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# In vitro In vivo comparison of two pH sensitive Eudragit polymers for colon specific drug delivery

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**Abstract**:
The aim of this study was to develop the polymer coated diclofenac tablet containing superdisintegrant for colonic drug delivery and compare the in vivo performance of two polymers for site specificity. Eudragit FS 3D and Eudragit S100 were used as pH sensitive polymers. Tablets were prepared to give fast release at specific site with the help of sodium starch glycolate as superdisintegrant. Tablets were coated separately with Eudragit FS 30D and Eudragit S100 in various thicknesses and evaluated for in vitro drug release using changing pH method. X ray imaging was used to monitor the placebo tablets throughout the gastrointestinal system. In vitro release studies reveals that Eudragit FS30D coated tablet with 10%w/w coating level start release of drug at pH 6.8 after suitable lag time in the same pH which corresponds to colonic arrival time, as compare to Eudragit S100 coated tablet which release only at higher pH , approximating the transverse colon. In vivo study shows that Tablet coated with Eudragit FS30D with 10%w/w coating level and Eudragit S100 with 10% coating level disintegrated in cecum region. Thus Eudragit FS30D coated tablet may be a promising system for the treatment of colonic disease where pH may decrease and drug also start to release at the same pH after suitable lag time as well as release of drug at the beginning of colon so drug will be available in solution or disperse form for local and systemic effect throughout the colon.

**Key words:** Eudragit S100, Eudragit FS30D, X ray studies, colon drug delivery.

## Introduction:

The importance of colon–specific drug delivery system has been well recognized and documented. In addition to providing more effective therapy of the colon related diseases such as irritable bowel syndrome, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, colon specific delivery has potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs [1]. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of small intestine. Due to the distal location of the colon in gastrointestinal tract, a colon specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Such a system can be formulated utilizing some specific conditions existing in the colon in comparison to other parts of the gastrointestinal tract. Overall, the physiological changes along the gastrointestinal tract can be generally characterized as a continuum, with decrease in enzymatic activity, motility and fluid content and increase in pH as we move from esophageal end to the rectum [2]. Research interest in the area of colonic drug delivery has been fuelled by the need to better treat pathologies of the colon that range in seriousness from constipation and diarrhea to the debilitating inflammatory bowel diseases ( Ulcerative colitis and Crohn's disease ) through to the colon carcinoma , the third most prevalent form of cancer in both men and women [3] .Targeted drug delivery to the colon would therefore ensure direct treatment at the disease state , lower dosing and a reduction in systemic side effects. Beside the local treatment, the colon can also be utilized as a portal for the entry of drugs into the blood stream for the purpose of systemic therapy. Drugs that are degraded and poorly absorbed in the upper gut may be preferentially absorbed from the colon because of the lower levels of luminal and mucosal digestive enzymes, as compared with the small intestine. Furthermore, colonic drug delivery may also be used as a means of achieving chronotherapy for diseases such as asthma and arithritis [4]. Most of the conventional

drug delivery systems for treating the colon disorders such as IBD e.g. Ulcerative colitis, Crohn's disease, infectious diseases (e.g. amoebiasis) and colon cancer are failing as the drugs do not reach the site of action in appropriate concentrations. Thus, an effective and safe therapy of these colonic disorders, using site specific drug delivery systems is a challenging task to pharmaceutical technologist. In the recent times, the colon-specific delivery systems are also gaining importance for the systemic delivery of protein and peptide drugs. The peptide and protein drugs are destroyed and inactivated in acidic environment of the stomach and by pancreatic enzymes in the small intestine. These drugs are usually administered by parentral route, which is inconvenient and expensive. Due to negligible activity of brush border membrane peptidase activity and less activity of pancreatic enzymes, the colon is considered to be more suitable for delivery of peptides and proteins in comparison to small intestine. Besides this low hostile environment, the colonic transit time is long (20 -30 h) and the colonic tissue is highly responsive to the action of absorption enhancers, which make the colon a promising site for the delivery of protein and peptide drugs for systemic absorption. Thus, colonic delivery of analgesic peptides, contraceptive peptides, oral vaccines, insulin, growth hormone, erythropoietin, interferon and interleukins was attempted for systemic absorption. Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed. Suppositories are only effective in the rectum because of the confined spread and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore, oral administration is preferred, but for this purpose many physiological barriers have to be overcome. Absorption or degradation of the active ingredient in the upper part of the gastrointestinal tract is the major obstacle and must be circumvented for successful colonic drug delivery [5].The targeting of orally administered drugs to the colon is accomplished in several ways such as prodrugs, pH controlled drug release, time controlled drug release, enzyme controlled drug release, and pressure controlled drug release [6,7].

