Design and Evaluation of pH sensitive Minitablets for Chronotherapeutic Delivery of Theophylline

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A pH-sensitive tablet in capsule system intended to approximate the chronobiology of nocturnal asthma is proposed for site specific release to the colon. The system comprising of Eudragit S-100 coated minitablets was designed for chronotherapeutic delivery of theophylline in view to specifically target the nocturnal peak symptoms of asthma. The drug-loaded core minitablets were produced by wet granulation procedure using alcoholic solution of PVP K 30 as a binder. Different coat weights of Eudragit S-100 were applied to the drug loaded core minitablets in a conventional coating pan to produce the pH sensitive minitablets. SEM revealed a distinct continuous acrylic coat free from cracks or pores. *In vitro* dissolution studies performed following pH progression method demonstrated that the drug release from the coated minitablets depended on the coat weights applied and pH of the dissolution media. The studies showed that a coat weight of 10% weight gain was sufficient to impart an excellent gastro resistant property to the tablets for effective release of the drug at higher pH values.

Chronotherapeutics refers to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm[1]. Asthma is a chronic obstructive lung disease characterized by airways inflammation and hyper-reactivity. In most patients, the condition worsens at night with acute exacerbation being most common. Clinical and epidemiological studies verify that asthma is several hundred folds more likely at night than during the day with disturbance of sleep at least once weekly in approximately 75% of those afflicted[2]. The heightened risk of asthma at night coincides with the trough of the circadian rhythms of airway patency, cortisol, epinephrine and sympathetic tone, along with the peak of the rhythms in air way inflammation, hyper reactivity and cholinergic tone[2]. Cyclic environmental factors also seem to be involved as triggers of acute episodes of the disease occurring nocturnally. These include supine posture overnight affecting pulmonary dynamics, day-night differences in antigen exposure, night time gastric reflux, late asthma reactions and perhaps specific biological processes that occur during sleep.

The possibility of deferring the drug release for a programmed time interval after oral administration of the dosage form is considered as a promising tool for handling, among recently highlighted chronopathologies, especially those presenting nocturnal and early morning symptoms[3].

The site-specific delivery of drugs to the colon has implications in a number of therapeutic areas, which include topical treatment of colonic disorders such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon and irritable bowel syndrome[4]. A colonic drug delivery system would additionally be valuable when a delay in absorption is therapeutically desirable in treatment of chronic medical conditions like nocturnal asthma, which is reported to be circadian rhythm dependent[4].

In recognition of this, it was thought to design a pH-sensitive tablet in capsule system of theophylline to specifically target the nocturnal peak symptoms of asthma. Theophylline was selected as a drug candidate considering its short half life[5] (7-9 h), good oral bioavailability[5] (96%) and good colonic absorption[6]. The system when administered in the evening was aimed to achieve an elevated theophylline level overnight when the risk of asthma is found to be maximum.

Colon specific delivery can be achieved with a suitable

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mechanism that triggers off the drug release upon reaching the colon. The physiological changes in the pH of the gastrointestinal tract have been extensively exploited to convey the actives to the colon. Methods based on pH sensitive delivery such as delayed onset dosage forms could be a simple and practical means for colon targeting. Several polymers particularly Eudragit S-100[7] and Eudragit™S[8] have been investigated for colonic delivery. Since the pH of the colon in normal subjects varies from 6.4±0.6 to 7.5±0.4[9], these polymers have been designed to be soluble at pH values higher than 7, keeping in mind the pH prevalent in the large intestine.

A multiparticulate system presents several advantages in comparison to single unit forms in that they exhibit higher colonic residence time and more predictable gastric emptying[10]. The aim of the present investigation was to work out the feasibility of the combination of tableting and acrylic pan coating to produce a pH-sensitive tablet in capsule system of theophylline for colon targeting. The major objective was to modulate drug release of these coated multiparticulates to specifically target the nocturnal peak symptoms of asthma.

