ejpmr, 2015,2(4), 1143-1158

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM OF CELECOXIB CONTAINING POLYMER COATED CAPSULE DOSAGE FORM

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Article Received on 12/06/2015 **Article Revised on 04/07/2015** **Article Accepted on 26/07/2015**

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ABSTRACT

In this context, a polymer surface encompassed capsule dosage form of celecoxib was investigated & personalized for colon-targeted delivery of drugs. The sandwich replica of the system was designed by imparting the essences of time-release function and a pH-sensing function to a hard gelatin capsule. The technical traits of the system are fabricated to contain an organic acid together with an active ingredient in a capsule coated with a three-layered film consisting of an acid-soluble polymer, a water-soluble polymer, and an enteric polymer. In order to prioritize the suitable formulation, various formulation factors were investigated through a series of in vitro dissolution studies. The results are complied as: (1) various organic acids can be used for this system invariably; (2) a predictable timed-release mechanism of a drug can be attained by tailoring the thickness of the Eudragit E 100 layer; and (3) the outer enteric coating with CMEC lends acceptable acid-resistibility. The result out comes postulate & suggests that this approach can provide a beneficial and practical means for colon-targeted delivery of drugs. This engineered structure has a proven benefit in various fronts for the end organ (colon), getting optimum concentration of drug to cause the therapeutic improvisation in the segment of malignancy & its associated risks within it.

KEYWORDS: Colon-targeted delivery; hard gelatin capsule; Organic acid; Eudragit E 100; CMEC; Celecoxib.

1. INTRODUCTION

Inspite the presence of various delivery systems, colon as a site, caters some distinct beneficial features on account of a near neutral pH, a much longer transit time; lessen digestive enzymatic activity and a much greater responsiveness to absorption enhancers.[1] Colon specific drug delivery has been increasingly expanding the researchers attention in mammoth for not only in the gastrointestinal segment but also the systemic area of approach as well. Besides, colonic delivery of drugs may be extremely significant when setback in drug absorption is required from a therapeutic view point, e.g. in case of diurnal asthma, angina pectoris and arthritis.[2] Currently available drug delivering methodologies are quite seldom in releasing or targetizing the drugs in the upper gastro intestinal tract as for as its absorption and degradation is concern. So a sophisticated alternative stratagem is quite essential to cope up with the aforementioned issues. Ever since the issue, inconsistent massive approaches have been made in the last decade to stabilize a connotation in full move towards the colon region is in existence. In deliberate concern vis-a-vis the physiological conditions of the gastrointestinal tract, various systems have been developed based on different principles, including pH-triggered,[3, 4] time-controlled[5-8] and microbially controlled deliveries.[9-12]

Dually the cause of concern for the colon specific drug delivery outstands in two fronts either large scale reproducibility or the confronting the regulatory constraints before it put forward to the clinicians contentment. The implications in terms of pharmaceutical feasibility concern as for the material selection & pivotal batches using improved practicality. A microbial cleavage strategy utilizing the high enzymatic activity of microflora in the large intestine may be one of the most promising approaches in terms of an excellent site-specific. However, at this juncture, the aforementioned approach does not prove to be handy because the preparation of the systems usually meets the use of new pharmaceutical additives, such as polymers containing azo-bonding and other materials which are microbial degradable in the large intestine. And so only the feasibility of the product reaching the consumer end is quite complicated and perplexed has impelled as many researchers to rejuvenate the therapy module itself in betterment on stood.

In spite more practical technologies, possessing contemporary & conventional coating pointing towards drug release are seldom enough to meet the release requirement, as it releases all its contents promptly after gastric emptying time. Subsequently the exploitation of superior pH enteric coating polymer has been in a while, to strive out in delaying the drug

release pattern, reason that a miniature fluctuation in pH or ionic condition sounds huge.[3,13,14] The stained-release or timed-release approach, in which drugs are released on the basis of time-controlled principle, is also insufficient because the large variation of gastric emptying time in humans makes it difficult to achieve sufficient and reliable colonic availability of a drug by those methods. The most hopeful tool for controlled- release approaches aforementioned illustrations are thought quite practical in terms of huge scale ups, continued improvisation of site selection of drug is as essential as its dosage.

Indeed, we contemporarily endeavored to design a new colon-targeted delivery system in capsule dimension, which was designed to possess a pH-sensing function and a timed-release function. In this conjuncture, the concept for the design of this novel device and the core notion of drug release are introduced, and the potential for colonic delivery of drugs will be elicited through a cascade of in vitro studies.

Celecoxib is widely indicated drug for the treatment of various colonic diseases, especially inflammatory bowel diseases, ulcerative colitis and Crhon's disease. More over celecoxib inhibit both types of Cyclo-oxygenase (COX-1 and COX-2), celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme for arthritis and other inflammatory diseases. The selected candidate has got low bioavailability and subsequent clinical inefficacy is always a concern for the clinicians. Having the fact in mind the current method of pH sensing and time dependent release, is a better alternate to improve the bioavailability.