Enteric coatings are well-known and several marketed IBD products rely on them to delay release in an attempt to increase local drug delivery. They have proven useful in IBD patients. Indeed, current understanding of the pH profile along the GIT of patients with active IBD suggests that accurate control over the site of release, particularly from the terminal ileum onward is difficult based on pharmacokinetics alone, when using pH-sensitive polymer coatings. It is possible to treat the IBD effectively by orally administering the drug through the colon specific drug delivery which may act systemically as well as locally. Eudragit S100 have been successfully tried for the colon specific drug delivery but it target drug delivery in the colon only at high alkaline pH [8,9] and intestinal pH may decrease in the colonic disease [10] which affects the colon specific drug delivery based on pH approach. Eudragit FS30 has been shown to give more specific result as compare to other polymer. Therefore we have done the comparative utility of the above polymers in developing suitable dosage form, exhibiting minimum drug release in the upper regions of the GIT in order to provide targeted drug delivery to the colon even in low pH condition simulating pH in colonic disease. The first objective was to design an enteric coated tablet which will release the drug

specifically and instantly in the colon and second was to evaluate their effects in vivo and in vitro. The Diclofenac sodium designed core tablet contain superdisintegrant to release the drug instantly at the target site and compensate intersubject variation in GI transit time since large variations in gastric emptying times [11] and passage of formulation across the ileo-caecal junction without drug release have been reported [12]. For this purpose varying concentration of polymers were applied, core tablet was prepared with superdisintegrant and effect of the coating on drug release and site specificity in different pH condition was evaluated *in vitro* as well as confirmed by *in vivo* trials in human volunteers.

**Materials and Methods**:

Diclofenac sodium was obtained as a gift sample from the Arti Pharmaceuticals Ltd., Mumbai. Eudragit FS 30D and Eudragit S100 was obtained from the Degussa India Pvt. Ltd. Mumbai, as a gift sample. HPMC 15 cps was provided by the Colorcon India Pvt. Ltd. Other excipients like talc, magnesium stearate, sodium starch glycolate, dichlormethane, isopropyl alcohol used to prepare tablets and for coating was of standard pharmaceutical grade and all chemical reagents used were of analytical grade and procured locally.

**Preparation and evaluation of diclofenac sodium core tablet:**

Three different tablet formulation of diclofenac sodium were prepared by using wet granulation technique (F1, F2, and F3). In this, polyvinyl pyrolidon solution (3%w/v) in isopropyl alcohol was used as binder. The formulations details are shown in Table 1. Total weight of each tablet was 200 mg that contains 50 mg of Diclofenac sodium IP. The Tablets were compressed on 8 mm standard concave punch on single rotary tablet compression machine (Rimek, Mumbai) and characterized after preparation. Twenty tablets were tested for weight variation (Mettler Toledo), thickness (Vernier Caliper), friability (Rosche friability tester), and hardness (Monsanto hardness tester). The drug content was measured spectrophotometrically, for this purpose 10 tablets were individually weighted and then each of them was crushed and dissolved in 150ml ethanol and diluted with distilled water. The samples were assayed spectrophometrically (Jasco V-530) at 276 nm. In order to see effect of superdisintegrant on site specificity and release pattern, core tablets (F1) were prepared without superdisintegrant and processed similar as above.

**Preparation of non aqueous Eudragit S100 coating solution** [13]

***Preparation of S100 dispersion***: The solution of Eudragit S100 was prepared by dissolving 9.75g of Eudragit S100 dry polymer in the mixture of 62ml of isopropyl alcohol (IPA) and 3.75ml of water at room temperature (Table2).

***Preparation of Eudragit S100 organic coating solution:*** In the 72.19ml of IPA 1.88g of talc and 0.94ml of plasticizer are added with constant stirring, after a homogenous mixture was obtained, dispersion of Eudragit S100 was added with a continuous stirring. The final coating solution was stirred for a 10 min.

