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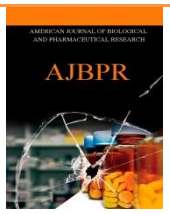

DESIGN AND EVALUATION OF A CHRONOMODULATED DRUG DELIVERY FOR THE TREATMENT OF NOCTURNAL ASTHMA

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ABSTRACT

The purpose of this research was to formulate and develop a pulsatile dosage form to mimic the circadian rhythm of the disease. Thus this study attempts to design and evaluate a chronomodulated drug delivery of a bronchodilator drug Terbutaline Sulphate by using Eudragit S100 as polymeric coating to core tablet. Fifteen batches of core tablet were prepared by direct compression. Using microcrystalline cellulose and sodium starch glycollate showed rapid disintegration. Eudragit S100 was used as coating polymer as it has pH dependent solubility. These coated tablets showed increase in the lag time with increase in the coating level. The lag time increases from 2 to 8 hrs for the coating of 1-7 % respectively

INTRODUCTION

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems. These systems are beneficial for the drugs having chrono-pharmacological behaviour where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in GIT. Drugs used in asthmatic patients and patients suffering from rheumatoid arthritis are also discussed along with many other examples [1-2]. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. It has been reported that more shocks and heart attacks occur during morning hours. The level of cortisol is higher in the morning hours, and its release is reported to decline gradually during the day.

Blood pressure is also reported to be high in the morning till late afternoon, and then drops off during night. Patients suffering from osteoarthritis are reported to have less pain in the morning than night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours [3]. The release of some drugs is preferred in pulses. A single dosage form provides an initial dose of drug followed by one release-free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release [4-7].

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So objective of present investigation is to formulate and develop a pulsatile dosage form to mimic the circadian rhythm of the disease. Thus this study attempts to design and evaluate a chronomodulated drug delivery of a bronchodilator drug Terbutaline Sulphate, for the treatment of nocturnal asthma. It was aimed to have a lag time of 8 hours i.e., the system is taken at bed time and expected to release the drug after a period of 8 hours i.e. at 4.00 am where asthma attacks are more prevalent.

MATERIALS AND METHODS

Materials

Terbutaline Sulphate was obtained as gift sample by Shimoga Chemicals Pvt. India. Eudragit S 100 was obtained as gift sample by Evonik Pvt.Ltd.Mumbai.All other materials and solvents used were of analytical grade.

Methods

FTIR spectrums of drug and drug: excipient /polymer and its interpretation

The dry sample of Terbutaline Sulphate was mixed by triturating with dry potassium bromide (A.R. Grade) and placed in sample cell. The IR spectrum of the drug sample was recorded and the spectral analysis was done[8-10]. IR spectrums were given in (fig no.1-3).

Formulation of core tablet

The core tablets were prepared with selected excipients by direct compression on single punch tablet compression machine. Accurately weighed quantities of drug and other ingredients like sodium starch glycolate, lactose, and magnesium stearate were mixed by triturating in glass mortal-pestle. The blend was directly compressed at weight of 150 mg using 7 mm diameter punch as showed in (table no.1). The compositions of the formulation batches containing different ratios of polymers chosen on trial and error basis.

Preliminary studies for powder blend used for preparation of core tablet

The flow properties of powder blends were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated. The core tablets were coated with a polymethacrylate co-polymer with pH dependent solubility. Which will keep the core tablet protected from the gastric environment and will release the drug in the lower part of the small intestine where the pH will go above 7. The polymethacrylate co-polymer Eudragit S100 having solubility at pH 7 will dissolve in the intestinal pH. As the intestinal fluid will penetrate in the core tablet, the super disintegrant will cause the tablet to release the drug by rupturing the coating. Di-butyl phthalate was used as plasticizer to make the coating more pliable. The coating solutions were prepared in 10 % extra quantity to overcome the handling waste and coated with solutions given in (table no.2). The batches coated to gain % wt.from1to5 [11].

Coating of Terbutaline Sulphate core tablet

Coating was carried with help of spray gun. The parameters are shown in (table no.3). Formulation no. 15 was selected from core tablet formulation and that was coated till desirable result.

