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PREPARATION AND EVALUATION OF COMPRESSED COATED TABLETS USING POLYELECTROLYTE COMPLEX FOR TARGETED DELIVERY OF ANTI-AMOEBIC DRUG

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An unwanted absorption of anti-amoebic drug at upper gastrointestinal tract (GIT) causes numerous side effects and requires higher doses to get therapeutic effect. The primary goal of this study was to develop a secnidazole colon targeted drug delivery system (CTDDS) employing compressed coated tablets (CCT) coated with polyelectrolyte complexes (PECs). The optimized PEC was formulated by using varying ratios of cationic and anionic polymers which have the ability to resist a wide range of pH environment from stomach to colon (acidic, neutral to basic). The in vitro release profile of drug was studied in various simulated physiological conditions i.e., gastric, intestinal and colonic environment. For in vivo evaluation, barium sulfate imaging x-ray technique was used to evaluate the transit behavior of formulation in GIT. The results obtained from physical evaluation have demonstrated uniform diameter, thickness, desired hardness (> 4 kg/cm^2), and friability (not more than 1.0%). The Korsmeyer-Peppas model suggested the kinetics of drug release as 'n> 0.89' which indicates super case–II transport mechanism. In vivo images have confirmed that the tablet formulations were not disintegrated in the upper stomach and degraded in the colonic area.

Keywords: *Polyelectrolyte complex, Compressed coated tablets, Anti-amoebic drug, Cationic anionic polymers, Targeted delivery.*

INTRODUCTION

Amoebiasis, normally an infection caused by *Entamoeba histolytica* present in the large intestine (colon) can cause colitis along with the chronic diarrhoea after invading the wall of colon and reaching to different organs such as liver, lungs, brain, or other through blood. It can prove to be fatal if not treated. Its exposure can be exceedingly high in endemic areas: a 40 percent annual incidence was calculated among youngsters in a Bangladeshi slum[1-4]. Secnidazole, 1-(2-methyl-5-niroimidazole-1-yl) propan-2-ol is a relatively newly added in Indian pharmacopeia as an antiprotozoal agent and approximately equipotent to metronidazole but due to upper gastrointestinal tract absorption, it is required in large dose (1 gm) and causes various side effects such as vomiting, glossitis, anorexia, nausea, metallic taste and epigastric pain[5&6].

The most critical challenge to prepare oral formulation is that they must have adequate biopharmaceutical properties to deliver the medicament in such a way, that the site of action can achieve a therapeutic concentration, which could be attained by targeted drug delivery system (TDDS) only. Colon targeted drug delivery system (CTDDS) is the most common system of TDDS, but in case of CTDDS, drug should be prevented to come in contact with the upper GIT environment.

The frequency of dose can be reduced by the colon targeting for the management of local

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ailments, viz. ulcerative colitis, colon cancer, Crohn's disease and infections, etc. where systemic circulation of drug is not required[7&8]. The polymers are quite important in the formulation of CTDDS. They restrict the drug from being released in the middle and upper GI tracts, but promote the release of drug in the colon. Most of polymers used in CTDDS have tendency to get easily hydrolyzed/swelled up in acidic, neutral or alkaline pH of various parts of GIT and release their medicament, especially polymers at cationic (chitosan and poly-l-lysine) and anionic (Na-alginate, pectin) state. However, in polyionic state, the polymers can resist a wide range of pH environments[9].

The present research work was aimed to formulate compressed coated tablets using polyionic complex as a coating material to get negligible to no release of drug in the upper GIT and selective release in lower GI region for achieving an improved localized action with minimized side effects which arises due to absorption of drug in upper GIT.

MATERIALS AND METHODS

Materials

Barium sulphate, sodium alginate, directly compressible lactose (Tablettose 80), pectin and pepsin were purchased from CDH, New Delhi, India. Poly-l-lysine and chitosan were purchased from Sigma Aldrich, Germany. Secnidazole (purity> 99%) was procured from Unichem lab, Mumbai, India as a gift sample. Dawley albino rabbits (female and male with average weight of 225-265 g) were obtained from Institute of Pharmaceutical Sciences, G.G. Central University, Bilaspur, C.G., India. The animals were kept in laboratory *ad libitum*. The animals were maintained in a 12 hrs light-dark circle. All animal procedures were performed in accordance with the protocols approved by Institutional animal ethical committee of Institute of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur, India (994/GO/Ere/s/06/CPCSEA).

Preparation and evaluation of Polyelectrolyte Complex (PEC)

Cationic (chitosan and poly-l-lysine) and anionic (Na-alginate, pectin) polymers were separately dissolved in pH 2, 4, 5, 6 and distilled water, respectively in equal strength (1%) and mixed in various ratios 1:1 to 1:9 to produce PECs[10-12]. These mixtures were incubated for 24 hrs at 37 ± 2 ºC and centrifuged at 15000 rpm for 20 min, the supernatant's viscosity was measured by Brookfield Viscometer (Disc Spindles model, Brookfield, Australia) at 25 ± 2 ºC. Deionized water was used to wash the precipitate and vacuum dried and weighed separately. The optimal ratio of polymers to produce desired PEC was assumed when the equivalent viscosity of supernatant and solvent was achieved with a maximum weight of dried PEC. Subsequent to various physicochemical studies (such as weight of precipitate, viscosity of supernatant liquid and spectra of FTIR (Cary 630 FTIR) of dried precipitate), the optimized PEC of different polymers were evaluated for its swelling properties by using different pH environment according to the modified method described in previous reports[13&14]. The specified quantity (100 mg) of PEC was placed into a teabag and dipped for 2 hrs in 100 ml of solution (pH 1.2) followed by pH 7.4 aqueous buffers at 37 ± 0.5 ºC until a constant weight is achieved. The procedure was repeated with empty teabag and compared with PEC to find the degree of swelling.

$$\text{Degree of swelling (DS)} = (\alpha_{\text{tea bag with material}} - \alpha_{\text{empty tea bag}}) \quad \text{(Eq. 1)}$$

where, $(\alpha) = \{(W_\infty - W_0) / W_0\}$

Here, W_∞ is the weight of the hydrated material and W_0 is the weight at time 0 in dry state.

