepared by direct compression method using microcrystalline cellulose (MCC). These tablets were coated with pH sensitive polymers like Eudragit S-100, cellulose acetate succinate(CAS) and Ethyl Cellulose (EC) at fixed concentration with different coating level (10% & 20%).The prepared tablets were evaluated for lag time and in vitro drug release. FTIR studies revealed that there was no interaction between drug and polymer. Lag time with Eudragit S-100 at (20% coating level) was 5 hrs, Cumulative drug released from the formulation ranged from 91-96% within 8-10 hrs. Drug released followed first order kinetics. The rapid release of the drug after a lag time consistent with requirement for chronotherapeutics was achieved. This approach provides a useful means for pulsatile/programmable release (with single pulse) of 5-Fluorouracil and may be helpful for patients suffering from cancer.

Key words: 5-Fluorouracil, Pulsatile drug delivery, Colo rectal cancer, Chronotherapeutics, lag time.

INTRODUCTION

Controlled drug delivery systems are receiving more and more attention as they control the rate of drug release and sustain the duration of therapy[1]. Oral controlled release drug delivery system has a number of advantages over conventional release delivery preparation. However they are not useful in certain diseases like cardiovascular diseases, asthma, arthritis, and peptic ulcers etc. which exhibit circadian rhythm, where constant drug levels are not preferred but need a pulse of therapeutic concentration in a periodic manner which acts as push for the development of PDDS[2].

A timed, pulsatile delivery system provides one or more rapid release pulses at predetermined lag times or at specific sites resulting in better absorption of the drug, and thereby providing more effective plasma concentration time profile[3].

Large-amplitude circadian rhythms have been mapped for some tumors. The rhythmic circadian changes in tumor blood flow and cancer growth are observed, both when tumors are small and growing most rapidly and when they are larger and growing slowly. The goal of circadian- modulated chemotherapy or "chronotherapy" is to find times for drug delivery that results in low toxicity to the host and high toxicity to the cancer cell, increase the maximum drug tolerance, and ultimately result in better tumor management[4,5].

Colorectal cancer (CRC) is a lifestyle-related illness. It exhibits a well-defined precancerous (usually polypoid) growth phase that progresses in parallel with a characteristic sequence of molecular genetic changes[6].

5- Fluorouracil is a antineoplastic drug which is white in colour and crystalline. Its molecular formula is $C_4H_3FN_2O_2$ and is distributed throughout the body tissue and fluids including crossing the blood-brain barrier to appear in the cerebrospinal fluid and disappear from the plasma within about 3 hours[7].

MATERIALS AND METHODS

5- Fluorouracil was obtained as a gift sample from Naprod Life Sciences Pvt. Ltd. (Mumbai, India). Eudragit S-100 was obtained as gift samples from Evonik Pvt. Ltd. Mumbai. Ethyl cellulose was gifted by Colorcon Asia Pvt. Ltd., (Goa, India). Cellulose acetate succinate was gifted by Arihant trading, Mumbai. Microcrystalline cellulose, Crospovidone, Croscarmellose sodium and Sodium starch glycolate was gifted by Cipla Ltd. Mumbai. All other excipients used were of analytical grade.

Preformulation studies of pure drug

Identification of 5- Fluorouracil was carried out by Infrared Absorption Spectroscopy.

Preparation of core tablet

Tablets of 5- Fluorouracil were made by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 minutes by trituration using glass mortar and pestle. Microcrystalline cellulose (MCC) was used as direct compressing agent. Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate were used as disintegrating agents. Aerosil and Talc were used as lubricants. Tablets were compressed in Minipress Tablet Compression Machine using 8mm round concave punches. (Rimek minipress-11 MT, Karnavati Engineering Ltd., Ahmedabad, India). The composition of core tablets is given in **Table 1.**

Evaluation of powder blend

Blended drug/polymer mixture of all the formulations were subjected for precompressional evaluation such as bulk and tapped density, compressibility index Hausner's Ratio and angle of repose[8].

Evaluation of Core Tablets

Prepared core tablets were evaluated for physical properties like uniformity of weight determined by using a Sartorious electronic balance (Model CP- 224 S), hardness by using a dial type hardness tester (Model 1101, Shivani Scientific Ind), friability by using a Roche friabiliator (Camp-bell Electronics, Mumbai), disintegration time by using a disintegration test apparatus (Electrolab ED-2 Bowl USP, Mumbai), diameter and thickness by using vernier caliper etc.

