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Colonic Delivery of a Systemic Cephalosporin.

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ABSTRACT

Cefaclor was formulated for localized colon-targeting action. This was done by compression of 250 mg of cefaclor with Polyvinylpyrolidone as a binder and pore former. Two ionic super disintgrants were investigated, sodium starch glycolate (Explotab) and crosscarmellose (Ac-di-sol). Cefaclor tablets were film coated with Eudragit S100, which is a pH responsive polymer, to give release of the drug at pH higher than 7. Cefaclor tablets were coated with different levels Eudragit S100. The film coated tablets were examined for weight, thickness, and content uniformity. They were also investigated for *in-vitro* dissolution at three different stages in bio-relevant media simulating Gastrointestinal tract. Drug release was dependent on the film coat thickness. It was concluded that cefaclor can be formulated for colonic delivery.

Keywords: colonic delivery; Inflammatory Bowel Disease; Eudragit S100; antibiotics; cefaclor; Bio-relevant dissolution media.

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INTRODUCTION

Antibiotics have played a definite role in treating specific, episodic or persisting bacterial infections that are localized in the colon. Bacterial infections in colon can cause major complications such as intra-abdominal abscesses or small intestinal bacterial overgrowth which either causes or accompanies inflammatory bowel disease (IBD). This arises the use of antibacterial agents in the treatment of these diseases as modulator of the gastrointestinal flora or as adjuvants in the treatment of localized colon infections [2, 3]. Antibiotics act through different pathways: They inhibit bacteria linked to the pathological process of the disease, in addition to lowering the luminal and/or mucosal bacterial overgrowth. The modification of the intestinal flora may reduce the strength of certain symptoms accompanying IBD, including extended pain and diarrhea [4].

IBD pathogenesis is localized majorly in large and small intestine where high drug concentrations are required. Unrequired drug levels in the blood can lead to side effects. The optimal IBD treatment is one delivering localized effect and minimal blood concentrations[5].

Colonic Targeted drug delivery systems is the treatment of choice to reduce systemic absorption and tailor conventional therapy for localized colonic delivery. Elevated levels of luminal bacterial concentrations in the colon require use of local action antibiotics such as sulfasalazine and mesalamine, [6]. Studies showed that broad-spectrum antibiotics like ciprofloxacin, metronidazole, rifamycin*or* cotrimoxazole improve clinical outcomes in patients with IBD[7, 8].

Development in formulation to be able to use different classes of antibiotics normally used for systemic action to give local intestinal action, and delivering the antibiotic to site of action can bypass all side effects due to unrequired elevated blood drug levels. Colonic delivery of broad-spectrum antibiotics can help the physician with a wide range of choices to overcome microbial resistance developed due to long treatment periods, fear of over dosing or toxicity[9, 10]. One of the known strategies for colonic delivery is the use pH responsive polymers such as Eudragit S100 or Eudragit L which dissolve at pH higher than 7 and pH 6 respectively. Drug delivery approaches for pH dependent systems currently on the market based on polymer coatingwith Eudragit S100 for IBD are coated 5-ASA tablets (Asacol®) and Eudragit L coated 5-ASA tablets (Salofalk®, Claversal®, Mesazal®, Calitoflak®) which represent pH dependent release systems which release the active substance upon the dissolution of the polymer coating, at pH 7 or pH 6 for Eudragit S100 and Eudragit L coating[11].

Cefaclor is an effective broad spectrum, second generation cephalosporin. The usual adult dose is 250 to 500 mg every 8 hours; and has proven to be safe up to 4 g daily[12]. Cefaclor is classified in BCS class III (high solubility and low permeability). It is effective against many different bacterial organisms such as Staphylococcus aureus, Streptococcus pneumoniae, Haemophilusinfluenzae, E. coli, and many others[13].

The scope of this work is to design cefaclor tablets for colonic targeting through coating with pH sensitive polymer to resist release through GIT and give triggered drug release upon reaching alkaline pH of the colon through dissolving of enteric coat of the tablet.