**Coating of Diclofenac sodium tablets with Eudragit S100 non aqueous coating solution:**

The coating dispersion was passed through sieve 0.25 mm aperture diameter before use. The spray rate and the bed temperature during the coating process were 2 gm/min (till the end of process) and 30- $35^0$C respectively. The various coating parameters controlled during coating process are given in Table 3. Before coating the tablets were preheated to the $40^o$C bed temperature for 15 min. The tablets were coated to a 5, 10, 15, and 20 % w/ w total weight gain.

***Preparation of Aqueous dispersion containing Eudragit FS 30 D:***

To prepare the Eudragit FS 30 D coating dispersion a 30 % (w/w) aqueous Eudragit FS 30 D dispersion was used. Polysorbate 80 as a wetting agent and glyceryl monostearate as a glidant were added to water and the mixture was heated at $60^0$ C by stirring for 10 min at 50 rpm until a fine homogenous dispersion was obtained. After cooling, this dispersion was gently added to Eudragit FS 30 D dispersion and mixed by magnetic stirrer. For this coating dispersion no plasticizer was needed in the formulation since it exhibits a minimum film-forming temperature of $14^0$ C and low glass transition temperature [14].

***Coating of tablets with Eudragit FS 30 D aqueous dispersion:***

Core tablets were initially coated with HPMC (15cps) to form barrier in between the diclofenac core tablet with superdisintegrant and outer Eudragit FS 30D aqueous coating in order to avoid seepage of moisture into core tablet. The coating dispersion of Eudragit FS30D was passed through sieve 0.25 mm aperture diameter before use. The spray rate and the bed temperature during the coating process were 2 gm/min (till the end of process) and 30-$35^0$C respectively (Table 3). Before coating the tablets were preheated to the $40^o$C bed temperature for 15 min. The tablets were coated to a 5%, 10, 15 % and 20% w/ w total weight gain.

**Drug release study of Eudragit S100 and Eudragit FS30D coated Diclofenac sodium tablets**

The dissolution studies of coated tablets were carried out in a USP XXIII dissolution apparatus II (DA 6D Veego) at a rotation speed of 100 rpm in a 933.3 ml medium at $37^0$ C. The tablets(n=6) were transferred to dissolution medium and aliquots were collected at selected time intervals, filtered through whatmann filter paper no. 41 and analyzed by UV spectrophotometer (V-530 Jasco) at 276 nm. The continuous changing pH dissolution method was used for simulating conditions of the GI tract. Initially tablets were added in 700 ml of 0.1 N HCl (pH 1.2) for 2h. At the end of 2 h 233.3 ml of tribasic sodium phosphate solution was added to all the dissolution vessels and the pH was adjusted to 6.5, 6.8 and 7.2 by using 2M NaOH or 2M HCl till third and forth and till the end of study respectively.

Eudragit FS 30 D is a relatively new pH-dependent methacrylic acid polymer for colonic delivery purposes. The earlier reported threshold pH values for Eudragit FS 30D polymer was 6.8 [8], 7.2 or above [9] and 7.5 [15]. In order to test the suitability of Eudragit FS 30 D in comparison with Eudragit S100 for colon targeting, the pH dissolution profile of the tablets with the 10% and 15% coating level were investigated in 0.2M phosphate buffers at pH 6.8 and 7.2, after 2 h incubation in 0.1M HCl till more than 90% of drug release occur **.** Dissolution study was performed with USP XXIII dissolution apparatus II (DA 6D Veego) at a rotation speed of 100 rpm in a 900 ml medium at $37^0$ C. The tablets(n=3) were transfer to dissolution medium and aliquots were collected at selected time intervals, filtered through Whatmann filter paper no. 41 and analyzed by UV spectrophotometer (V-530 Jasco) at 276 nm.same method as.

**Result**

**Evaluation of diclofenac sodium core tablets:**

The tablet formulations prepared as per table1 were evaluated for physical properties. The tablet from all the formulations exhibited similar strength. Formulation F3 containing 5% of superdisintegrant was considered useful, which showed disintegration time of less than one minute ($0.50 \pm 0.36$).

