Research Article

PREPARATION AND COMPARATIVE CHARACTERIZATION OF DRUG RELEASE FROM TWO DIFFERENT CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS OF SALBUTOMOL FOR NOCTURNAL ASTHMA

Papola Vibhooti * **Rajan G, Bisht Seema, Kothiyal Preeti**

Shri Guru Ram Rai Institute of Technology & Sciences Dehradun, Uttarakhand, India

*Corresponding Author: Email papola.vibhooti@gmail.com

ABSTRACT

Coating with pH dependent polymers,based on the metabolic activity of colonic bacteria. Colonic bacteria degraded the prodrugs and polysaccharides enzymatically and then the drug releases into the colon. Previously several polysaccharides have been reported as carriers to colon-specific drug delivery. Oral compression coated tablets (CCT) compose of an inner solid core that contains an active pharmaceutical ingredient and any other pharmaceutically acceptable carriers or excipients which is substantially covered with an outer layer that dissolves or disintegrates slowly to produce the pre-determined lag time. The advantage of this manufacturing technique is that it is simple, inexpensive and it is not hazardous to the environment since it does not require the use of high amounts of organic solvents. ***Purpose****:* a) The aim of the present study was to to check the effect of chitosan on drug release and targeting it in colon by using the principle of compressed coat. b) Effect of Coating with ph independent polymer eudragit S100 on release in colon area. ***Method:*** a) Compression coated tablets of Sallbutamol were prepared by wet granulation method using chitosan and b) coating of core tablet with Eudragit S100 .

Keywords: Preparation and Comparative characterization of drug release from two different chronotherapeutic drug delivery systems of salbutomol for nocturnal asthma.

INTRODUCTION

Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety, and efficacy. These days, drug delivery companies are engaged in the development of multiple platform technologies to get competitive advantage, extend patent life, and increase market share of their products. Although the small intestine is the primary site for drug absorption and is therefore a preferred area of the GI tract to target with various controlled-release technologies, considerable interest has been shown in the past few years in **colon** targeting of drugs. The main reasons for this interest are the reduced proteolytic activity in the colon, which may be advantageous in targeting certain drugs. The pH-controlled release coatings that are insoluble at the lower pH of the stomach and dissolve in the lumen of the small intestine. To achieve release in the colon, the start of the drug release is controlled by increasing the thickness of the coating, allowing a pH- and time controlled polymer dissolution and drug release. These pH-sensitive enteric polymers dissolve in a pH between 6 and 7 and thus release the drug as soon as the pH of the intestine reaches 6 or 7. Some of these enteric polymers are cellulose acetate phthalate, HPMC phthalate, and Eudragit L and S.

Time-controlled release coating in which the lag time depends upon coating thickness and drug release can be accomplished by changes in osmotic pressure or disruption of the coating by swelling of the core. A review of the chronobiology of asthma highlighted that airway resistance, broncho constriction, exacerbation of symptoms and

worsening of lung function, increase progressively at night. It has been reported that risk of asthma attacks is 100 fold greater during the night time hours (around 2.00 am) than during other times of day, an observation which has nicely been confirmed in modern epidemiologic studies in asthmatic patient.

Press-coated systems: Delayed-release and intermittent-release formulations can be achieved by press coating. Press coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. Materials such as hydrophilic cellulose derivatives can be used and compression is easy on a laboratory scale.

Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and COPD. It is 29 times more selective for beta2 receptors than beta1 receptors giving it higher specificity for pulmonary beta receptors versus beta1-adrenergic receptors located in the heart. Salbutamol is generally used for acute episodes of bronchospasm caused by bronchial asthma, chronic bronchitis and other chronic broncho pulmonary disorders such as chronic obstructive pulmonary disorder (COPD). It is also used prophylactically for exercise-induced asthma.

Material and methods:- Salbutamol was obtained from Windlas pharmaceuticals,Dehradun,India . Chitosan was purchased from Alembic Pharma, Baroda, India. Eudragit S100 , Avicel ph 101 (micro crystalline cellulose), cross carmellose sodium, povidone K30, magnesium state, ethanol, ammonia,tri ethyl citrate, tween were obtained from Central Drug House Pvt. Ltd., New Delhi .

The **instruments** used were as follows: Dissolution test apparatus (Tablet Dissolution Tester USP TDT -06P , paddle), Disintegration test apparatus (Tablet Disintegration Tester Machine (I.P. STD, India), FT-IR Spectrometer (Perkin Elmer Spectrophotometer), UV- Visible Spectrophotometer (ELICO SL210 Double beam) , Hot Air Oven (HICON THERMOSTAT oven memert type), Digital weighing balance (SHIMADZU), Tablet compression machine (I.P/B.P/U.S.P. standard) 12 Station (Karnavati Engineering, Ahmedabad, India), Hardness tester (Monosanto), Friability tester (digital friability tester HICON grover enterprises India), Hydraulic pellet press (Type KP SR.No.1363).