Preparation and evaluation of compressed coated tablets using PEC

Preparation and evaluation of the core tablets

The composition mentioned in Table 1 was used to prepare core tablets by using direct compression method by the tablet punching machine (compaction force: 4000 kg) to produce 9.01 ± 0.1 mm diameter, 1.5 ± 0.1 mm thickness and 300 ± 10 mg weight (n=10). The content uniformity, hardness and friability were measured for core tablets[15-17].

Preparation and evaluation of the coating core tablets

The coating of core tablets was done as per method suggested by Yassin *et al.*[18] and Sridhar *et al.*[19] with various modifications. The core tablets were compressed coated into different coat compositions given in Table 2.

Table 1: Composition of core tablets.

S.No.	Component	Quantity (mg)	
		Normal tablet	**Animal study**
1.	Drug (Secnidazole)	200	-
2.	Barium Sulphate	-	20
2.	Directly compressible lactose (Tablettose 80)	85	8.5
3.	Magnesium stearate	5	0.5
4.	Talc	10	1.0
Total weight		300	30

Table 2: Coating composition of PEC.

	PEC of Chitosan:pectin			PEC of Chitosan:Na alginate			Poly L Lysine:pectin			PEC of Poly L Lysine: Na-alginate			Anima l study
Formulation code→ Ingredients(mg)↓	CC P1	CC P2	CC P3	CC A1	CC A2	CC A3	CP P1	CP P2	CP P3	CP C1	CP C2	CP C3	
PEC	250	300	350	250	300	350	250	300	350	250	300	350	35.0*
DCL	235	185	135	235	185	135	235	185	135	235	185	135	13.5
MS	5	5	5	5	5	5	5	5	5	5	5	5	0.5
Talc	10	10	10	10	10	10	10	10	10	10	10	10	1.0
Total weight (mg)	500	500	500	500	500	500	500	500	500	500	500	500	50

DCL - Directly compressible lactose (Tablettose 80), MC - Magnesium stearate, ***-** CCP3, CCA3, CPP3, CPC3

The cavity (diameter 11 mm) was filled with one third amount of coating mixture. The core tablet (diameter 9 mm) was cautiously positioned in the middle of the die cavity and was filled with the residual amount of the coat formulation. The force of 5000 kg was applied to compress the core tablet using flat, plain punches of 11 mm round.

The post compression properties of compressed coated tablets[19&20] were evaluated for thickness, weight uniformity, hardness and disintegration time.

Evaluation of swelling behavior of compressed coated tablets

The compressed coated tablets, formulated by different PEC, drug and excipients were evaluated for quantitative swelling properties[21&22] in different acidic and alkaline medium. Briefly, pre-weighed tablets were kept into teabag dipped in 100 ml of acidic (pH 1.2) medium for 2 hrs and then in aqueous buffers of pH 7.4 at 37 ± 0.5 ºC to get a constant weight. The extent of swelling was determined as per Equation 1.

***In-vitro* dissolution test**

The randomly selected compressed coated tablets equivalent to 200 mg of secnidazole were subjected to the dissolution study using USP rotating XXIII dissolution rate test apparatus (DT-06, Erveka, Germany) at 100 rpm and 37 ± 0.5°C. The pH of the dissolving medium was changed at various time intervals to simulate GI transit conditions[20&23]. Briefly, the dissolution medium consisted of 900 ml of simulated gastric fluid (SGF), pH 1.2 for 2 hrs, followed by replacement with 900 ml of Sorenses's phosphate buffer medium (pH 7.4). Since 3-4 hrs is the transit time of small intestine[24] and for the evaluation of colonic bacterial enzyme susceptibility of prepared formulation, the continue studies were carried out with simulated intestinal fluid (pH 7.4 phosphate buffer) in presence or absence of 2% and 4% of rat caecal bacteria, up to 24 hrs . The withdrawal of aliquot sample were done at different time interval and filtered. The filtrate

was analyzed in UV spectrophotometer analysis (λ_{max}= 310 nm). For each sample, the dissolution studies were repeated three times. The kinetics of drug release was analyzed.

***In-vivo* transit behavior of colon targeted compressed coated tablets**

The core tablets were prepared for the non-invasive technique of X-ray studies to observe the transit behavior of selected compressed coated tablets (CCP3) in albino rabbits using radio contrast agent ($BaSO_4$), as per the methods reported by Yassin *et al.*[18], Kadiyam and Muzib[25], and Amidon *et al.*[26]. For animal studies, the animals were free to access water overnight. Before the test sample was administered, radiograph was taken to make sure the lack of radio-opaque material in GIT. The tablet was administered orally to animal with 50 ml of water. By using X-ray system (Siemens, Model No. 3064581-B-5310, Germany), radiographic images were taken in a standing position of animal and printed on X-ray film. For proper observation of the movement of tablet, all the images were taken in the same position of X-ray source and animal. The radiographs of the abdomen was taken at 0 hr, 0.15 hr, 1 hr, 3 hrs, 6 hrs , 10 hrs, 12 hrs, 14 hrs, 18 hrs and 20 hrs after the ingestion of the tablet.

RESULTS AND DISCUSSION

Results

The composition of ingredients for the compressed coated tablets was given in Table 3 using optimized PEC by direct compression technique (Fig. 1). The excipients were mixed and core tablets were prepared by tablet punching machine (compaction force: 4000 kg) to get 9.01 ± 0.1 mm diameter, 1.5 ± 0.1 mm thickness and 300 ± 10 mg weight (n= 10). The optimized formulations were selected for compression coating. The coatings of core tablets were prepared as per method suggested by Krishnaish *et al.*[27], and Sinha *et al.*[28] with few modifications, and the composition of ingredients was taken as per Table 1. The core tablets were compressed coated with the coat composition shown in Table 2. The die cavities were filled with one third quantity of formulation for coating. Subsequently, the core tablet was placed at the centre of the formulation already filled in the die cavity and covered with remaining amount coat formulation. The material was compressed by punching with 11 mm round, flat and plain punches with a force of 5000 kg into core tablet. Various quality control tests were performed to evaluate the physical properties (thickness, weight, hardness and disintegration time) of the compressed coated tablets to confirm its suitability[19&20].

