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Formulation and evaluation sustain Release Tablets Theophylline

K. P. Sampath Kumar[1,*] and Debjit Bhowmik[2]

[1]Department of Pharmaceutical Sciences, Coimbatore Medical College, Coimbatore- 641 014.

[2]Nimra College of Pharmacy, Vijayawada, Andhra Pradesh.

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ABSTRACT

Colon is an ideal site for delivering drugs for both systemic and local action. The aim of the study is to formulate a sustained release tablet dosage form for theophylline, which is used for treating nocturnal asthma. Theophylline tablets were prepared by direct compression method and coated with Eudragit S100 and HPMC inorder to avoid the drug release in the upper gastro intestinal tract. Tablets were characterized by the following parameters like hardness, friability, film property, weight variation, uniformity of drug content and *in vitro* dissolution studies were performed by half dilution method. The coated tablets remain intact drug release up to 5 hours. An accelerated stability study was carried out at ambient condition and 45ºC with 75% relative humidity. In conclusion the coated theophylline tablets was found to be better alternate for the conventional tablets to release the drug in the mid night and early in the morning which is desirable features for treating nocturnal asthma.

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Introduction

Drug targeting at a specific site is one of the innovative approaches by reducing quantity of drug and minimizing the systemic side effects. Now days, colonic drug delivery via oral convenient route has got great attention as many drugs have been delivered successfully to specific site for treating colonic disease such as ulcerative colitis, irritable bowel disease, Crohn's disease and carcinomas.. Colon is an ideal site for those delivering drugs for both local as well as systemic action . It has being investigated as a potential site for delivery of proteins and peptides and other drugs such as nifedipine, theophylline, isosorbide etc . The colon is an attracting interest as a site, where poorly absorbed drug molecules have better bioavailability . Additionally, it has a longer retention time than other oral sites and it offers a near neutral pH, reduced in the presence of digestive enzymes . The pH-dependent systems exploit the generally accepted view that pH of the human gastrointestinal (GI) tract increases progressively from the stomach (pH 2–3), small intestine (pH 6.5–7) to the colon (7.0–8.0) . Taking advantage of the highest pH value of the colon content, the dosage form containing the active drug in a core is coated with pH-dependent material which dissolves at the specific pH of the colon. But recent studies using sensitive and reliable equipments contradict the traditional view and provide evidence of a fall in pH at the GI region between ileum and colon. Apparently, the colon has a lower pH value (6.5) than the small intestine (7.0–7.8), and the jejunal region of some individuals has a higher pH (range 6.1–7.2) than the small intestine or colon of other individuals . Accordingly, high individual variability in physiological pH of the GI tract is a matter for concern. In fact, in a recent in vitro study, demonstrated that coating with a pH-dependent polymer Eudragit™ S100) would result in either delivery of the drug at the duodenum, or not at all, depending on individual pH variability of the GI tract . It is one of the successive methods to achieve better targeting drugs to colon, so the prepared formulations have remain intact the release in stomach and gastrointestinal tract (GIT), which deliver at cecum of the large intestine. This preferred colonic site may be useful in treatment of diseases susceptible to diurnal rhythm such as asthma, arthritis or inflammation etc. An ideal formulation may deliver slowly or longer release rate have been absorbed successfully to the specific site of colon. However, the different coated dosage forms, especially the enteric coated dosage forms are more popular for targeting drugs to the colon . The pH sensitive enteric polymers play a major role to deliver the drugs to the specific pH environment and it protects the drug or formulation in the hostile environments . The dosage forms were present in longer time in different fluid environment, the incorporated drug which may diffuse by means of penetration. So the swelling polymer hydroxy propyl methyl cellulose (HPMC) coating may be protected the drug diffusion in the hostile environment. Most of the multilayer coated tablet, capsules , pellets and granules were reported for colon targeting drug delivery systems.