Spectroscopic studies:

a)   FT-Infrared spectroscopy:

Infrared spectroscopy were taken by using KBr pellets technique using a Perkin Elmer Spectrophotometer in the wavelength region of 4000 to 400 cm^{-1}.10 mg of the sample and 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at 10 kg/cm2 using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm-1 to 400 cm-1 in Shimadzu FT-IR spectrophotometer. Samples were prepared for drug ibuprofen, polymer chitosan, and physical mixture of drug and polymer. The spectra obtained were compared and interpreted for the functional group peaks.

b)   U.V Spectroscopy in different medium (acidic, basic, and water)

The standard stock solution was prepared by dissolving Salbutamol in 0.1N HCl , 6.8 ph buffer and in purified water separately to make final concentration of 200µg/ml. Different aliquots were taken from stock solution and diluted with different media separately to prepare series of concentrations from 10-80 µg/ml. The λmax was found by UV spectrum of Salbutamol in 0.1NHCl 6.8 pH buffer and

Table No.1 Linearity of Salbutamol in different media

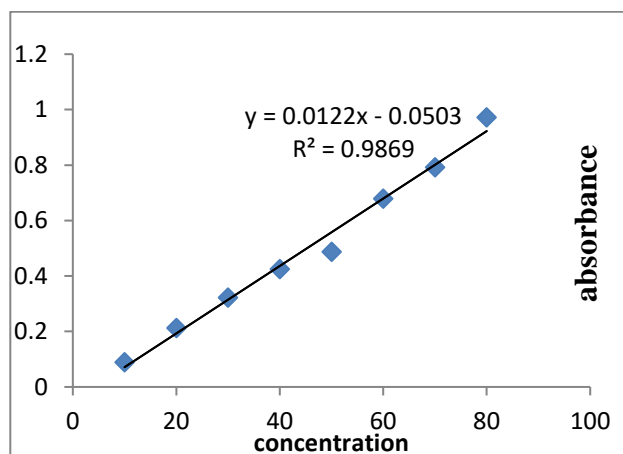| Salbutamol Conc. (µg/ml)	UV Absorption in different media		
	Water	0.1 N HCl pH 1.2	Phosphate Buffer pH 6.8
0	0	0	0
10	0.0651	0.0881	0.1845
20	0.0714	0.2119	0.2467
30	0.1237	0.3215	0.309
40	0.1727	0.4247	0.4119
50	0.1988	0.4872	0.5128
60	0.2294	0.6789	0.5737
70	0.2436	0.7915	0.75333
80	0.2833	0.9713	0.8722
R^2	**0.980**	**0.986**	**0.982**
Slope	**0.003**	**0.012**	**0.010**
Intercept	**0.016**	**- 0.050**	**-0.025**

Fig 1. Standard curve of salbutamol with hydrochloric acid
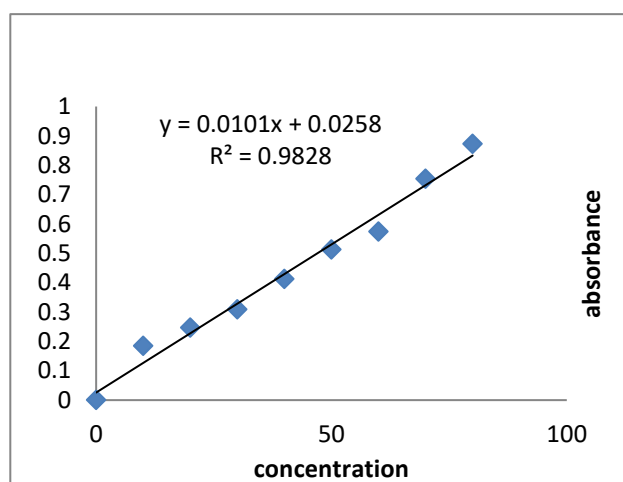

Fig 2. Standard calibration curve of salbutamol in phosphate buffer.
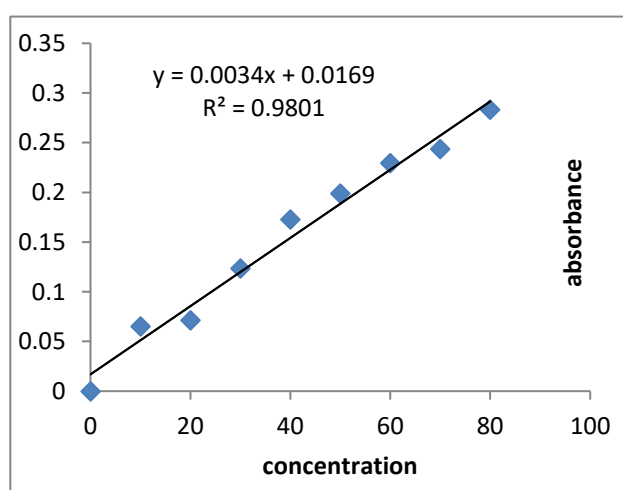

Fig 3. Standard calibration curve of salbutamol in Water.

purified water, in the range of 200-400 nm and it was found to be 276 nm. Absorbance was measured at 276 nm. The calibration curve was prepared by plotting absorbance versus concentration (μg/ml) of Salbutamol.

RESULTS AND DISCUSSION

Figures 1, 2, and 3 illustrate the linearity of the calibration curves of salbutamol in **distilled water, 0.1 N HCl**, and **phosphate buffer pH 7.4**, respectively, based on the data shown in Table (1). The linear regression equations parameters were very close with slope equal to **0.003** in the case of water , **0.012** in case of 0.1 N HCl and **0.010** in the case of phosphate buffer. The values of R^2 were almost similar in the three Medias and equal to **0.980, 0.986 and 0.982.**This is acceptable since salbutamol is known to exist as unionized in all over the GIT normal pH range (1-7.5).