2. Design of dosage form

When the physical and physiological conditions of the human gastrointestinal tract are considered, a site-specific oral drug delivery seems to be achieved by appropriately integrating a combination of pH-sensing functions and time-controlled release functions into a single pharmaceutical. These two functions of the CTDC could improve the above-mentioned drawbacks of pH-triggered system and time-controlled system. That is, since the gastric emptying time greatly varies depending on various factors, the drug release in the stomach must be minimized. Imparting a pH sensing function to the pharmaceutical should be effective for this purpose. Meanwhile, the passage of pharmaceuticals in the small intestine is known to be less variable, i.e. about 3 ±1 h.[15] After gastric emptying, therefore, the time-controlled release function must be effective to deliver the drug to the target site in

the intestine. Thus the colon-targeted delivery capsule (CTDC) was designed according to the above-mentioned concept.

The fundamental structure of the CTDC is shown in Fig. 1. The technical characteristics of this device are to contain an organic acid in a hard gelatin capsule together with an active ingredient, and to coat the capsule with three different polymeric layers; an inner layer consisting of cationic polymer dissolving in acidic fluid, a water-soluble intermediate layer, and an outer layer consisting of enteric materials dissolving at pH>5.[16] Here, the intermediate layer is provided to prevent the direct contact of the cationic polymeric layer and the anionic polymeric layer. The expected in vivo behavior of CTDC in the gastrointestinal tract is illustrated in Fig. 2. After ingestion of the capsule, drug release can be completely prevented in the stomach due to the acid-resistibility of the outer polymeric layer.

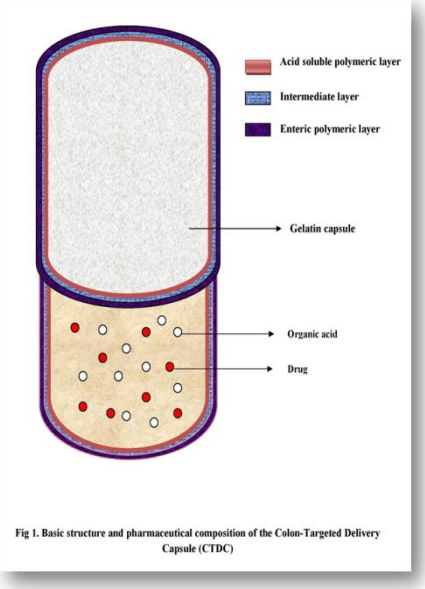
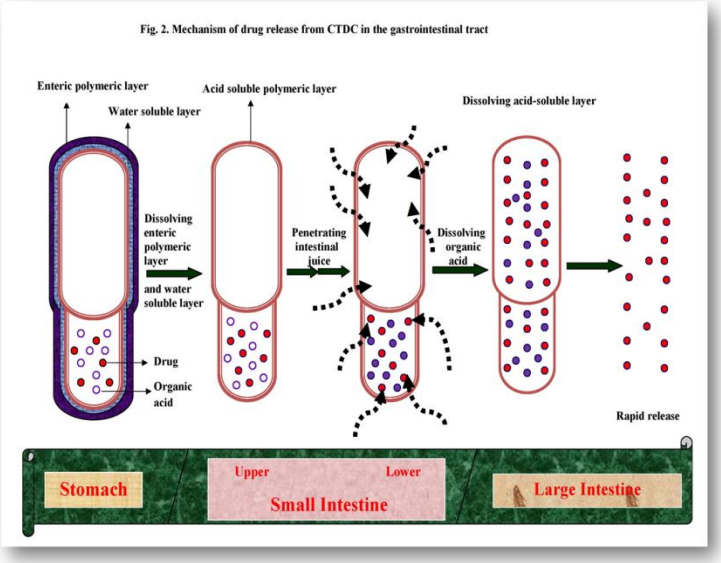


Fig 1. Basic structure and pharmaceutical composition of the Colon-Targeted Delivery Capsule (CTDC)



After gastric emptying, the outer layer and the intermediate layer quickly dissolve, but the inner polymeric layer still remains and effectively prevents the drug release in the intestine. However, when the micro-environmental pH inside the capsule gradually decreases according to the dissolution of organic acid, and when the inner polymeric layer was finally dissolved by the acidic fluid, the drug content was quickly released. The onset of the drug release, therefore, can be controlled by the thickness of the inner polymeric layer. When sufficient acid-resistibility and the suitable thickness of the inner layer are given to adjust the onset time of drug release to 3±1 h, a site-specific drug release to the proximal colon will be realized.

3. MATERIALS AND METHODS

3.1. Materials

Authenticated sample of celecoxib was procured from ideal lab Pvt Ltd, Pondicherry. Hard gelatin capsules (#0, #1, #2, #3 and #4) were purchased from Goutham Pharma Pvt Ltd, Chennai. Eudragit E 100 (Vikram Thermonik Pvt. Ltd. Hyderabad) was used as a cationic polymer which is soluble in a low pH aqueous medium up to pH 5, Carboxy methyl ethyl cellulose (Hetro Lab, Hyderabad) was used as an enteric polymer. Hydroxy propyl methyl cellulose (Chemfield Pharmaceuticals Pvt. Ltd, Mumbai) was used as a neutral water-soluble polymer. Ethyl cellulose (Himedia Laboratories Pvt Ltd. Mumbai) was used as a sealing agent for the hard gelatin capsule. Citric acid, fumaric acid, Maleic acid, Succinic acid and tartaric acid were used as the pH adjusting agents and were purchased from Adlab Pharmaceuticals, Pondicherry. All other chemicals and solvents were of reagent grade.