Theophylline was reported many literature as an anti-asthmatic drug. Nocturnal asthma causes severe breathing problems in the time between the mid-night and the early morning. Hence, once in daily dose tablet would be highly useful as they maintain the drug level through out the specific time and also improve patient compliance. Theophylline has been used as one of a drug of choice for treating nocturnal asthma, which had apparent circadian rhythms and peak symptoms in the early morning . The aim of this present work was to assess the suitability of such an approach for achieving better targeting delivery of theophylline at colon, by using protective polymers coating. Hence, the prepared theophylline coated tablets were found to be better release at the time of mid-night and early in the morning which is desirable features for treating nocturnal asthma.

Materials and Methods

Materials

Theophylline was purchased from Sigma chemicals, USA. Eudragit™ S100 was purchased from Germany, Poly vinyl pyrrolidine (PVP-K30), HPMC were received as a gift from Cassel research laboratories ltd, Chennai, Acetone, and ethanol and hydrochloric acid were procured from Nice chemicals, Mumbai. Trisodium orthophosphate was purchased from

Tele:

E-mail addresses: drkpsampathkumar@gmail.com

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S.D.Fine Chemicals, Mumbai. All other chemicals used were in analytical grade.

Methods

Preformulation study

This was done to find out the possible interaction between the selected drug Theophylline and polyvinyl pyrrolidine (PVP-K30) and Eudragit™ S100 polymer. Briefly, the small quantity of drug, physical mixture of drug-Eudragit™ S100 and drug-PVP-K30 were taken triturated separately with 400 mg of potassium bromide. Each triturated sample was taken in to pellet marker, compressed at 10kg/cm² using hydraulic press and the pellets were scanned from 4000 cm^{-1} to 400 cm^{-1} in Perkin Elmer FT-IR Spectrophotometer. The obtained spectra were interpreted and compared with standard spectra.

Preparation of theophylline compressed tablets

The theophylline compressed tablets were prepared by direct compression by using Poly vinyl pyrrolidine (PVP-K30) as main filler and different proportions starch 1500 (F1-0%, F2-10%, F-20% and F4-30%) were added as disintegrant. Other manufacturing excipients such as talc 2% and magnesium stearate 1% (shown in tab.1) were also added and thoroughly mixed with Kalwaga mini cube mixer. An ideal mixture was directly punched in to tablets weighing about 250 mg containing 100 mg of theophylline, at 12 g/min flow rate; which were compressed in Rimach mini press-I, 10 station single rotary tablet punching machine, using 6 mm diameter concave punches and a compression force of 500-600 kg/cm².

The different batches of compressed theophylline tablets were tested for hardness by Monsanto hardness tester; weight variations by standard method, friability was carried out by Rochi friabilator, disintegration time and uniformity of drug content were done as per pharmacopoeial standard specifications.

Preparation of coating solutions

Solution-I

Coating solution was prepared by simple solution method . Coating solution-I was prepared by dissolving 6% w/w of Eudragit™ S100 as an enteric polymer, 2.6% w/w of titanium dioxide as opacifier, 2% diethyl phthalate as plasticizer and acetone and isopropyl alcohol mixture was used as solvent. Titanium dioxide was triturated in a glass mortar with small amount of solvent mixture and filtered through muslin cloth in to the polymer solution already prepared with half parts of solvent acetone and isopropyl alcohol mixture. Diethyl phthalate was added and made up the volume with rest of the solvent mixture (tab: 2); this mixture was constantly stirred for one hr with 3 paddle mechanical Remi stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a clear coating solution was obtained (Table.no: 3).

Solution-II

Coating solution-II was prepared by dissolving 6.5% of HPMC as an enteric polymer, Titanium dioxide as opacifier, amaranth as colorant; Poly ethylene glycol 400(PEG 400) as plasticizer and Purified water was used as an aqueous solvent. This mixture was constantly stirred for one hr with 3 paddle mechanical Remi stirrer at the rate of 1000 rpm; the stirred coating solution was again filtered through muslin cloth, a clear coating solution was obtained (Table.no: 3).