**Table 1. Composition of Diclofenac sodium core tablet.**

| *Sr. No.* | *Ingredients (mg/tablet)* | Formulations | | |
|---|---|---|---|---|
| | | **F1** | **F2** | **F3** |
| 1 | Diclofenac sodium IP | 50 | 50 | 50 |
| 2 | Sodium Starch Glycolate | - | 5 | 10 |
| 3 | Microcrystalline cellulose | 10 | 10 | 10 |
| 4 | Talc | 5 | 5 | 5 |
| 5 | Magnesium stearate | 4 | 4 | 4 |
| 6 | Lactose monohydrate | 131 | 126 | 121 |

Formulations F1 represent control, without superdisintegrant and F2, F3 with two different concentration of superdisintegrant.

**Table 2 Formulation details of Eudragit S100 coating solution.**

| Sr. no. | Ingredients | Quantity (gm) |
|---|---|---|
| ***A. S100 Dispersion*** | | |
| 1 | Eudragit S100 | 9.75 |
| 2 | IPA | 62 |
| 3 | Water | 3.75 |
| ***B. Eudragit S100 coating solution*** | | |
| 4 | Coating Dispersion A | 70 |
| 5 | Plastsizer | 0.94 |
| 6 | Talc | 1.88 |
| 7 | IPA | 72.19 |

**Table 3 Coating parameter Eudragit S100and Eudragit FS 30D coating.**

| Parameters | Specification | |
|---|---|---|
| | **Eudragit S100** | **Eudragit FS 30D** |
| Batch size | 50 gm | 50 gm |
| Spray rate | 2 gm/min | 2 gm/min |
| Nozzle diameter | 1 mm | 1 mm |
| Atomizing air pressure | 0.5 bar | 1 bar |
| Air inlet temperature | 50-60$^{o}$ C | 30-35$^{0}$ C |
| Pan speed | 30-40 RPM | 50-60 RPM |
| Preheating of core tablets | 10 min | 10 min |

Coating parameters followed during pan coating of diclofenac core tablet with Eudragit S100 and Eudragit FS30D.

The mean drug content of all formulation was found to be in the range of 99-102%.Formulation F3 was selected for coating processes.

**In vitro drug release study of Eudragit S 100 and Eudragit FS30D enteric coated formulation containing super disintegrant**

Figure 1 and 2 showed the drug release profile of the Eudragit S100 and Eudragit FS30D enteric coated Diclofenac sodium tablets respectively. The tablets with 5% w/w coating level start the drug release after 2 h lag time and showed more than 80% drug release within 5 h. Tablets with 10% w/w coating level of Eudragit S100 showed lag time of 5 h and 100% of drug release after this lag time in less than 2 h; whereas

**Table 4 Dissolution test method in phosphate buffer at different pH**

| System code | Polymers | Coating level (w/w) | pH of 0.2 M phosphate buffer |
|---|---|---|---|
| A1 | Eudragit FS 30 D | 10 % | 6.8 |
| A2 | Eudragit FS 30 D | 10 % | 7.2 |
| A3 | Eudragit FS 30 D | 15 % | 6.8 |
| A4 | Eudragit FS 30 D | 15 % | 7.2 |
| A5 | Eudragit S100 | 10 % | 6.8 |
| A6 | Eudragit S100 | 10 % | 7.2 |
| A7 | Eudragit S100 | 15 % | 6.8 |
| A8 | Eudragit S100 | 15 % | 7.2 |

Formulations of diclofenac core tablet coated with 10%w/w and 15%w/w coating level and dissolution media used for drug release studies. A1-A8 represents different formulation code

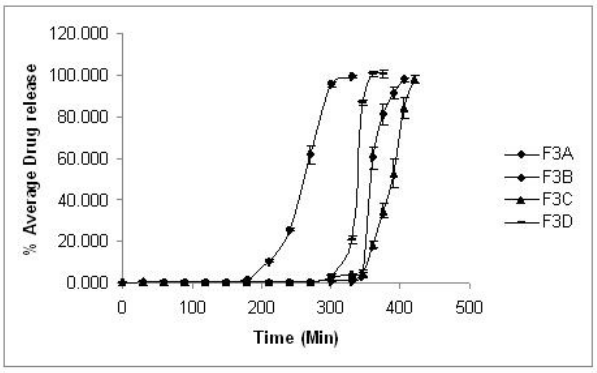


**Figure 1** Cumulative % release of diclofenac from tablet coated with Eudragit FS 30D containing different coating level (weight gain) 5%w/w, 10%w/w,15%w/w, 20%.Bars represent standard deviation.