3.2. Preparation of CTDC

Hard gelatin capsules were filled with the powder mixture of Celecoxib, organic acid, etc., were prepared for the experiment purpose. The capsules are subjected for the sealing with Ethyl Cellulose 5% (w/w) in Ethanolic solution, the core capsules obtained were spray-coated with three polymeric films successively in the order of Eudragit E-100, HPMC, and CMEC, using a coating machine (Sakthi instruments Ltd, Pan coater). The formula for the polymeric coating solution and the operating conditions for coating for each layer are described in Table 1. The type of organic acid, the amount of organic acid loaded in a capsule, and the amount of each coating film were changed for optimizing the formulation. In this research, the four trials, namely F1A, F1B, F1C and F1D were carried out to optimize the best formulation. The formulation of CTDC is presented in Table 2.

Table: 1 Formula for coating solution and standard operating conditions for the coatings of Eudragit E-100, HPMC and CMEC

Formula (w/w%)	**Spray Solution**		
	EUD Coating	**HPMC Coating**	**CMEC Coating**
	Eudragit 5% Ethanol 95%	HPMC 5% Water 95%	CMEC 5% Ethanol 57% Water 38%
Operating Conditions			
Blower temperature (°C)	40	50	60
Exhaust temperature (°C)	30	35	40
Spray pressure (kg/cm^2)	1.5	1.5	1.5
Spray rate (g/min)	2.5	1.8	2.5
Rotating speed of coating pan (rpm)	20	20	20

Table: 2 Formulation of Celecoxib CTDC

Name of Ingredients	Formulation (mg) F1			
	F1 (A)	F1 (B)	F1 (C)	F1 (D)
Empty Gelatin Capsule Weight	63	63	63	63
Amount of Drug loaded	20	20	20	20
Borax	10	10	10	10
Succinic acid	0	25	50	75
Eudragit	23	26	30	34
HPMC	21	23	24	26
CMEC	165	175	190	200
Wt. of Capsule without Coating	93	118	143	168
Wt. of capsule after coating	302.0	342.0	387.0	428.0

3.3. Measurement of film thickness

The thickness of all the three layers of the capsules after the coating was measured using a micrometer screw gauge (Mitutoyo) instrument ranging 0-25 mm with the precision 0.001mm. Ten different positions were measured for each capsule to obtain a mean thickness.

3.4. Adjustment of pH inside the CTDC

The pH inside the CTDC was adjusted by filling 100 mg of buffering agents consisting of various ratios of the mixture of succinic acid and borax into the #2 capsule shells. The pH value to be attained in the capsule during the dissolution process was estimated by determining the pH value of the solution dissolving 2.7 g of buffering agent in 10 ml of pH 6.8 (which corresponds to the ratio of the actual volume of the capsule and the content of buffering agent loaded in the capsule).

3.5. Drug content and content uniformity

The drug content and uniformity of celecoxib was determined by UV-spectrophotometer. Methanol was used to dissolve the drug for content uniformity assay. The content of 20 capsules was removed and grind into fine powder. Then powder equivalent to 20 mg of celecoxib was accurately weighed and transferred in to 100ml volumetric flask. About 75 ml of methanol was added and stirred well. This solution was adjusted with methanol to 100ml. The above solution was used as stock solution and filtered using filter paper. 5 ml was taken from the above stock solution and adjusted to 100ml with methanol. Then the absorbance was measured at 253nm and amount of drug present in each capsule was calculated by using the following formula.

$$\text{Amount present} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} X \frac{\text{Standard weight}}{\text{Standard dilution}} X \frac{\text{Sample dilution}}{\text{Sample weight}} X \frac{\text{Potency}}{100} X \text{ Average weight}$$

$$\% \text{ Amount present} = \frac{\text{Amount present}}{\text{Label claim}} \text{ X } 100$$

3.6. In vitro release study

The drug release profiles from capsules were investigated according to the procedure described in the Indian Pharmacopoeia (the paddle method). The capsules were placed in a vessel with 900 ml of the pH 1.2 and pH 6.8 at 37 ± 2°C rotating at 100 rpm. The released amount was periodically determined by the spectrophotometric method. All the experiments were carried out in more than triplicate. The morphological change of capsules during dissolution testing in the pH 6.8 was observed using a Digital binocular microscope (Labomed Nerland). The percentage amount of celecoxib release was calculated by using the following formula

$$\text{Amount release (mg)} = \frac{\text{Absorbance}}{\text{Slope}} X \frac{\text{Dilution Factor X Total volume of dissolution medium}}{1000}$$

$$\% \text{ Amount release} = \frac{\text{Amount release (mg)}}{\text{Label claim}} X 100$$

