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Site specific delivery of 5-aminosalicylic acid and prednisolone for treatment of ulcerative colitis

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ABSTRACT

The present work was to evaluate the effects of pH sensitive polymers (Eugragit S100 and Shellac) on 5-aminosalicylic acid and prednisolone release from tablets to optimize the coating concentration for colonic delivery. Coating formulation was designed based on the full factorial design. Two indecent variables were used in different concentrations by factorial design. In-vitro dissolution studies, it was found that formulation G4 showed 99.26% of 5-ASA in 18 hours and 99.48% of prednisolone in 24 hours, which lies within the acceptance criteria of 80%. That study conclude that the 1% coating concentration of shellac on inner and 10% coating concentration of Eudragit S100 shows the complete release of drugs to colon for treatment of ulcerative colitis.

Keywords: Eudragit, 5-ASA, prednisolone, shellac, ulcerative colitis.

INTRODUCTION

Site specific drug delivery system is much more advanced and beneficial over the conventional drug delivery system. Site specific delivery of drugs to the colon is valuable in the treatment of colon diseases whereby high drug concentration can be achieved while minimizing side effect that occur because of release of drugs in the upper GIT or unnecessary systemic absorption (1). The transit of pre orally administered formulation through the gastrointestinal (GI) tract is highly variable and depends upon various factors. For example factor like disease state of the lumen (diarrhoea, diabetes, peptic ulcer etc), concomitant administration of other drugs (domperidone, cisapride, metoclopromide etc), body posture (vertical or supine) and food type (fat and protein content) can influences the gastric empting rate (2).

Colon targeted drug delivery differs from ordinary enteric coating (that are designed to merely avoid drug release in the stomach) in that the tablet or capsule is specially formulated to channel greater quantity of drug release to the colonic compartment, thus preventing or reducing drug release until the dosage form reaches the colon. Although the large intestine is difficult to access through per oral delivery it is still favoured as the appropriate site to tackle local colon related diseases (3) because of following reasons, Near neutral pH (4), Much longer transit time (5), Reduced digestive enzymatic activity (6), Greater responsiveness to absorption enhancers, The opportunity ensure direct treatment at the disease site, lower dosing and to reduce adverse effects in the treatment of colonic diseases (7).

Colon is divided into the caecum, ascending colon, transverse colon, rectum and anal canal. The caecum has a dilated portion, which is blinded interiorly and is continuous with the ascending colon superiorly. Ascending colon passes upwards from the caecum to the level of the liver where it bends acutely to the left at the right colic flexure to become transverse colon. The transverse colon, that extends across the abdominal cavity, in front of the duodenum and the stomach to the area of the spleen. The descending colon passes down the left side of the abdominal cavity then bends towards the midline. Pelvic colon describes an S-shaped curve in the pelvic, then continuous downwards

to become the rectum (8). The use of pH dependent polymers coating to delayed release of the drug has been studied.

The pH dependent systems exploit the generally accepted view that pH of the human GI tract increases progressively from the stomach (pH 1 to 2.5 at fasting, which increases to 5 during digestion), small intestine (pH 6 to 7) at the site of digestion, and increases to 7 to 8 in the distal ileum and large intestine (pH 5.5 to 7.2). The coating of pH-sensitive polymers to the tablets, capsules, or pellets provide delayed release and protect the active drug from gastric fluid (9). In this technique, the tablets were coated with pH sensitive polymers that dissolve at colon pH. In the terminal ileum, the pH is approximately 6, whereas in colon, the pH is closer to neutral (approximately 7) (10).
Ulcerative colitis (UC) is a chronic disease in which the lining of the colon (the large intestine) becomes inflamed. The inflammation almost always affects the rectum and lower part of the colon (11). Corticosteroids, sulphasalazine as well as its derivative like 5-amino salicylic acid and immunosuppressant are mainly used in medical treatment (12). The factor which cause that disease are, genetic factors, immunologic factors, microbiological factors, physiological factor (13). For unknown reasons, ulcerative colitis is more common in the people who live in northern climates and in developing countries, e.g. North America, Great Britain and Scandinavia, compared to those who live in southern climates (11). Symptoms of UC include diarrhea (typically four episodes per day), abdominal pain/cramping (mild tenderness, lower abdominal cramping), blood in stool (amount depends on the disease severity), fatigue (excessive blood loss and anemia), fever (low grade in severe cases), weight loss, decreased appetite (14).