Table 3: Degree of swelling and swelling kinetics of various PECs for 6 h at pH 1.2 and 7.4 buffers

PEC	Percentage degree of swelling at pH 1.2 for 2 hrs	Percentage degree of swelling at pH 1.2 and 7.4 for 6 hrs	Kinetics of swelling			Diffusion mechanism
			K(min^{-1})	R	n	
Chitosan:Pectin	76.74 ± 0.44	83.05 ± 0.95	2.547	0.966	0.554	Anomalous transport
Chitosan:Na-alginate	81.13 ± 0.68	87.34 ± 1.15	3.330	0.974	0.592	Anomalous transport
Poly L Lysine: Pectin	85.07 ± 0.75	91.07 ± 1.24	4.154	0.972	0.744	Anomalous transport
Poly L Lysine: alginate	85.91 ± 0.96	91.86 ± 1.33	4.137	0.980	0.730	Anomalous transport

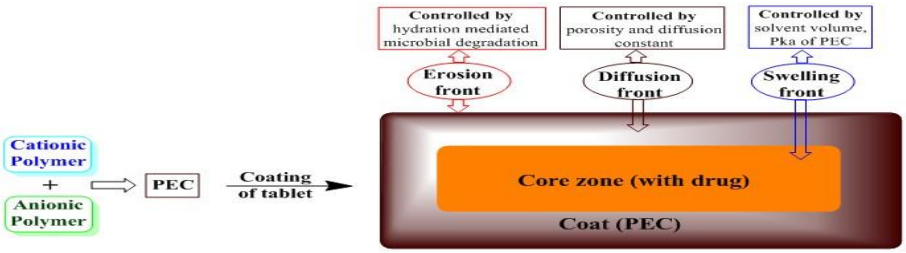

Fig. 1. Drug release behavior of compressed coated tablets.

The effect of concentration of polymers and pH of solvent on the weight of precipitate and viscosity of supernatant were evaluated (Fig. 2). It was assumed that the most effective ratio between polymers at various pH was achieved, when the supernatant viscosity was close to one and maximum weight of precipitate obtained, which showed the maximum polymer was contributed in the formation of PEC[29-31]. FTIR studies also confirmed the formation of PEC (Fig. 3). Pectin/ Na-alginate showed the characteristic peaks, i.e., asymmetric stretching band near 1589 cm^{-1} for COO^- group and band near 1416 cm^{-1} for symmetric stretching. Chitosan and PLL have showed intense peak near 1640 cm^{-1}, 1530 cm^{-1}, 2925 cm^{-1} and 2850 $cm.^{-1}$. The combination of polyanion and cation result in the formation of peaks for amide on 1645$cm^{-1,}$ 1532 cm^{-1}, 1549 cm^{-1} and 1403 cm^{-1} which were intense near their pKa value.

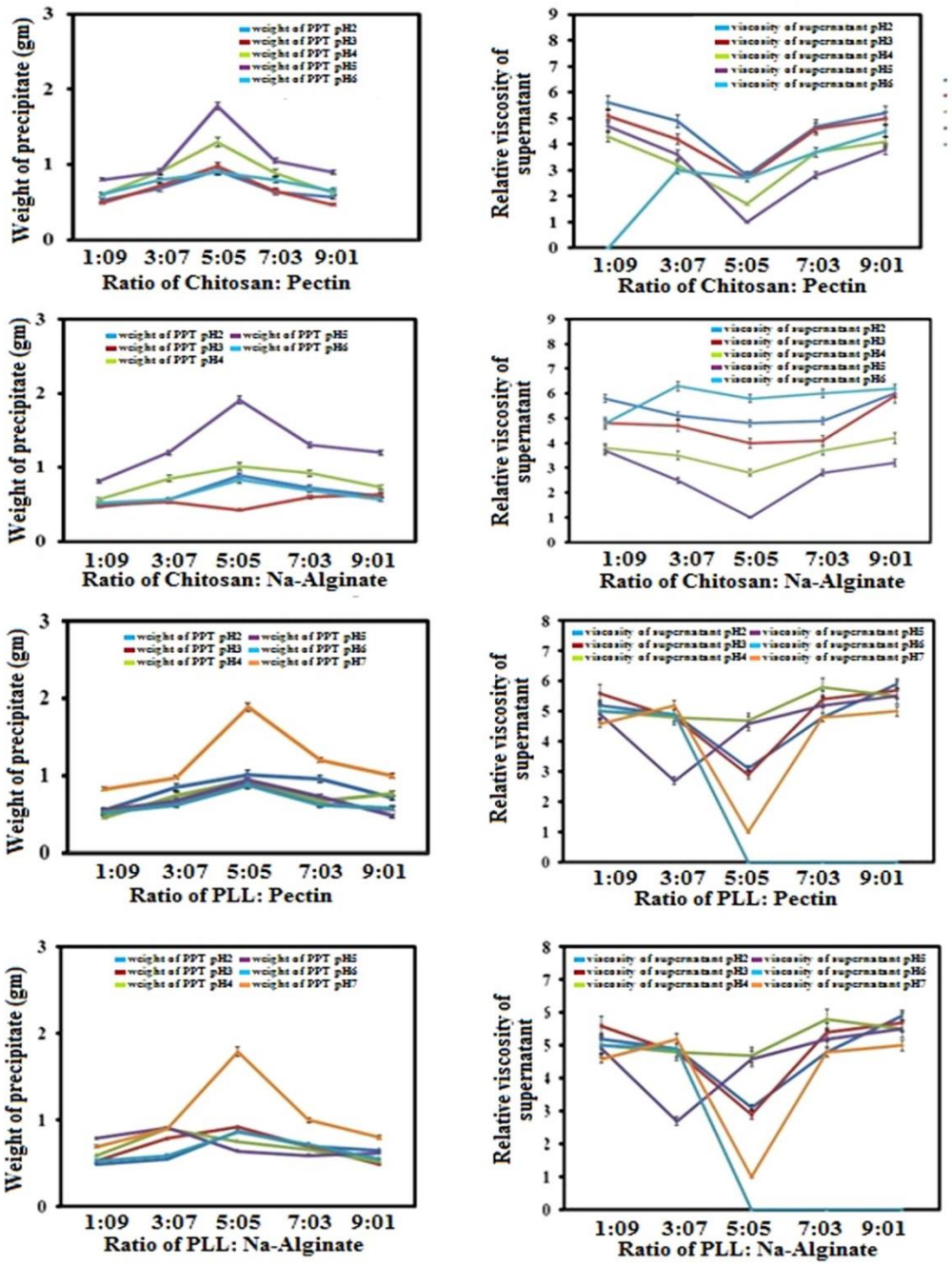

Fig. 2. Effect of polymer ratio of Chitosan and Pectin (a-b), Chitosan and Na-Alginate (c-d), PLL and Pectin (e-f) and PLL and Na-Alginate (g-h), with respect to pH on PEC formation.

