Research Article

Formulation and Evaluation of Fluticasone Propionate Colon Targeted Tablet

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ABSTRACT

The aim of present investigation deals with the development of time-dependent and pH sensitive press-coated tablets for colon-specific drug delivery of Fluticasone propionate (FP). Fp is glucocorticoid exerts a potent anti-inflammatory action when administered topically. The drug has been evaluated for the treatment of irritable bowel diseases (IBD) conditions such as Crohn's disease and ulcerative colitis. To overcome of poorly water soluble drug formulated as solid dispersion with different hydrophilic carriers. The Solid dispersions (SDs) of FP with Pluronic® F-127 and PEG 6000 were prepared in three different ratios of 1:5, 1:10, and 1:15 by the solvent evaporation method and evaluated to deliver FP to the colon in a pre-solubilized form. The selected formula of SDs was compressed into core tablets using drug compatible excipients and then press-coated tablet with the polymer mixture of HPMC K15 (time dependent) and Eudragit® L100 (pH-responsive polymer). Differential scanning calorimetry and scanning electron microscopy and powder X-ray diffraction, and Fourier transform infrared spectroscopy proved drug amorphization in SDS. The 1:15 FP/Pluronic® SDs showed the greatest improvement in solubility and dissolution. The best result of press coated tablet was given at HPMC k15 to Eudragit L100 at polymer ratio 5:5 with coat weight 350 mg. This formula resisted pre-colonic pH values and showed an adequate lag time for the intended colonic targeting (5 hrs), followed by release phase in phosphate buffer at pH 7.4. The proposed coated tablets may provide a colonic delivery system for FP with improved dissolution for local action.

Keywords: Fluticasone propionate; Solid dispersion; Pluronic F-127; Colon targeted; Press-coated; Eudragit L100; HPMC k15.

INTRODUCTION

Site-specific drug delivery systems offer several advantages over the traditional drug therapies and due to this, a great deal of research has been carried out on these systems during the last few decades.[1] The success of a colon-specific drug delivery system (CDDS) depends on the drug's physicochemical properties, the type of delivery system, all other factors which may influence the GI transit time, as well as the degree of interaction between the drug and the GI tract. It is essential for oral CDDS to protect the drug from being released in the stomach and small intestine. Thus, the approaches used in developing a CDDS are aimed at delaying the drug release until the system reaches the colon, with some strategies demonstrating better success than others.[2]

Among the various pharmaceutical approaches used to target drugs to the colon are pH-dependent, time-dependent and bacterially degradable polymers. pH, time response systems are easier to prepare but limitations of these systems are variable physiological and pathological conditions of GIT.[3] The combination of pH and time-controlled systems are prepared by enteric coating with high threshold pH materials, the enteric coating on press coated tablets and blends of extended release and enteric polymers. Compression coating technique is an alternative technique to spray coating technique for the application of high molecular weight polymers. A thick coat can be applied to the core tablet and it is solvent free. Various materials can be applied on the core tablet by compression coating technique like HPMC, hydroxypropyl cellulose, Eudragit. Drug release modified systems can be prepared by this technique.[4]

Steroids are commonly prescribed for acute exacerbations of both ulcerative colitis (UC) and Crohn's disease (CD), but prolonged use can lead to undesirable systemic side-effects.[5] Fluticasone propionate a new generation glucocorticoid exerts a potent anti-inflammatory action when administered topically.

The drug has been evaluated for use in different irritable bowel disease (IBD) conditions with encouraging results when administered orally, almost 100 % of the drug is subjected to first pass metabolism and metabolized via the cytochrome P-450 system in liver[6,7]. Its poor aqueous solubility does not allow its transport to the mucosal surface, which eventually leads to poor absorption with oral administration. The poor absorption of the drug along with high first pass metabolism leads to the negligible oral bioavailability (<1 %) of the drug. First pass metabolism is the fundamental reason for the safe use of potent topical glucocorticoids in IBD conditions.

The local action of the drug can be improved by facilitating local transport of the drug to the colonic mucosal surface, which in turn can be achieved by improving the aqueous solubility of the drug.[8]

To enhance the solubility of poorly soluble drug and improvement dissolution for local action, FP was prepared as solid dispersions by solvent evaporation method using, pluronic F-127 and PEG6000 as hydrophilic carriers, then press-coated with polymeric mixture of pH-dependent and time-dependent polymers as a coating

material for colon-targeted drug delivery to optimized drug release profile in colon.