5-Amino salicylic acid is an anti-inflammatory drug. It has been used to treat inflammatory bowel disease, such as ulcerative colitis and mild to moderate crohn's disease. Chemically, called as 5-Amino-2-hydroxybenzoic acid and molecular formula is $C_7H_7NO_3$ (as shown in figure 1). It is soluble in 0.1N HCl, sparingly soluble in hot water, slightly soluble in cold water and alcohol. Prednisolone is an adrenocortical steroid. Chemically called 11 β, 17α, 21-trihydroxy-1,4-Pregnadiene-3,20-dione molecular formula is $C_{21}H_{28}O_5$ (as shown in figure 2). It is soluble in ethanol (95%) and in methanol, sparingly soluble in acetone, slightly soluble in chloroform, very slightly soluble in water (15, 16).

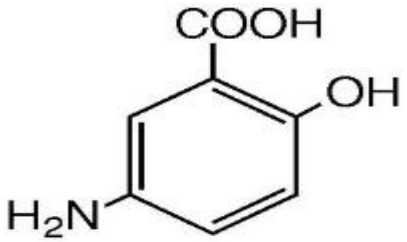

Figure.1: Structure of 5 - ASA

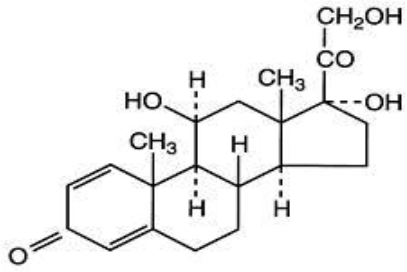

Figure. 2: Structure of Prednisolone

MATERIALS AND METHODS

2.1 Material

The compounds obtained as gift samples: Prednisolone from La Pharma Pharmaceutical Limited, Ludhiana, India. Micro crystalline cellulose (B.P) from Juko Orchem Pvt. Limited, Chennai, India. 5-aminosalicylic acid and polyvinyl pyrrolidone from Himedia Laboratories, Mumbai, India. Eudragit S100 from PC Chem, Mumbai, India. Shellac from CDH India. All the other chemical and ingredients were used as laboratory grade.

2.2 Method

2.2.1 Tablet Preparation

Tablets were prepared by direct compression method, using lactose as the main filler. Starch was used as binder and microcrystalline cellulose as a disintegrant. In this technique first of all the ingredients were weighed accurately and mixed geometrically. All the ingredients were passed into sieve no 60 for the complete mixing with each other. Tablets weighing 500 mg and containing 300 mg of 5-aminosalicylic acid and 10 mg of prednisolone were punched on multi punch tabletting machine using a 12 mm concave die-punch as shown in Table 1. Tablets were tasted for weight variation, friability, hardness, thickness, diameter and drug content as shown in Table 2 & 3.

Table 1: Formula for 1 tablet (500mg) prepared by direct compression method

Sr. No.	Ingredients	Quantities for 1 tablet (mg)	Quantities for 50 tablets (mg)
1	5-aminosalicylic acid	300	15000
2	Prednisolone	10	500
3	PVP	40	2000
4	MCC	100	5000
5	Lactose	35	1750
6	Talc	10	500
7	Magnesium stearate	5	250

Table 2: Evaluation parameter of prepared tablets

Sr. No.	Evaluation parameters	Results
1	Weight variation (IP)	Passed
2	*Thickness (mm) ± S.D	6.12 ± 0.04
3	*Diameter (mm) ± S.D	12 ± 0.00
4	*Hardness (kg/cm^2) ± S.D	6.0 ± 0.5
5	Friability (%)	0.274 ± 0.06

* Average of Three Determinations

Table 3: Drug content uniformity of prednisolone & 5-aminosalicylic acid

Sr. No.	Prednisolone (%) ± S.D	5-ASA (%) ± S.D
1	98.8	101.5
2	99.1	100.8
3	97.4	99.3
Mean (n=3)	98.43 ± 0.90	100.43 ± 1.10

The drug content of prednisolone and 5-aminosalicylic acid were found within the specified IP limits (85 to 115%).