The physicochemical evaluations such as film thickness, film weight and film solubility were also carried out from the same coating solutions.

Coating of theophylline compressed tablets

About 100 gm of compressed theophylline tablets were de-dusted and loaded in a 9 cm width fabricated mini stainless steel coating pan which was fixed on Kalwega VDM4 model apparatus; 30 rpm speed was maintained. The tablets loaded bed was pre-heated at 60°C. The prepared Eudragit™ S100 (6%w/w) coating solution was sprayed on the tablet bed; spray gun nozzle 0.52mm diameter, air pressure at 50 kg/cm², spray rate 1.5 ml/min and the hot air was applied inside coating pan at 40-60°C. The coating process was continued until the desired tablet coating weight was achieved. The coated tablets were kept in dehumidity chamber for 24 hrs, to prevent coating damage and studied for its standard evaluations such as weight variations, uniformity of drug content and *in vitro* dissolution study. Half parts of Eudragit™ S100 coated tablets were again coated with hydroxy propyl methyl cellulose (6.5% w/w) polymer solution for double layered tablets: inside pan temperature 90-100°C and other same parameters were followed in previous coating method. The double layer coated tablets were also kept in dehumidity chamber for 24 hrs and studied for its weight variations, uniformity of drug content and *in vitro* dissolution study.

Physicochemical evaluations of coating films

The polymeric films were prepared by casting the acetone-isopropyl alcohol (2:1) polymer solution onto the Teflon sheets mounted on a leveled glass plate (10X10 cm^2 area and total solid content 3gm). The films were dried for 24 h at room temperature under a special cover with reduced solvent evaporation to obtain smooth homogenous films. The dried films were peeled from the Teflon surface, cut into 1 X 1 cm^2 area. The prepared polymeric films were studied for film thickness, film weight and film solubility. The thickness of dry films determined in five positions with a thickness screw cage. The 1cm X 1cm coating films were selected and separately weighed the films by Sartorious-India digital balance; the average film weight was calculated.

The film solubility was studied with different pH medium such as pH 1.2, 3.0, 6.8 and 7.2. The 1 X 1 cm^2 coating film was selected, weighed and transferred in a beaker containing 20 ml of specified pH medium, which was mixed in a magnetic stirrer for 1 hr at 37˚C. Finally the films were collected, dried, weighed and film solubility was calculated.

Viscosity of the coating solutions

Both the prepared Eudragit™ S100 (6%w/w) and HPMC (6.5%w/w) coating solutions were studied the viscosity by Brookfield DV-II+ Viscometer.

Uniformity of drug content

20 theophylline tablets were weighed (coated and uncoated) and crushed as powder in a mortar and pestle. 50 mg equivalent of theophylline tablets crushed powder was weighed and transferred into conical flask containing 100 ml pH 6.8 buffer solutions. It was allowed to shake for 4 hrs and temperature was maintained at 37˚C. Finally, the samples were filtered (20 µm size Whattman filter paper) and centrifuged in Remi centrifuge at 4000 rpm for 30 minutes: a clear liquid was collected. The drug content was analyzed λ maximum at 271nm in Simadzu-Japan UV 160A Spectrophotometer and drug content was calculated.

In vitro dissolution study

This study was accomplished by half dilution method , with different transit time from stomach to colon, were carried out with different pH conditions (pH 1.2 for 2 hrs, pH 3.0 for 1 hr, pH 5.6 for 1 hr, pH 6.4 for 1 hr, pH 7.2 for 1 hr and pH 6.8 for up to 18 hrs) were maintained for the entire dissolution study. It was carried out by USP XXIII Type 2 (basket) method; 500 ml of pH 1.2 medium was initially used and different pH medium was maintained by the addition of another phosphate buffer

solutions (tab. no: 4) without stopping the process (without addition of any enzymes). The basket stirring rate at 75 rpm and the temperature was maintained at 37˚C. The 5ml of the sample was withdrawn from the dissolution media and same pH medium was replaced, the collected samples were centrifuged in Remi centrifuge at 4000 rpm for 30 minutes: a clear liquid was collected. The percentage drug releases were analyzed and calculated λ maximum at 271nm in Simadzu-Japan UV 160A Spectrophotometer.

