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Formulation and Evaluation of Colon Targeted Osmotically Controlled Drug Compressed Dosage Forms for Treatment of Colon Cancer

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Abstract: 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. Colon specific drug delivery systems are designed to obtain targeted drug delivery to the large intestine (colon) 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 proposed work prepared and evaluated an osmotically controlled colon targeted solid formulation containing 5FU. The 5FU and osmogens containing core tablets was coated with pH sensitive polymers (total weight gain 10%), thus remain intact throughout the GI tract and release the drug specifically near the colon region. Thus, preparation of colon specific microspheres of 5-fluorouracil improved the therapeutic efficacy of the drug by local action and reduce side effects by minimizing the systemic absorption of drug. The proposed research investigation is the combinational approach to protect the drug and development of osmotic pressure. The system will retain the drug at GIT environment upto colonic region and intact amount of drug release at specific site with application of osmotic pressure. The proposed system is industrial approachable, novel technical process, economically cheap for social human being mainly for elder patients suffering with colon cancer.

Keywords: Colon specific drug delivery, Solid dispersion, 5-Fluorouracil, Colon cancer, Drug formulation

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Introduction

The oral controlled release dosage forms used for the treatment of acute diseases or chronic

illnesses has been achieved by delivery of drugs to the patients for many years. These drug

delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body (Lee, 2000). Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. Many conventional drug delivery systems have been designed by various researchers to modulate the release of a drug over an extended period of time (Madhu and Kumar 2009). The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GI) and so on (Prescott 1989). However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract (Jain and Kori, 2018). The oral route for drug delivery is the most popular, desirable and most preferred method for administering therapeutic agents for systemic effects because it is a natural, convenient and cost effective manufacturing process. Oral route is the most commonly used route for drug administration. Although different routes of administration are used for the delivery of drugs, oral route remains the preferred mode. Even for sustained release systems, the oral route of administration has been investigated the most because of flexibility in designing dosage forms. Present controlled release drug delivery systems are for a maximum of 12 h clinical effectiveness. Such systems are primarily used for the drugs with short elimination half life (Krishnaiah and Satyanarayan, 2001). Drugs can

be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form (Mishra *et al.*, 2006). Osmotic controlled drug delivery system delivers the drug to a large extent and the delivery nature is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. Osmotic controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents (Verma *et al.*, 2002). Among the controlled release devices, osmotic controlled holds a stable place because of its reliability to deliver the API at predetermined zero order rate for prolonged period of time so these are used as the standard dosage forms for the constant delivery of contents. Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. Osmosis is an aristocratic bio phenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilizes the principles of osmotic pressure for delivery of drug. Osmotic pumps offer many advantages over other controlled drug delivery system (Thakor *et al.*, 2010). Osmotic Pump Controlled Release Preparation is a novel drug delivery system with eternally drug delivery rate as characteristic and controlled with the osmotic pressure difference between inside and outside of the semipermeable membrane as drug delivery power. Recently, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system results. Subsequently, water diffuses into the core through the

microporous membrane, setting up an osmotic gradient and thereby controlling the release of drug (Jain *et al.*, 2022). Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure. Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus, a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug (Zentner *et al.*, 1985). Osmotic drug delivery systems for oral use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems (Cortese and Theeuwes, 1982). The objective of present work was to prepare colon specific osmotic pressured 5-fluorouracil that will improve the therapeutic efficacy of the drug by local action and reduce side effects by minimizing the systemic absorption of drug. The major objective of the present work was to prepare, optimized and characterized eudragit L-100 coated Osmotic control colon targeted drug delivery system (OCCTDDS) encapsulating the 5-fluorouracil for site specific colon drug delivery.

Materials and Methods

Solid dispersion:

The solid dispersion (SD) of drug 5-fluorouracil (5-FU) exposed to an aqueous medium, with carrier and gets form of fine colloidal particles. The SD was prepared by cogrinding dispersion process as mixture of solvent system which was available on previous process solvent evaporation

method. The dissolution medium solution (0.5 ml) was triturated with drug (100 mg) and Polyethylene glycol (PEG) (10 mg), propylene glycol (PG) (20 mg), and polyvinylpyrrolidone (PVP) (30 mg) until a creamy homogeneous mixture was obtained. The prepared drug 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 manually.