Table 1. Composition of 5- Fluorouracil core tablets

Ingredients (mg/tablet)	Formulations F1	F2	F3
5- Fluorouracil	50	50	50
Microcrystalline cellulose	65	65	65
Lactose	129	129	129
Crospovidone	2	*	*
Croscarmellose sodium	*	2	*
Sodium starch glycolate	*	*	2
Talc	2	2	2
Aerosil	2	2	2
Total	250	250	250

Tablet dosage forms assay

Tablet containing 50 mg of drug was dissolved in 100 ml of phosphate buffer pH 6.8 and 7.4 (simulated intestinal & colonic fluid respectively). The drug was allowed to dissolve in the solvent, the solution was filtered, and 1ml of filtrate was suitably diluted with respective buffer and analyzed spectrophotometrically at 266 nm. The amount of 5-Fluorouracil was estimated by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each batch of formulation[9].

In vitro disintegration test for tablet

The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 SIF (simulated intestinal fluid) and pH 7.4 SCF (simulated colonic fluid) maintained at $37^0 \pm 2^0$C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at $37^0 \pm 2^0$C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate[10].

Preparation of enteric coated tablet

Preparation of coating solution

Coating solution was made using different pH sensitive polymers like Eudragit S100, Cellulose acetate succinate and Ethyl cellulose. Polymeric content in the coating solution was kept constant as 10%w/v. Required quantity of polymers were dissolved in mixture of solvents (acetone & isopropyl alcohol) and stirred on magnetic stirrer to get homogeneous coating solution. Dibutyl phthalate was added in above solution as plasticizer (2% as polymer based) and Titanium dioxide (5% as polymer based) was added as an opacifying agent. After getting homogeneous coating solution coating was done on tablets.

The process conditions were as follows:

Table 2. Detail list of Parameter Value

Parameter	Value
Inlet temperature	40-45 ^{0}C
Exhaust temperature	30-35 ^{0}C
Spray rate	3-5 ml /min
Spray nozzle diameter	1 mm
Distance (Tablet bed-spray gun)	10 – 15 cm
Pan speed(RPM)	20

The core tablets were coated with above coating solution at coating level of 14 % and 24 % respectively on basis of % weight gain by core tablet.

The % weight gain calculated by using the following equation:

$$\%\text{weight gain} = \left(\frac{W_t - W_0}{W_0}\right) \times 100$$

Where Wt is the weight of the tablets after coating, W_0 is the initial weight of tablets. The tablets were dried in an oven at 50^{o}C for 12 hr and these tablets were subjected for evaluation. Composition of coating solution is tabulated in **Table 3**.

Table 3. Composition of coating solution. [1]Quantity in gms [2]Quantity in ml

Ingredients	CT 1	CT 2	CT 3	CT 4	CT 5	CT 6
[1]Eudragit S 100	50	50	*	*	*	*
[1]Cellulose acetate succinate	*	*	50	50	*	*
[1]Ethyl cellulose	*	*	*	*	50	50
[2]Dibutyl phthalate	1	1	1	1	1	1
[1]Titanium dioxide	2.5	2.5	2.5	2.5	2.5	2.5
[2]Isopropyl alcohol	250	250	250	250	250	250
[2]Acetone	250	250	250	250	250	250
% Coating	14	24	14	24	14	24

Evaluation of pulsatile release tablets

Dissolution studies of the coated tablets

Drug release studies of coated tablets were carried out using USP XXIII dissolution test apparatus I. Initially tablets were placed in 900 ml of 0.1 N HCl for 2 hours maintained at 37 ± 0.5^0C, 75 rpm followed by pH 6.8 phosphate buffer for 3 hours and pH 7.4 for 5 hours. Aliquots of predetermined quantity were collected manually at definite time intervals replacing with fresh buffer to maintain sink condition and analysed for drug content using a UV-visible spectrophotometer at λ max of 266 nm[11].

Data analysis

To analyse the mechanism for the drug release and release rate kinetics of the dosage form, the data obtained from in vitro drug release studies was fitted in to zero order and first order[12].

RESULTS AND DISCUSSIONS:

Drug polymer compatibility studies were conducted by FTIR spectroscopy and the results are presented in figure 1 and figure 2. The results indicated that were was no interaction between the drug and the polymers.

Evaluation of powder blend

Angle of repose, compressibility index and Hausner's ratio were found to be between 20.33 to 22.22, 12 to 12.30 and 1.21 for all formulations respectively. These results suggested that powder blend had good flow properties.