4. RESULTS AND DISCUSSION

4.1. Examine of various organic acid on the drug release behavior of drug-loaded CTDC

To select the suitable organic acids for the CTDC, and also to investigate the amount of influence of organic acid species on drug release behavior, Eudragit E 100-coated capsules (no enteric coating in this case), containing either Maleic acid, succinic acid, tartaric acid, fumaric acid, or citric acid was used. In this experiment, the loaded amount of organic acid and the thickness of the Eudragit E 100 layer were tentatively fixed at 75 mg and 0.062 mm, respectively. The release profiles of celecoxib, from those capsules in the pH 6.8 are compared in Fig 3. The result shows that the duration of lag time differed depending on organic acid species; for instance, the maleic acid-loaded capsule gave the shortest lag time of about 2 h; in the cases of succinic acid and tartaric acid, the lag time observed was about 2.5 h; and in the cases of fumaric acid and citric acid, the lag time was found to be 5 h and 4.5 h respectively. In all cases, celecoxib was quickly released after a distinctive lag time, suggesting that either of the organic acids can be utilized as the pH adjusting agent for

CTDC. Though the reason for this phenomenon is still obscure, it might depend on the difference in the dissolution kinetics of the individual organic acids and/or the pH value attained in the capsule. However that may be, this result suggests that the onset time of drug release could be controlled by organic acids to some extent. Also, through this study, we found that succinic acid is likely to be a suitable organic acid for practical use, due to less hygroscopicity and good powder properties of this compound; i.e. ease in processing and minimizing influence on drug stability.

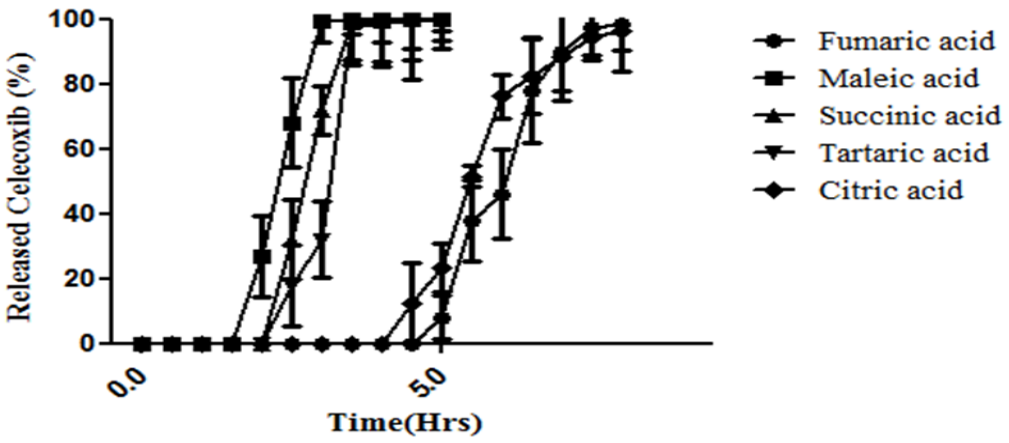


Figure 3: Effect of organic acids on drug released behavior of celecoxib loaded CTDC

4.2. Effect of Succinic acid on drug release

To elucidate if the addition of organic acids into the capsules is indispensable for the preparation of CTDCs, two types of celecoxib-loaded hard gelatin capsules were prepared, firstly only one formulation without succinic acid and secondly with different ratios of 25mg, 50mg, 75mg (three formulations) in the presence of succinic acid, were experimented. Both types of capsules were spraycoated with Eudragit E 100, HPMC and CMEC; and the thickness of the capsules was increased from 0.042mm to 0.30mm, 0.047mm to 0.31mm, 0.054mm to 0.34mm, 0.062mm to 0.36mm. In addition the weight of the capsules increased from 25mg to 165mg, 26mg to 175mg, 30mg to 190mg, 34mg to 200mg per capsule. As was shown in Fig 4, Formulation F1 (A) drug loaded capsule deprived of succinic acid, merely provided a very slow drug release profile of 2.4% at 5 th hour and 16.2% at 12th hour respectively. On the other hand, the drug loaded capsules [F1 (B, C &D)] containing succinic acid with different ratio provided a distinct lag time of about 3 hours. That means the drug release profile of F1 B, C & D are 32.2%, 85.5% and 94.5% and 91.5%, 93.8% and 95.0% at the interval of 3 rd hour and 12th hour respectively. Fig. 4 is a comparison of drug release

characteristics of both preparations in the pH 6.8. As was shown, both types of capsules gave completely different dissolution profiles as mentioned. Thus, the capsules deprived of succinic acid merely provided a very slow drug release profile, whereas the one with succinic acid provided a distinctive lag time of about 3 h. Among these, the Formulation containing 75mg of succinic acid F1 (D) provided a very rapid drug release profile and a distinctive lag time of about 3 hrs. The remaining formulation with succinic acid provided a very good drug release profile and a same distinctive lag time of about 3 hrs but the somewhat less release profile when compared to F1 (D). It may be due to the concentration of Succinic acid. All the drug loaded capsules were released rapidly within a comparably short time thereafter from the initial time. This result suggests that succinic acid plays a pivotal role in obtaining such an unusual release profile of celecoxib.