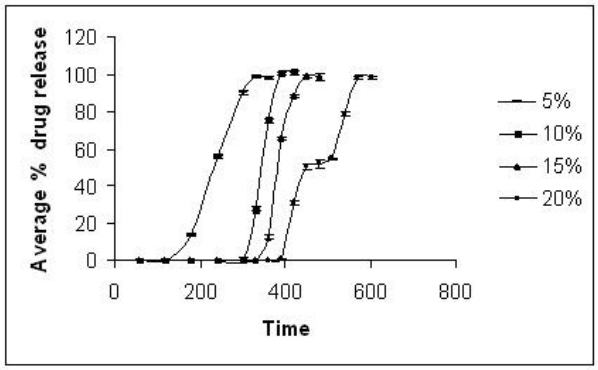


**Figure 2** Cumulative % release of diclofenac from tablet coated with Eudragit S100 containing different coating level (weight gain):5%w/w, 10%w/w, 15%w/w.20%.Bars represent standard deviation

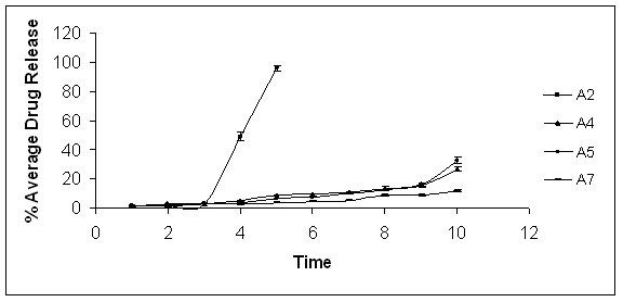


**Figure 3** Cumulative % release of diclofenac from tablet coated with Eudragit FS 30D with coating level of 10%w/w A2 and coating level of 15%w/w A4. Eudragit S100 with coating level of 10%w/w A5 and coating level of 15%w/w A7 at pH 7.2.Bars represent standard deviation.

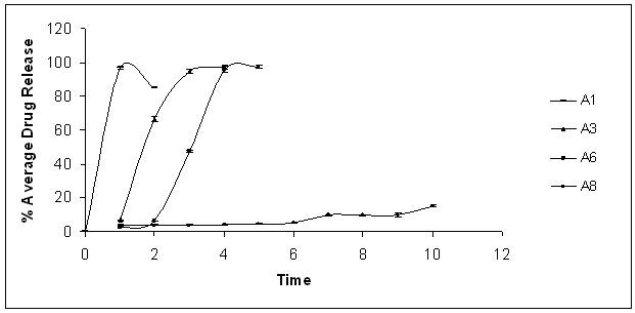


**Figure 4** Cumulative % release of diclofenac from tablet coated with Eudragit FS 30D with coating level of 10%w/w A1 and coating level of 15%w/w A3. Eudragit S100 with coating level of 10%w/w A6 and coating level of 15%w/w A8 at pH 6.8.Bars represent standard deviation.

**Table 5 In vivo study result of tablets with different coating level**

| Subject. no. | Polymers | Coating level (%w/w weight gain) | Location after 5.30h | Status |
|---|---|---|---|---|
| 1 | Eudragit FS 30D | 10 | ----- | Disintegrated |
| 2 | Eudragit FS 30D | 15 | Transverse colon | Intact |
| 3. | Eudragit S 100 | 10 | ----- | Disintegrated |
| 4. | Eudragit S 100 | 15 | Transverse colon | Intact |

Formulation with 10%w/w coating level of Eudragit S100 and Eudragit FS 30D remain intact till 5h in cecum (initial segment of colon)and found disintegrated after 5.30h X ray, whereas Formulation with 15%w/w coating level of Eudragit S100 and Eudragit FS 30D remain intact till 5.30h in transverse colon.