METHODOLOGY

Preparation of salbutamol core tablets : Each core tablet (average weight **270** mg) for invitro drug release studies consisted of salbutamol as active material 200 mg, microcrystalline cellulose as diluents 53mg , crosscarmellose sodium as disintegrant 10mg , povidone K30 as binder 5 mg and magnesium stearate as lubricant 2mg. Initially, amounts of each content were weighed and sieved through 630 μm sieve. Except for magnesium stearate, they were transferred to a lab scale granulator, allowed for dry mixing for 5 minutes at medium speed, and granulated with sufficient quantity of water to get uniform soft granules. The resulted wet mass was immediately passed through 2500 μm sieve. The prepared granules were dried in lab scale fluid bed drier (FBD) with an inlet air temperature of 55°-60°C till the (loss on drying) LOD percentage reached around 4%. The dried granules were passed through 900μm sieve and lubricated with magnesium stearate for 5 minutes blending. The tablets were prepared by compressing the thoroughly mixed materials using 1.8cm round, flat and plain punches on a single station tablet machine. The thickness of the core tablet was 1.1cm mm and their crushing strength was checked. It was about 3 Kg/cm2.

Table no.2 Formula chart of core tablet

Ingredient	Mg/tablet	Function of ingredient
Salbutamol	200	Active material
Avicel ph 101	53	Diluents
Crosscarmellose sodium	10	Disintegrants
Povidone K30	5	Binder
Magnesium stearate	2	Lubricant
Purified water	As required	Granulation solvent
Total weight	270	

1. Preparation of salbutamol compression-coated tablets with chitosan:

Preparation of chitosan granules: Chitosan was granulated by the wet method using PVP K30 before using in compression. Simply, chitosan were mixed thoroughly with PVP K30. Gradually, ethanol 96% was added till the formation of wet cohesive mass. Granulation time was 5 minutes. The obtained granules were spread over the stainless steel tray and allowed for drying over night at ambient temperature and finally sieved through 500 μm sieve to give uniform granules.

Compression-coating procedures: The produced salbutamol core tablets from the previous part were subjected to compression coating with chitosan granules. Half the amount required for the coat was placed in the die. The core tablet was carefully positioned in the center of the die and then the other half was added. The granules were compressed around the core using constant compression force. This was achieved by adjusting the distance between the upper and lower punches to be constant.

2. Preparation film coated salbutamol tablets using Eudragit S100:

Core tablets of salbutamol were subjected to film coating with various thickness of Eudragit S-100 by controlling the weight gain from 5% to 20%. In vitro release study at variant pH values was performed to mimic the extreme pH changes likely to prevail in the GIT. For Eudragit- S100, 12.5% (m/V) Eudragit S-100 (ES) was prepared using *iso*propyl alcohol and PEG-400 (1.25% m/m) as plasticizer.

- **Agitation frequency (Hz):** 15.2 Hz.
- **Air temperature (°C):** 40°C.
- **Airflow (m/s):** 11 m/s.
- **Pump speed:** 4 rpm.
- **Atomising air pressure (bar):** 1.0 bar.
- **Height of spray head (mm):** 150 mm (second graduation).

Evaluation parameters:

1. Evaluation of salbutamol core tablets

Uniformity of weight: The uniformity of weight was carried out for the core tablets. Twenty tablets were weighed individually. The average weight, standard deviation and coefficient of variation percent were calculated. Results are shown in table (3).

Uniformity of thickness: The thickness of core tablets was measured for twenty tablets using vernier caliper. The mean thickness, standard deviation and coefficient of variation percent were calculated .Results are shown in table (3).

Hardness: Twenty tablets were randomly sampled and tested for hardness using Monosanto . The mean hardness, standard deviation and coefficient of variation percent were calculated. Results are shown in table (3).

Friability: Twety-five tablets were randomly sampled and brushed to remove adhering dust using a soft brush. They were accurately weighed and placed in the drum of digital friability tester (HICON grover enterprises). The drum was rotated for a time period of four minutes at a speed of 25 rpm. At the end of rotation period, the tablets were removed from the drum, carefully brushed to free from adhering dust and weighed. The percent loss of weight was calculated using equation (1) and taken as the measure of friability. Results are presented in Table (3).

% Friability = Initial weight – Final weight x 100…………….………(1)

Disintegration Test: Disintegration studies were carries in the Talet Disintegration Tester Machine (I.P. STD. Six tablets were placed in the basket, one in each of the six tubes, and the apparatus was operated. The immersion fluid was water and the temperature was maintained at 37°C ±2 °C. The tablets were visualized till complete disintegration. Result are shown in Table No. (3)

properties. According to USP, the uniformity of dosage form is only expressed by the uniformity of weight for label amounts higher than 25 mg. The mean hardness value **was 8 Kp** which is high enough to withstand further coating processes either compression or film. The core tablets exhibited a very low friability with only **0.1%** (Table 3). In addition, the tablets showed a very fast disintegration time

Table No. 3 Salbutamol core tablet characteristics

Physical properties	Mean	Range	Standard deviation	***RSD(%)
Uniformity of weight (mg)	269.5	268-271	0.919	0.34
Uniformity of thickness (mm)*	3	2-3.5	0.012	0.4
Hardness (kp)	8	7.9-8.1	0.031	0.38
Disintegration time (seconds)	20	18-22	0.11	0.55
Friability % **	0.1%			

* Tablet thickness should not deviate by ± 5%.