2.2.2 Tablet coating

Coating solutions were prepared using the usual concentrations of polymers used for coating. In case of Eudragit-S100 5%, 10%, 15% (m/V) was prepared using isopropyl alcohol and PEG-400 as plasticizer. In the case of coating with shellac, 1%, 2%, 3% (m/V) solution in ethanol (95%) was used. The tablets were coated with polymers, by using full factorial design at three different concentrations as shown in Table 4 & 5. The desired volume of coating solution was spray on the tablets in coating pan. The tablets were coated and dried with the help of inlet air (temperature 35-45°C). The coating process was repeated till the desired level of coating was achieved. The percent mass increase of the tablets upon coating was taken to be indicative of the coat thickness as shown in Table 6.

Table 4: Optimization of the coating concentration by using full factorial design

Ingredients	Lower (-1)	Middle (0)	Upper (+1)
Shellac (X_1)	1%	2%	3%
Eudragit S100 (X_2)	5%	10%	15%

Table 5: Formulation batches of full factorial design

Batch No.	X_1	X_2
G1	1%	5%
G2	2%	5%
G3	3%	5%
G4	1%	10%
G5	2%	10%
G6	3%	10%
G7	1%	15%
G8	2%	15%
G9	3%	15%

Table 6: Evaluation parameters of the coated tablets

Sr. No.	Batch	*Hardness	*Thickness	*Diameter	*Weight variation
1	G1	6.66 ± 0.28	8.09 ± 0.09	14 ± 0.1	Passed
2	G2	6.83 ± 0.28	8.12 ± 0.03	14.06 ± 0.05	Passed
3	G3	7.0 ± 0.00	8.13 ± 0.03	14.13 ± 0.05	Passed
4	G4	7.16 ± 0.28	8.17 ± 0.02	14.26 ± 0.06	Passed
5	G5	7.16 ± 0.28	8.18 ± 0.01	14.33 ± 0.05	Passed
6	G6	7.5 ± 0.5	8.18 ± 0.02	14.43 ± 0.11	Passed
7	G7	7.66 ± 0.28	8.19 ± 0.02	14.53 ± 0.06	Passed
8	G8	8.0 ± 0.00	8.19 ± 0.01	14.6 ± 0.1	Passed
9	G9	8.0 ± 0.5	8.20 ± 0.02	14.63 ± 0.05	Passed

**Average of three determination*

2.2.3 Dissolution studies

Dissolution studies were carried out on all the formations according to the USP apparatus 1, i.e. basket type at 100 rpm and at a temperature of 37±0.5˚C. Initial studies were carried out in 900 ml of 0.1N HCl (pH 1.2) for 2 hours, followed by replacement of that solution with 7.4 pH phosphate buffer for 3 hours and finally that was replaced with 6.8 pH phosphate buffer and then study was continued up to 24 hours. The samples were withdrawn at predetermined time intervals and replaced with fresh media. Then the samples were analysed using UV-Spectrophotometer at the λmax of 302 nm and 283 nm.

2.2.4 Data analysis

The raw dissolution data were analyzed using Q-absorption method and Q-point method.

RESULTS AND DISCUSSION

The optimized G batch was prepared (as shown in Table 1), and all the parameters were evaluated. The parameters were evaluated like hardness, friability, weight variation, thickness, diameter within the IP limits. The drug content of 5-aminosalicylic acid was 100.43 ± 1.10 and prednisolone was 98.43 ± 0.90, which were found within the specified IP limits (85 to 115%). These prepared batches were coated with different concentrations of polymers (Eudragit S100 and shellac). That coated batches were evaluate by hardness, thickness, diameter of tablets (as shown in Table 6).

The expected in vitro release pattern selected for the colon targeting was not more than 20% of drug release up to the end of small intestine (5 hrs) and more than 80% of drug release up to 18 hrs. Figure 3-11 shows the dissolution profile of shellac and Eudragit S100 containing different concentration of polymers coating of 5-ASA and prednisolone coated tablets. In vitro dissolution of batch G1-G3 shows more than 20% drug release within 5 hours and complete drug release in 12-15 hours. In-vitro dissolution of batch G4-G6 shows 10% drug release within 5 hours and completes drug release 18-24 hours. in case of batch G7-G9 shows less than 6% drug release in 5 hours and complete drug release in 60-80% drug release in 24 hours.