MATERIALS AND METHODS

Cefaclor monohydrate kindly gifted from Pharco Pharmaceuticals Co., Alexandria, Egypt; Eudragit S100, Evonik Industries AG, Darmstadt, Germany; Sodium starch glycolate (Primojel) kindly gifted from Cid pharmaceuticals, Giza, Egypt; Crosscarmellose kindly gifted from Pharco Pharmaceuticals Co., Alexandria, Egypt; Polvinylpyrrolidone K30 (PVP),El-Nasr Pharmaceutical Chemicals Co., Cairo, Egypt; Sodium bicarbonate, monopotassium dihydrogen phosphate, disodium hydrogen phosphate and concentrated hydrochloric acid, Nasr pharmaceuticals,Cairo, Egypt; Methanol, analytical grade, Nasr pharmaceuticals,Cairo, Egypt; Magnesium stearate, Loba Chemicals, Mumbai, India; Dibutylphathalate, Loba Chemicals, Mumbai, India.

Preparation of cefaclor tablets:

Cefaclortablets were prepared either by using cefaclor powder alone or by mixing of cefaclor powder with Polyvinlypyrolidone at concentration level 2% w/w. Two super disintegrants were investigated,

crosscamellose sodium (Ac-di-sol) and Primojel (Explotab). All powders were mixed and methanol was usedas a granulating solvent. The mixture was passed through sieve size #20 over a foil sheet and left to dry overnight. After drying of the granules, 1% w/w magnesium stearate was added and mixed manually. The prepared granules were kept in airtight container and the container was covered with aluminum foil till use[14].

Compression of cefaclor tablets:

Each tablet was weighed individually and pressed using a laboratory size single station tablet press with 8mm flat punch (Single punch machine, Karishma Pharma Machines, Mumbai, India). Compression force was adjusted by pressing of avicel powder to give tablets of hardness 50 N to 60N.

Enteric Coating of cefaclor tablets:

Cefaclor tablets were coated by dip coating in apre-prepared solution of Eudragit S100 and dibutyl phthalate(plasticizer) in methanol then the tablets were left to dry on non-sticking paper at room temperature. Tablets were coated with different levels of Eudragit S100 as follows: 0.5%, 2%, 4%, 6%, 8% and 12% w/w[15-18].

Physical properties of film coated cefaclor tablets:

Tablet weight variation, tablet thickness and drug content were calculated according to British Pharmacopeia**.** [19].

***In-vitro* release studies of Eudragit S100 coated tablets:**

Eudragit S100 film coated tablets were tested for drug release using USP dissolution Apparatus II, (Agilent 708-DS Dissolution Apparatus, Agilent Technologies, USA) paddle rotation was kept at 100 rpm and temperature was adjusted at 37±0.5°C all through the test period.

Dissolution was conducted following a three-stage process. The first stage was performed in simulated gastric fluid. The dissolution medium was1000 milliliters and pH was adjusted to 1.2 for 2 hours. During the second stage, the test was performed in simulated intestinal fluid. The test time was three hours and the pH was raised to 6.8. Raising of pH was done by adding 4 grams of monopotassium dihydrogen phosphate, 3 grams of disodium hydrogen phosphate and 10 milliliters of 20%w/v sodium hydroxide to the acidic dissolution medium[20]. During the third stage, the test was completed in simulated large intestine/ distal small intestine pH until the end of the experiment. The pH of the dissolution medium was raised from 6.8 to 7.4 by addition of 4 milliliters of 20% w/v sodium hydroxide. The test was done for each formula in triplicates. At the end of every hour five milliliters sample was collected and replaced by freshly prepared dissolution medium according to the pH the test is performed at. The samples were filtered through a 0.45µ membrane filter. Cefaclor was assayed spectrophotometrically at λ max 265. *In-vitro* drug release profiles of cumulative percentage of cefaclor released against time were plotted[21, 22].