MATERIALS AND METHODS

Materials

Fluticasone propionate avicel 102 were obtained from hyperchemella, D-mannitol, Crospovidone, Croscarmellose sodium, magnesium stearate, talc were obtained from Aladdin chemistry china, pluronic F-127 was obtained from Sigma-Aldrich Co., USA,PEG6000from Sinopharm chemical reagent Co., China, Eudragit L100 were purchased from Evonik Company, Germany and HPMC K15 was manufactured from Jiangsu yew pharmaceutical Co., Ltd.

Methods

Determination of Fluticasone Propionate Saturated Solubility

Phase solubility studies were carried out as per the method described by Higuchi and Connors.[9]

Thus; an excess amount of FP about (25mg) was added to 5ml of phosphate buffer pH 7.4 containing different ratio from pluronic F-127 and PEG 6000 in sealed glass tube.

The suspensions were placed in shaker water bath for 24 hr at 37 °C and 50 rpm.

After removal from the shaker water bath, the tubes were left to stand for 2 hr to allow the un-dissolved matter to settle.

The solutions were filtered through a 0.45 µm filter membrane and the concentration of FP dissolved was determined by UV-spectrophotometer at their specified λ_{max}[10]

Preparation of FP Solid Dispersion

Solid dispersions of FP in two hydrophilic carriers at three different weight ratios were prepared by the solvent evaporation method by using ethanol as common solvent.

The calculated amount of polymer and drug was dissolved separately in the required amount of solvent ethanol and mixed under mechanical agitation.

The solvent was eliminated using a rotary evaporator under reduced pressure.

The solid dispersions, when dried, were grinded using a mortar and pestle then passed through 300 µm sieve and stored in desiccators until use, and the optimum one for each carrier was compared with the physical mixture (PM) and pure FP.

SD and PM of different weight ratios are listed in Table 1.

Table 1: Formulation of FP Solid Dispersions Prepared By Different Methods with Different Carriers

Formulation code	Carriers	Drug: Carriers Ratio(w/w)	Method of Preparation
SD 1	Poloxamer 407	1:5	Solvent evaporation
SD 2		1:10	Solvent evaporation
SD 3		1:15	Solvent evaporation
PM 1		1:15	**Physical Mixture**
SD 4	PEG 6000	1:5	Solvent evaporation
SD 5		1:10	Solvent evaporation
SD 6		1:15	Solvent evaporation
PM 2		1:15	**Physical Mixture**

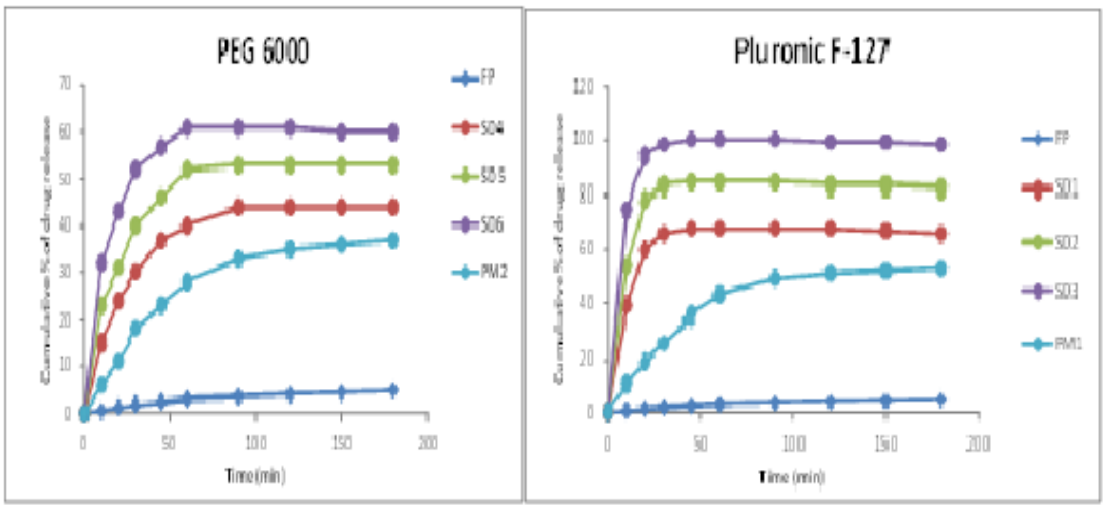

Figure 1: Effect of Using Different Carrier Ratio and Type on Drug Release in Phosphate Buffer pH7.4 at 37 °C