Preparation of colon targeted tablet:

The core tablet prepared with drug containing solid dispersion and osmogens, microcrystalline cellulose (Avicel, 102) by direct granulation method for optimized the behavior of osmotic controlled nature of formulation. The wet mass was passed through a mesh # 10 and dried at 60 °C for 1 h in a hot air oven. The dried granules were sized by passing through a sieve # 14 and mixed with magnesium stearate and talc mixture. These lubricated granules were compressed into tablets on single-station punch machine (Table 1).

Coating of colon targeted (CT) tablets by pH sensitive polymers:

The core tablets were again coated by pan coating machine with a perforated pan. The spray pan coating method was used for coating involves with polymeric solution containing Eudragit L100 along with TEC (5% w/v) and dissolved in ethanol: water (1:1) mixture and stirred gently for a period of 10 min using magnetic stirrer. Dispersion was transferred to a filtering flask and air bubbles were removed using a vacuum pump and used for coating purpose. The temperature of inside pan coater was regulated and maintained by circulating hot air by hot air blower fitted at upper end of burette stand. Speed of pan rotation was regulated by key present at rotatory vacuum evaporator. The coating of pH sensitive polymers was done upto getting 10% weight gain of total weight of tablet.

Table 1: Composition of uncoated tablet formulations prepared by wet granulation method

Ingredients	FOCT1	FOCT2	FOCT3	FOCT4	FOCT5	FOCT6
Solid dispersion	260	260	260	260	260	260
Microcrystalline cellulose (Avicel pH 102)	50	50	50	50	50	50
Dibasic calcium Phosphate dihydrate (DBP)	50	50	50	50	50	50
Mannitol	150	0	0	75	75	0
Sodium chloride	0	150	0	75	0	75
Potassium chloride	0	0	150	0	75	75
Purified Talc	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10
Polyvinyl pyrrolidone K-30	10 % w/v in isopropyl alcohol					
Total weight	530 mg					

Characterization of OCCTDDS tablets:

Flow properties of granules: The flow properties of granules were characterized in terms of Carr's index, Hausner's ratio and angle of repose. The Carr's index (I_C) and Hausner's ratio (H_R) of granules were calculating according to following equation:

$$\text{Carr's Index } (I_C) = \rho_{\text{Tapped}} - \rho_{\text{Bulk}} / \rho_{\text{Tapped}}$$

$$\text{Hausner's ratio } (H_R) = \rho_{\text{Tapped}} / \rho_{\text{Bulk}}$$

The angle of repose (θ) was measured by fixed height method. This was calculated by following equation:

$$\text{Angle of repose } (\theta) = \tan^{-1} 2 H / D$$

Where H is the surface area of the free standing height of the powder heap and D is diameter of heap that formed after powder flow from the glass funnel.

Thickness: The thickness of coated OCCTDDS tablets was determined using a screw gauze, and the results are expressed as mean values of ten determinations.

Uniformity weight: 20 coated OCCTDDS tablets were sampled from each batch and accurately weighed using an analytical balance (D5

14300857/E I300, Shimadzu Corp. Manufacturing, Philippines).

Hardness: 20 coated OCCTDDS tablets were sampled from each batch and individually tested for hardness using the Stoke-Monsanto hardness tester. The tablet hardness is expressed in kg/cm².

Friability: The friability test of coated OCCTDDS tablets was performed on 10 tablets at 25 rpm for 4 min using Roches Friability Tester (Model 9509/ZEC-Z). The percentage of friability was calculated based on the weight lost after the test. A maximum loss of weight (from a single test or from the mean of the three tests) was not greater than 1.0 %.