** Friability should not more than 1%.

*** RSD = SD/mean ×1

Dissolution of salbutamol core tablets in water:
The dissolution of salbutamol core tablets was made according to USP -30- NF25, 2007 using USP – TDT - 06P (paddle). The dissolution medium was 900 ml distilled water maintained at 37±0.5°C and the rotation speed was 50 ±1 r.p.m. Six Tablets were tested and samples were analyzed at appropriate time intervals (5, 10, 20, 30, 45 minutes) and replaced with fresh and preheated at 37 °C dissolution medium. Data are shown in Table (4).

with mean value of only **20 seconds. According to the** data shown in Table (**4**), the prepared core tablets exhibited a rapid dissolution in water giving **100% release after only 5 minutes** which is considered accepted according to the USP - 30-NF25, 2007 criteria (100% dissolution in less than 45 minutes).

2.   Evaluation of salbutamol compressed coated tablets:-
All the prepared compression coated tablets were evaluated for the uniformity of coat thickness and the in vitro release characteristics.

Uniformity of coat thickness: The thickness of twenty coated tablets was measured using a micrometer and the coat thickness was obtained by subtracting the mean thickness of the core tablets from the mean thickness of the coated tablets and dividing by two. Results are presented in Table (5).

In vitro release: The release of salbutamol from the prepared chitosan compression-coated tablets was carried out in two pH media: 1.2 for two hours and 7.4 for three hours to evaluate the ability of the system to resist both the gastric and intestinal conditions. Three tablets from each formula were individually tested. The dissolution medium was 700 ml

Table No. 4 Dissolution of salbutamol core tablet in water

Time (min)	Average UV Absorbance	Cumulative % Dissolved
5	0.1016	64.19
10	0.2391	167.325

Results and Discussion: The results of physicochemical evaluation of prepared core tablets are shown in Table 3. The tablets were evaluated for uniformity of weight and thickness, hardness, friability, disintegration and dissolution tests. Table (3) represents all the characteristics of the core tablets. They showed **RSD% less than 1%** with all the

Table no 5. Coat-thickness for the compression-coated formula

	F1	F2	F3
Average thickness of 20 core tablets (mm)	3mm	3mm	3mm
Average thickness of 20 coated tablets (mm)	3.27 mm	3.32 mm	3.50 mm
Average coat layer thickness(mm)	0.27 ± 0.015mm	0.32 ± 0.008mm	0.5 0± 0.013mm

Table no. 6 In vitro release profile of theophylline from different compression coated tablet formula in varying pH media

Salbutamol average % of drug release ± SD				
Media	Time (min)	F1	F2	F3
0.1 N HCL **pH 1.2**	0	0	0	0
	5	49.40	0	0
	10	86.64	0	0
	20	107.41	0	0
	30	130.40	0	0
	45	-	0	0
	60	-	0	0
	90	-	11.47	0
	120	-	13.55	0
Phosphate buffer **pH 7.4**	150	-	15.07	0
	165	-	37.46	0
	180	-	53.43	0.133
	240	-	57.56	0.133
	255	-	61.68	1.4
	285	-	65.81	1.54
	300	-	69.93	2.26

0.1 N HCl (pH 1.2) for 2 h and 900 ml of Phosphate buffer pH 7.4 for 3 h. The stirring rate was 50 rpm±1 and the temperature was maintained at 37± 0.5°C. Samples of 5ml were withdrawn manually every half-an-hour till six hours and replaced with fresh preheated (at 37°C) dissolution medium. Samples were measured spectrophotometrically at λ= 271 nm. The amount released was calculated from the regression line of the standard calibration curve developed in the same medium. Data are shown in Table (6) and Figure (4).

RESULTS AND DISCUSSION:

Three compression coated formulae were prepared individually with constant compression force by adjusting a constant distance between the upper and lower punches. This explains the high similarity in the coat thickness among each batch with very low standard deviation values. The average coat thicknesses were **0.27, 0.32,** and **0.5 mm** for batch, F1, F2, and F3, respectively. The total weight of the coat layer were **280, 320, 380 m**g per tablet for F1, F2, and F3, respectively.

Table (6) represent the release profile of salbutamol from three compression coated tablet formulae, F1, F2, and F3. The first acidic two hours to represent the average gastric residence time and the next 3 hours at pH 7.4 represents the average intestinal residence time.