Evaluation of coated tablet

Hardness

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing packaging and shipping. Hardness tester (Monsanto tester) was used to measure hardness of tablets. The whole experiment was performed in triplicate. It is expressed in Kg/cm^2 [12-15].

Friability

An adequate resistance for powdering and friability are the necessary requisites for consumer acceptance. This test was carried out by using tablet friability test apparatus (Roche). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed.

Weight variation

The weight variation test is done by taking 20 tablets randomly and they were weighed accurately. The composite weight divided by 20, provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 %. And none should deviate by more than twice that percentage. The average weight and standard deviation of the tablets were calculated. Allowable limit for weight variation was as per IP guidelines.

Thickness and Diameter of tablets

Thickness permits accurate measurements and provide information on the variation between tablets. Ten tablets were taken and the thickness was measured using a vernier-caliper. The tablet thickness should be controlled within a ±5% variation of a standard value.

Content of uniformity

The TBS core tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 250 mg was weighed accurately and mixed in 100ml of pH 7.4 buffer solution. The mixture was shaken properly. The undissolved matter was removed by filtration through Whatman filter paper No.41. Then the serial dilution was carried out. The absorbance of the solution was measured

at 276 nm. The concentration of the drug was computed from the standard curve of the Terbutaline sulphate in phosphate buffer pH 7.4.

Disintegration test

Disintegration test was carried out as described under procedure for uncoated tablets in USP. One tablet each was placed in each of six tubes of the basket of the assembly. Apparatus was operated using water, maintained at 37 ± 20 c as the immersion fluid.

***In-Vitro* dissolution study**

The In-Vitro dissolution studies of the pulsatile tablet formulation of Terbutaline sulphate were carried out using dissolution test apparatus USP-II paddle type. The dissolution medium consisted of 900 ml of standard buffer of pH 1.2 for the first 2 hours, followed by pH 7.4 for the remaining time period up to 8 to 10 hours. The temperature of the medium was maintained at 37±0.5^{0}C. The speed of rotation of the basket was kept at 100 rpm. Aliquots of 1 ml were withdrawn after every half and hrs for a total of 10 hrs. These samples were diluted to make up the volume of 10ml with pH 1.2 buffer for first 2 hours and then by pH 7.4 buffer. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by U.V. visible spectrophotometer, by measuring the absorbance for the samples solutions at 272 nm (for pH 1.2) for Terbutaline sulphate. The dissolution characteristics of each samples was studied, after accounting for loss in the initial concentration of the drug – Terbutaline sulphate while changing the buffer. The release studies for each formulation were conducted in triplicate, indicating the reproducibility of the results [16].

Accelerated Stability study

The stability study of optimized formulation was carried out at accelerated condition of 40 ± 2ºC and 75% ± 5%R.H. for a period of one month. The tablet were individually wrapped using aluminium foil and packed in ambered screw capped bottle and kept at above specified condition in incubator for a period, and analyzed at 7th, 14th, 21st, and 30th days for their changes in various physical properties[17].

RESULT AND DISCUSION

IR spectra for Terbutaline Sulphate, physical mixture of Microcrystalline cellulose and Sodium starch glycolate, drug and IR Spectrum of Core Tablet, Are given in [fig.1-3.] Major functional groups of Terbutaline Sulphate (C=N Stretching Stretching) at 1716, (C=O Stretching) at 1670, (NH Bending) at 1568, (Xanthenes ring) at1485, can be seen in spectra of individual drugs as well as in spectra of physical mixture. So there is no interaction between Terbutaline Sulphate and physical mixture.

Physical evaluation of powder blend used for preparation of core tablet

The angle of repose of lubricated granules granules were found in the range of 26.11±0.04 to 30.89±0.05. Angle of repose less than 30° gives the good flow property to the powder blend. Bulk density depends upon particle size, shape, and tendency of particles to adhere together. The values for bulk density and tapped density were found to range from 0.38±0.05 to 0.52±0.04 and from 0.44±0.03 to 0.7±0.06. The values of compressibility index found in the range of 6.12±0.04 to 11.11±0.05 respectively. These values for compressibility index (5 -15) indicated excellent flow properties of granules and this was further supported by values of angle of repose. Generally, compressibility index values up to 15 % result in good to excellent flow properties. Results are given in (table no.4).