RESULTS AND DISCUSSION

Preparation of cefaclor tablets:

During preliminary studies, cefaclor was used alone without adding any excipients, considering that it is a water soluble drug (10 mg/ml)[23] and can dissolve into dissolution medium by passive diffusion. Unsatisfactory release profiles were recorded and this required addition of excipients to attain the required release profile. Incorporation of 2% w/w PVP had proven to have good binding effect. In addition, PVP was reported to be a hydrophilic tablet binder with release enhancing effect.PVP is classified as a pore former by forming “percolating” channels inside the tablets which helps the process of diffusion through water filled pores.

Diffusion is enhanced in both directions, firstly diffusion of drug to dissolution medium and secondly opposite diffusion of water to the inside of the core tablets[24, 25].

Crosscarmellose and primojel were both investigated as superdisintegrants to aid drug release on reaching colonic pH. Crosscarmellose caused many problems during compression and coating. Crosscarmellose caused capping and fragmentation of edges on storage. Primojel has proven to be more suitable. After preliminary testing, 0.2%w/w primojel was the concentration of choice for the required dissolution profile. At high concentrations of primojel, premature release of the coated tablets occurred.

Choice of primojel and crosscarmellose was done as both disintegrants are ionic and were reported to have limited water uptake in acidic media. The strong decrease in swelling capacity of chemically modified starches and celluloses in acidic medium, was reported to be due to the converting of the carboxymethyl sodium moieties to its free acid for both substances to acidic groups. Since the acid form has less hydration capacity than its corresponding salt form. These carboxylic groups ionize in the acidic media and lose their liquid holding capacity. Primojel was chosen to be the disintegrant of choice in the investigated formulae as it has shown better compressibility, more stability on storage, handling and coating of cefaclortablets. Crosscarmellose has been reported to have 10 fold the swelling energy of primojel which explains why on storage or during coating any moisture uptake caused fragmentation of the edges of the tablet and quick bursting of coated tablets when exposed to dissolution medium. [26, 27]

A key difference in the chemistry of sodium starch glycolate (primojel) from that of crosscarmellose, is that some of the carboxymethyl groups themselves are used to cross-link the cellulose chains, the process being accomplished by dehydration. This makes crosscarmellose more eager for moisture uptake which explains that during handling and storage it showed less stability than primojel[28].

The incorporation of a disintegrant helped in pulsatile (release of drug after certain lag time) release of the drug through the enteric coat. Once the pH threshold is passed, the fluid will cross though fissures and cracks in the dissolved coat and will hydrate the incorporated disintegrant. The disintegrant will perform a disruptive effect on the enteric coat firstly and will swell upon contact with water by binding with water molecules in their polymeric network. This swelling will rupture the coating polymer and form cracks in the coating through which water can penetrate further into the tablets. Secondly, the disintegrant particles may themselves form the route for water penetration. In this way the coating will rapidly be completely disrupted and the drug can be released fast even if the external coat has not fully dissolved.[29]

Enteric Coating of the cefaclor tablets:

Table 1 displays the composition of different formulae of film coated tablet with different coating levels of Eudragit S100.

Table (1): Composition of different formulas of core tablet coated with different coating levels of Eudragit

Formula	Coating Polymer	Coating level w/w%	Composition of core tablet	Other excipients
F1	S100	12	cefaclor	----------
F2	S100	8	cefaclor	----------
F3	S100	6	cefaclor	----------
F4	S100	4	cefaclor	----------
F5	S100	2	cefaclor	----------
F6	S100	0.5	cefaclor	----------
F7	S100	2	cefaclor	2%PVP +0.2% Primojel
F8	S100	4	cefaclor	2%PVP +0.2% Primojel
F9	S100	6	cefaclor	2%PVP +0.2% Primojel
F10	S100	8	cefaclor	2%PVP +0.2% Primojel

Physical properties of cefaclor tablets

The average weight and standard deviation were found to be 259.7±5.8 mg.

The average thickness was found 4 ± 0.01 mm.The average drug content was 254.2±6.51mg.

***In-vitro* release studies of Eudragit S100 film coated cefaclor tablets:**

The study of the coated tablets is based on consecutive pH changes of the environment to simulate bio-relevant media. To establish bio-relevant pH conditions throughout the test, a sequential pH-gradient was used. The test setup in this study was created to simulate transit through the GI tract in the fastingstate with residence times of 2h in the stomach and 3h in the small intestine and the rest of the test was performed in pH7.4.