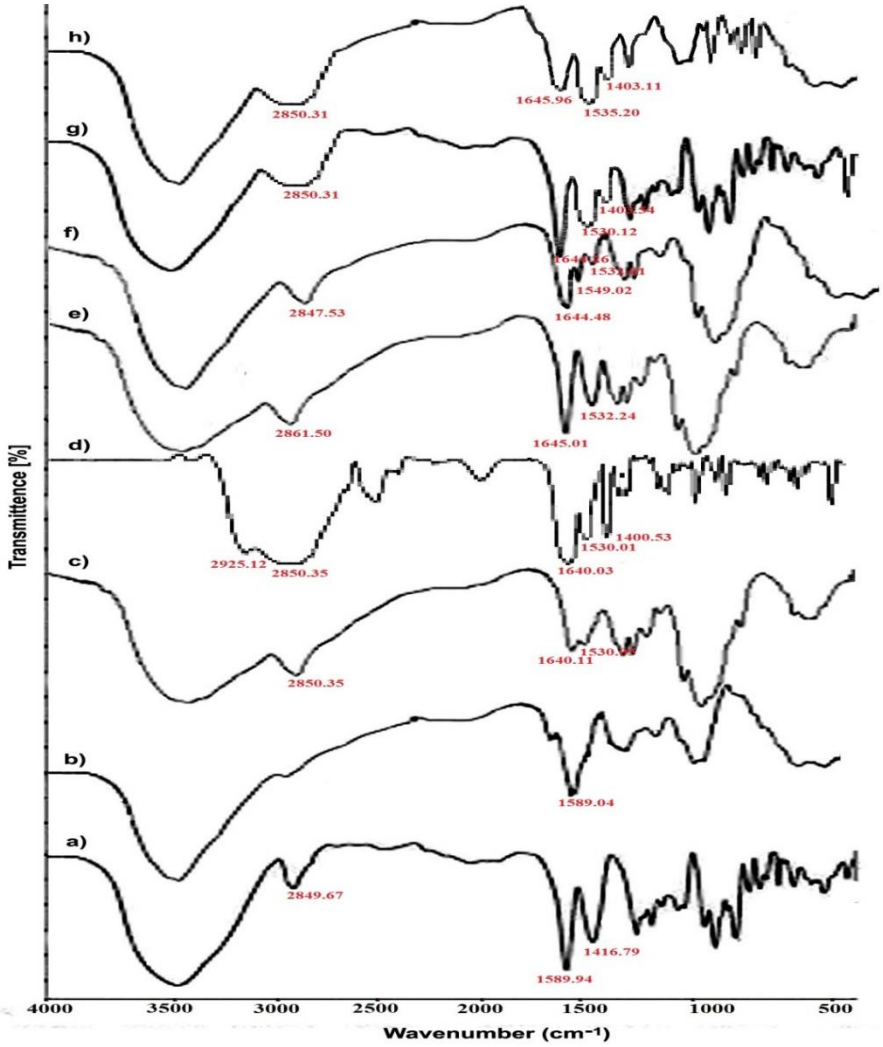

Fig.3. FTIR spectra of a) Pectin; b) Sodium alginate; c) Chitosan; d) Poly-l-lysine; e) PEC of chitosan & pectin; f) PEC of chitosan & alginate; g) PEC of poly-l-lysine & pectin; h) PEC of poly-l-lysine & sodium alginate.

These results were confirmed by the swelling study of PEC, as shown in Table 3. The maximum swelling was found in PEC of PLL and Na-alginate (91.86 ± 1.33) and minimum swelling was found in PEC of chitosan and pectin (83.05 ± 0.95). The swelling kinetics (Table 3) suggested that the solvent migration in polymers followed anomalous transport of solvent. It was noted that none of the PEC collapsed or fragmented during swelling study and showed resistance to upper GIT fluid.

The results of pre and post compression properties of compressed coated tablets were evaluated as per Indian pharmacopoeial standard[32] (Tables 4 and 5), that confirmed the use of PEC mixture as a polymer for the preparation of CTDDS formulation. The swelling behavior and kinetics of various CCT were tabulated in Table 6, and *In-vitro* dissolution data were demonstrated in Fig. 4. All the formulations had a minimum 3 h of lag time for various gastric and intestinal fluids. On observation of drug release, a significant difference ($p < 0.001$) occurred with 4% of rat caecal content after 24 h, when compared to the dissolution studies carried without rat caecal content of all formulations. However, in comparison to the 4% rat caecal content, less significant difference ($p > 0.05$) was observed with 2% rat caecal content after 24 h of the dissolution studies. The drug release was assisted or mediated by enzymes present in rat ceacum, as suggested by the results.

Table 4: Pre-compression or flow properties of different powder mixture used for direct compression tablets of PEC.

S. No.	Formulation	Angle of Repose (θ)	Carr's Index (%)	Hausner ratio
1.	CCP1	22.02	18.10	1.35
2.	CCP2	22.84	18.68	1.40
3.	CCP3	23.12	18.11	1.42
4.	CCA1	21.02	16.20	1.20
5.	CCA2	21.19	16.32	1.22
6.	CCA3	21.22	16.58	1.25
7.	CPP1	24.00	20.30	1.63
8.	CPP2	24.56	20.75	1.65
9.	CPP3	25.41	21.98	1.70
10.	CPA1	25.88	21.10	1.51
11.	CPA2	26.20	21.58	1.65
12.	CPA3	26.80	22.0	1.70
13.	Core tablet material	22	12.10	1.21

Table 5: Physical parameters of compressed coated Secnidazole tablets.