F1 :The results showed a very fast release for F1 in the acidic medium. This indicates the inability of the chitosan coat at this thickness to retard dissolution in the acidic medium. The tablet disintegrated rapidly before forming any gel layer. On the other hand, at higher coat thicknesses F2 and F3, showed complete protection for drug release in the acid phase with no release.
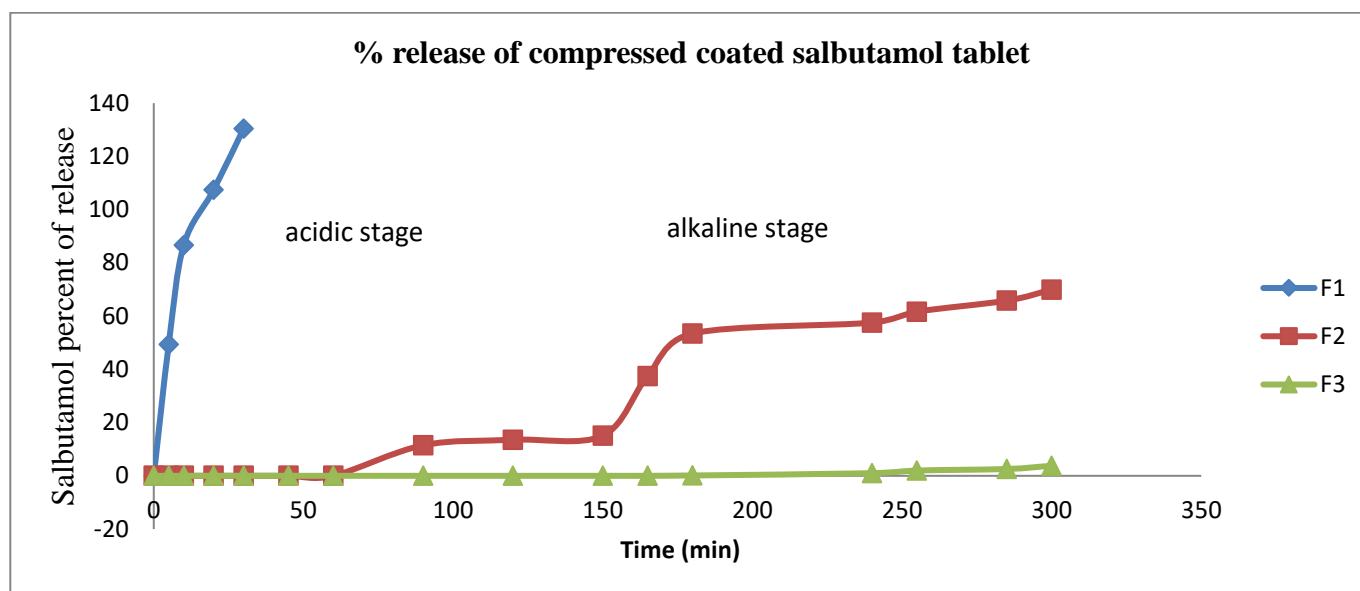
% release of compressed coated salbutamol tablet

Fig No. 5. Dissolution comparison of F1,F2,& F3 in dissolution media without cecal content.

F2: In the alkaline phase, only F2 showed gradual release to small amount reaching **57.56%** in 4 hours followed by markedly higher rate of release in the next hour giving a total amount equal to **69.93%.** The increase in the value of the S.D. during the fifth hour occurred because one of the three tested tablets exhibited much higher rate of release than the other two indicating high variability at this level of coat thickness.

F3: This was not the case with F3, in which all the tested tablets showed almost complete protection during the alkaline phase with amount released 3.48%. All of the tested tablets from F2 and F3 showed the formation of a transparent swelled outer gel layer with inner core clearly seen inside as shown in Figure (5).

The mechanism of release postulated that the gel porosity of chitosan allows penetration of salts and enzymes from the media to the core. Thus, the salt will neutralize the gel pH, while enzymes will degrade the polymer which increase the matrix porosity; all these mechanisms tend to enhance the drug release (Kawadkar, 2007). It is clear that there is a minimum coat thickness necessary for achieving reasonable resistance in the gastro intestinal medium and as the coat thickness increase, the protective properties increase and the variabilities diminish. This is in agreement with what previously reported by Park et al., (2002), Yassin et al., (2001) and Yassin, (2003). They showed that granulation of chitosan with 10% PVP results in protection against the acidic

solubility of chitosan and obviatethe need for further enteric coat.

3.   Evaluation of eudragit S100:

The tablets were coated with two or three different concretrations. The desired volume of coating solution was poured on the prewarmed tablet (batch size 50 g) bed in a pan coater. The tablets were coated and dried with the help of inlet air (temperature 35–45 °C). The coating process was repeated till the desired level of coating was achieved. The percent mass increase of the tablets upon coating was taken to be indicative of the coat thickness.

Uniformity of weight:The uniformity of weight was tested for each formula. For the test tablets were weighted individually. Mean, standard deviation (±SD).Results are shown in Table (8).

Uniformity of thickness: The uniformity of film-coat thickness was determined by measuring the thickness of ten tablets from each of the prepared batches using micrometer and the mean film-coat thicknesses (T) were obtained using the following formula:

$$T = \frac{\text{Mean thickness of the coated} - \text{Mean thickness of the uncoated}}{2} \dots\dots (2)$$

The mean thickness, standard deviation (±SD), and relative standard deviation (RSD) were calculated. Results are shown in Table (9).

In-vitro release: The release of salbutamol from different coated formulae was monitored using standard USP apparatus (Paddle method). Three tablets from each formula were individually tested. The release study was performed in variant pH media to simulate the pH changes in the GIT. During the first two hours, the dissolution medium was 600 ml of 0.1 N HCl (pH 1.2) representing the stomach medium. Then, the pH was changed to pH 6 by the addition of 100 ml of (10.2% w/v) trisodium phosphate dodecahydrate solution. The release profile was studied at this pH for one hour to simulate the medium of the upper part of the small intestine. After that, the pH was adjusted to pH 7.5 for the next successive two hours by the addition of another 100 ml of (5.3% w/v) trisodium phosphate dodecahydrate solution to represent the middle and terminal intestinal medium. Then the medium pH was adjusted to pH 6.8 for the last four hours representing the colonic medium. This was achieved by the addition of 100 ml of (0.0047% w/v) of HCl solution. The stirring rate was 50 rpm±1 and the temperature was maintained at 37± 0.5°C.