The USP dissolution methods are different for extended-release dosage forms (performed at pH 7.5 only) and delayed-release tablets (performed at PH 1.4 for 2h, pH 6.0 for 1h, and finally at pH 7.2). In both methods stated, change of dissolution medium for different drugs depends on the stated monograph of each drug rather than simulating actual transit time through the GIT.USP method includes removal, drying of tablets and change of dissolution medium.[30] Reported GIT transit times are for tablets are 2.7±1.5 hours in the stomach and 3.1±0.4 hours in the small intestine with total transit time around 5.8 hours till reaching the large intestine.[31] The aforementioned transit times are not reflected in the USP methods for ***extended-release*** and ***delayed release*** which perform dissolution testing at only pH 7.5. In this study, the method used is simple and reproducible for delayed/pulsatile release dissolution testing without having to change the medium and adjustment of dissolution medium volume can be controlled for accurate calculation of the percentage of drug released. The method is based on a modification of USP method used for dissolution of delayed release of enterically coated Asacol™ tablets. It was reported that on using USP methods for modified /delayed release, Eudragit S100 of Asacol tablets gave different results when applying both USP methods for delayed and extended release. Applying a method based on sequential change of pH of medium has proven to be efficient [32].

Cefaclor tablets in this study, coated with Eudragit S100, were formulated to resist release at different pH media through the GIT and to give 100% release after 7to 8 hours on reaching the triggering pH of the colon. Dissolution test used had to consider different stages of GIT transit times and gradual change of pH through the GIT. Figures 1 and 2 illustrate different release profiles of different formulae (F1 to F10) investigated in this study.

Release profiles of formulae from F1 to F6

Figure (1) displays the cumulative percentage of cefaclor released during different stages of dissolution, when cefaclor was used alone with no excipients. Release profiles from F1 to F6 show that all formulae released less than 10% of the drug within the first two stages of dissolution. During stage III of dissolution, release rate increased. F1, F2, F3, F4, and F5 released 8.933±0.35%, 36.9±4.4%, 47.8±2.6%, 58.3±3.1%, and 67±2.2% respectively. While F6 released more than 30% of the drug in the first two stage and reached 74±4.58% after 8 hours. None of the aforementioned formulae fitted the required release profile.These results required the addition of other excipients to the cefaclor tablets to help disruption of the tablet and give a pushing effect to release the drug yet not allowing for premature release. Despite cefaclor being a water-soluble drug, passive diffusion was not enough to give required release profiles.

Release profiles of formulas F7 to F10

Figures (2) illustrates dissolution profiles of formulae F7 to F10.
Figure (3) displays cumulative percentage of drug released during different stages.

The results of aforementioned formulae (F1 to F6) required the addition of other excipients to the cefaclor tablet to help disruption of the tablet and give a pushing effect to release the drug yet not allowing for premature release.

The results indicate that addition of PVP and primojel improved release.

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Formulas ***F7 and F8*** coated with Eudragit S100 at level of coating 2% and 4% w/w respectively, released 49.9%and 27.9% of the drug at the end of the stage II and gave 100% release of cefaclor after 6 hours (during the first hour of Stage III).

In spite of the fact of releasing 100% of the drug, these formulas were considered to give premature release of drug in stage II.