Evaluation of core tablets

The tablets showed hardness values ranging from 4 to 5 kg/cm2. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In present study, the friability values for all the tablet formulations were found to be <1%, indicating that the friability is within the prescribed limits. The pharmacopoeial limits for deviation for tablets of more than 150 mg are ± 5%. The values are found between 151±0.55-161±0.65. The average percentage deviation for all tablet formulations was found to be within the specified limits and hence all formulations complied with the test for weight variation. Tablets from all batches showed thickness values in the range of 1.48±0.07to 1.51±0.09mm. Good uniformity in drug content was found within and among the different types of tablet formulations. The values ranged from 97±1.12 % to 101±1.023 % of labelled amount. Hence the tablet prepared passes the pharmacopoeial limit. As per the requirements of pulsatile tablets the core tablet should give rapid and transient release. The tablets prepared by using lactose using microcrystalline cellulose shows disintegration time between 15 to 63 second. Where Sodium starch glycolate was used as superdisintegrant in both case. The studies showed that the tablet hardness affects the disintegration time, harder the tablet more the disintegration time. Hardness from 4 to 5 gives best disintegration results being in its own limits and showed in (table no.5).

Evaluation of coated tablet

The tablets showed hardness values ranging from 4 to 5 kg/cm2. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less

than 1% of their weight are generally considered acceptable. In present study, the friability values for all the tablet formulations were found to be <1%, indicating that the friability is within the prescribed limits. The pharmacopoeial limits for deviation for tablets of more than 80 mg are ± 7.5%. The values are found between 148±1.12 and 169±0.06. Tablets from all batches showed thickness values in the range of 1.37±0.3 to 1.6±0.5 mm. good uniformity in drug content was found within and among the different types of tablet formulations. The values ranged from 97±1.12 % to 101±1.023 % of labeled amount. Hence the tablet prepared passes the pharmacopoeial limit. After coating with impermeable anionic polymer i.e. eudragit S100 the disintegration time of the tablet was increased. The disintegration time increased with increase of percentage level of coating with polymer. The tablet didn't disintegrated or showed any crack on it in simulated gastric fluid for 1 hrs after that it showed increase in the disintegration time from I hr. to 7 hr. minutes. given in (table 6).

In vitro Dissolution studies:

In Vitro Dissolution profile for formulations CT1 to CT6

The dissolution profile of all batches shows increase in the lag time with increase in the Percent weight gain. The weight gain directly increases the coating thickness so the lag time too. The aim of the study was to develop a tablet which will be protected from gastric environment and will release the drug rapidly in the intestine after 7-8 hours of administration. So the above batches showed increase in lag time from 2 hr to 8 hr. with respect to their coating level and showed in (fig.no.4).

Scanning electron microscopy:

The coating of optimised batch were examined by scanning electron microscopy as shown in (fig.no.5) a illustrating the microphotographs of formulation CT 7 at lower and higher magnification. The coated surface was spherical with no visible major surface irregularity. Few wrinkles and inward dents were appeared on the surface of tablet. It may due to collapse tablets during the coating process.

Accelerated stability study

Accelerated stability studies (AST) was carried for optimized formulation CT5 by exposing it to 40°C/75% RH for one month and analyzed the sample at the interval of 7,14,21,28 days. The sample was analyzed and showed in (table no.7).

Table 1. Formulation of core tablet

Formulation Code	Ingredient in %					
	TBS	MCC	SSG	Lactose	Mg Stearate	Talc
F1	10	60	1	26	2	1
F2	10	60	2	25	2	1
F3	10	60	3	24	2	1
F4	10	60	4	23	2	1
F5	10	60	5	22	2	1
F6	10	60	6	21	2	1
F7	10	60	7	20	2	1
F8	10	60	8	19	2	1
F9	10	60	9	18	2	1
F10	10	60	10	17	2	1
F11	10	60	11	16	2	1
F12	10	60	12	15	2	1
F13	10	60	13	14	2	1
F14	10	60	14	13	2	1
F15	10	60	15	12	2	1