Samples of 5ml were withdrawn manually at appropriate time intervals (1, 2, 3, 3:15, 3:30, 3:45, 4, 4:30, 5, 5:30, 6, 6:30, 7, 8 and 9 hours) and replaced with fresh preheated (at 37 °C) dissolution medium.

Samples were measured spectrophotometrically at 271 nm. The amount released was calculated from the regression line of the standard curve developed in the same media. Data are shown in Table (10) and Figure (6).

Film coating process by Eudragit S was giving a uniform tablet building weight for each formula. From Table (8), it is obvious that all the investigated salbutamol tablets coated with different thicknesses of Eudragit S-100 met the requirement of B.P (2008), which states that, not more than two tablets deviate in weight by more than ± 7.5 percent from the average weight (for tablets more than 130 mg and less than 324 mg), and no single one deviate by more than ±15 percent. The average weight values were 281.7 ± 2.53, 298.23± 0.6, 310.64 ± 1.06, and 324.14 ± 1.2 concerning those tablets of formula F4, F5, F6, and F7, respectively.

Batch No.	F4	F5	F6	F7
Time (min)	6	11	15	19
%weight gain	5%	10%	15%	20%
Average core tablet weight (mg)	270.12	270.12	270.12	270.12
Average coated tablet weight (mg)	281.7	298.23	310.64	324.14

Table no.7 Specifications of the prepared film coated formulae

Formula	%weight gain	Average weight (mg)	Range	SD	RSD%
F4	5%	281.7	280.12-287.5	2.53	0.89
F5	10%	298.23	297-299.45	0.6	0.201
F6	15%	310.64	309.06-312.4	1.06	0.34
F7	20%	324.14	323.06-326.1	1.2	0.37

Table no.8 Uniformity of weight of salbutamol coated tablets with Eudragit S100

Formula	%weight gain	Film coated thickness (mm)	Range	SD	RSD %
F4	5%	0.095	0.09-0.1	0.025	0.6
F5	10%	0.175	0.17-0.185	0.031	0.71
F6	15%	0.275	0.25-0.305	0.052	1.14
F7	20%	0.40	0.35-0.465	0.061	1.27

Table no.9 Uniformity of coat thickness of salbutamol coated tablets with Eudragit S100

Table (9) showed that the prepared salbutamol tablets coated with different thicknesses of Eudragit S had acceptable limits of thickness uniformity. The mean film thickness values were 0.095 ± 0.025, 0.175 ± 0.031, 0.275 ± 0.052 and 0.4 ± 0.061 mm for formulae F4, F5, F6 and F7, respectively.

Formula F4 showed the lowest RSD % of thickness followed by F5, F6 and F7. It is clear that the increase in % weight gain is linearly parallel to the increase in coat thickness.

The release profiles of salbutamol from F4, F5, F6, and F7 is presented in Table (10), and Figure (6). **F4** with only 5% coat showed 100% salbutamol release during the first hour

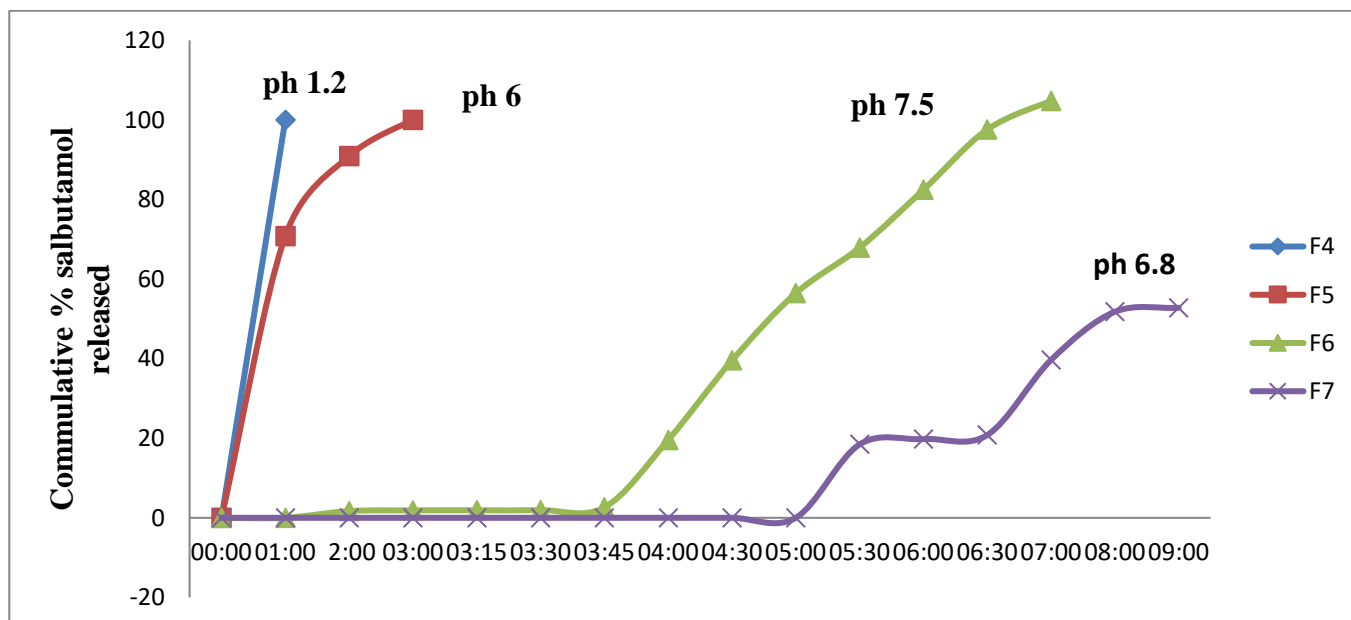| Time (hr)	Media pH	Cumulative Salbutamol % Released			
		F4	F5	F6	F7
1:00	1	100	70.8	0	0
2:00	1	-	90.9	1.68	0
3:00	6	-	104.6	1.87	0
3:15	7.5	-	-	1.9	0
3:30	7.5	-	-	1.93	0
3:45	7.5	-	-	2.6	0
4:00	7.5	-	-	19.56	0
4:30	7.5	-	-	39.56	0
5:00	7.5	-	-	56.45	0
5:30	6.8	-	-	67.89	18.45
6:00	6.8	-	-	82.43	19.79
6:30	6.8	-	-	97.58	20.80
7:00	6.8	-	-	104.78	39.67
8:00	6.8	-	-	-	51.78
9:00	6.8	-	-	-	52.79