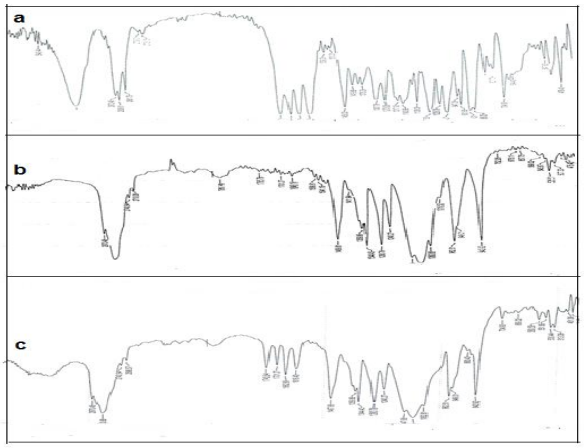

Figure 2: FTIR Spectra of a) FP, b) Pluronic F-127 and c) SD3

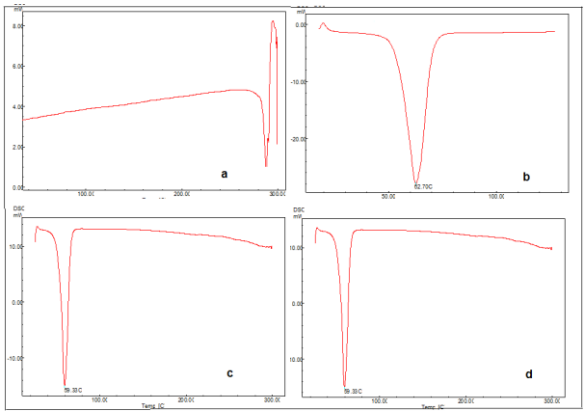

Figure 3: DSC Thermograms of a) Pure FP, b) Pluronic F-127, c) PM1, d) SD3 (1:15 Pluronic F-127)