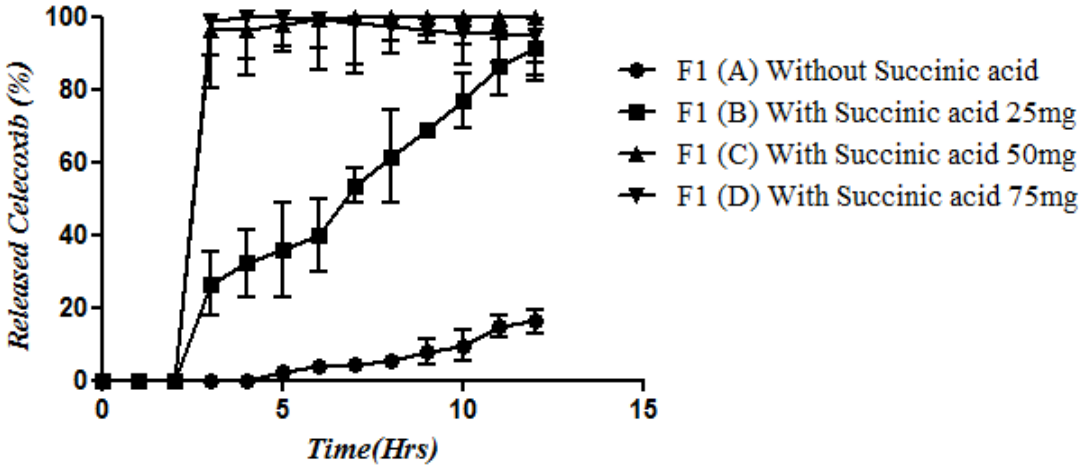


Figure 4: Comparison of drug release characteristics of celecoxib loaded hard gelatin capsules, with or without loaded succinic acid

4.3. Effect of pH and Lag time relationship of drug release

To study the effect of micro-environmental pH inside the capsule on the drug release behavior of CTDC was studied . For this experiment, various Eudragit E 100 coated capsules (without enteric coating in this case) containing both succinic acid and/or borax at different ratios were prepared. The thickness of the Eudragit E 100 layer was tentatively fixed at 0.062mm. The addition of borax with succinic acid, has given a superior pH microenvironment inside the capsule. The relationship between pH inside the capsule and lag time in the pH 6.8 is shown in Fig 5. Above pH 5, the lag time of the Eudragit E 100-coated capsules increased as pH increased, but the drug release rate was slower. Below pH 5, however, the lag time was almost stable. The refractive point observed at about pH 5 was in

accordance with the upper limit of the soluble pH range of Eudragit E 100. From this result and Fig. 5, it was ascertained that the drug release from CTDC was triggered by dissolving the Eudragit E 100 layer when the micro-environmental pH inside the capsule decreased below 5.

To conclude succinic acid functioned as a pH-adjusting agent to change the superior microenvironment pH inside the capsule in addition of borax, by which the timed-collapse of the Eudragit E 100 layer was achieved. Therefore, the lag time could be influenced by various factors, including organic acid species, loading amount of organic acid, coating amount of Eudragit E 100 and anything affecting the dissolution kinetics of the polymer.