MATERIALS AND METHODS

Theophylline anhydrous was a gift sample from Eros Pharma Pvt. Ltd., Bangalore and Eudragit S-100 was generously donated by Rohm Pharma, Darmstadt, Germany. Lactose, polyvinyl pyrollidone K 30 (PVP K 30) sodium starch glycollate (SSG) and triethyl citrate (TEC) were kindly donated by Zydus Health Care Ltd., Bangalore. The rest of the chemicals of analytical grade were supplied by S. D. Fine Chemicals, Mumbai.

Formulation of core mini tablets of theophylline:
The conventional wet granulation procedure was employed to formulate core mini tablets of theophylline[3]. The ingredients consisting of anhydrous theophylline, lactose and intragranular portion of SSG were passed through 60 mesh (250 µm) separately and dry mixed in a planetary mixer (model PMS, M/s Karnavathi Engineering, Ahmedabad). The dry mixing was carried out at a slow speed (50 rpm) for 10 min. and the blend was granulated with 10% w/v alcoholic solution of PVP K-30 at a high speed (150 rpm) for 5 min. The resulting wet mass was immediately processed in a wet granulator (model WSG, M/s Karnavathi Engineering, Ahmedabad) fitted with 16 mesh screen (1000 µm). The granules obtained were dried for 1 h in a thermostatic hot air oven maintained at 40-45° to a moisture content of 2 to 3%. The dried granules were passed through the same sieve (1000 µm) to break the lumps and blended with extra granular portion of SSG, required amount of fines, magnesium stearate and talc. The lubricated granules were compressed into mini tablets weighing 25 mg using 4 mm shallow biconcave punches in a rotary tablet press (Rimek mini press, model RSB-4, M/s Karnavathi Engineering, Ahmedabad) to a hardness of 2 kg. The composition of the core mini tablet of theophylline is shown in Table 1. The compressed mini tablets were dedusted and evaluated for various tablet properties before the process of acrylic film coating.

Acrylic film coating of the drug-loaded mini tablets:
A non-aqueous film coating procedure was employed to apply Eudragit S 100 on to the drug loaded mini tablets[7]. Triethyl citrate was dispersed in water and added to isopropyl alcohol with stirring using a variable speed propeller stirrer (M/s Remi Udyog, Mumbai). Eudragit S100 was added to the mixture and stirring was continued to obtain homogeneous solution. Purified talc of size fraction 100/120 (150 µm/125 µm) was dispersed in the coating solution and stirring was maintained at a low speed through out the coating process.

Drug loaded mini tablets were charged into a conventional coating pan (model CPS, M/s Karnavathi Engineering, Ahmedabad). The coating dispersion was intermittently applied using a pilot type spray gun (model 630, Bullows, Mumbai) fitted with a 1 mm spray nozzle. The spray dispersion application rate was maintained at a rate of 5-10 g/min at an atomization air pressure of 4 kg/cm^2. An infra red lamp was focused on the tablets so as to maintain the bed temperature between 35 and 40°.

TABLE 1: CORE MINI TABLET AND COATING DISPERSION COMPOSITION ALONG WITH THE PROCESSING CONDITIONS FOR ACRYLIC FILM COATING

Core mini composition (% w/w)	Coating dispersion composition (% w/w)	Processing conditions tablet
Theophylline 40	Eudragit S 100 6.00	Bed temp 35-40°
Lactose 46	Triethyl citrate 0.6	Spray rate 5 g/min
PVP K30 04	Purified talc 3.0	Spray nozzle dia. 1 mm
SSG 06	Water 5.0	Spray pressure 4kg/cm^2
Magnesium stearate 02	Isopropyl alcohol Q.S	Pan speed 20 rpm
Talc 02		

The composition of the core minitablets and coating dispersion along with the processing conditions for acrylic film coating of theophylline-loaded mini tablets

Four batches of coated mini tablets T_1, T_2, T_3 and T_4 were produced by applying the acrylic dispersion on the surface of core mini tablets till 5%, 10%, 15% and 20% of practical weight gain was achieved. The detailed processing conditions for acrylic film coating are outlined in the Table 1.