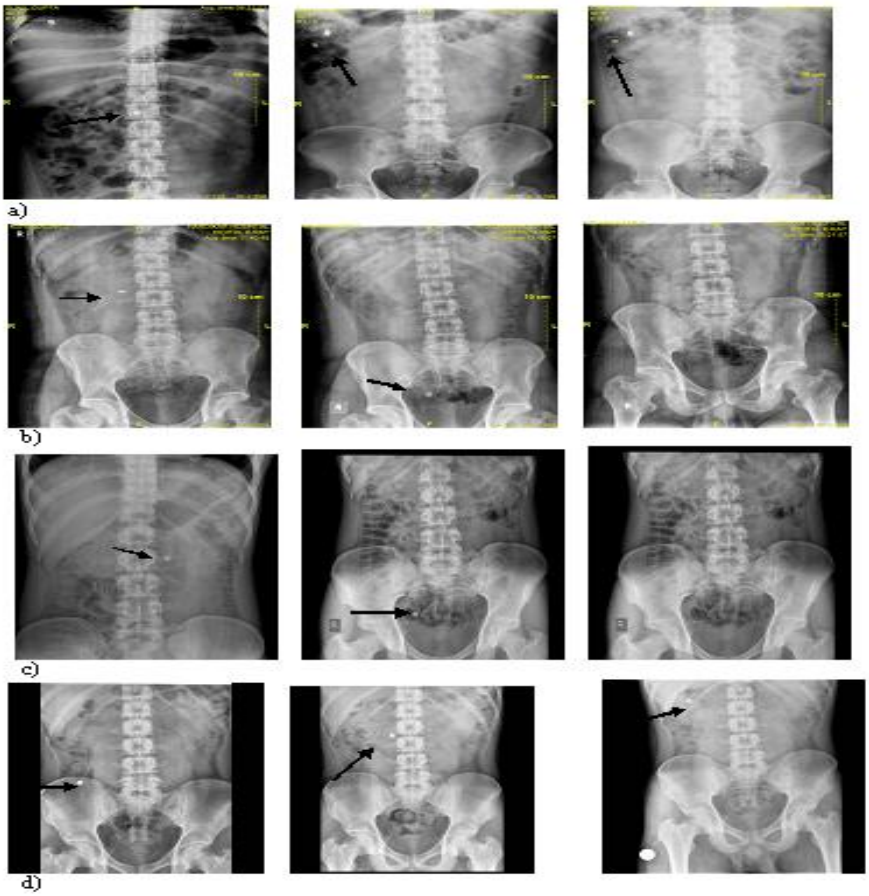


**Figure 5** X ray after 2h, 5h and 5.30h of position of placebo tablet coated with Eudragit S100 and Eudragit FS30D in four different subject a) Eudragit S100 coating level 15%w/w, b) Eudragit S100 coating level 10%w/w, c) Eudragit FS30 D coating level 10%w/w, d) Eudragit FS30D coating level 15%w/w.In subject b and c tablet not observed after 5.30h which indicate disintegration of tablet in colon.

FS 30D 10% w/w coated tablet showed 100% of drug release within 30 min after a lag time . Formulations with 15% and 20% w/w coating level showed 6 h and 6.5 h lag time respectively and after this lag time these formulations showed 100% drug release within 1.5 to 2.5 h.

**Comparison of in vitro drug release study of Eudragit FS 30 D coated tablets and Eudragit S100 coated tablets**

It was observed that within 1 h 100% drug was released from Eudragit FS 30D 10% w/w tablet at pH 7.2 (A2), Eudragit S100 10% w/w tablet in pH 7.2 (A6) remained intact for 2 h and completely disintegrate after 2.5 h.

At pH 6.8 only 3% of Diclofenac sodium was released after 3 h from 10% w/w Eudragit FS 30D tablets (A1), at $4^{th}$ h drug release was found to be 45%. The tablet coated with Eudragit S100 with coating level of 10% w/w at pH 6.8 (A5), 15% w/w at pH 6.8 (A7) and 7.2 (A8) remained intact for 6 h and showed less than 10% drug release. Formulation with Eudragit FS 30D coating level of 15% w/w shows 100% drug release after 3 h at pH 7.2 (A4)) but showed only 24% drug release after 10 h at pH 6.8.(Figure 3,4)

**In vivo studies:**

In vivo studies reveal that after X ray examination tablet coated with Eudragit S100 with coating level of 10%w/w, after 2h and 5h remains intact in stomach and cecum respectively and found disintegrated after 5.30h ,whereas tablet with 15% coating level remains intact even after 5.30h in transverse colon. Tablet coated with Eudragit FS30D 10%w/w coating level was found to be intact after 2h and 5h in stomach and cecum respectively and found disintegrated after 5.30h and tablet with Eudragit FS30D 15%w/w coating level was intact after 5.30h in transverse colon. At the end of 5h tablet with 10%w/w coating level of both the polymer was in ileum in intact position (Fig 5 and Table5).