Drug content: Ten coated OCCTDDS tablets were finely powdered, and a quantity of powder equivalent to 100 mg of 5FU was accurately weighed. The weighed sample was transferred to 100 ml volumetric flasks containing approximately 50 ml of various solvents. The flasks were shaken for solubilizing the drug and sonicated for 10 min. The solutions were filtered through a 0.45 μ m membrane filter and the absorbance taken at simulated intestinal fluid (pH 6.8) containing 4% w/v rat caecal medium using double beam UV spectrophotometer (Shimadzu-1800).

Disintegration test: The disintegration test of coated OCCTDDS was performed using disintegration test apparatus (9508/TEC-1, Indian Equipment Corp. Mumbai). The tablets were placed in the tubes of the assembly and assembly was suspended in the beaker containing 900 ml of 0.1 N HCl and assembly operated for 2 h without the disc. After 2 h the 0.1 N HCl was replaced with phosphate buffer pH 6.8 and discs were added in each tube of the assembly containing the tablets and assembly operated further for 60 min.

Bursting time: Bursting time of coated OCCTDDS was determined as the time after which tablet was not able to withstand the internal pressure and the tablet opened up. The test was carried out in the dissolution media by keeping the tablets in buffer (pH 6.8) at 100 rpm at 37 ± 0.5 °C. The test was carried out using 6 tablets from each formulation.

Water uptake: Water uptake of OCCTDDS tablets was performed by a piece of filter paper (10 X 10 cm) folded twice to give a 5 X 5 cm square, placed in a glass petri dish and added 5.0 ml of distilled water. An accurately weighed tablet was placed on the moist paper for 5 min and then reweighed. Five tablets from each batch were tested. Results are expressed according to the equation below

$$\text{Water uptake (\%)} = \frac{\text{Weight increase of tablet (mg)}}{\text{Initial tablet weight}} \times 100$$

Swelling studies: Swelling ratio of OCCTDDS tablets was determined using following equation:

$$\text{Swelling Ratio (\%)} = \frac{(A_t - A_0)}{A_{\text{tablet}}} \times 100$$

Where A_t , weight of the tablet and basket at time t (g); A_0 , weight of the tablet and basket at the beginning (g); A_{tablet} , weight of the dry tablet (g).

The prepared tablets were placed in the wire basket of six basket dissolution apparatus. The basket was immersed in a beaker containing 0.1 N HCl (900 ml) for 2 h. Then the dissolution medium was replaced with phosphate buffer pH 7.4 (900 ml) and allowed to stand for 3 h. Then again dissolution medium was replaced with phosphate buffer pH 6.8 (900 ml) allowed to stand for 3 h

and allowed to swell at 37 °C. The tablets were removed and changes in weight were measured before and after swelling.

In vitro dissolution study: The *in vitro* release profile of OCCTDDS tablets and the entrapped drug from the coated tablets were studied by the *in vitro* dissolution study. The coated tablet placed in basket of IP dissolution rate test apparatus (apparatus type II, 50 rpm, 37 ± 0.5 °C). The basket was immersed in a beaker containing 0.1 N HCl (900 ml) for 2 h as the average gastric emptying time is about 2 h, then the dissolution medium was replaced with phosphate buffer pH 7.4 for 3 h as the average small intestinal transit time is about 3 h. The susceptibility of gum combination coats to the colonic environment was assessed by replacing the dissolution medium by phosphate buffer pH 6.8 (900 ml) saline to maintain colonic pH condition. Aliquotes were withdrawn periodically and analyzed for drug content by using UV spectrophotometer, the absorbance was taken at λ_{max} 262.0 nm in 0.1 N HCl, λ_{max} 266.0 nm in pH 7.4 phosphate buffer, λ_{max} 266.0 nm in pH 6.8 phosphate buffer and λ_{max} 267.0 nm in simulated intestinal fluid (pH 6.8) containing 4% w/v rat caecal medium using double beam UV spectrophotometer (Shimadzu-1800).