Evaluation of tablets:

Scanning electron microscopy (SEM) has been extensively employed to study the morphology and surface topography of the coated tablets[11]. The morphology and surface topography of coated minitablets were examined by SEM (model JSM-840A, SEM-Jeol, Japan). The samples to be examined were mounted on the SEM sample stab using a double-sided sticking tape. The samples mounted were coated with gold (200 A°) under reduced pressure (0.001 torr) for 5 min using an ion sputtering device (model JFC-1100 E, Jeol, Japan). The gold coated samples were observed under the SEM and photomicrographs of suitable magnifications were obtained.

Weight variation of the core/coated tablets was determined by official method[12]. The percentage practical weight gain for each batch of coated tablets was computed from the average tablet weight of each batch. Ten mini tablets used for the weight variation test were further subjected for determination of the average tablet thickness[13]. The thickness of ten randomly selected core/coated tablets from each batch was individually recorded in mm using a digital caliper (Mitutoyo digimatic caliper, Mitutoyo Corporation, Japan). The mean and standard deviation values were calculated from each value recorded.

Hardness of ten randomly selected core mini tablets previously used for weight variation test and tablet thickness determinations were measured using a Stokes Monsanto hardness tester[13]. The percentage friability of the core tablets was determined by following the USP procedure[13]. Friability was determined by subjecting a sample of core tablets equivalent to 6.5 g to abrasion in automated USP friabilator (model EF-2, Electrolab, Mumbai) for 100 rotations (25 rpm for 4 min). The dedusted tablets were weighed and percentage friability was calculated from the difference in the weight of mini tablets before and after the friability test.

The disintegration test of the acrylic coated tablets was carried out using USP XXIII disintegration tester[14] (model ED-2, Electrolab, Mumbai). Six coated mini tablets were placed individually in each tube of the apparatus; the disintegration test was performed initially in pH 1.2 without the discs for 1 h. After 1 h, the same tablets were tested for disintegration in pH 7.5 with the discs. The temperature of the water bath was maintained at 37±0.5° through out the test. The disintegration time for the tablets was recorded in seconds.

Ten mini tablets were randomly selected and allowed to equilibrate with 0.1 N HCl overnight and the solution was filtered (0.45 µm) after 24 h. The samples were suitably diluted and assayed spectrophotometrically at 269 nm against the blank in the same solvent system. Drug content uniformity was determined following the official procedure[12].

Dissolution studies of the coated mini tablets were carried out in triplicate employing USP XXIII dissolution rate test apparatus-1 (model TDT-06T, Electrolab, Mumbai) following pH progression method simulating the gastrointestinal tract conditions[15]. Ten mini tablets were loaded into the basket of the dissolution apparatus, the pH changes were performed starting with 900 ml of 0.1 N HCl for 2 h, mixed phosphate buffer of pH 5.5 for 1 h, phosphate buffer of pH 6.8 for 2 h, followed by mixed phosphate buffer of pH 7.5 till the end of the test. The temperature of the dissolution fluid was maintained at 37±0.5° with a stirring speed of 100 rpm. Aliquots of the dissolution medium were withdrawn at 1 h. interval for a period of 7 h and the sampled volume was replaced with equal volume of buffer maintained at the same temperature. The samples withdrawn were suitably diluted, filtered (0.45 µm) and assayed spectrophotometrically at 269 nm for samples of pH 1.2 and 271 nm for rest of the samples. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.

The IR spectrum of the coated mini tablets was recorded and compared with that of theophylline to confirm the chemical integrity of the drug in the mini tablets[16]. The samples were powdered and intimately mixed with dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength region of 400 to 4000 cm^{-1} in a FTIR Spectrophotometer (model 460 Plus, Jasco, Japan).