Table 2. Formulation of coating solution

Coating Material (%)	CT 1	CT 2	CT 3	CT 4	CT 5	CT6	CT7
Eudragit S100	1	2	3	4	5	6	7
Avg.% Wt Gain	1	2	3	4	5	6	7
Di-butyl phthalate	2	2	2	2	2	2	2
Solvent (ml)	100	100	100	100	100	100	100

Table 3. Parameter for coating

Parameter	Formulations				
	CT1	CT2	CT3	CT4	CT5
Inlet temp (^{o} C)	55	55	55	55	55
Outlet temp (^{o} C)	40	40	40	40	40
Nozle diameter (mm.)	1	1	1	1	1
Automization pressure (bar)	**1**	**2**	**3**	**4**	**5**
Spray rate (g/min.)	20	17	15	13	14
Pan Speed/min.	25	25	25	25	25

Table 4. Physical evaluation of powder blend used for preparation of core tablet

Formulation	Angle of Repose (Ǿ)	Bulk Density (g/cm^2)	Tap Density g/cm^2)	% Compressibility
F 1	26.11±0.04	0.42±0.06	0.47±0.03	7.54±0.03
F 2	26.88±0.03	0.48±0.06	0.51±0.05	6.12±0.04
F 3	28.45±0.03	0.47±0.04	0.48±0.03	8.92±0.03
F 4	28.67±0.02	0.51±0.05	0.58±0.04	7.94±0.05
F 5	27.02±0.03	0.43±0.06	0.57±0.05	9.09±0.03
F 6	27.78±0.03	0.52±0.04	0.54±0.05	11.11±0.05
F 7	28.29±0.04	0.52±0.04	0.44±0.03	10.63±0.07
F 8	30.89±0.05	0.48±0.05	0.58±0.06	7.54±0.03
F 9	29.23±0.04	0.38±0.05	0.64±0.04	8.77±0.03
F 10	28.93±0.03	0.5±0.04	0.70±0.05	8.00±0.03
F 11	28.77±0.02	0.51±0.05	0.58±0.06	7.95±0.05
F 12	28.32±0.04	0.49±0.04	0.43±0.03	10.43±0.07
F 13	26.02±0.04	0.41±0.06	0.47±0.03	7.34±0.03
F 14	29.23±0.04	0.38±0.05	0.64±0.05	8.77±0.03
F 15	28.90±0.03	0.40±0.04	0.69±0.07	8.02±0.03

Table 5. Evaluation of core tablets

Formulation	Hardness (kg/cm^2)	Weight Uniformity (mg) ± SD	Friability (%)	Thickness	Uniformity of content	Disintegration time (sec.)
F1	4.8	151±0.62	0.621	1.50±0.33	100±1.02	63
F2	4.9	152±0.90	0.554	1.51±0.33	101±1.12	60
F3	4.8	156±0.89	0.741	1.49±0.32	101±1.04	57
F4	4.5	153±0.23	0.358	1.51±0.31	98±0.98	55
F5	4 .6	155±0.97	0.558	1.51±0.09	99±0.94	53
F6	4 .3	158±0.44	0.658	1.51±0.27	102±1.26	51
F7	4 .7	160±0.56	0.554	1.49±0.29	100±1.01	47
F8	4 .4	155±0.06	0.741	1.48±0.07	101±1.02	42
F9	4 .3	152±0.52	0.358	1.51±0.32	97±1.12	40
F10	3.9	152±0.62	0.558	1.50±0.31	98±0.99	36
F11	4.5	156±0.89	0.721	1.50±0.35	100±1.04	33
F12	4.3	151±0.85	0.348	1.49±0.32	99±0.98	31
F13	4.4	161±0.65	0.598	1.48±0.34	98±0.94	24
F14	4.6	156±0.99	0.657	1.51±0.09	100±1.26	20
F15	4.2	151±0.55	0.553	1.51±0.29	99±1.01	15

n=3

Table 6. Evaluation of coated tablet.