S No.	Formulation code	Physical test			
		Hardness kg/cm^2	Percentage friability	Average weight (mg)	Percentage Drug content
1.	CCP1	6.88 ± 0.57	0.19 ± 0.06	830 ± 9.0	99 ± 0.3
2.	CCP2	6.20 ± 0.83	0.20 ± 0.08	815 ± 3.0	100 ± 0.5
3.	CCP3	5.90 ± 0.32	0.24 ± 0.03	812 ± 5.0	102 ± 0.3
4.	CCA1	6.68 ± 0.35	0.25 ± 0.04	826 ± 2.0	98 ± 0.8
5.	CCA2	6.10 ± 0.32	0.31 ± 0.05	832 ± 7.0	99 ± 0.3
6.	CCA3	6.00 ± 0.15	0.30 ± 0.07	821 ± 4.0	101 ± 0.6
7.	CPP1	6.42 ± 0.27	0.19 ± 0.05	813 ± 6.0	98 ± 0.4
8.	CPP2	6.03 ± 0.35	0.21 ± 0.05	808 ± 5.0	101 ± 0.3
9.	CPP3	5.84 ± 0.22	0.32 ± 0.08	806 ± 2.0	103 ± 0.6
10.	CPA1	5.88 ± 0.33	0.21 ± 0.01	816 ± 7.0	98 ± 0.2
11.	CPA2	5.60 ± 0.24	0.26 ± 0.03	809 ± 5.0	100 ± 0.2
12.	CPA3	5.55 ± 0.12	0.32 ± 0.05	806 ± 2.0	104 ± 0.3
13.	Core tablet	4.58 ± 0.22	0.51 ± 0.05	300 ± 9.0	104 ± 0.31

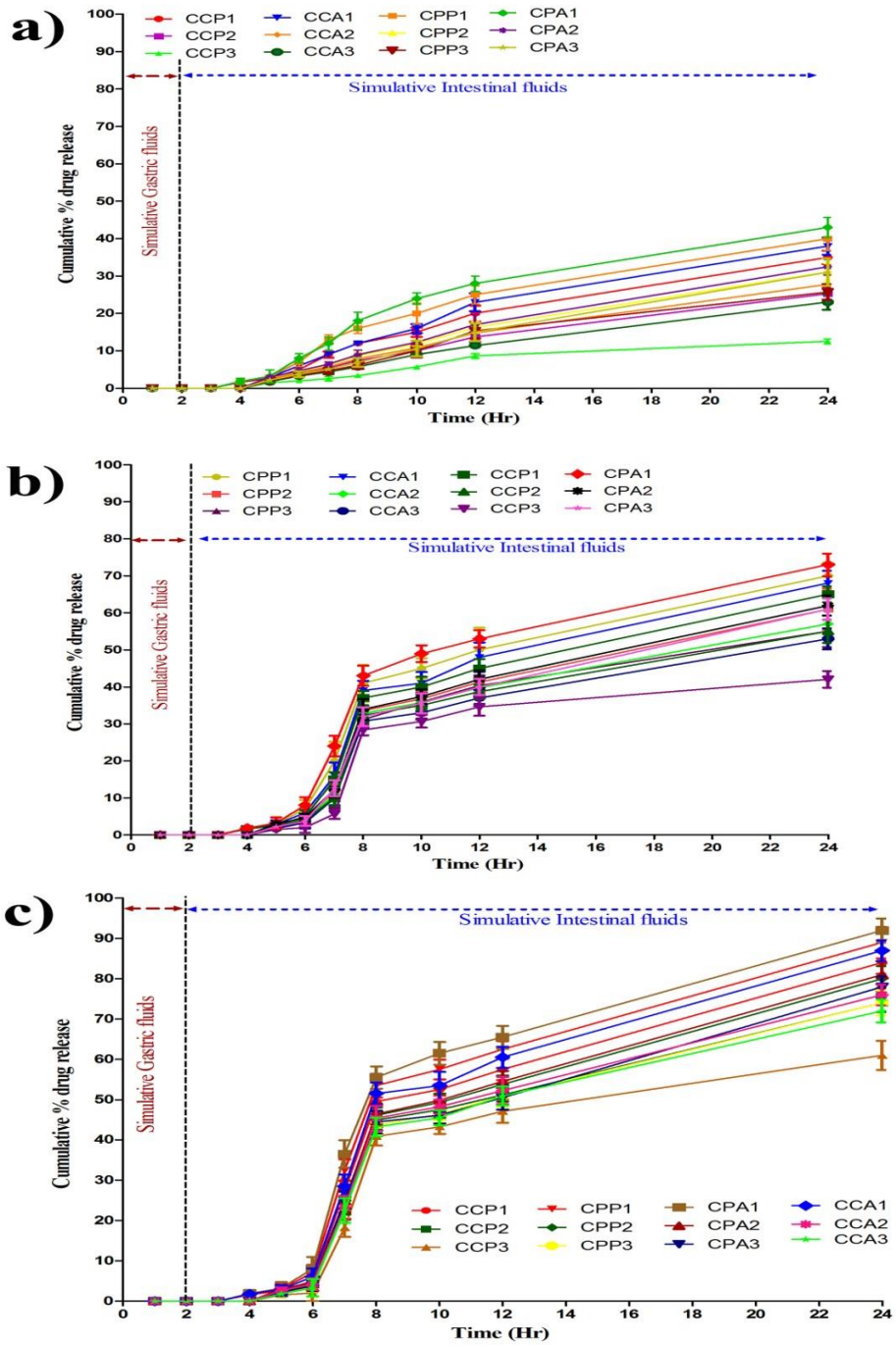

Fig. 4. Cumulative percentage drug release (CPR) of drug release from compressed coated tablets, without rat caecal content (a), with 2% Rat caecal content (b) and formulations in simulative gastric and intestinal fluid with 4% rat caecal content (c).