RESULTS AND DISCUSSION

A wet granulation procedure was employed to produce mini tablets of theophylline. Lactose was selected as filler

in the formulation as tablets containing lactose are reported to show fast disintegration, good friability and low weight variation with no signs of sticking, binding and capping[17]. The formula was designed to have sufficient SSG as a disintegrant with the intention to minimize the disintegration time and to generate a pulsed release during the dissolution. SSG was incorporated in two steps, 3% (w/w) was added as the intragranular portion and dry mixed before the wet granulation step and the remaining 3% (w/w) incorporated as the extragranular portion during the lubrication step. The two step method of addition of disintegrant is reported to produces more complete disintegration[17] as the extragranular portion of SSG was known to cause immediate disruption of the tablet into precompressed granules (disintegration) while the intragranular portion produces further erosion of the granules to the primary particles (deaggregation). The disintegration time is reported to be independent of compressional force applied when SSG was used as a disintegrant[17]. PVP K30 is an excellent and versatile all purpose binder which was used at a concentration of 4% (w/w) of the dry mass during the wet granulation step. Since it is recommended to granulate soluble powders with alcoholic solution of PVP K 30[17], an alcoholic solution of the binder was used to ensure the mini tablets produced were hard enough to withstand further processing including the acrylic film coating process in the conventional coating pan. Magnesium stearate was incorporated as a glidant and antiadherent, whereas talc acts as a lubricant and glidant.

The physical properties of the core mini tablets are outlined in Table 2. The core tablets passed the friability test as the friability of the core mini tablet was found to be within the specified limit of 1%. The tablets showed no evidence of capping, cracking, cleavage or breaking after tumbling in the Roche friabilator. The mean value of thickness and hardness for the entire batch of core tablets was found to be 1.49±0.04 mm and 1.85±0.34 kg, respectively. The hardness of the mini tablets was found to vary from 1.5 to 2.5 kg indicating that they possessed sufficient mechanical strength to withstand further processing including the acrylic film coating process in the conventional coating pan. The presence of optimum amounts of moisture (2-3% w/w) and PVP K30 in the in the precompressed granules were the contributing factors for the low friability and good hardness of the core mini tablets[13].

TABLE 2: THE PHYSICAL PROPERTIES OF THE CORE MINI TABLETS CONTAINING THEOPHYLLINE

Physical properties	Mean±SD
Weight[a] (mg)	25.20±0.93
Thickness[b] (mm)	1.49±0.04
Hardness[b] (kg)	1.85±0.34
Friability[a] (%)	0.059±0.02
Disintegration time[c] (min)	5.00±0.17
Drug content[b] (mg)	10.00±0.13

The values represent mean±SD of [a]n=20, [b]n=10 and [c]n=6

The core mini tablets passed the disintegration test for uncoated tablets as they were found to disintegrate in 5.00±0.17 min. The quick disintegrating time of the core mini tablet can be attributed to the presence of the super disintegrant SSG in optimum concentration in the formulae.

The batch of the core mini tablets was found to pass the weight variation test with an average tablet weight of 25.20±0.93 mg. The core mini tablets passed the content uniformity test with an average assay value of 10.00±0.13 mg. The uniformity in content could be related to the low weight variation of the core tablets which could be due to the narrow size distribution and free flowing nature of the pre compressed granules. The core mini tablets showed no signs of sticking or binding during compression.

Eudragit S-100 is a pH sensitive polymer having a threshold pH of 7.0 which has been designed to deliver the drug to the colon exploiting the change in the physiological pH of the gastrointestinal tract. A non-aqueous acrylic coating procedure was adopted to apply the pH sensitive polymeric coating on the drug loaded mini tablets. Isopropyl alcohol was used as a solvent for the coating dispersion considering its high flash point (15°), low boiling point (82.3°), low heat of evaporation (667 J/g) and low risk of toxicity[18]. Talc was incorporated at a concentration of 50% w/w of the polymer as it is reported to reduce the porosity of the acrylic film coatings and lower their water permeability. Talc reduces the stickiness of the coating by forming lattice structures as these particles are easily embedded in the polymer layers significantly reducing the sticking during the film forming process. Since, Eudragit S is a brittle polymer, triethyl citrate was used at a concentration of 10% w/w of the polymer dry weight to lower the glass transition temperature and promote formation of a good elastic film. Since, triethyl citrate was a hydrophilic plasticizer; water was incorporated (5% w/w) to the spray dispersion to avoid phase separation between the polymer and plasticizer during film formation. The coating dispersion was sufficiently diluted to have 6.00% w/w of the dry

polymer content with the intention to overcome any possible formation of aggregates during the pan coating process.