Coated Formulation	Hardness	Weight variation (mg) ± SD	Disintegration time (in hr.)	Thickness	Friability	Uniformity of content
CT 1	4 .3	152±1.12	1	2.8±0.02	0.554	98±0.98
CT 2	4 .7	153±1.123	2	2.9±0.02	0.741	99±0.94
CT 3	4 .4	155±1.09	3	3.0±0.04	0.358	102±1.26
CT 4	4 .3	157±0.05	4	2.9±0.03	0.558	100±1.01
CT 5	3.9	159±0.97	5	3.0±0.03	0.658	101±1.02
CT6	4.00	159±0.98	6	3.1±0.05	0.554	987±1.12
CT 7	4 .2	162±.58	7	3.0±0.03	0.554	98±0.98

Table 7. Accelerated stability study of CT 7 formulation.

Sr.N0.	Days	% Drug remaining 5-8°C	% Drug remaining 27±2 °C	% Drug remaining 40±2 °C
1.	0	100 ± 0.010	100 ± 0.14	100 ± 0.17
2.	15	99.97 ±0.13	99.86 ± 0.21	99.63 ± 0.20
3.	30	99.80 ± 0.05	99.81 ± 0.16	99.46 ±0.16
4.	45	99.74 ± 0.12	99.79 ± 0.11	99.29 ± 0.09
5.	60	99.68 ± 0.15	99.75 ± 0.12	99.13 ± 0.18
6.	75	99.85±0.02	99.78±0.12	99.45±0.04
7.	90	99.45±.23	99.58±0.13	99.65±0.15

Figure 1. FT-IR Spectrum of Terbutaline Sulphate.

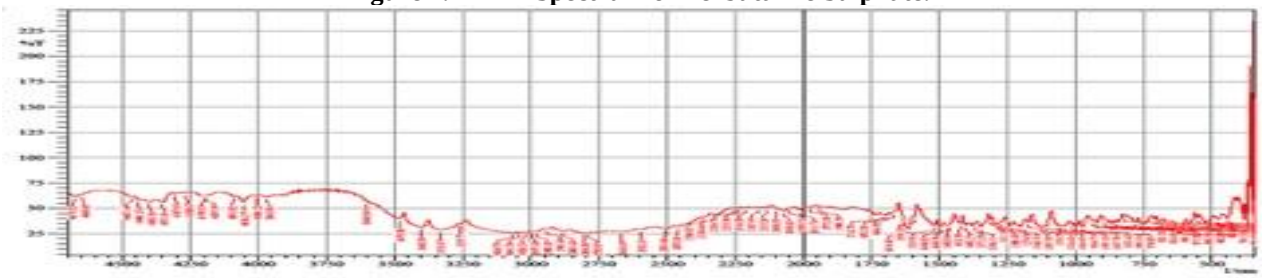


Figure 2. FT-IR Spectrum of TBS, SSG & MCC.