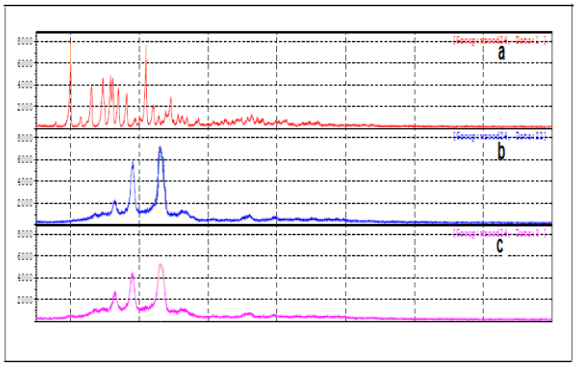

Figure 4: X-Ray Diffraction (XRD) Patterns of a) Pure FP, b) PM and c) SD3

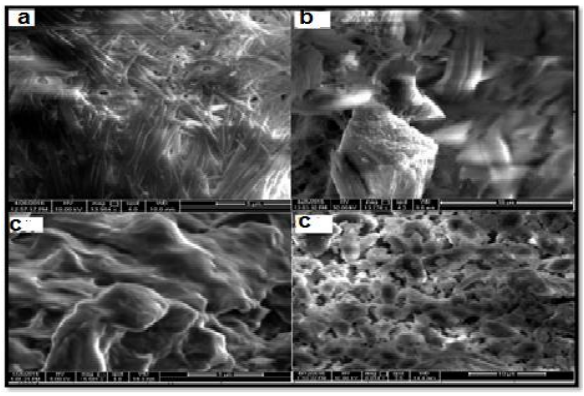

Figure 5: SEM of a) Pure drug, b) Physical Mixture and c) SD3

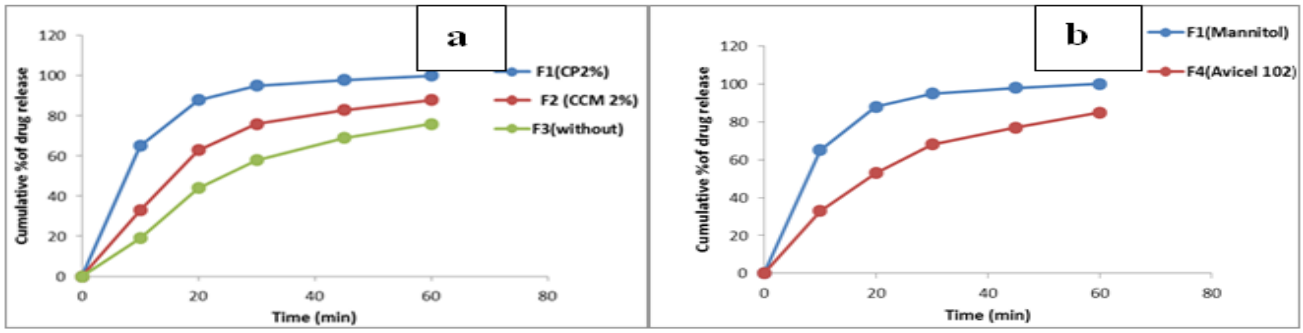

Figure 6: a): Effect of super disintegrates type, b) Effect of Different Type of Diluent, on Release of FP from Core Tablets in Phosphate Buffer pH 7.4 At 37°C.

Table 2: Press-Coated For Colon Targeting Drug Delivery System

Ingredients(mg)	C1	C2	C3	C4	C5	C6
HPMC K15M	241.5	206.5	173.5	207.9	178.2	148.5
Eudragit L100	105	140	173.5	89.1	118.8	148.5
Mg-stearate	3.5	3.5	3.5	3	3	3
Core:Cote ratio	1:1.75	1:1.75	1:1.75	1:1.5	1:1.5	1:1.5
HPMC:Eudragite ratio	7:3	6:4	5:5	7:3	6:4	5:5
Coat weight (mg)	350	350	350	300	300	300

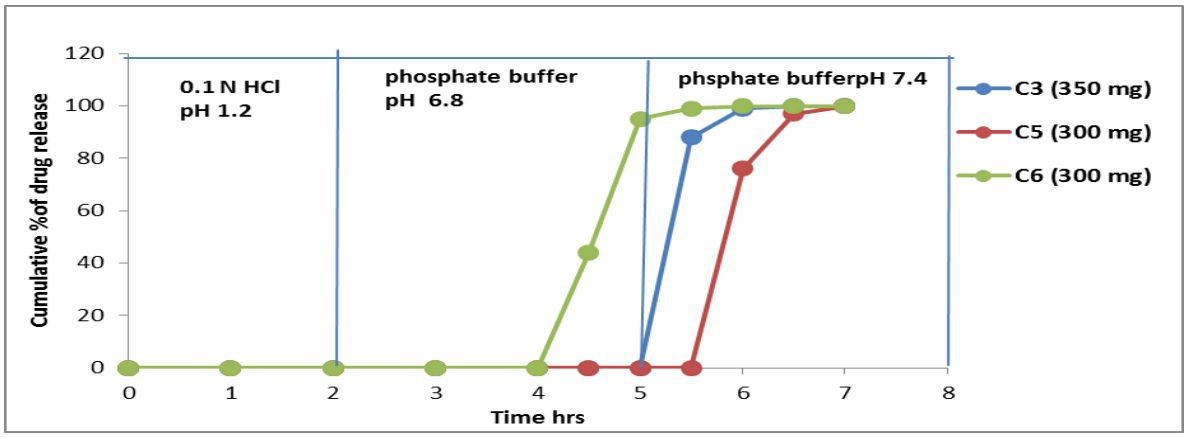

Figure 7: *In vitro* Release of Fluticasone Propionate from Press-Coated Tablet and Effect of Coat Thickness of Drug Release in 0.1N HCl (PH 1.2), Phosphate Buffer 6.8 and Phosphate Buffer 7.4 at 37 °C.

Evaluation of the Prepared Solid Dispersion

Determination of Drug Content

Accurately weighted amount of FP solid dispersion equivalent to 5 mg of FP was dispersed in 50 ml ethanol and subjected to centrifugation at 3000 rpm for 10 min then withdrawn the supernatants and diluted with ethanol.

The drug solution was analyzed for drug content by UV-spectrophotometry.[11]

Fourier Transforms Infrared Spectroscopy (FTIR)

Samples of pluronic F-127 (poloxamer 407) and the best formula (SD3) (equivalent to about 5 mg of FP were grinded, mixed with dry potassium bromide and pressed in the form of discs using a hydraulic press.