As higher temperatures stimulate sticking due to the softening tendencies of the polymer, the bed temperature was maintained close to room temperature or slightly higher (35-40°) using an infra red lamp. With the aim to get fine spray droplets the spray nozzle of 1 mm was used at an atomization air pressure of 4 kg/cm^2. The sticking tendency of the mini tablets was overcome by setting the pan rotation speed to 20 rpm and empirically controlling the spray dispersion application rate. The coating dispersion flow during the coating process was continuous with no spray system blocking during the process.

The surface morphology and cross sectional view of the coated mini tablet (T_4) as revealed by scanning electron microscopy are shown in figs. 1a and 1b, respectively. The coated surface free from cracks or pores was visualized under high magnification (2000 X). The cross sectional of the coated minitablets revealed a distinct, continuous and dense coat measuring approximately 75 µm in thickness. An acrylic coat thickness of about 30-50 µm is reported to be sufficient to provide excellent resistance to the gastric fluid[19].

The properties of the coated minitablets are portrayed in Table 3. The average tablet weight for the coated mini tablets T_1, T_2, T_3 and T_4 were found to be 26.56, 27.84, 29.07 and 30.51 mg respectively. The tablet weight variation was found below 2% for different batches of coated tablets. The percent practical weight gain calculated from the average tablet weight was found to be 5.40, 10.48, 15.36 and 21.07 for T_1, T_2, T_3 and T_4, respectively.

The mean thickness of the coated mini tablets was found to be 1.52, 1.56, 1.60 and 1.64 mm for T_1, T_2, T_3 and T_4, respectively. The tablet thickness of the coated mini tablets increased with the increase in the coat weights applied. The percentage increase in the tablet thickness was found to be 2.01, 4.70, 7.38 and 10.07% for T_1, T_2, T_3, and T_4, respectively.

All the batches of the coated tablets passed the disintegration test for enteric-coated tablets. The mini tablets tested remained intact in pH 1.2 for a period of 1 h showing no signs of cracks or fracture. Same tablets disintegrated within 40 min in pH 7.5. The disintegration time for the coated mini tablets in pH 7.5 are portrayed in Table 3. The disintegration time in pH 7.5 was found to increase with increase in the percent weight gain. The integrity of the coated mini tablets in pH 1.2 could be

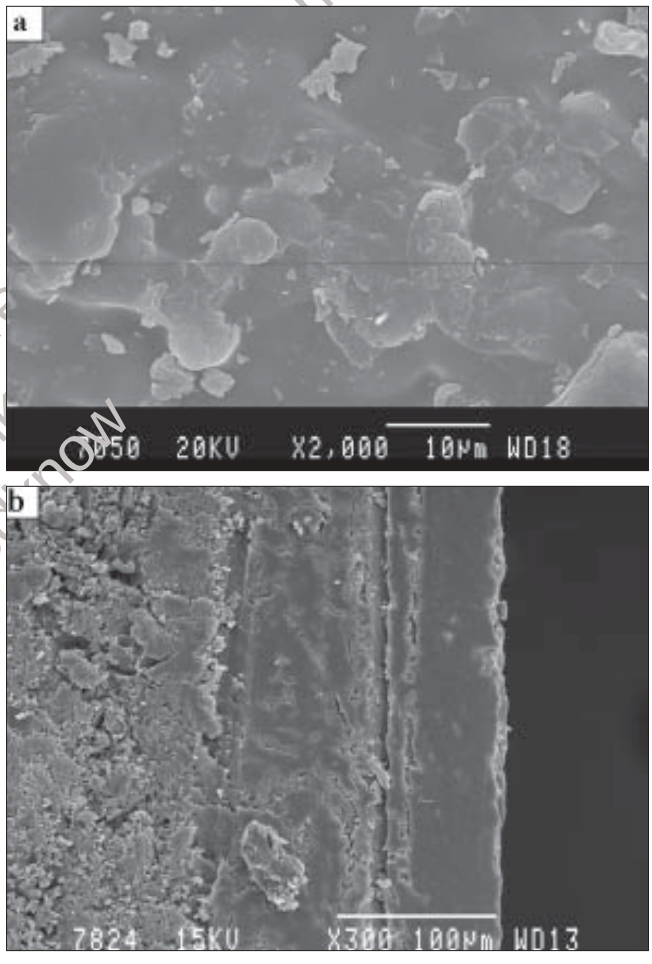

Fig. 1: SEM Photomicrographs.
Surface morphology (a) and cross sectional view (b) of Eudragit S coated minitablets containing anhydrous theophylline as revealed by scanning electron microscopy