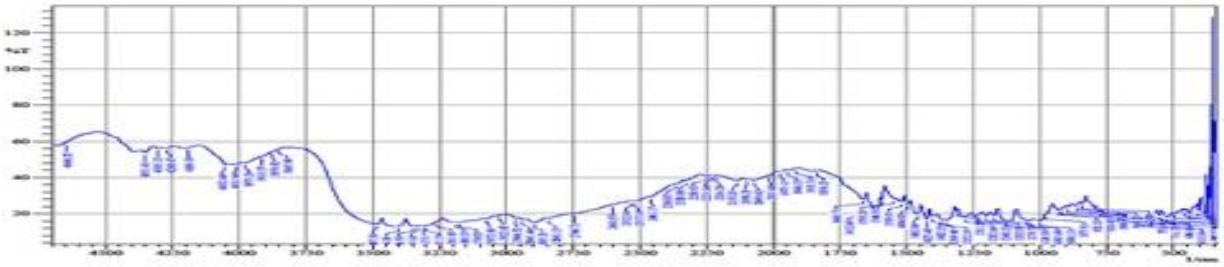


Figure 3. FT-IR Spectrum of Core Tablet

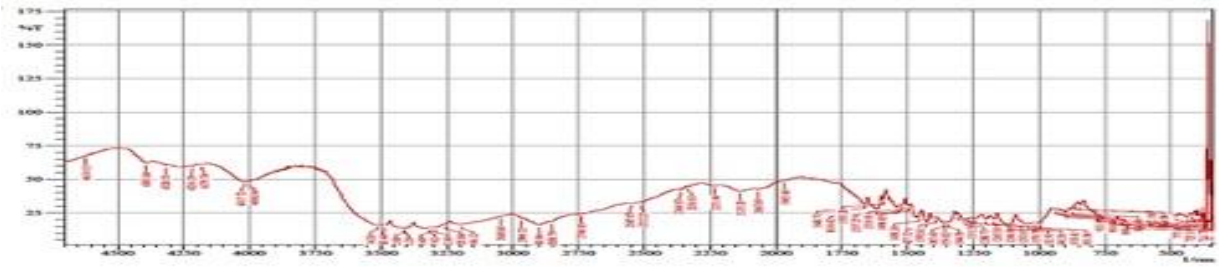


Figure 4. Dissolution profile of coated tablet.

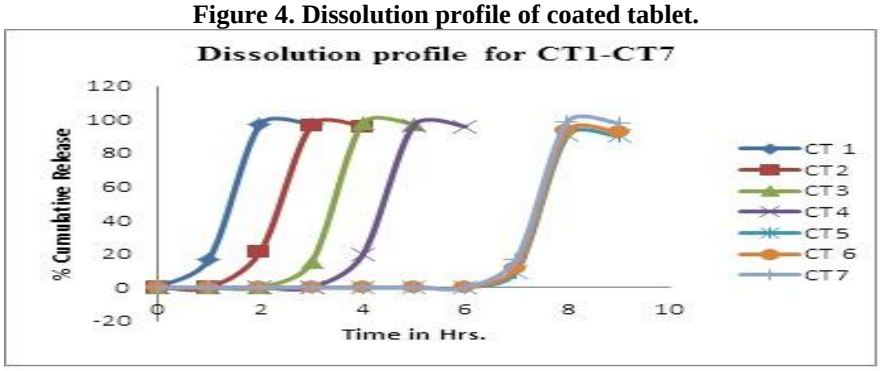
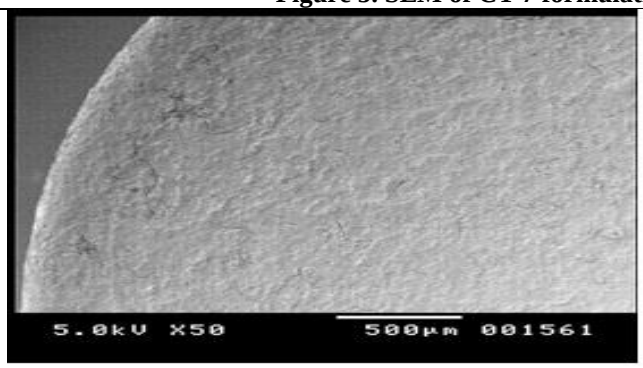
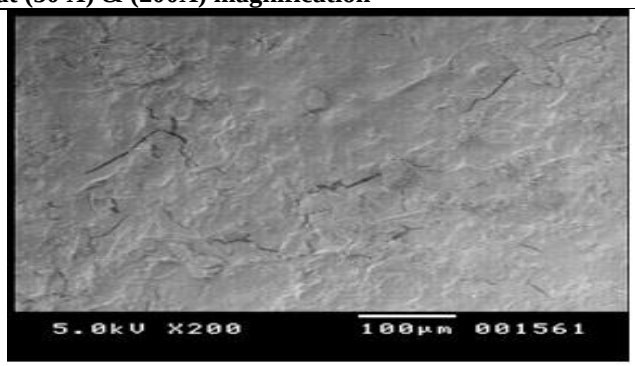


Figure 5. SEM of CT 7 formulation at (50 X) & (200X) magnification





CONCLUSION

In the present work Eudragit S 100 alone is used for coating. Batches were coated in different percent weight gain from 1-7 percent. These coated tablets showed increase in the lag time with increase in the coating level. The lag time increases from 2 to 8 hrs for the coating of 1-7 % respectively. This study was utilized to optimize the formulation; the present work concludes that there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc.

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