The discs were analyzed by FTIR spectroscopy (Shimadzu, Japan) from 4000 - 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermal analyses were performed using DSC (PerkinElmer, USA). Approximately 5 mg of each sample pure FP, Pluronic F-127, SD3 and the corresponding physical mixture of drug and polymer were used. Each sample was placed in a sealed aluminum pan and heated at a scanning rate of 10°C/min from 20°C to 300°C.

Powder X-Ray Diffraction (PXRD)

Powder X-ray diffractometry was carried out using XRD system (Philips Analytical PW 3710), which was operated with Ni-filtered Cu-K_α radiation at 4°/min with diffraction angle (θ) from 3 to 50° at 50 kV and 150mA for the sample holder of the glass plate.

Scanning Electron Microscopy (SEM)

Samples were mounted on a double-faced adhesive tape and sputtered with thin gold palladium layer by sputter coater unit. Crystal properties were observed with a scanning electron microscope (SEM Tescan, Vega III, Czech).

Dissolution of SDs and PMs

The dissolution of FP from the different formula of solid dispersion was carried out in USP-II dissolution apparatus in 900 mL phosphate buffer pH 7.4 maintained at 37±0.5°C and rotation speed of 100 rpm, 5 mg of FP or its equivalent in the physical mixture or solid dispersion was dispersed on the dissolution medium surface. Samples (5 ml) were withdrawn at regular intervals, for up to 3 hr, and each withdrawn sample was replaced with an equal volume of fresh release medium. The samples were filtered through a 0.45µm filter and analyzed by UV spectrophotometrically at their specified λ_{max} of the drug. Triplicate runs were carried out and the amount of drug dissolved was calculated.[12,13]

Manufacturing of Colon Targeted Core Tablet of FP

FP core tablets average weight 200mg was prepared by direct compression method. Using about 80mg of FP solid dispersion (equivalent 5mg of FP), crospovidone and crosscarmelose as superdisintegrants 2% in each formula, mannitol and avicel as diluent, talc 2% as gladient, and finally mg stearate1% as lubricant.[14]

Preparation of Press-Coated Tablets (Dry Coating)

The different type of polymers combination in different ratio and different coat thickness were used to get appropriate lag time. Core tablets were covered with different coated polymers HPMC K15 and Eudragit L100 (ED) mixture in different ratio with the coat weight of 350mg and 300mg as shown in Table 2.

For compression coating, 50% of coat weight powder was first placed in the die cavity. Then, careful putting off the core tablet in the center, flow by the addition of the remainder 50% of the coated powder mixture.

The coating material was compressed around the core by a single station tableting machine using 11mm round concave punches.[15]

Physical Characterizations of FP Core Tablets and Press-Coated Tablets

The development of FP core and press-coated were studies for their for compressional characteristics like weight variation, hardness, friability using reported procedure.[16]

***In-vitro* Dissolution Study for Core Tablets**

The dissolution of FP core tablet from different formula was carried out the same as for powder solid dispersion of FP as mention above except the duration of dissolution for up to 1hr.

***In-vitro* Dissolution Study of Press-Coated Tablets**

The in-vitro dissolution studies were carried out in USP-II dissolution apparatus at a stirring speed of 100 rpm in 900 mL of dissolution-media-maintained-at-37±0.5°C. To mimic the GIT transit, the dissolution was carried in different bio-relevant media representing pH of the particular anatomical region. Sample aliquots withdrawn at specific time intervals, were analyzed at 239 nm using UV-spectrophotometer.[17]

Statistical Analysis

The results of the experiments are given as mean values ± SD. Statistical analysis was performed by applying Graph Pad Prism Version 7 by choosing one-way analysis of variance ANOVA, and t-test followed by Turkeys test (pairwise comparisons) at which significant results ($p<0.05$) and non-significant ($p>0.05$).

RESULTS AND DISCUSSION

The measured solubility of FP in phosphate buffer pH7.4 (0.16±0.0003 µg/ml) indicates that the drug is practically insoluble compound in this buffer.[18] The solubility enhancement with pluronic F-127 >PEG6000,This markedly higher solubility may be attributed to the higher solubilizing capacity, higher hydrophilic/lipophilic balance value (HLB= 18-23) of this copolymer surfactant which makes it highly water soluble carrier and finally the micellar solubilization of the drug especially when its concentration exceeds the critical micelle concentration (CMC) which was reported to range from 5 to 6.7 g/L.[19]