Packing of Theophylline coated tablets

Prepared single and double layer coated tablets were packed in 0.30 mm thickness glossy poly vinyl chloride (PVC) foil and 0.09mm aluminum foil by Pharma equipment-India blister packing machine. The 10 mm concave mould drum, speed at 10 rpm, 90-100˚C vacuum air inlet a mould, sealing temperature 60˚C and 20 tablets/ blister was maintained during the packing process.

Stability Studies

The Theophylline tablet blisters were stored at different temperature such as ambient temperature (temperature in the working area) 20- 29º, at 35ºC±2 in an incubator and 45ºC and 75% relative humidity (RH). The storage conditions were selected to appropriate conditions of finished product. Stored samples were with drawn different time intervals such as 0, 15, 30, 45 and 90 days and evaluated for loss on drying and uniformity of drug content remaining. The loss on drying was studied by drying 1 gram of crushed tablets powder at 60ºC for 4 hrs in vacuum using a pre-dried (60º for 30 min) petridish. The sample was kept in a desiccator to attain room temperature. The percentage loss was calculated. The uniformity of drug content was evaluated periodically using sample size of 10 tablets. The percentage theophylline content remained on 15, 30, 45 and 90 days were calculated taking the theophylline content 100% on initial day (0 day). The percentage drug content remaining of theophylline was analyzed and calculated as per the procedure followed in uniformity of drug content. The percentage theophylline remaining of prepared formulations are given in tab.7.

Result and Discussion

Selection of tablets by direct compression method

Based on the Preformulation study from the IR spectral interpretation the polymers and excipients were selected. The IR-spectral interpretation did not give any interactions with drug and polymer**.**

The theophylline tablets with polyvinyl pyrrolidine as main filler as well as sustaining pharmaceutical material and starch 1500 (0%, 10%, 20% and 30%) as disintegrating agent. The manufacturing excipients such as talc and magnesium stearate (shown in tab. 1) and which had been directly compressed into theophylline tablets. All the formulated theophylline uncoated tablets (TF1, TF2, TF3 and TF4) were subjected to various physicochemical parameters. The hardness of the prepared compressed tablets ranges from 6.1±0.91to 6.5±0.56 kg/cm² tested by Monsanto harness tester; friability 0.091 ±0.51 to 0.109 ±0.91 was done by Rochi friabilator and weight variation was found the ranges from 2.86 to 3.34. All the results were compared with pharmacopoeial standards and comply within the limits. Uniformity of drug content of the prepared theophylline compressed tablets was done by using pH 6.8 phosphate buffer at 37ºC and the percentage drug content were 98.26 ±1.9% (TF-I), 96.93±1.21 (TF-2), 97.99±1.17(TF-3) and 98.08±1.93 (TF-4).

Effect of single layer enteric polymer coating of theophylline tablets

Since the drug targeting at the colonic environment was achieved by means of pH sensitive protective coating with Eudragit™ S100 polymer by simple pan coating method. The core tablets of theophylline were found the release from the acidic media to colonic medium by mimicking the release up to 8-12 hrs. But an enteric polymer Eudragit™ S100 single layer coated tablets which maximum remain intact the release up to 5 hrs but the administered tablets were protected for prolong period in different fluid hostile environment. So the drug theophylline was slightly diffused by means of drug penetration at the biological fluids environment.

Effect of both enteric and swelling polymers coating of theophylline tablets

The in vitro simultaneous release profiles of both enteric polymer Eudragit™ S100 and swelling polymer HPMC coated theophylline tablets are shown in fig. 3.The drug release showed in maximum release at the alkaline pH medium used. The in vitro release profile of double layer coated theophylline tablets were found to remain intact the drug release up to 5 hrs, so the coated drug formulation was completely protected from the hostile environment by means of protective double layer polymers coating.