Evaluation of core tablets

The formulated tablets were subjected for evaluation according to official specifications for shape, thickness, hardness, friability, weight variation, drug content and *in vitro* disintegration time. The results are tabulated in Table 3. *In vitro* disintegration for batch F1, F2 & F3 was found to be 35, 50 & 55 seconds respectively. Batch F1 was considered as optimum formulation as it showed least disintegration time. Hence further study was planned using formulation F1 as core tablet.

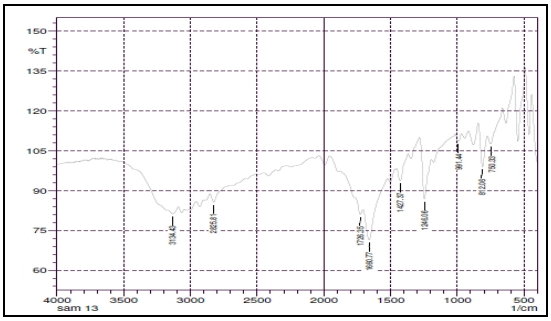

Figure 1: IR spectrum of 5-Fluorouracil pure drug

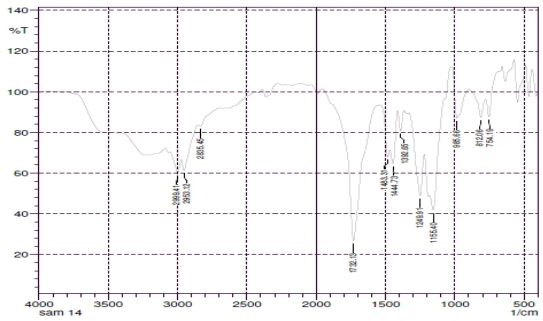

Figure 2: IR spectrum of drug + MCC + Crospovidone + Lactose

Table 4. Post-compression evaluation of the prepared tablets

Batch	F1	F2	F3
Uniformity of thickness (mm) (n=3)	4.3 ± 0.1	4.2 ± 0.2	4.1 ± 0.1
Weight variation (mg) (n=10)	250 ± 2.23	252 ± 2.32	248 ± 2.45
Hardness (kg/cm2) (n=3)	4.3 ± 0.2	4.5 ± 0.2	4.1± 0.2
Friability (%) (n=6)	0.84 ± 0.05	0.80 ± 0.05	0.86 ± 0.05
% Drug content (n=3)	96.21 ± 0.23	96.16 ±0.25	96.33±0.34
Disintegration time (sec)	35	50	55

Evaluation of pulsatile release tablets

In vitro drug release studies

All the pH sensitive polymers used in the present study (Eudragit S-100, Ethyl cellulose and Cellulose Acetate Succinate) showed no drug release in the first two hrs in the gastric environment. Later a different drug release profile was evident for each polymer.

A plot of % drug release versus time showed that the dissolution rate was inversely proportional to the coating level applied. Lag time of 3 hours was achieved with a coating level of 10% (CT 1- Eudragit S 100) and the % drug release in the initial 3 hrs of dissolution media pH 6.8 phosphate buffer was 72.32%. As the coating level was increased to 20 % (CT-2- Eudragit S 100), there was a significant increase in the lag time upto 5 hrs and there was absolutely no drug release in pH 6.8 phosphate buffers. At 6th hr, burst effect was observed it was because coating concentration was increased and the coat became more impermeable and finally retarded the drug release.

The formulation with 10 % coating level (CT 3 Cellulose Acetate Succinate- CAS) showed a lag time of 2 hrs and % drug release in initial 3 hrs of dissolution media pH 6.8 phosphate buffer was 60.32%. As the coating level was increased to 20% (CT 4 CAS) the lag time was increased to 4 hrs and inversely the drug release was reduced to 35.64%. All the coated tablets showed a nearby complete drug release in 10 hrs.

A lag time of 3 hours was achieved with a coating level of 10% (CT 5 Ethyl cellulose-EC) and the % drug release in the initial 3 hrs of dissolution media pH 6.8 phosphate buffer was 77.08%. As the coating level was increased to 20% (CT 6-EC), there was a significant increase in the lag time upto 5 hrs and there was absolutely no drug release in pH 6.8 phosphate buffer. Drug release started in pH 7.4 dissolution media. This may be attributed to the fact as the coating level was increased, the drug release was retarded suggesting that the thicker film formed by EC was quiet impermeable in pH 6.8 phosphate buffer solution.