The results obtained from *In-vitro* drug release study were supported by *in vivo* study performed using $BaSO_4$, as a strong opaque agent. The Fig. 5 (a, b, c and d) showed the presence of the tablet movement in GIT of the experimental rabbits. After 1 hr of dosing, it was observed (Fig. 5b) that the tablet remained in the stomach with no sign of drug release. Similarly, after 6 hrs, it indicated the presence of formulation on the proximal part of the small intestine with small white spots. Fig. 5c shows the colonic distribution of opaque material in rabbit after 10 hrs, and finally after 20 hrs of dosing. It exhibited (Fig. 5d) high opacity in the colonic region and showed degradation of coating and dispersion of radioactive material. The images were selected based on clarity.

Table 6: Percentage degree and kinetics of swelling of different formulations of compressed coated tablets.

Formulation	Percentage of degree of swelling		Kinetics of swelling			Order of release (n) solute diffusion mechanism
	pH 1.2 for 2hrs	pH 1.2 and 7.4 for 6 hrs	k	R	n	
CCP1	145 ± 2.64	245 ± 3.10	8.42	0.998	0.65	Case II (relaxation controlled) transport
CCP2	135 ± 2.50	235 ± 2.98	11.95	0.989	2.41	
CCP3	65 ± 1.22	125 ± 2.42	9.45	0.980	1.86	
CCA1	165 ± 2.72	435 ± 4.12	7.92	0.967	1.44	
CCA2	155 ± 2.69	425 ± 4.10	9.40	0.983	1.74	
CCA3	115 ± 1.30	225 ± 2.90	7.63	0.944	1.40	
CPP1	345 ± 3.88	645 ± 5.42	7.59	0.993	1.46	
CPP2	335 ± 3.60	635 ± 5.52	8.36	0.988	1.62	
CPP3	235 ± 3.01	460 ± 4.50	8.36	0.997	1.62	
CPA1	345 ± 3.80	675 ± 5.85	7.05	0.997	1.34	
CPA2	335 ± 3.66	665 ± 5.60	7.65	0.996	1.46	
CPA3	255 ± 3.15	515 ±4.91	7.52	0.996	1.43	

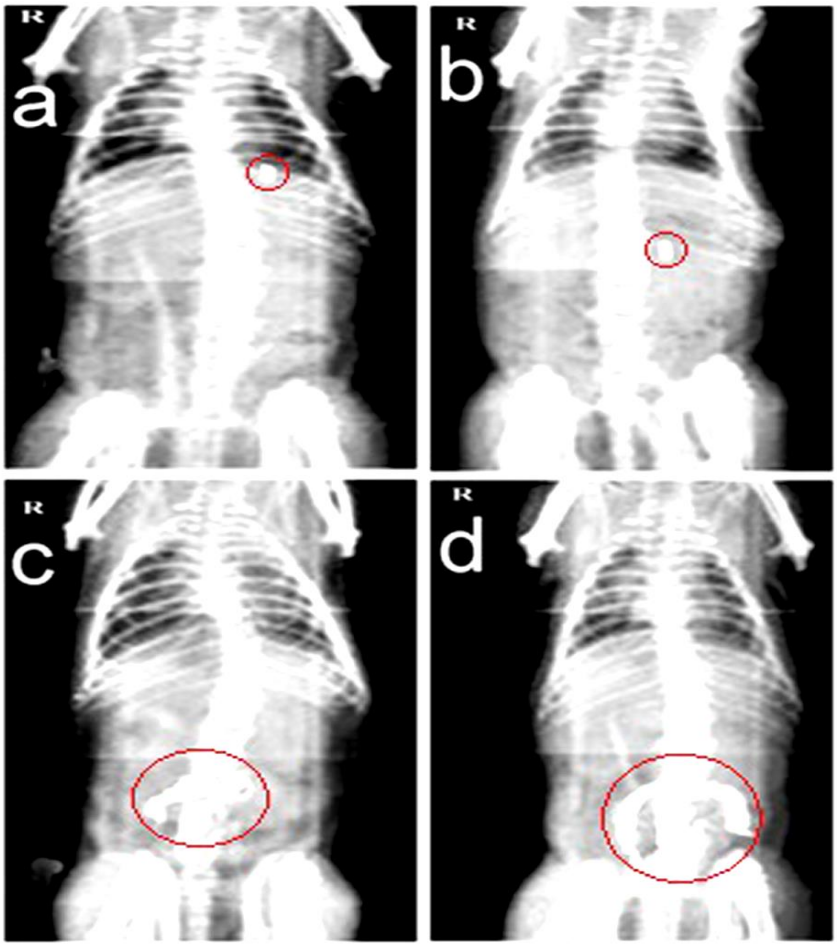

Fig. 5. Various X-Rays images of rabbit's GIT after 1 h (a), 6 h (b), 10 h (c) and 24 h (d) of ingestion time.

The polyelectrolyte complexes of polyanion and cation were formed by electrostatic interaction between negatively charged pectin/Na-alginate (COO^-) and positively charged chitosan/PLL (NH_3^+). The optimum concentration for PEC was ascertained by changing the concentration of polyanion: polycation (1:9, 3:7, 5:5 and 9:1). If the viscosity of supernatant is close to 1, the PEC is found to be maximum. The polyelectrolyte swelling is controlled by various factors especially properties of polymers such as pKa of ionic monomer, concentration of ionizable monomer, charge of ionizable monomer, degree of ionization, and properties of solvent medium like pH, ionic strength and counter ions. The optimized PEC (with ratio 5:5) of chitosan:pectin and chitosan:Na-alginate showed maximum resistance in both acidic and alkaline pH but significant difference was observed in swelling of PEC of PLL with pectin and chitosan. Similar results were also observed by various researchers during the formulation of PEC[33]. The kinetics of swelling was defined by using the equation 2.

$$In\ (W_t/ W_\infty) = In k + n\ ln t \ldots\ldots\ldots\ldots\ldots\ldots (Eq.\ 2)$$

Where, W_t and W_∞ represent the amount of water absorbed by polymer in time t and in the equilibrium. "n" is the diffusion exponent, which describes the mode of water transportation into system. All the PEC exhibited the n values more than 0.5, since a value of n= 0.45 indicates a fickian diffusion mechanism, while if it reaches the value 0.45<n> 0.89, it suggests the diffusion is a non-fickian or anomalous type i.e., a combination of diffusion and erosion. In the special case where n= 1, the transport mechanism is generally type II and is based on fact that the solute's migration occurs at a constant speed and is purely controlled by the relaxation of the chains. This equation was applied to initial swelling state and has a linearity when the ln (W_t/ W_∞) is related to function of the ln (t) up to fractional swelling value less than 0.60[31,34&35].