Release profile study: Release profile of OCTDDS tablets was characterized for release lag time (T_{lag}) and release rate k . Release data within the linear range were selected and fitted to a zero-order mathematical model: $Q = C + kt$. Where Q is the release percentage at time t ; k is the slope of the fitted linear equation and here represents release rate; and C is the intercept of the linear equation. T_{lag} is defined as the time of the start of drug release and calculated here from the fitted equation, setting $Q=0$: $T_{\text{lag}} = -C/k$. The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable for T_{lag} and k calculation.

Results and Discussion

The formulations FOCT1 to FOCT6 containing solid dispersion equivalent to 100 mg of 5 FU as

Table 2: Physical characteristics of formulations OCCTDDS

Formulation code	Carr's index ⁿ (%)	Hausner's ratio ⁿ	Angle of repose (θ) ⁿ	Tablet Thickness (cm)		Average Weight (mg)	Hardness (kg/cm ²)
				Thickness	Diameter		
FOCT1	13.13±0.018	1.12±0.011	24.1±0.11	0.801±0.002	1.12±0.011	634.2±0.090	5.21±0.19
FOCT2	14.14±0.012	1.15±0.012	22.2±0.11	0.811±0.006	1.12±0.010	638.3±0.150	5.81±0.09
FOCT3	14.11±0.012	1.13±0.012	23.1±0.11	0.801±0.003	1.12±0.009	633.2±0.158	6.11±0.20
FOCT4	14.21±0.011	1.17±0.011	21.1±0.13	0.816±0.005	1.12±0.002	636.8±0.117	6.02±0.13
FOCT5	13.12±0.011	1.11±0.012	22.1±0.12	0.830±0.003	1.12±0.012	635.9±0.118	6.51±0.25
FOCT6	13.11±0.013	1.13±0.011	23.2±0.12	0.808±0.001	1.18±0.001	646.8±0.189	6.25±0.35

Table 3: Physical characteristics of formulations OCCTDDS

Formulation code	Drug Content (%)	Disintegration Time (h)	Bursting time (h) ⁿ	Water uptake (%)	Swelling ratio (%)		
					0.1 N HCl	pH 6.8	pH 7.4
FOCT1	99.3±1.00	2.23±0.014	4.38±0.17	174.8±1.87	143	232	79
FOCT2	99.2±1.01	2.47±0.012	4.32±0.13	178.7±1.73	142	248	91
FOCT3	98.9±0.98	2.34±0.012	4.45±0.10	147.5±1.76	151	251	89
FOCT4	99.1±1.01	2.28±0.011	5.08±0.19	142.6±1.73	208	316	109
FOCT5	99.6±1.01	2.10±0.013	5.25±0.15	229.4±1.92	199	276	99
FOCT6	98.8±0.83	2.48±0.013	5.20±0.18	121.5±1.76	177	278	97

active medicament by wet granulation methods technique containing. The core tablets prepared containing mannitol in various ratios of sodium chloride or potassium chloride as osmotic agents for optimization of osmogens. The formulations were incorporated at varying concentrations of Avicel PH 102 was used as diluents and directly compressible vehicle at different concentrations to

prepare all the tablets at a constant weight of talc and magnesium stearate was added as lubricant and glidant in all the formulations. The direct compression process was found to be suitable for compressing powder blends as osmotic tablets. All the batches of tablets were compressed under identical conditions to minimize processing variables. The core osmotic tablet was converting