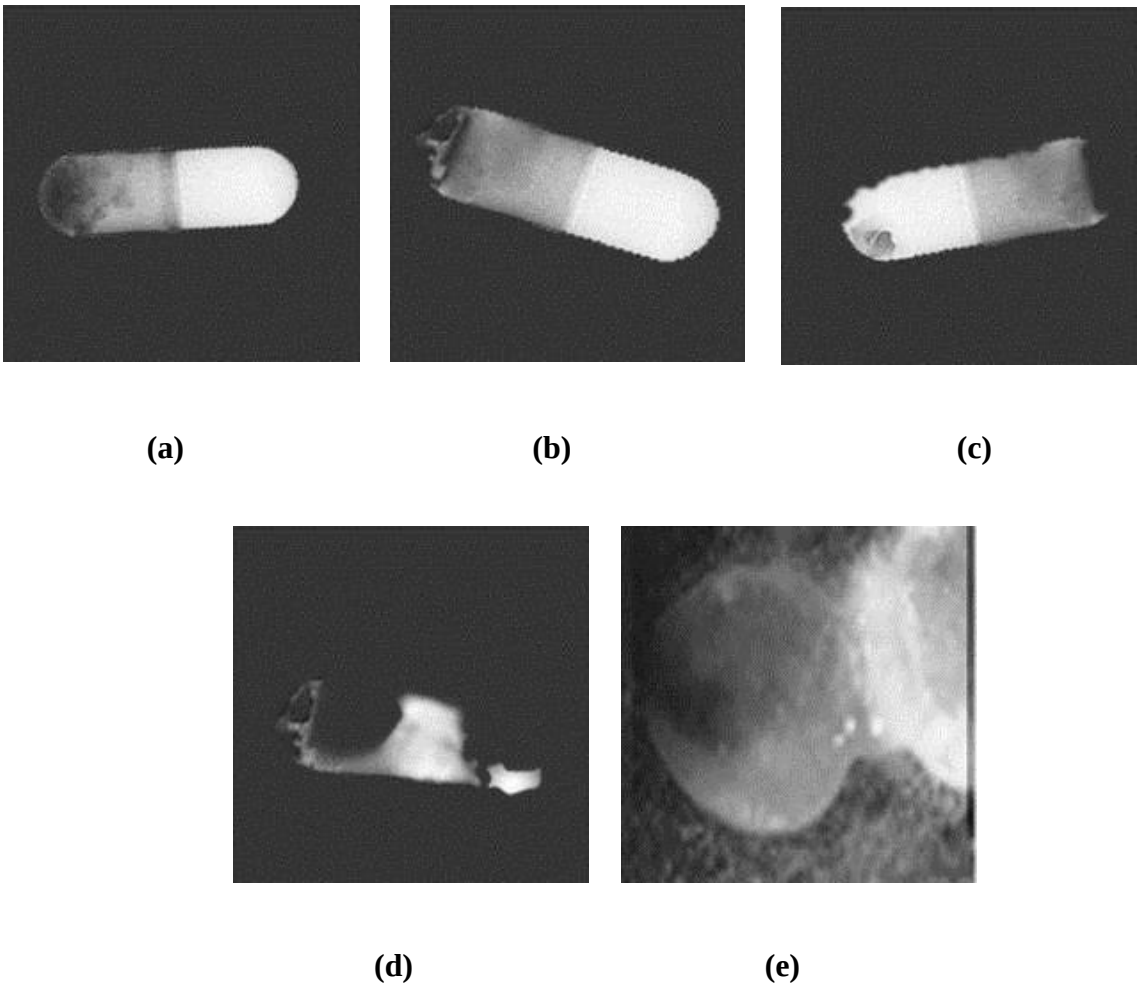


Fig 5: Microscopic observation of CTDC during the dissolution process in the IP 2nd fluid (pH 6.8).

Succinic acid-containing capsule: (a) 2.6 h after starting the dissolution test; (b) after 3.1 h (about 2% of celecoxib was released); (c) after 3.5 h (about 75% of celecoxib was released); (d) after 3.9 h (celeccoxib release was already completed). Succinic acid-free capsule: (e) 18 h after starting the dissolution test (about 16% of celecoxib was released).

4.4.Effect of the loading amount of succinic acid

To scrutinize the effects of the loading amount of organic acid on the duration of lag time and the drug release rate thereafter, Eudragit E 100-coated capsules containing various amounts of succinic acid were prepared and tested for celecoxib release. The observed lag times for preparations are listed in Table 3. As was expected, acid content affected the drug release behavior of the capsules. When the loading amount of succinic acid was less than 50 mg (i.e., 25 mg) per capsule, the lag time was gradually delayed with decreasing the acid content. But, when at 50 mg of succinic acid lag time considerably shortened as compared with the 25 mg of succinic acid. On the other hand, 75 mg of succinic acid load has given a shortened lag time with the constant drug release; almost the results of lag time and drug release profiles are comparable and slightly higher, with the 50 mg of succinic acid utilization. It was concluded that the lag time of capsules might be controlled by the loading amount of Sucscinic acid to certain extent, and the adequate amount of succinic acid for CTDCs was estimated at 75 mg to obtain a constant lag time and a quick release.

Table: 3 Effect of Succinic acid content in lag time (n=3)

Succinic acid content (mg)	Lag time (hr)			Average (hr)	Variation (hr)
	1	2	3		
0	11.5	13.2	14.5	13.07	3
25	3.8	4.5	5.2	4.5	1.4
50	3.2	3.5	3.7	3.47	0.5
75	3.1	3.2	3.3	3.2	0.2

4.5. Effect of the coating amount of Eudragit E 100

To examine the effect of coating amount of Eudragit E 100 layers of lag time, celecoxib-loaded capsules (size #0, #1, #2, #3, #4), each of which contained 20 mg of celecoxib and 75 mg of succinic acid, were coated with Eudragit E 100 in various coating amounts. When the coating amount of Eudragit E 100 was varied from 10 mg to 100 mg and the thickness increased linearly from 0.018 mm to 0.182 mm. The lag time observed in the dissolution test

for celecoxib loaded capsules in the pH 6.8 was delayed with increased coating, and a very good linear relationship was found between the coating amount and lag time (Fig. 6). This suggests that the onset time of drug release from CTDC could be controlled quantitatively over a quite wide range by altering the coating amount of Eudragit E 100. When Eudragit E 100 coating was applied to various sizes of hard gelatin capsules, a good linear relationship was also found between film thickness and lag time for each capsule size, and the regression lines were almost coincident with each other (Fig. 6), suggesting that the lag time is predictable in terms of the film thickness of Eudragit E 100 layer irrespective of capsule size.

The selection of the capsule size for a commercial product is made during product development. The choice is determined by the requirements of the formulation, including the dose of the active ingredient and the density and for characteristics of the drug and other components. For best bioavailability of the powder, a loosely packed capsule is preferred because the powder disperses easily as the capsule shell dissolves. In this research the optimized formulation is capsule #2.