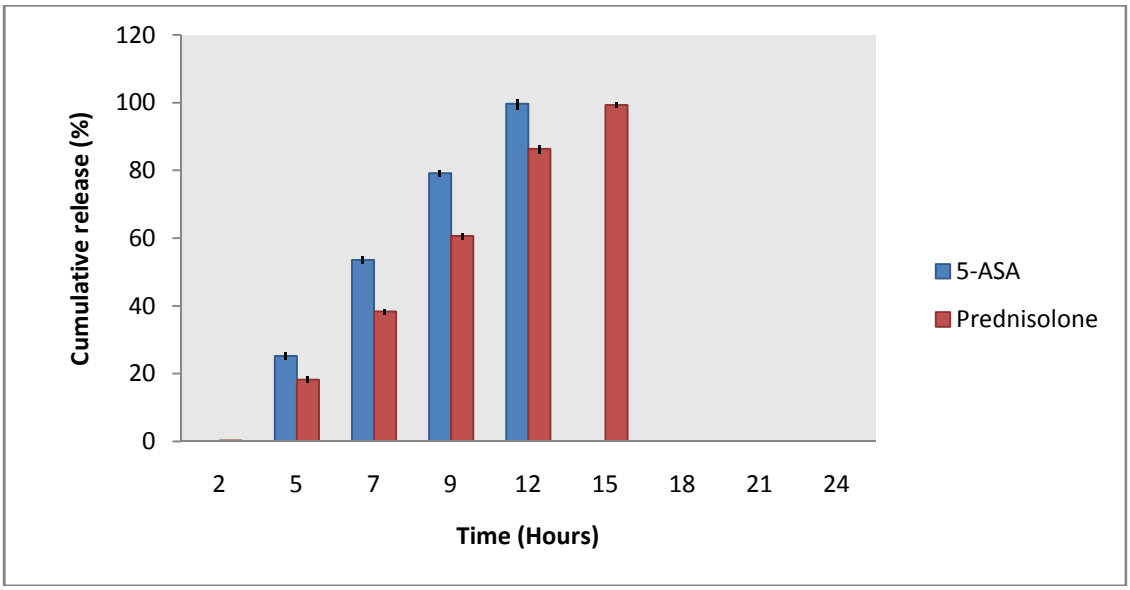

Figure 3: Percentage cumulative release profile of formulation G1

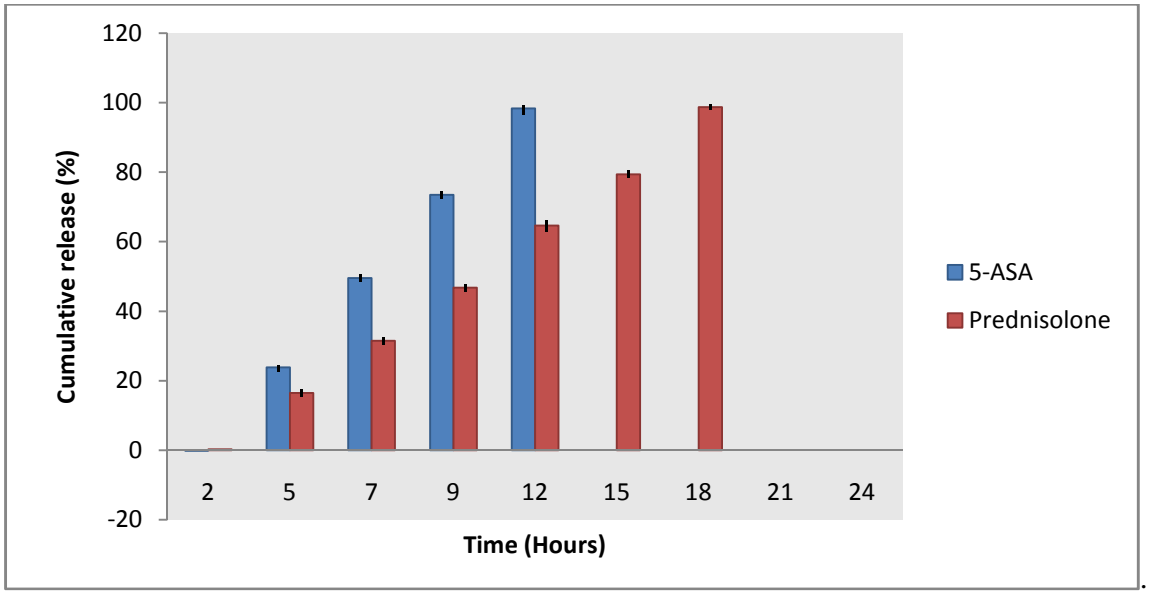

Figure 4: Percentage cumulative release profile of formulation G2

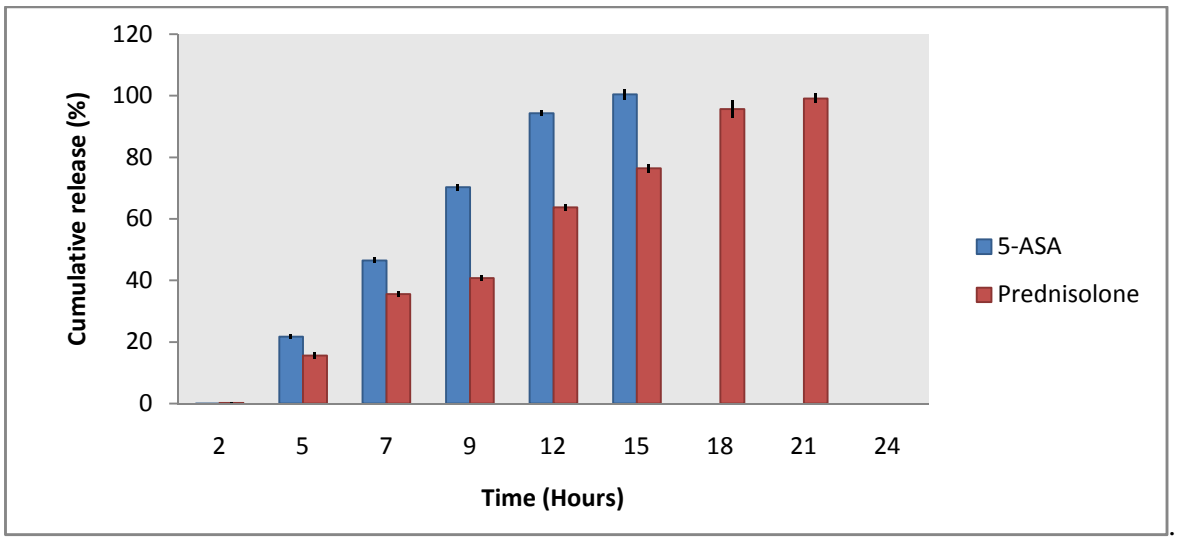

Figure 5: Percentage cumulative release profile of formulation G3

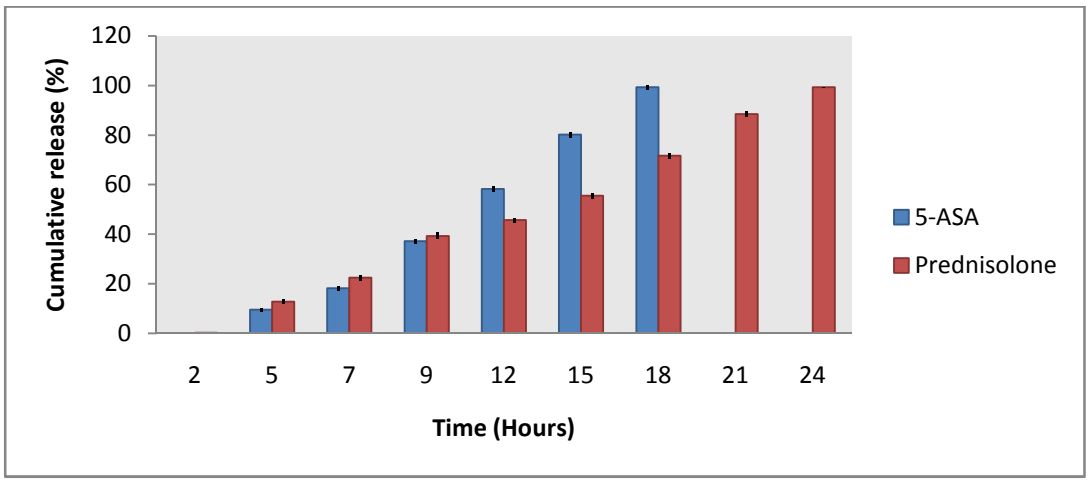