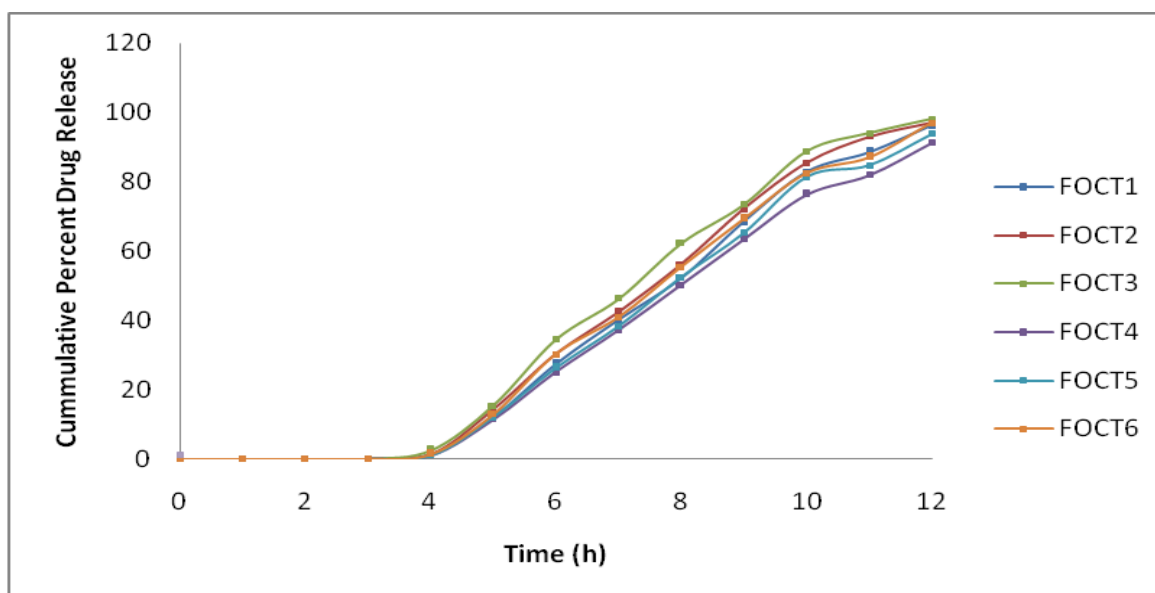


Fig. 1: Zero order *in vitro* drug release study of various OCCTDDS tablets.

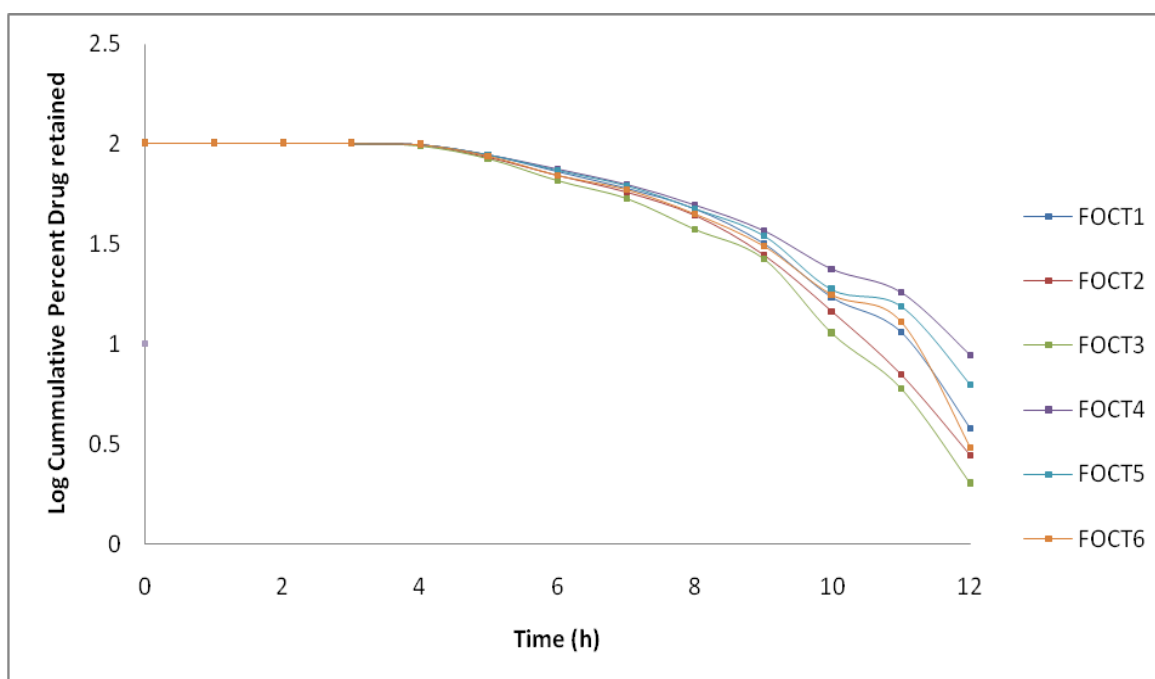


Fig. 2: First order *in vitro* drug release study of various OCCTDDS tablets.