The lag time and *in vitro* drug release profiles for all three polymer solutions at constant concentration and variable coating levels indicate that lag time is directly proportional and dissolution rate is inversely proportional to the coating level applied. At a coating level of 20% of Eudragit S 100 (CT 2) and Ethyl cellulose (CT 6) are proved to be the most appropriate pH sensitive polymers for pulsatile drug delivery. The drug release profile showed sigmoidal release pattern which is considered to be an ideal for the pulsatile drug delivery system as shown in figures 3, 4 and 5.

The results of *in vitro* dissolution studies obtained from these formulations were plotted in zero order and first order kinetics to study the mechanism of drug release. Correlation coefficient (r) value was highest for the first order release equation in all the 6 batches thus indicating first order release kinetics which is depicted in figure 6.

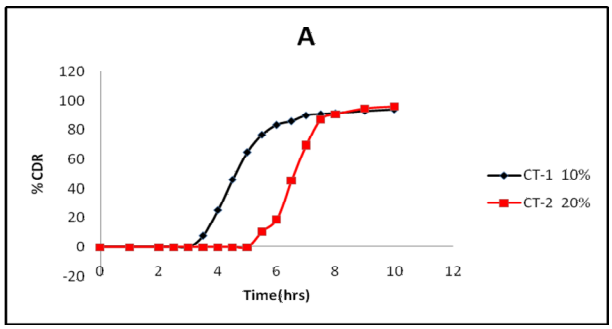

Figure 3: in vitro drug release profile of Eudragit S-100

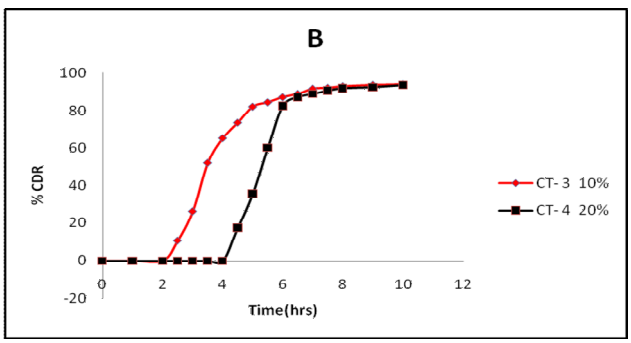

Figure 4: in vitro drug release profile of Cellulose Acetate Succinate

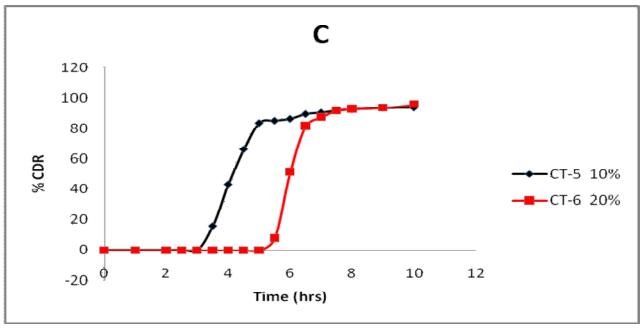

Figure 5: in vitro drug release profile of Ethyl cellulose

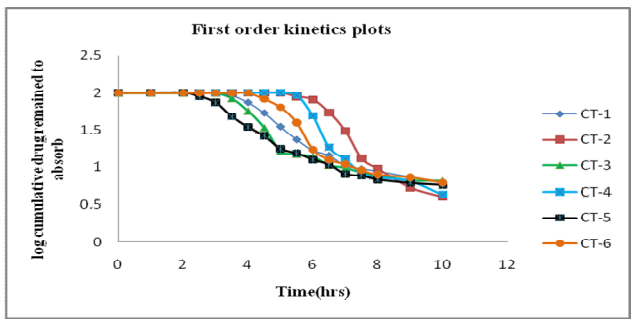

Figure 6: First order kinetics plots of formulations

CONCLUSION

Finally a successful attempt was made to formulate and evaluate 5- Fluorouracil pulsed tablet, which enables to

release the drug in a controlled manner for prolonged period of time after a lag time as required for chronotherapy. pH sensitive polymers delayed the drug release. Thus this approach can provide a useful means for pulsatile/programmable release (with single pulse) of 5-Fluorouracil and may helpful for patients suffering Colo rectal cancer.

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