Figure 6: Percentage cumulative release profile of formulation G4

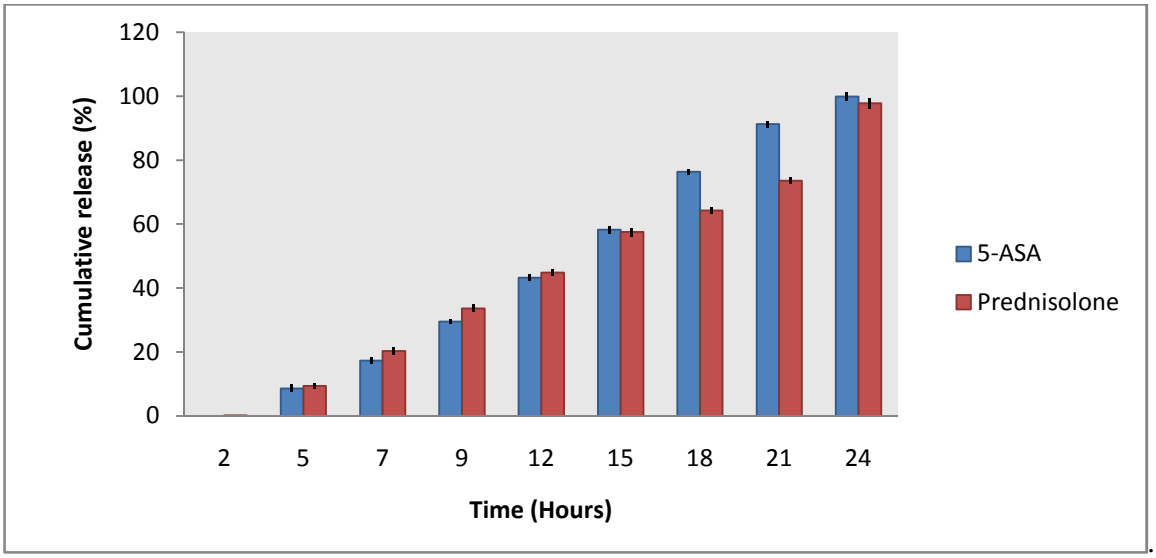

Figure 7: Percentage cumulative release profile of formulation G5

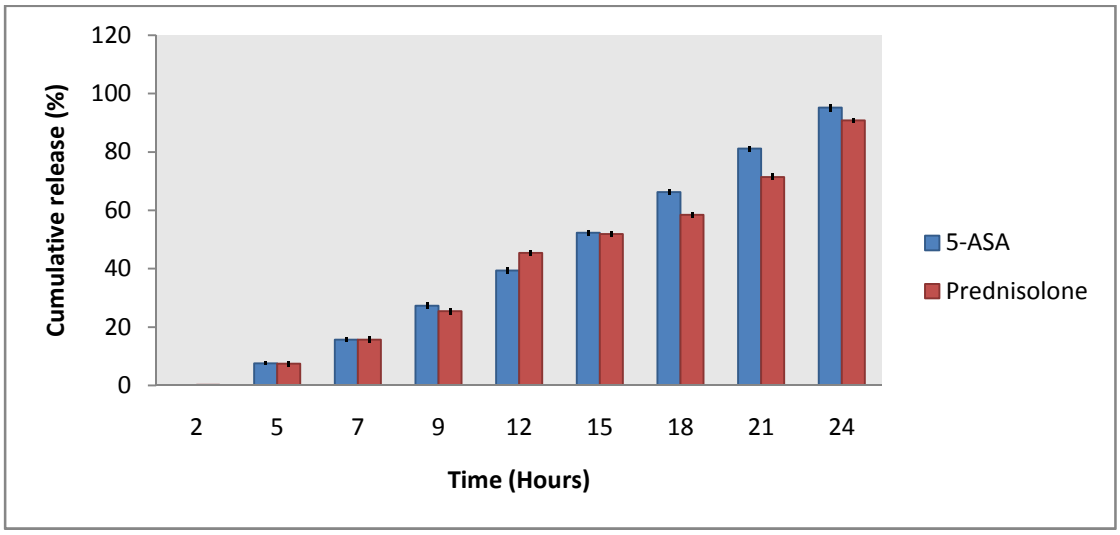

Figure 8: Percentage cumulative release profile of formulation G6

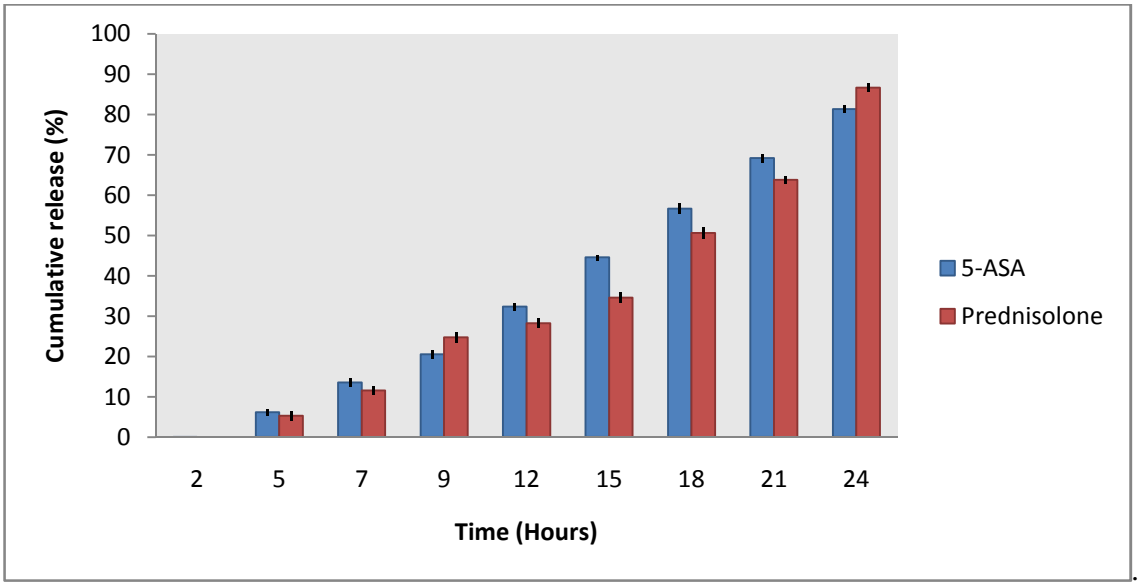

Figure 9: Percentage cumulative release profile of formulation G7