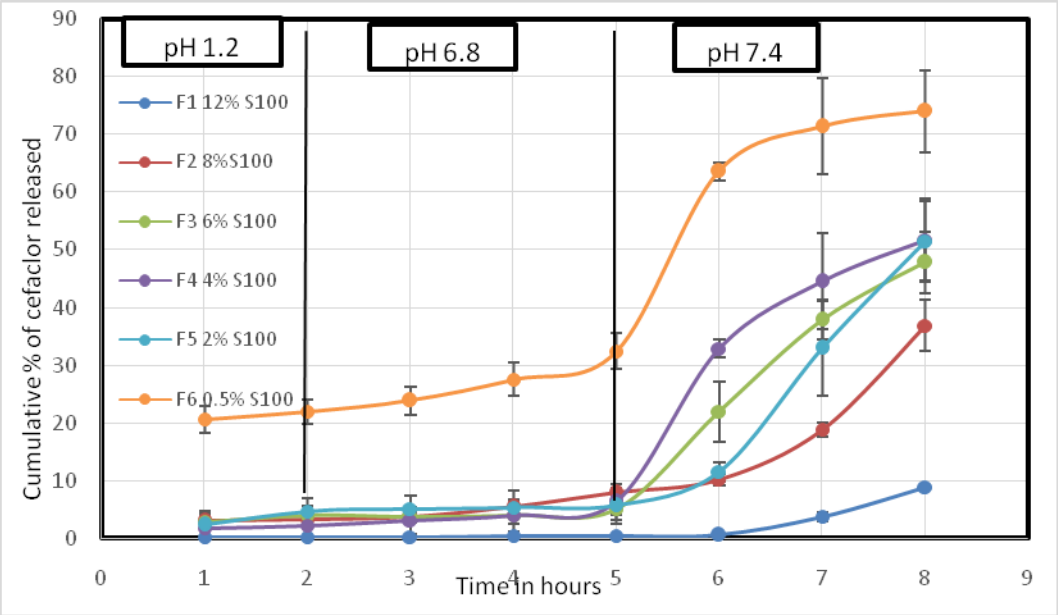

Figure 1: Release profiles of film coated tablets of cefaclor (no excipients) with different coating levels of Eudragit S100

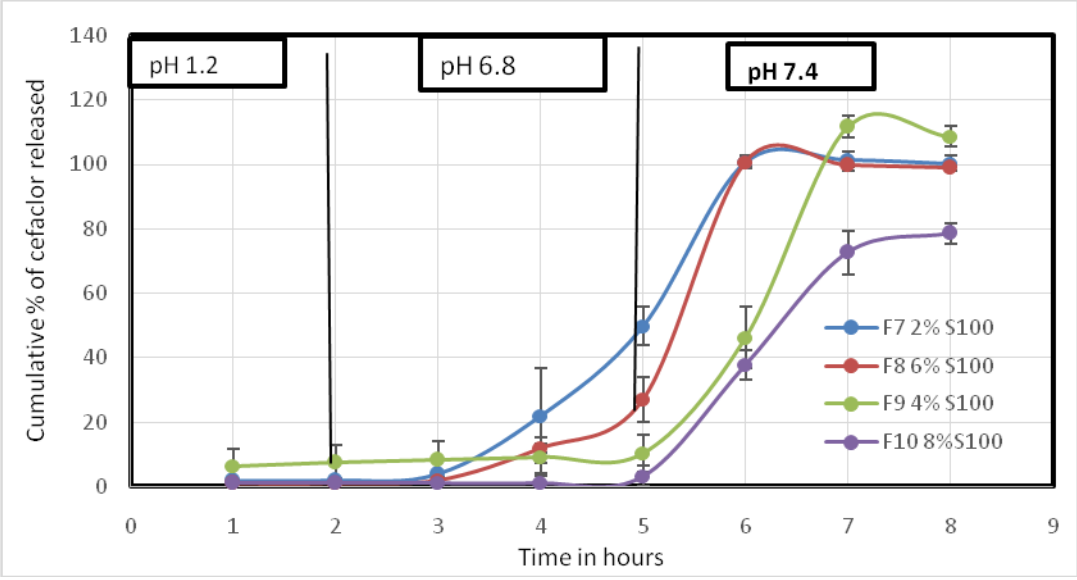

Figure 2: Release profiles of film coated tablets of cefaclor after addition of 2% PVP and 0.2%primojel coated with different coatinglevels of Eudragit S100