Effect of the physicochemical parameters of prepared coating solutions

In order to test the parameter of physicochemical evolution of coating solution-I (Eudragit™ S100) and coating solution-II (HPMC) were studied in different parameters such as film weight, film thickness and film solubility, which were depicted in tab. 5. Both the tablet coating solutions were done by simple procedures and usual our standard laboratory techniques. The effect of physicochemical parameters such as film weight, film thickness and film solubility were also affected the release profile of the prepared formulations. The solubility of the prepared film should soluble in the specific pH medium, the high film thickness and weight of the coated film also varies the solubility of the film. The enteric polymer Eudragit™ S100 films were found to completely soluble in pH 7.2, sparingly soluble in pH 6.8 and insoluble in pH 1.2, 3.0, 5.6 and 6.4. The HPMC polymer film was slowly soluble in all pH medium. The physicochemical properties of the films are shown in tab. 5.

Choice of in vitro dissolution by half dilution method

The *in vitro* dissolution studies of the core tablets, single Eudragit™ S100 coated tablets and Eudragit™ S100 as well as HPMC double layer coated theophylline tablets were done by half dilution method. The core theophylline tablets showed better sustained release from acidic fluid medium to colonic fluid medium between 10 to 18 hrs (pH 1.2 for 2 hrs, pH 3.0 for 1 hr, pH 5.6 for 1 hr, pH 6.4 for 1 hr, pH 7.2 for 1 hr and pH 6.8 for up to 18 hrs). The above said prepared tablets had different ratios of starch (TF1-0%, TF2-10%, TF-20% and TF4-30%) as disintegrating agent. F4 uncoated tablets had the 30% of starch which was comparatively found more release than other formulations and it was showed maximum release 98.34% within 14 hrs and F1 uncoated tablet was formulated without any starch and it was showed better sustained drug delivery and reported the release 62% up to 18 hrs (Fig:1). However, the 20% and 30% starch contents of compressed theophylline tablets were found to be better release than other batches but the 0% and 10% starch contained tablets were found sustained release at the colonic environment.

Table 1. Formula for compressed theophylline tablets

S. No	Ingredients used	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
1	Theophylline	100	100	100	100
2	PVP-K30	130	105	80	55
3	Starch	0	25	50	75
4	Talc	10	10	10	10
5	Magnesium stearate	10	10	10	10

Table 2. Evaluations of compressed tablets

Formulations	Hardness	Weight variation	Friability	Tablet weight gain	% drug content
F-1	6.5±0.56	±2.86	0.039	-	98.31(1.10)
F-2	6.7±0.71	±2.92	0.051	-	96.93(1.21)
F-3	6.1±0.91	±3.34	0.109	-	97.99(1.17)
F-4	6.3±0.53	±2.93	0.132	-	98.08(1.93)
F-5	-	±3.01	-	4.98	98.39(2.01)
F-6	-	±2.82	-	5.21	97.01(1.65)
F-7	-	±3.09	-	5.01	98.11(2.21)
F-8	-	±3.12	-	5.19	98.00(1.89)
F-9	-	±3.09	-	10.31	98.26(1.26)
F10	-	±2.99	-	9.98	97.21(1.79)
F-11	-	±3.12	-	10.09	98.21(1.55)
F-12	-	±3.01	-	10.28	98.09(2.16)

Table 3. Composition for coating solutions

Coating solution formula- I		Coating solution formula- II	
Ingredients	**Quantity (% w/w)**	**Ingredients**	**Quantity (% w/w)**
Eudragit S100	6.0	HPMC	6.5
Titanium dioxide	2.6	Titanium dioxide	2.6
Diethyl phthalate	2.0	Amaranth	2.6
Acetone	59.4	PEG 400	2.9
Isopropyl alcohol	30.0	Purified water	85.4