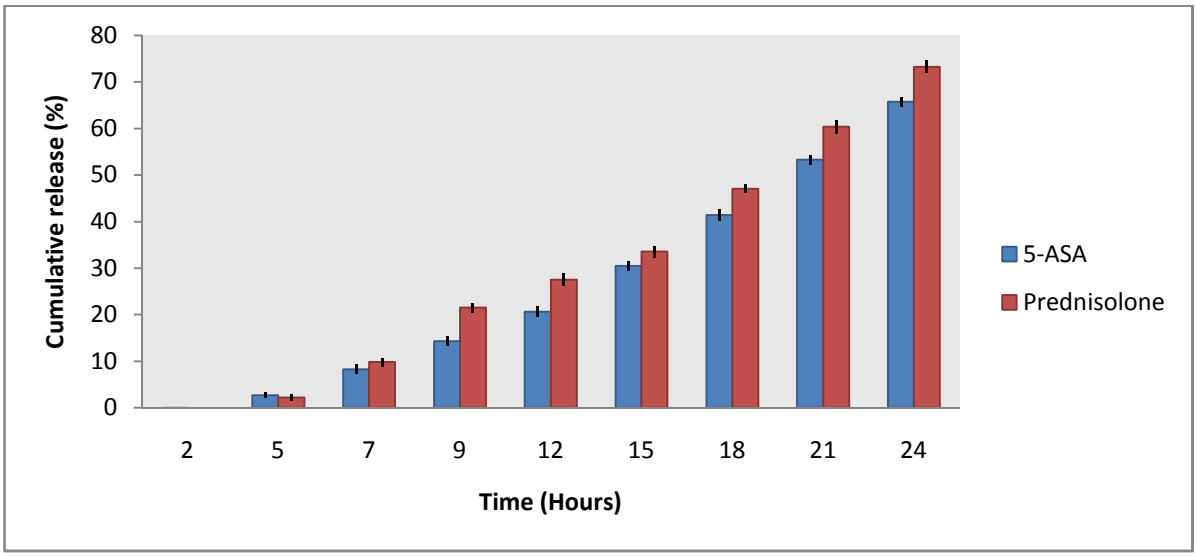

Figure 10: Percentage cumulative release profile of formulation G8

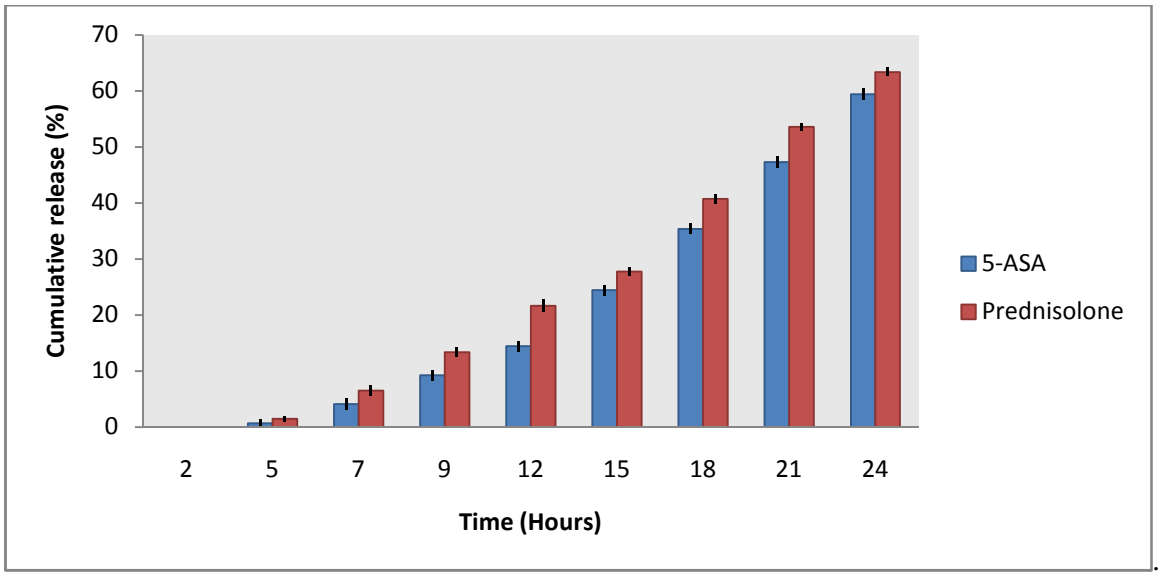

Figure 11: Percentage cumulative release profile of formulation G9

CONCLUSION

An attempt was made to formulate and develop colon targeted tablets for the treatment of ulcerative colitis. By using pH sensitive coating polymers colon targeting of the drug was achieved. For the treatment of ulcerative colitis, combination of two drugs 5-aminosalicylic acid and prednisolone was used. Nine batches G1 to G9 of eudragit and shellac coated tablets were developed. Tablets were formulated and evaluated for thickness, diameter, drug content and for tests mentioned as above. From in-vitro dissolution studies, it was concluded that formulation G4 showed 99.26% of 5-ASA in 18 hours and 99.48% of prednisolone in 24 hours, which lies within the acceptance criteria of 80%. All the data collected from stability studies showed physical and chemical compatibility of ingredients within the formulations.

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