The average weight of the tablets was found to be in the range of 812± 5.0 to 832±7.0 mg that was within the Indian pharmacopoeial limits[32]. All the tablets showed hardness more than 4 kg/cm^2. The higher hardness values were found in the combination of chitosan and pectin formulation. The previous study[35&36] suggested that the polysaccharide polymer had good compression properties and they could be used as binders, disintegrating agents and diluents in the formulation of tablets. The percentage of degrees of swelling of various compressed coated tablets is shown in Table 3. The maximum swelling was found in the compressed coated tablets of the formulation CPP1 (345 ± 3.88), while minimum swelling (65 ± 1.22) was observed in case of formulation CCP3, in 2 hrs swelling studies in pH 1.2. Similarly, the maximum percentage of swelling degree was exhibited by the formulation CPA1 (675± 5.85), while minimum swelling was observed in the formulation CCP3 (125± 2.42), in 6 h swelling study (2 h in pH 1.2, and then in pH 7.4). The previous research works[13,29] suggested that at acidic pH, free amino group of chitosan or PLL were completely protonated and increased the osmotic difference between polymer matrices and solvent, leading to an increase in the swelling of the tablet formulation. In case of alkaline pH, Na-alginate or pectin showed maximum swelling. But due to the formation of polyelectrolyte complexes, free amino group of chitosan and PLL and carboxylic group of Na-alginate and pectin were reduced, which decreases the swelling.

In the present formulations, an increase in the concentration of PEC of coating solution causes decline in the water uptake, which conformed the resistance of the tablet formulation at wide pH range, which is a prime and essential requirement of colon targeted drug delivery system. The equilibrium component "n" derived from kinetics of swelling as a diffusion exponent represents the mode of transport of solvent and behavior of formulation with varying pH environment. The results of swelling kinetics were shown in Table 3. It indicates the non fickian or anomalous type of diffusion (Type II).

The results of *In-vitro* drug release of all formulations conformed that the coating protects the release of drug present in core material not only from gastric fluid but also from intestinal fluid. The first 10 h showed very minute drug concentration in dissolution media. It was followed by a linear increment in release rate that depends on the type and proportion of PEC. The enhanced concentration of coat decreases the drug release. It can be simply revealed by the increased hardness of tablets with higher concentration of PEC.

The decrease in drug release rate on the increased concentration of coat could be explained on the basis that a higher PEC concentration led to an increase in the hardness of the tablets and the capillary pore size gets reduced. The wicking property of tablet for solvent got reduced due to above consequences of porosity and thus affects adversely the swelling and drug release rate[19&34]. However, the reports suggested[36] that when aqueous miscibility of drug is low, the possibility of drug release from the polymeric matrix does not take place by diffusion but by surface erosion. In case of exposure of hydrophilic polyelectrolytes formulation to aqueous medium, the medium penetrate into the system and surface turns into a gel. The formation of gel is dependent on the ionization of PEC which strictly depended on the pKa value of polyanions and polycations[10]. When the penetration of the medium into the system continues, gel layer gets thickened and the system swells. Subsequently, the outer gel layer starts to regenerate. The thick gel surrounding the surface of the tablet is another important parameter that governs the diffusion of drug[13,29].

The previous research work suggests[34,37] that the release profile from the compressed coated tablets depends on the concentration of coat. Therefore, it was found that the compressed coated tablets having 50% PEC concentration, release their 30% drug before 12 h. However, in case of formulation CCP2, CCA2, CPP2 and CPA2, when comparing the amount of drug released at the end of the 12 hrs dissolution trial with 3% rat caecal content to the dissolution study with 6% rat caecal content, a significant difference ($p < 0.001$) was detected. It suggests that at 60% concentration of PEC, not only protect drug up to 6 h but the release of drug was specifically mediated by anaerobic microorganisms found in rat caecum.

A colon-targeted drug delivery system must deliver the drug to colon as well as it should protect its load to be released within stomach and the small intestine region. Since the physiology of colon and its environment, such as fluid scarcity, reduced motility, and the presence of microflora cannot be simulated in conventional dissolution testing apparatus, traditional *In-vitro* dissolution studies are less effective to predict bacterial triggered colon delivery system's *in vivo* performance. As a result, the release investigations were carried out in a distinct release medium (content of rat caecal at various concentrations) known as rat caecal content release media. Because of their resemblance to human and rodent colonic microbiota, rat caecal contents have been widely used as an optional dissolving medium to circumvent the limitations of traditional dissolution testing. Bacteroids and Bifidobacteria, two quantitatively dominating polysaccharides-degrading bacteria, have average log10 viable counts of 8.0 and 7.0 in human large intestine and 8.0 and 8.2 in rat caecum, respectively[38]. For the better stimulation of bacteria, the rat needs pretreatment of polymers or polysaccharides few days earlier. The drug release from sodium pectinate was previously reported[34&39] to be related to the concentration of rat caecal content in the dissolution medium, and the rat was primed with pectin to boost bacteria activity. Due to this, it demonstrated a distinct release pattern in 2 to 4% of the rat caecum. The results from an *In-vitro* drug release study were examined using the Higuchi model to study the release kinetics behavior of the drug from the matrix of compression coated tablets (Eq. 3).

$$F_t = K_H\, t^{1/2} \qquad \text{..... (Eq. 3)}$$

where, $F_t = (1-(W_t - W_0)$ is the fraction of drug dissolved in time t and K_H is the Higuchi dissolution constant. The formulation obeys the Higuchi model of drug release in presence (2% and 4%) and absence of rat caecal content, since all of them followed the linearity ($r^2 \geq 0.9$ and positive slope). However, in presence of rat caecal content, the formulation showed slight deviation ($r^2 = 0.8$ with positive slope) from linearity due to matrix swelling and drug diffusivity. It was dependent on the microbial degradation mediated erosion of polymer matrix, which was directly proportional to the concentration of rat caecal content and hydration of polymer matrix. To find out the mechanism of drug release, initially 60% of drug release data of compressed tablets were fitted in Korsmeyer–Peppas model (Eq. 4).

$$\frac{M_t}{M_\infty} = at^n \qquad \text{.....(Eq. 4)}$$

where, 'M_t / M_∞' is the fraction of drug released at time t, 'k' is the rate constant and 'n' is the release exponent. The plots of log cumulative percentage of drug release (LCPR)

with respect to log time were prepared and the 'n' value is used to characterize the different release mechanisms as given in Table 7 for the formulation of matrices by incorporating the initial 60% of drug release. The drug release mechanism followed the Korsmeyer Peppas model, where 'n' is the release exponent, which indicates the drug release mechanism. All the tablet formulation showed n> 0.89, i.e., super case–II transport. The drug transport mechanism in case-II relaxation release is linked to stresses and state transition in hydrophilic glassy polymers that swell in water or biological fluids. Polymer separation and erosion are also included in this phrase[40].