Table 4. In vitro dissolution by half dilution method

Time in hrs	0-2	2-3	3-4	4-5	5-6	6-24
Half of dissolution media replaced with buffer	-	6.0	6.0	7.6	7.6	6.0
pH of the dissolution media obtained during the process	1.2	3.0	5.4	6.4	7.2	6.8

Table 5. physicochemical evaluations of Eudragit S100 and HPMC coating films

Film thickness (mm)		Film weight in g (1cmX1cm)		Film solubility at 37º C		
Eudragit S100	**HPMC**	**Eudragit S100**	**HPMC**	**pH used**	**Eudragit S100**	**HPMC**
0.39	0.46	0.109	0.136	1.2	Insoluble	Soluble
0.38	0.46	0.098	0.135	3.0	Insoluble	Soluble
0.38	0.47	0.099	0.141	5.6	Insoluble	Soluble
0.37	0.45	0.098	0.139	6.4	Insoluble	Soluble
0.38	0.46	0.100	0.137	7.2	Soluble	Soluble
0.38	0.47	0.102	0.138	6.8	Sparingly soluble	Soluble

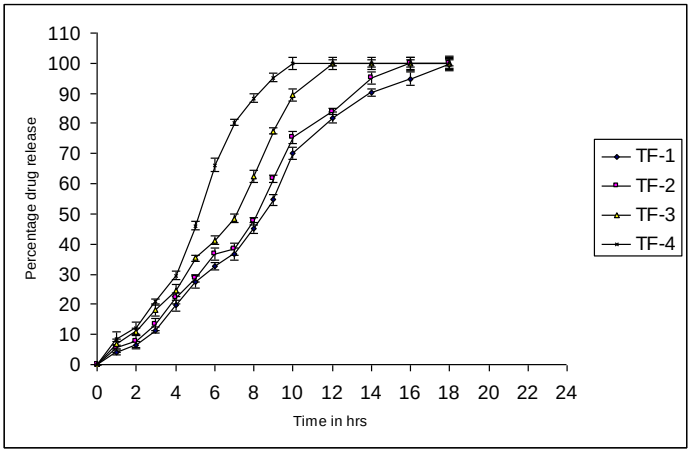

Fig 1. Shows in vitro release profiles of theophylline compressed tablets by dissolution-half dilution method. TF-1 (0% starch), TF-2 (10% starch), TF-3 (20% starch) and TF-4 (30% starch).

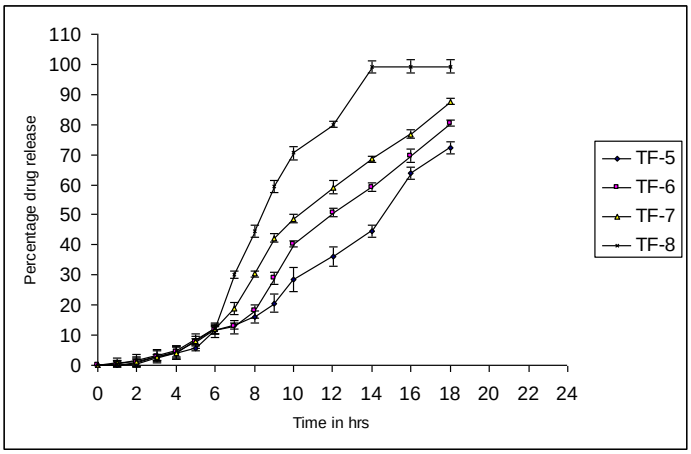

Fig 2. show in vitro release profiles of Eudragit S100 coated theophylline tablets by dissolution-half dilution method. TF-5 (0% starch), TF-6 (10% starch), TF-7 (20% starch) and TF-8 (30% starch).