TABLE 3: THE PHYSICAL PROPERTIES OF THE ACRLIC FILM COATED MINI TABLETS CONTAINING THEOPHYLLINE

Batch code	Weight[a] (mg)	% weight gain	Thickness[b] (mm)	D. T.[c] (pH 1.2)	D. T.[c] (min) (pH 7.5)
T_1	26.56±1.60	5.40	1.52±0.07	Intact	12′ 32″±34″
T_2	27.84±1.62	10.48	1.56±0.06	Intact	28′42″±1′27″
T_3	29.07±1.54	15.36	1.60±0.06	Intact	31′ 52″±1′ 21″
T_4	30.51±1.15	21.07	1.64±0.06	Intact	36′ 32″±1′30″

The values represent mean±SD of [a]n=20, [b]n=10 and [c]n=6

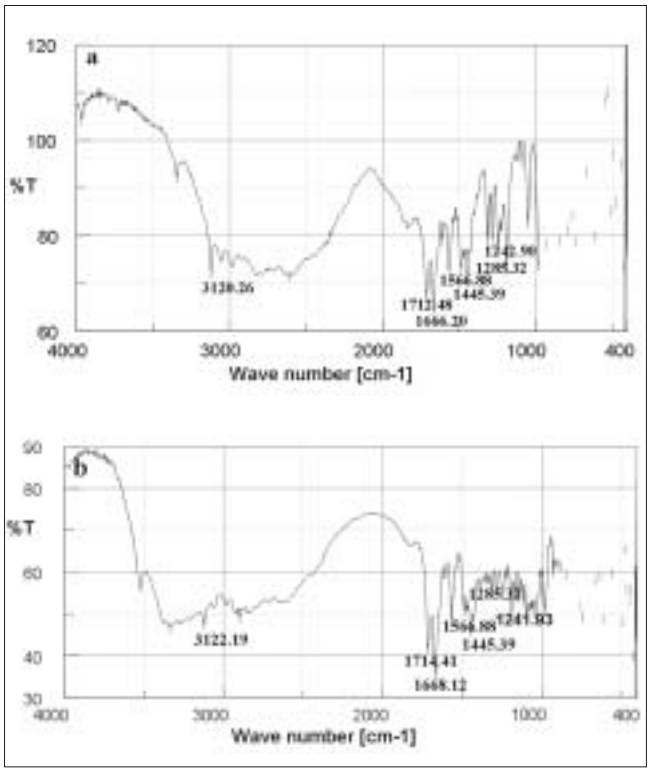

Fig. 2: IR Spectra.
IR Spectra of theophylline (a) and coated theophylline mini tablets (b)