to osmotic pump after coated by pan coating machine with a perforated pan. The core tablets were coated by pan coating machine with a perforated pan with polymeric solution containing Eudragit L100 pH sensitive polymeric layer to get weight 10% of total weight of core tablet. The prepared OCTDDS were characterizing by various evaluating parameters. The physical blends of

various 5FU osmotic controlled release tablets before compressing them as tablets were analyzed for their flow properties such as angle of repose and Carr's index were evaluated for all the physical blends of the formulations. The angle of repose and Carr's index values for various physical blends of the formulations are given in Table 2. All the physical blends of the formulations were

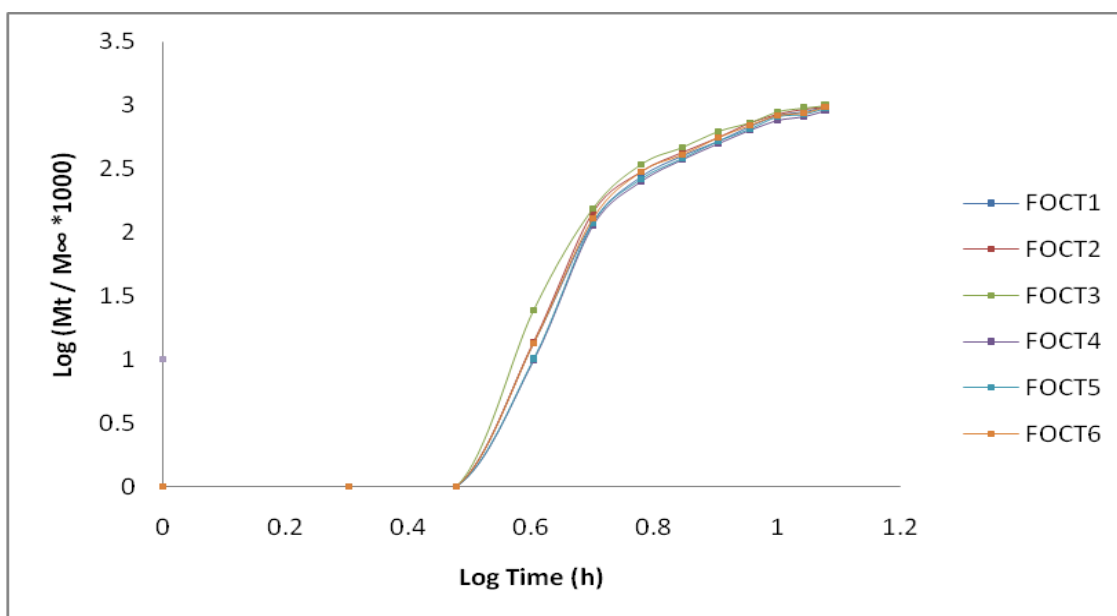


Fig. 3: Korsmeyer-peppas *in vitro* drug release study of various OCCTDDS tablets.