Fig no.6 Release profiles of theophylline from tablets coated with different percentage of weight building of Eudrait S-100, (F4= 5%), (F5= 10%), (F6= 15%), (F7= 20%) in several pH media

in the acidic medium while **F5** showed slightly more resistance with 90% release during the first two hours and complete release after three hours. **F6** with 15% coat showed complete resistance to both the acidic medium and the upper small intestine medium with almost no release (1.68%). After one hour in pH 7.5, the salbutamol release started to increase gradually and continued till it reached complete release after 7 hours from the beginning of the test. In the case of **F7** with the highest coat thickness (20% weight gain), no release was seen till five hours from the beginning of the test. Then, the release was slowly and gradually increased reaching a maximum of only 52.9% of the labeled amount at the end of the test (9 hours).

Results:

a)   Compressed coated tablet of chitosan

1) The developed core tablet formula of theophylline showed excellent physical characteristic and high hardness values to withstand further coating processes.

2) The compression coating technique was successful in producing colonic drug delivery tablets embracing number of advantages including: small in size, no need for hardening, cross-linking or film-coating.

3) The successfulness in protecting the coated tablet of salbutamol from the local environment of the gastro-intestinal medium is highly dependent on the coat thickness.

4) Granulation of chitosan with PVP was very effective in protecting against the effect of the stomach acidic medium on chitosan and obviates the need for further enteric coating.
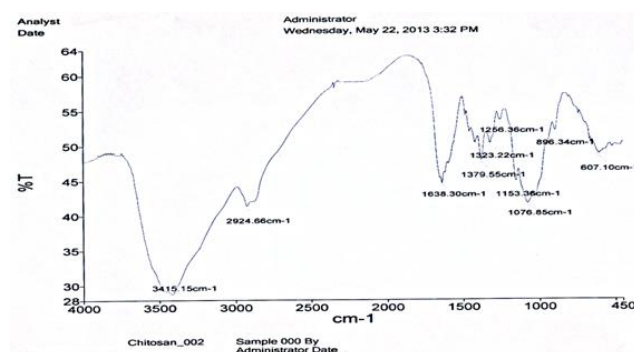
b)   Coating with eudragit S100

1) The prepared coating formula containing Eudragit S100 was suitable and useful for producing elegant film coats up to high coat thickness.

2) The adjusted coating process conditions were useful in producing a reproducible tablet film-coating using the Caliva Mini Coater in a relatively short time.

3) The resistivity of Eudragit S100 film coats to low pHs is highly affected by the film thickness.

4) A threshold of film thickness equals to 0.275 mm is necessary for the resistance against acidic pH.

5) The coat thickness should be optimized based on the required release profile. As the use of very high thicknesses may result in incomplete release which may result in lower bioavailability.
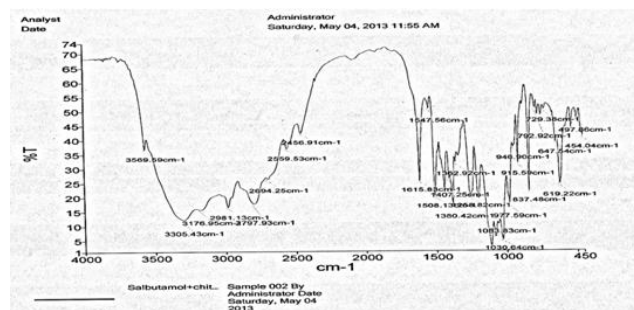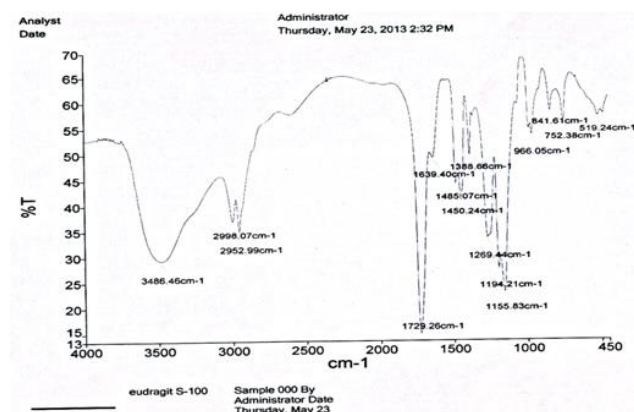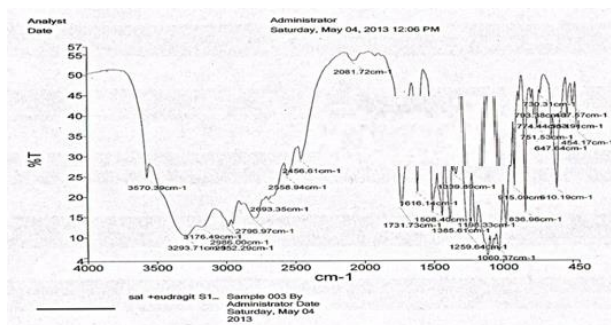
FTIR results:

a)   Salbutamol
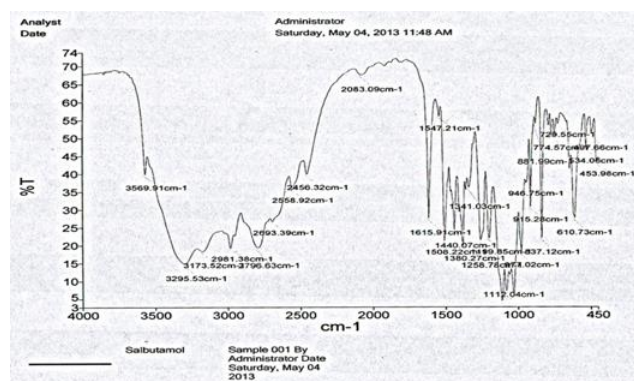
b)   Chitosan

c)   Salbutamol with chitosan

d)   Eudragit S100

e) **Sabutamol with eudragit S 100**

Conclusion: The measure of success for this project is to introduce a new drug delivery that can provide higher drug blood levels in the period of maximum disease intensity (2-6 am). Based on the above-mentioned findings both the prepared formulae F3 and F6 are considered promising in this regard. Probably, F3 is more successful as it provides the higher levels for longer duration.

REFERENCES

1. Alsarra, I.A., El-Bagory, I., Bayomi ,M.A.,(2005). Chitosan and sodium sulfate as excipients in the preparation of prolonged release theophylline tablets. Drug Dev. Ind. Pharm., May; 31(4-5):385-95.

2. Alvarez-Fuentes, J., Fernández-Arévalo, M., González-Rodríguez, M.L., Cirri, M., Mura, P., (2004). Development of enteric-coated timed-release matrix tablets for colon targeting. J. Drug Target., 12 (9-10):607-12.

3. Anderson, D.M., Brydon, W.G., Eastwood, M.A., Sedgwick, D.M., (1991). Dietary effects of sodium alginate in humans. Food Addit. Contam., 8: 237-248.

4. Anon, (1995). The British Guidelines on Asthma Management; Review and Position Statement. Thorax, 52:S2-S21

5. Bateman, J.R., Clark, S.W., (1979). Sudden death in asthma, Thorax, 34: 40– 44.

6. Bayomi, M.A., Al-Suwayeh, S.A., El-Helw, A.R., (2001). Excipient-excipient interaction in the design of sustained-release theophylline tablets: in vitro and in vivo evaluation. Drug Dev. Ind. Pharm., Jul; 27(6): 499-506.

7. Blask, DE., (1994). Chronobiology and the endocrine system. Lab Med. 25: 372-375.

8. Calhoum, W.J., (2002). Nocturnal asthma. Chest; 123; 399S- 405S.

9. Cannon, W.B., (1902). The movements of the intestines studied by means of rontgen rays.Am.J.Physiol.6, 251.

10. Cardizem LA® Package Insert. Biovail. Bridgewater, NJ. April 2004.

11. Christensen, J., (1981). Motility of the colon, in Physiology of the gastro intestinal tract, 1st ed., Vol 1, Jonson-LR, Ed, Raven Press, New York.

12. Chung, M., Ritberg, D.P., Gaffeney, M., Singleton ,W., (1987). Clinical Pharmacokinetics of nifidepine, gastro intestinal therapeutic system –a controlled release formulation of nifidepine. Am. J. Medicine, 83,Suppl 6 B: 10- 14.

13. Kawadkar, J., (2007). Colon Targeted Chitosan Microsphere Compressed Matrices for the Treatment of Ulcerative Colitis, pharmainfo.net, latest Reviews, vol.5, Issue 4 .34-35.

14. Kelmanson, I.A., (1991). Circadian variation of the frequency of sudden infant death syndrome and of sudden death from life-threatening conditions in infants. Chronobiologia., 18: 181–186.

15. Kerlin, P, Tucker, R., Phillips, S.F., (1983). Rapid intubation of the ileocolonic region of man. Aust. N.Z.J. Med., 13, 591-593.

16. Moore, J.G., Halberg, F., (1987). Circadian rhythm of gastric acid secretion in active duodenal ulcer: chronobiological statistical characteristics and comparison of acid secretory and plasma gastrin patterns in healthy and postvagotomy and pyloroplasty patients. Chronobiol. Int., 4: 101–110