**Discussion**:

Core tablet satisfied with official and unofficial requirement of quality control parameter so tablet has sufficient mechanical strength and drug content. Drug release study by continuous pH changing method reveal fast release of drug from Eudragit FS 30D coated tablet as compare to Eudragit S100 coated tablet which is due to Eudragit FS 30D dissolves in controlled manner above pH 6.5, it contain carboxylic as well as ester group in ratio of 1:10 [9, 13] and Eudragit S100 contain more percentage of carboxylic group as compare to ester group which require higher pH for hydrolysis and subsequent release of drug. Drug release study at pH 7.2 shows that more than 90% drug get released from Eudragit FS30D coated tablet within 1h, this can be consider as critical pH value for this polymer which is in agreement with Huyghebaert et al [16] and Chunsheng Gao et al [9].At pH 6.8 only 3% of Diclofenac sodium was released after 3 h from 10% w/w Eudragit FS 30D tablets (A1), which is considered to be the suitable transit time for the dosage form in small intestine. At $4^{th}$ h drug release was found to be 45% released, that means the dosage form assured the release of drug after suitable lag time at pH 6.8, this is beneficial in patients having low intestinal pH in IBD [10], and Eudragit S100 coated tablet release less than 10% release which is due this polymer require higher pH for dissolution [8,9].These results show that FS 30D is the more suitable enteric polymer for targeting the drug to the colon region because the patients with inflammatory bowel diseases may show decrease in the pH value of small intestine and colon. So there might be the chances that the formulation travels down the colon and excreted in intact form with very less amount of drug release. So it is necessary

for any formulation targeted at the colon region should release the drug after a suitable lag time (3-4 h) in the alkaline pH 6.5-6.8. As seen above FS 30D with 10% w/w (A1) showed the lag time of 3 h in the pH6.8 after this lag time it starts the drug release. The Eudragit FS 30D contains higher ratio of ester to carboxylic groups than Eudragit S100 [7,17] which gets dissolved in controlled manner at pH 6.8-7.2 [8,9,18],whereas Eudragit S100 contains higher ratio of carboxylic to ester group which get hydrolyzed only at higher pH. Therefore Eudragit FS 30D was considered as more suitable polymer for colon targeting than Eudragit S100 since it release the drug at low pH also after suitable lag time and drug release may start as tablets reaches the colonic region so the drug is available in dissolved or dispersed form for local and therapeutic effect.

For effective treatment of ulcerative colitis drug release should start from terminal part of ileocecal region or from the cecum, so drug will be available for action in disperse or dissolved form in all parts of colon to produce effective local as well as systemic effect. In vivo study reveals that Eudragit S100 coated tablet (10%w/w) disintegrate in cecum as well as Eudragit FS30D coated tablet disintegrated in the same region this indicates superdisintegrant helps in disintegration of tablet irrespective of pH threshold of polymer, since both disintegrated in cecum, whereas in vitro studies indicates Eudragit FS30D coated tablet start release at pH 6.8 after suitable lag time as compare to Eudragit S10 which release specifically at higher pH and this could be beneficial for patient with IBD, where pH may drop.

**Conclusion**:

A novel pH based drug delivery system for potential colonic delivery was developed using coating of aqueous polymethacrylatetes on core tablet containing superdisintegrant. The delivery system might prove successful for delivery of drug to the colon instantly and even in decrease pH condition of colonic disease. The superdisintegrant helps to disintegrate the tablet specifically in the colonic region irrespective of type of enteric polymers. Thus Eudragit FS30D coated tablet may be a promising system for the treatment of colonic disease where pH may decrease and drug also start to release at the same pH after suitable lag time as well as release of drug at the beginning of the colon so the drug will be available in solution or disperse form for local and systemic effect through the colon. This system can be easily manufactured on a large scale in reasonable processing time using conventional coating technique. The Eudragit FS30D coated delivery system does not require organic solvents for preparation; it results in reduced cost, less environmental pollution and reduced work hazard.

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