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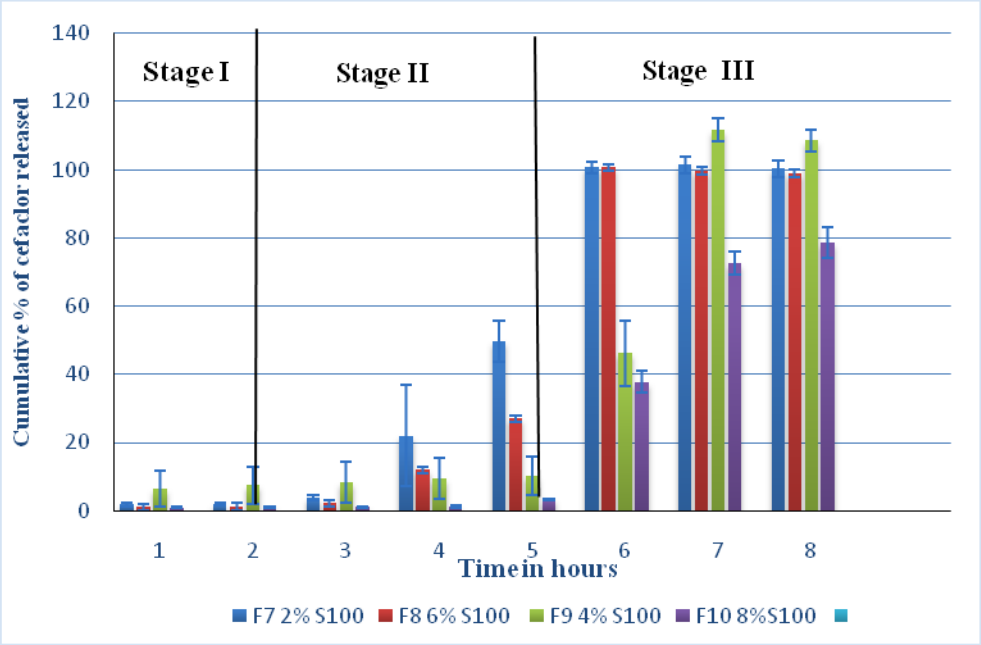

Figure 3: Cumulative % of cefaclor released during different phases of dissolution

Formula ***F9,*** with coating level 6% w/w of Eudragit S100, showed a better release profile. The cumulative percentage of drug released after 7 hours (second hour of stage III) was 100%. During the first two phases only 10% of the drug were released. These findings fit to the required release profile as dissolution of the cefaclor occurred on reaching the triggering pH in stage III.

In formula ***F10,***with coating level 8% w/w of Eudragit S100, the cumulative percentage of drug released after 8 hours (third hour of stage III) was 78.4%.

Addition of super disntegrant primojel (role and selection of primojel was discussed) enhanced drug release by swelling and disruption of cefaclor tablet therefore aiding release of drug. Action of super disintegrants depends on rapid uptake of water followed by rapid and enormous swelling. The difference in lag time between different formulas can be explained by the differences in the level of enteric coating withEudragit S100.

Eudragit S100 is a copolymer of methylacrylic acid and methylmethacrylate, containing about 30% of methacrylic acid units that tends to dissolve at pH 7 which makes Eudragit S100 the polymer of choice for tailored delivery at ileocecal area and formulating gastro-resistant dosage forms to protect the drug core system during its passage through the stomach and small intestine. The coating level was gradually varied. The variation in coating level is reported to be the main factor affecting the length of the lag time before the beginning of drug release. Since the pH-responsive polymers form the continuous phase in the coating film, no drug is released as long as the pH threshold is not passed. However, erosion is triggered once the pH threshold is passed and the fluid will rapidly reach the incorporated drug and excipients allowing drug release of the incorporated drug[21, 29].

CONCLUSION

Cefaclor is a broad spectrum cephalosporin which can be formulated for colonic delivery for treatment of localized colon inflammations and avoiding all side effects related to systemic action of the drug. Eudragit S100 can tailor drug release by adjusting the coating level and incorporation of appropriate excipients that can push drug release through the enteric coat on reaching the triggering pH of the coating polymer, showing resistance to release through different pH changes all through the GIT.

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