The results showed SD3 made up of pluronic F-127 having higher dissolution rate compared to other dispersions, physical mixtures and pure drug. The dissolution profiles of the solid dispersions are shown in Figure 1. The cumulative % of FP in physical mixtures as well as in solid dispersions was higher for both carriers as compared with pure FP. Pure FP showed a poor dissolution profile (i.e., only 4.9% of the drug was released at the end of 3 hours), whereas physical mixtures showed slight improvement due to the presence of the carrier in the respective mixtures. Dissolution profiles of all the solid dispersion for both carriers were shows that the pluronic F-127 shows better improvement in dissolution compare to PEG 6000 (i.e., significant improvement in dissolution was observed with an increase in carrier proportion). Solid dispersion with pluronic showed almost 100% drug release within 60 min, whereas solid dispersion with PEG 6000 shows almost 60% drug release within 60 min, indicating that solid dispersion with pluronic F-127 showed better a dissolution profile than PEG 6000. The significant higher dissolution of SD3 with ($p<0.05$) obtained from solid dispersion formulations was due to the formation of a high-energy amorphous form or increased solubility leading to super-saturation.

The increased solubility can be attributed to the dispersion of drugs at the molecular level and/or solubilization effects of the polymer. The drug remains in a metastable form for the considerable time in the supersaturated state and polymeric carrier, in turn, can stabilize the metastable state by preventing nucleation.[20,21]

Formula SD3 was chosen as the best formula since it showed higher drug solubility and percent drug release at the short period of time among other solid dispersion formulations; therefore, further characterization on this formula was done.

The content of fluticasone propionate was determined in all prepared solid dispersion formulas for each carrier and was found in the range (98-100) % of the theoretical calculated content which is within the limits of the official monographs of fluticasone propionate preparation of the USP30-NF25 (98 ± 2.5) % which indicates a uniform distribution of fluticasone propionate in the carriers as a result of the efficient method of preparation.[22]

The FTIR spectrum of selected formula (SD3) as shown in Figure 2 was examined and matched with those of, FTIR of fluticasone propionate and pluronic F-127 for the changes in position or intensity of peaks as an indication of interactions such as hydrogen bonding. In general, there is a reduction in the intensity and sharpness of the absorption bands of SD3 compared to FP alone as a result of the formation of intermolecular hydrogen bonding between drug and carrier.

Thermal analysis using DSC showed the presence of the single endothermic peak in the thermogram of SD3 as shown in Figure 3. From the thermograms of SD and physical mixture, it was observed that there was no peak corresponding to the melting point of drug, suggesting the amorphous form of FP in the solid dispersion as well as physical mixture. This result attributed to FP dissolution in the molten carrier during heating in DSC analysis may due to complete drug transformation from crystal to amorphous SD which was also confirmed by XRD and SEM results.

The PXRD patterns of FP, PM and selected formula SD3 are shown in Figure 4. The diffractogram of physical mixture of FP and pluronic F-127 had crystalline peaks, which appears to contribute by fluticasone propionate, while that of selected formula show halo pattern with intensive reduction of most peaks indicating the loss of crystallinity with state transformation to amorphous form

is present, these results came with good agreement with DSC study.

The results of SEM are shown in Figure 5 SEM Micrographs indicate that the pure drug is in crystalline form whereas physical mixture possesses amorphous particles and some crystals of the drug. In the case of the solid dispersion, the drug particles reduced in size, some have spherical shape might be one of the factors that are responsible for enhancing drug dissolution and solubility by providing a large surface area in addition to surrounding drug particles by pluronic F-127 particles. Particles are in an amorphous state, all these confirming formation of SD.

Post-Compression Parameters of Prepared Tablets

The result of post compression parameters of prepared core and press-coated tablets: Core thickness was (3.51-3.75) mm, press-coated thickness were (6.23-6.84) mm. Hardness of core tablets were (3.4-4) kg/cm^2, while the press-coated tablets hardness (9.5-9.9) kg/cm^2. The friability for both core and press-coated tablets below 1%. Weight variation and drug content of both core and press-coated tablets with a limited rang. All these results agree with requirements of USP and BP pharmacopeia.