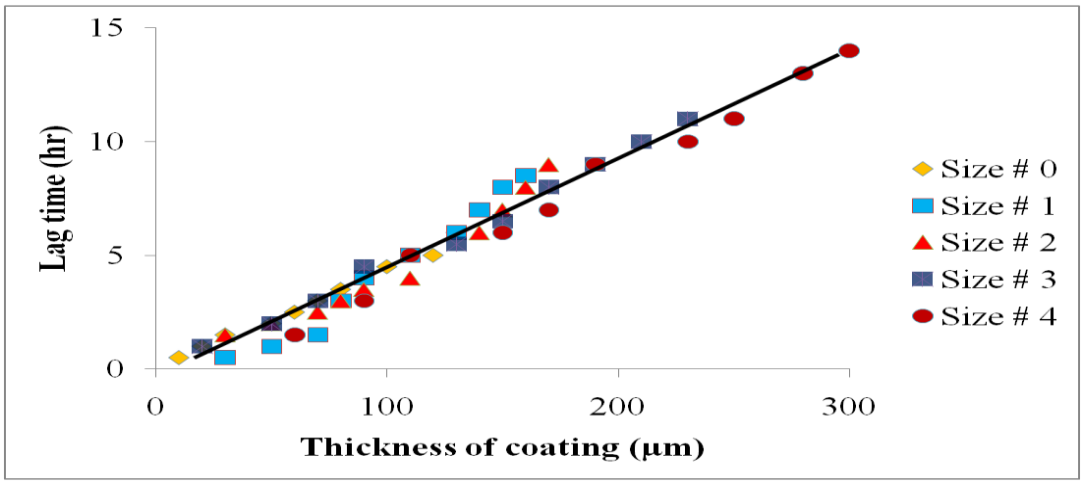


Figure 6: Relation between thickness of Eudragit E layer and lag time for various capsule sizes for celecoxib loaded capsules

4.6. Enteric protection with CMEC film coating

Eudragit E 100 coated capsules containing celecoxib and succinic acid, of which lag time in the pH 6.8 was set to about 3 h, were spray coated with HPMC and CMEC to complete the CTDC. Then, simulating the physiological condition in the human gastrointestinal tract, the CTDC was first immersed in the pH 1.2 for 8 h, and then the dissolution test was performed in the pH 6.8.

The results of CMEC coating, the lag time was observed for pH 6.8 was shown that with enteric coating, (without pretreatment) for CEL F1 (A), F1 (B), F1 (C) and F1 (D) released 12.6%, 25.8%, 28.9% and 32.5% at the end of 4th h; 72.7%, 75.9%, 76.9% and 82.7% at 8th h respectively. (Fig. 7-Fig. 10)

The result shown that with enteric coating (pretreatment by immersing in the 1st fluid for 8 h) in the pH 6.8 for CEL F1 (A), F1 (B), F1 (C) and F1 (D) released 19.2%, 39.8%, 64.2%, 88.2% at the end of 3rd h; and 82.8%, 86.2%, 88.4% and 97.2% of drug at the end of 8th h respectively. (Fig. 7-Fig. 10)

Enteric coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate/dissolve in the high pH environment of the intestinal fluid. In this research the effect of enteric coating on the dissolution behavior of CTDC was evaluated in the pH 6.8.

The value of lag time (3h) observed in the pH 6.8 was almost constant irrespective of the amount of enteric coating applied thereon, because the enteric coating layer quickly dissolved and hence it did not affect the dissolution behavior of the capsule in the pH 6.8.

Because, the lag time of capsule depends on the thickness of Eudragit E 100 (Fig. 6) coating. These above results suggest that enteric coated capsule CTDC (without pretreatment) varied by the penetrating rate of enteric coated capsule (pretreatment by immersing in the 1st fluid for 8 h), because the CMEC layer dissolved in pH 1.2 and the Eudragit E 100 layer dissolved in below pH 5. 5.

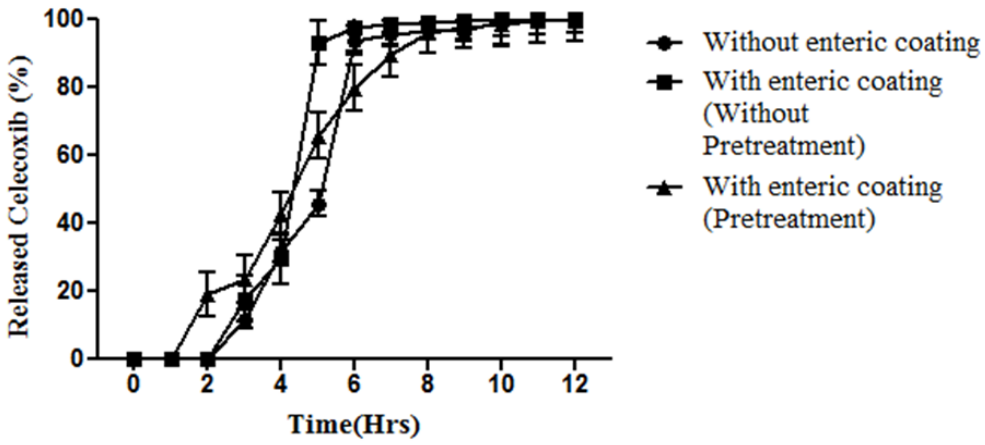


Figure 7: Influence of enteric coating on the drug release behavior (celecoxib – F1 [A]) in the IP 2nd fluid