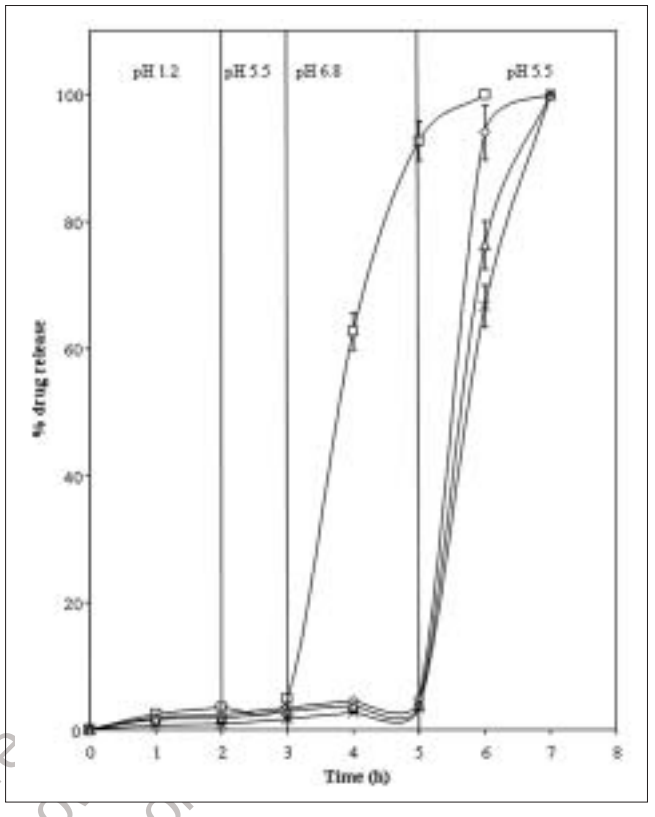

Fig. 3: *In vitro* release of theophylline from Eudragit S coated mini tablets following pH progression method.
Release profiles of theophylline from Eudragit S coated mini tablets T_1 (X), T_2 (△), T_3 (◇) and T_4 (□). Each point represents mean of three determinations

ascribed to the threshold pH of Eudragit S. It was observed that the disintegration time in pH 7.5 was found to increase with increase in the coat thickness or coat weights applied.

The IR spectra of the anhydrous theophylline and the coated mini tablets of theophylline are portrayed in figs. 2a and 2b respectively. The IR spectrum of the coated mini tablets depicts the characteristic peaks of theophylline at 3122.19 cm^{-1} (NH stretching), 1714.41 cm^{-1} (C=O stretching), 1668.12 cm^{-1} (C=C stretching), 1566.88 cm^{-1} (C=N stretching), 1445.39 cm^{-1} (C-H bending), 1285.32 cm^{-1} (C-N vibration), 1241.93 cm^{-1} (C-O vibration). These observations ruled out possible chemical interaction between theophylline and other excipients used.

The dissolution profiles of the coated mini tablets with different weight gains are displayed in fig. 3. The *in vitro* release studies were performed by pH progression method during which the pH of the medium was gradually increased to determine the influence of pH of the dissolution medium on drug release. It was noticed during the study that the drug release from coated mini tablets depended on coat weights applied as well as the pH of the dissolution medium. In case of tablets T_1, it was observed that coated tablets showed a limited drug release during the first three hours in pH 1.2 and 5.5 (4.88±0.26%). However the coated tablets failed to have any control on drug release in pH 6.8, as a rapid release phase was observed during which the tablets released most of their contents in two hours of dissolution in pH 6.8. It was noticed that the enteric effect of acrylic polymer was absent at pH 6.8 which could be due to the limited thickness of the acrylic coat corresponding to 5.40% weight gain.

The study revealed the fact that mini tablets T_2, T_3 and T_4 exhibited an excellent gastro-resistant and entero-soluble property. The tablets T_2 released 4.80±2.01% of the drug during the first five hours of dissolution in pH less than 7.0 which can be ascribed to the gastro resistant nature of Eudragit S 100 at the coat weight applied (10.48% weight gain). A pulsed release preceded the slow release phase during which the tablets released the entire drug within 2 h of dissolution in pH 7.5 which can be due to the threshold pH of Eudragit S 100 (7.0)[19] and the high drug solubility.

The tablets T_3 and T_4 released 3.92±0.2% and 3.42±0.17% of the drug, respectively during the first 5 h of dissolution.

The slow release was followed by pulsed drug release during which the entire drug was released in 2 h in pH 7.5. The studies showed that the gastro-resistant property of Eudragit S-100 became more pronounced with increase in the acrylic film thickness. A burst effect was clearly evident with these formulations at pH 7.5 which can be attributed to the enterosoluble nature of Eudragit S-100 as well as the high drug solubility in pH 7.5.

The results collectively indicate that tablet compression and pan coating can be employed to successfully develop a colon specific drug delivery system using a pH sensitive polymer. A coat weight of 10% w.g was just sufficient to impart an excellent gastro resistant property to the tablets and effectively release the drug at higher pH values. The pulsed release observed in most cases is highly desirable to target the nocturnal peak symptoms of asthma upon an evening administration of the multiunit system.

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