***In-vitro* Dissolution Study of Core Tablets**

Variable Effecting Release of FP from Core Tablets

Effect of Superdisintegrants Types

F1, F2 and F3 formula were designed to study the effect of Crospovidone, Crosscarmelose sodium, and without the addition of any disintegrants respectively on the drug release from the cored tablet as shown in Figure 6(a). There was significant difference ($p<0.05$) in the initial release of drug from these formulation among these formulas the F1 gave the best result of 100% release due to the rapid increase in dissolution of FP with the use of crospovidone, this result attributed to used crospovidone absorbs a huge amount of water when exposed to dissolution medium and promote the disintegration of tablets, by decrease the particle size, reduce the re-aggregation of the hydrophobic drug particles and the enhancement in the dispersibility of the drug particles can increase the dissolution rate of the drug. While croscarmellose has a tendency to swell with gel formation which makes a viscous layer at the surface of the tablet and prevent water penetration to the tablet and delay swelling.[23,24]

Effect of Diluent Types

F1 and F4 study the effect of using the different type of diluent on drug release from core tablet as shown in Figure 6(b). These formulas contain mannitol and avicel 102 as diluent respectively.

The results showed that formula contain mannitol as a diluent significantly increased the percent of drug release This might be due to the presence of hydrophilic soluble diluent (mannitol) which undergoes faster dissolution, in addition, the disintegration time of F1 is lower than the F4 about (7 min), as it is generally known that decreasing the disintegration time leads to increase in the dissolution rate because faster disintegration of tablets delivers a fine suspension of drug particles resulting in higher surface area and faster dissolution also F4 is harder than F1.[25]

***In–vitro* Dissolution Study of Press-Coated Tablet**

The requirement for *in vitro* release design for the colon targeting was no drug release up to the 5hrs to achieve this requirement combination of two polymer in a different ratio are used, no drug release in the first 2 hours in 0.1 N HCl (represent the pH 1.2 of stomach) and 3 hours in pH6.8 (small intestine) and began the drug release in 15 minute lag time and 100% release of the drug in the pH7.4 (pH of colon).

Variable Effecting Release of FP from Press-Coated Tablets

Effect of Combination of Time and pH Dependent Polymers on the Release of FP From The Press-Coated Tablet

Formula (C1-C3) used to study the effect of combination of two polymers in a different ratio HPMC k15 time-dependent polymer and Eudragit L100 pH dependent polymer at percent 7:3, 6:4 and 5:5 respectively with an objective to retard the initial premature drug release in stomach and, small intestine and should give majority of the drug release in the colon with press-coated powder weight 350mg. These formulas were compressed around the core tablet using 11mm die size.

The best result was obtained from Formula C3 as shown in Figure 7,which gave exact lag time 5 hours and 10 minutes in 7.4 phosphate buffers this result was attributed to that decomposing of Eudragit L100 when diffused of dissolution fluid inside press-coated tablet through HPMC k15 and formation of viscous layer gel around the core tablet but this percent is appropriate to release the core from press-coated tablet, another formula the percent of HPMC k15 was too high and still gave long lag time above 8 hours.this result was due to when increasing the percent of HPMC k15 lead to prolonging lag time.[26]

Effect of Coat Thickness on Lag Time of Press-Coated Tablet

Press-coated formulas (C4, C5, and C6) designed to study the effect of coat thickness on the lag time of press-coated tablets. The HPMC k15: Eudragit L 100 ratios were 7:3, 6:4 and 5:5 respectively. In these formulas; the weight of the coat was decreased from 350 mg to 300 mg. When decreased of coat thickness of press-coated tablet C4 formula still given higher lag time and C5 formula gave the lag time about 5 hours and thirty-five minutes in targeted area but this time still too high when compared with required target time 5 hours and ten minutes. Formula C6 was given low lag time and the

press-coated open at 4 hours and thirty minutes (2hr in stomach and 2hr and thirty minutes in small intestine this result was not targeted for my work.[27]

CONCLUSION

The successful prepared solid dispersion of Fluticasone propionate with pluronic F-127 in the ratio of 1:15 prepared by solvent evaporation method and further characterized by DSC, PXRD and SEM, and was reflected in the significant improvement in rate as well as the extent of *in vitro* drug dissolution, core tablets containing FP solid dispersion further coated with optimum proportion of HPMC and Eudragit in ratio 5:5 were able to prevent drug release in physiological environment of stomach and small intestinal and release 100% of the drug in the targeted area (physiological environment of colon).

The presence of Eudragit L100 in the coat reduces the initial swelling of HPMC with control the drug release in the targeted area.

Therefore this study lays a basis for use of novel combination of time and pH dependent polymers for press-coating of FP as one of the approach for targeting the drug to the colon for treatment ulcerative colitis and Crohn's disease.

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