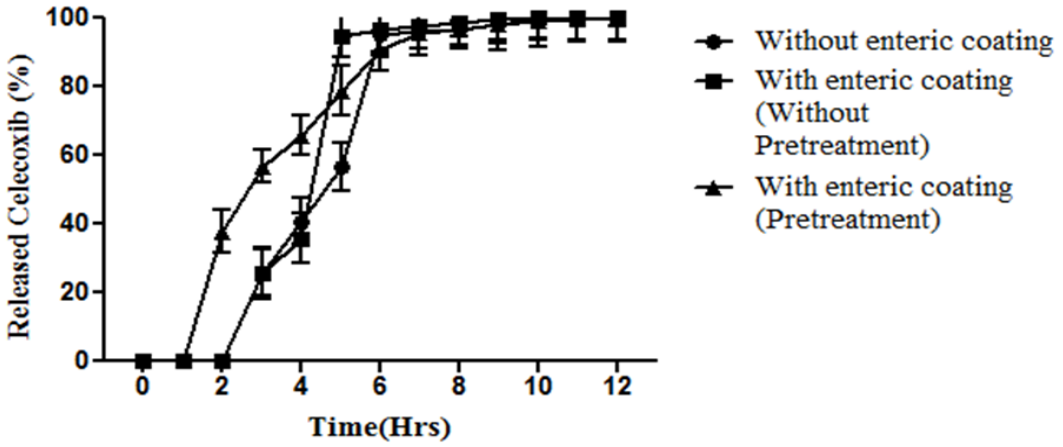


Figure 8: Influence of enteric coating on the drug release behavior (celecoxib – F1[B]) in the IP 2nd fluid

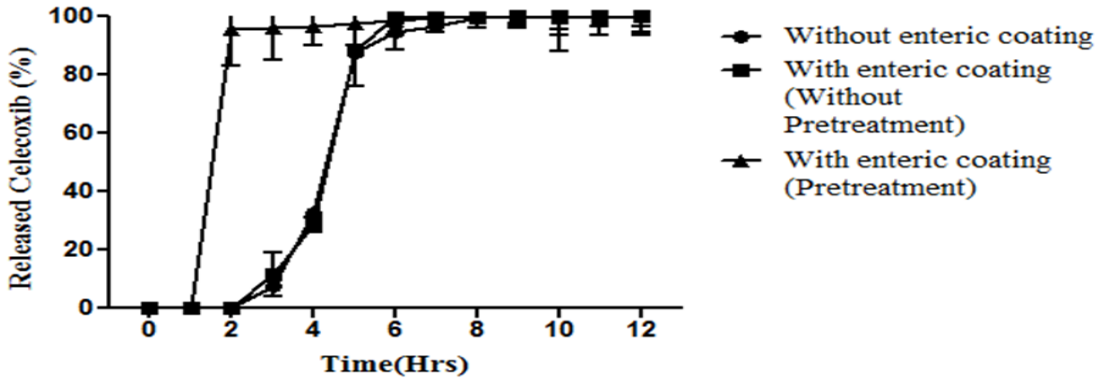


Figure 9: Influence of enteric coating on the drug release behavior (celecoxib – F1[C]) in the IP 2nd fluid

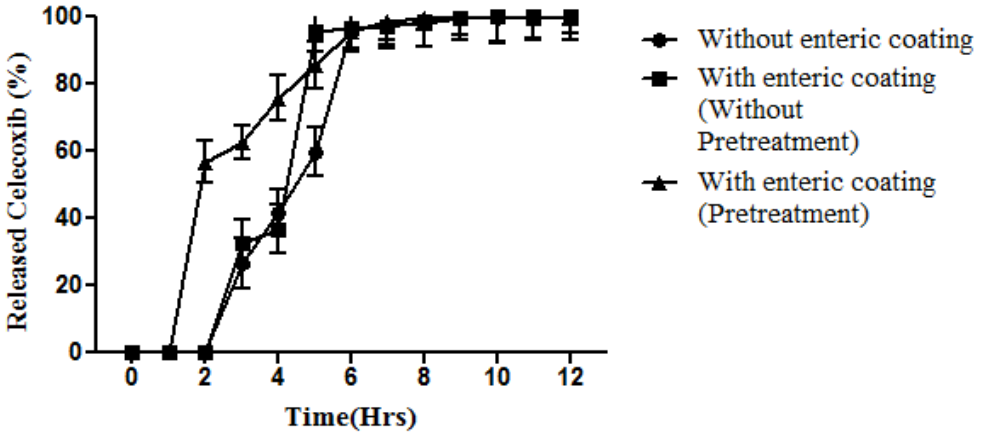


Figure 10: Influence of enteric coating on the drug release behavior (celecoxib – F1[D]) in the IP 2nd fluids

5. CONCLUSION

In this context, CTDC can be a useful mean for the colon targeted delivery of the both selected drugs. The effective stratagem of this technology involves: (1) Firstly, various organic acids can be used for this system; (2) Secondly, the predictable timed-release of drug can be attained by adjusting the thickness of inner layer; and (3) Thirdly, the outer enteric coating provided a satisfactory acid resistibility. The CTDC will be able to achieve a higher selectivity to the colon than other time controlled and pH-triggered systems, because it possesses the dual function of both pH-sensing and timing release of drugs. The CTDC has also a surplus advantage from the practical viewpoint, the reason that all the material used is identified as safe in actual usage and the fabrication techniques employed.

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