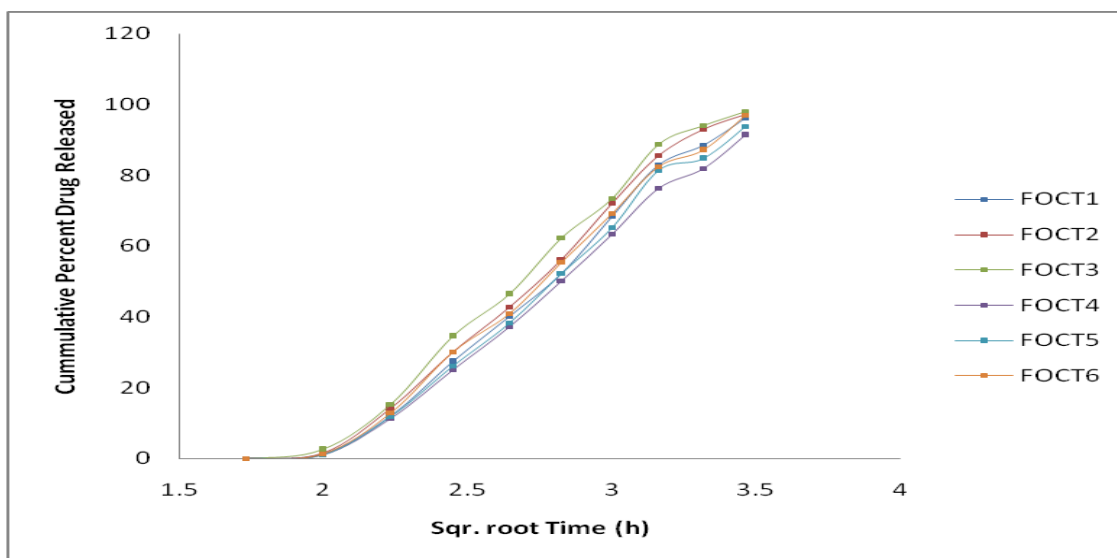


Fig. 4: Higuchi plot *in vitro* drug release study of various OCCTDDS tablets.

evaluated were evaluated for flow properties such as angle of repose and Carr's index before compression. The flow property values obtained for various powder blends were in the range of good to excellent flow characteristics. Thus all the powder blends were found to be stable and suitable for compression as osmotic controlled colon targeted tablets.

The prepared OCTDDS coated tablets of 5 FU were further subjected to evaluation of post compression parameters such as weight

uniformity, hardness, friability and drug content as per the compendial procedures (Table 3). Drug content estimated for all the tablet formulations was highly uniform with less than 1% variation. These studies revealed that all the tablet formulations were found to be stable and meeting I.P. specified limits for weight uniformity, friability and drug content. Thus, all the batches of tablet formulations were found to be stable and suitable for further studies. The Coated tablet showed smooth and uniform surface with pore exhibited

uniform aperture before dissolution and after dissolution the Figure 4 indicated slight erosion in the orifice indicated that the drug is released only through orifice by diffusion process.

The *in vitro* dissolution release study of prepared formulations were fitted in various kinetic models i.e. first order, Higuchi and Kormeyer Peppas plots were plotted and first order K value, Higuchi's K value and Kormeyer Peppas's n value with r^2 values were calculated as per the procedures mentioned (Figs. 1-4). The Zero order plots for FOCT1 to FOCT6 coated OCCTDDS tablets formulations were plotted and the values were in r^2 values in the range of 0.966 to 0.994 (Fig. 1). The Peppas's plot of all coated OCCTDDS tablets was confirmed 'n' values were in the range of 0.633 to 1.115 with r^2 value in the range of 0.981 to 0.999 (Fig. 3). The Zero order plot for FOCT4 tablet formulation was plotted and the value was r^2 value 0.966 and 'n' value was found to be with r^2 value 0.990 indicated near zero order release. However, drug release from the matrix osmotic tablets follows anomalous non-Fickian diffusion which indicates that erosion of the polymeric matrix followed by drug release by diffusion takes place.

Conclusion

Colon specific drug delivery systems are designed to obtain targeted drug delivery to the large intestine (colon) and provide local delivery for the treatment of colonic diseases and colon cancer, where it is necessary to attain high concentration of the drug. Colon specific drug delivery systems are designed to obtain targeted drug delivery to the large intestine (colon). 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 approaches for targeting drugs at specific site for specific local disease i.e. colon cancer are under innovative research field. The patients suffering with above

mentioned disease need high concentration or amount for treatment, which may produce more side effects and may not be able to treat by direct treatment. The osmotic controlled drug delivery systems have two principles; one utilize the osmotic pumping for controlled delivery of drugs at specific site with local action and other retain drug release up to colonic environment. Such an innovation will treat disease with less amount of drug with less side effect on human body.

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