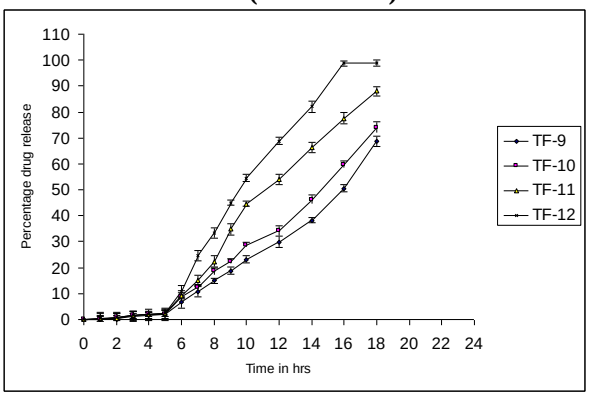

Fig 3. show in vitro release profiles of Eudragit S100 as well as HPMC double layer coated theophylline tablets by dissolution-half dilution method. TF-9 (0% starch), TF-10 (10% starch), TF-11 (20% starch) and TF-12 (30% starch).

Eudragit™ S100 coated tablets and Eudragit™ S100 as well as HPMC double layer tablets were almost showed remain intact their release up to 5 hrs and maximum release started from a pH 7.2 and 6 hr again changed to pH 6.8 colonic fluid medium without any enzymes, the release was carried up to 18 hrs.The Eudragit™ S100 coated theophylline tablets (TF5, TF6, TF7and TF8and Eudragit™ S100 as well as HPMC double layer coated tablets (TF9, TF10, TF11 and TF12) were also studied its *in vitro* dissolution by same half dilution method and released were found in 5 to 7% (Fig: 2) and less than 1-3% (Fig: 3) up to 5hrs respectively, without any coating damage. The Eudragit™ S100 coated theophylline tablets were found more drug diffusion in presence of different fluid environment before 5 hrs. But the Eudragit™ S100 as well as HPMC double layer tablets were highly protected from the fluid environment by means of swelleble HPMC coating polymer. The maximum drug release started at pH 7.2 (5hr), sustained release was showed from 6 hr at pH 6.8 (colonic fluid medium without any enzymes) for more than 18 hrs. . The Eudragit™ S100 coated theophylline tablets were found the release of TF5=72.35, TF6=80.34 TF7=87.58 and TF8=99.32 and Eudragit™ S100 as well as HPMC double layer coated tablets were found the release of TF9=68.73 TF10=73.94, TF11=88.04 and TF12=98.86. Hence, once a daily theophylline coated tablet to be taken at 6 pm or after the dinner at 9 pm, which will expected the release start at the time between mid might and early morning. So the selected theophylline coated tablets were found to be better release at the time of mid-night and early in the morning which is desirable features for treating nocturnal asthma.

Effect of packaging and stability studies

Generally all the prepared coated theophylline tablets were blister packed in polyvinyl chloride foils with aluminium foil as per the marketed formulation standard. The different storage conditions were selected to appropriate conditions of finished products. The temperatures such as ambient temperature (AT), 35ºC (controlled temperature and 45ºC and 75% relative humidity conditions, which was stored the preparations and tested for its loss on drying and percentage drug content periodically at 0, 15, 30, 45 and 90 days. The losses on drying and percentage drug contents are depicted in tab. 6 and tab. 7 respectively. Based on the loss on drying report was found minimum moisture content in storage conditions of AT and 35ºC. The maximum moisture was absorbed in 45ºC and 75% relative humidity condition due to the moisture penetrates through the packaging material and coating material. The percentage drug content of the stored formulations were found very less loss was showed in AT and 35ºCb and maximum drug loss was showed in 45ºC and 75% relative humidity due to the high temperature and high humidity condition.

Conclusion

The prepared theophylline coated formulations are able to achieve the drug delivery targeting at colon followed by oral administration, and provide a promising strategy to control drug release targeting the desired lower gastrointestinal region. So the selected theophylline coated tablets were found to be better release at the time of mid-night and early in the morning which is desirable features for treating nocturnal asthma.

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