However, in the case of formulation in presence of 4% rat caecal content, the correlation coefficient has slight lower value in comparison to the absence and presence of 2% rat caecal content. It might be due to the fast hydration and erosion by high concentration of caecal content in the alkaline media[14&37]. The disappearance of the tablet in the colon region had revealed unambiguous evidence for the degradation of tablet in the colon by anaerobic bacteria. However, Fig. 4 showed the presence of tablet in the stomach region as a spot appearance, thereby indicating the protection or non-degradability of formulation in the stomach. Similarly, there was no evidence of the breakage of tablet after 6 hrs, which confirmed the protection of the tablet in the small intestine. The previous reports[19,27,336] suggested that if any formulation is not degraded in first 6 hrs, it has the maximum probability to reach colon in an intact form. X-ray imaging is widely utilized to monitor numerous oral drug delivery methods throughout the human and animal gastrointestinal tracts[18,41]. After 8 to 9 hrs, the changes in shape of the tablet were observed. After 10 h of post administration, the white spot seemed bigger and confirmed the degradation of formulation in the intestinal region. The tablet degradation was confirmed by visualizing a big spot of X-ray images at the colonic region of the experimental animals.

Table 7: Kinetic modeling of drug release from compressed coated tablets in various simulated gastric and intestinal pH without rat caecal content.

Formulation code	Higuchi		Korsmeyer-Peppas	
	r^2	K_H	r^2	N
CCP1	0.932	9.6	0.865	1.4
CCP2	0.916	6.6	0.810	1.2
CCP3	0.915	3.3	0.703	0.9
CCA1	0.931	10	0.870	1.4
CCA2	0.925	7.8	0.844	1.2
CCA3	0.922	5.08	0.819	1.1
CPP1	0.934	11	0.873	1.4
CPP2	0.918	8.4	0.851	1.3
CPP3	0.914	6.5	0.834	1.2
CPA1	0.927	12	0.860	1.5
CPA2	0.918	8.8	0.850	1.3
CPA3	0.913	7.4	0.842	1.2

Diffusion coefficient (mg/ml); diffusion rate g/h X 10^3

Conclusion

The findings of our investigation suggested that the compressed coated tablet formulation of secnidazole prepared by the combination of polyanionic and polycationic polymers (5: 5 ratio of polymer i.e. Chitosan: Pectin, Chitosan: Na-Alginate, PLL: Pectin, PLL-Na-Alginate) possesses promising approaches to colon target drug delivery. Polyelectrolyte complex (PEC) coated compressed tablets has sufficient capacity to resist the release of drug in varying pH environment, i.e., acidic, basic and neutral pH, but when it comes in contact with rat caecal enzymes, it starts to release its load due to bacterial degradation of PEC complex, which further confirmed its targeted approach to colon. During PEC formation, the free amino groups of chitosan and PLL, as well as the carboxylic groups of Na-alginate and pectin, were reduced, reducing swelling and drug release rate. The optimized formulation made from PEC of Chitosan: Pectin (CCP3) shown promising results for colon targeted drug delivery. Therefore, it was concluded that PEC coated compressed tablets offered a significant, cost-effective and site-specific targeting to colon for the treatment of amoebiasis. For commercial use of these PEC formulation for colon targeted drug delivery, additional stability and pilot plant scale up studies are required.

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نشرة العلوم الصيدلية
جامعة أسيوط

تحضير وتقييم الأقراص المضغوطة المغلفة باستخدام مركب متعدد الإلكتروليت للايصال المستهدف لعقار مضاد للأميبا

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يؤدي الامتصاص غير المرغوب فيه للعقار المضاد للأميبا في الجهاز الهضمي العلوي (GIT) إلى العديد من الآثار الجانبية ويتطلب جرعات أعلى للحصول على تأثير علاجي. كان الهدف الأساسي من هذه الدراسة هو تطوير نظام توصيل دوائى مستهدف للقولون (CTDDS) لعقار سيكنيدازول باستخدام أقراص مغلفة مضغوطة (CCT) مغلفة بمجمعات الإلكتروليت (PECs). تمت صياغة PEC الأمثل باستخدام نسب مختلفة من البوليمرات الموجبة والأنيونية التي لديها القدرة على مقاومة مجموعة واسعة من بيئة الأس الهيدروجيني من المعدة إلى القولون (الحمضية ، المحايدة إلى القاعدية). تمت دراسة انطلاق العقار في المختبر في مختلف الظروف الفسيولوجية المحاكاة ، مثل بيئة المعدة والأمعاء والقولون. للتقييم في الجسم الحي ، تم استخدام تقنية الأشعة السينية لتصوير كبريتات الباريوم لتقييم سلوك العبور للصيغة في الجهاز الهضمي. أظهرت النتائج التي تم الحصول عليها من التقييم الفيزيائي قطرًا موحدًا وسمكًا وصلابة مرغوبة (> ٤ كجم / سم ٢) وقابلية للتفتت (لا تزيد عن ١,٠٪). اقترح نموذج Korsmeyer-Peppas حركية إطلاق الدواء كـ "n> ٠,٨٩" مما يشير إلى آلية نقل الحالة الفائقة II. أكدت الصور في الجسم الحي أن تركيبات الأقراص لم تتحلل في الجزء العلوي من المعدة وتتحلل في منطقة القولون.