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Original Article

Design, Evaluation and Comparative Study of Pulsatile Release from Tablet and Capsule Dosage Forms

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Abstract

The objective of present research was to design, evaluate and compare drug release from two different dosage forms in pulsatile drug delivery system (DDS) for Metoprolol tartarate (MT) as tablet and capsule. 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. Conclusively, the current study attained the successful comparison of drug release from two different pulsatile drug delivery systems.

Keywords: Drug delivery system; Release study; Metoprolol; Pulsatile.
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1. Introduction

Drug delivery systems with a pulsatile-release pattern are receiving increasing interest for the development of drugs for which conventional controlled drug-release systems with a continuous release are not ideal [1, 2]. These systems are beneficial for the drugs having chronopharmacological behaviour where night time dosing is required and for the drugs having high first-pass effect [3] and for several diseases (e.g. bronchial asthma, hypertension, rheumatic disease and myocardial infraction) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and cortisol) infuenced by circadian rhythms, delayed or pulsatile drug release could be an optimal approach. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism e.g. β-blockers [4-7]. A pulsatile-release profile is characterized by a time period of no release (lag time) followed by a rapid and complete drug release. The objective of present research was to design, evaluate and compare pulsatile drug release from tablet and capsule dosage

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forms. The tablet consisted of a Eudragit S100 coated core tablet which was compression coated with immediate release layer containing drug and super disintegrant. This compression coated tablet was then enteric coated with Eudragit L100-55 polymer to allow the drug release in small intestine. And the capsule consisted of metoprolol tartrate (MT) loaded sugar beads with dual pulse in which 50% of the sugar beads were coated with Eudragit L100-55 and remaining 50% were coated with Eudragit S-100 polymer. Pulsatile drug-delivery systems can be classified into site-specific systems in which the drug is released at the desired site within the intestinal tract (e.g., the colon) or time-controlled devices in which the drug is released after a well-defined time period [8]. The release of the drug as a pulse after a lag time has to be designed in such a way that the drug should be released as a pulse with rapid and complete drug release. This research covers an approach for the site specific drug delivery from the multipaticulate system which releases drug in pulse with a predetermined lag time depending on the pH dependant dissolution of the enteric polymers.

2. Materials and methods

2.1. Materials

Metoprolol tartarate was obtained as a gift sample from Astra Zeneca (Bangalore, India). Hydroxypropyl methylcellulose (Shinetsu Chemical Co. Ltd. Mumbai, India), cross-carmellose sodium (Singlet chemical corporation, Mumbai, India), microcrystalline cellulose (Ideal Cures Pvt Ltd., Mumbai, India), sugar beads no-10 were purchased from Shrikrishna Homeo-Pharmacy (Pune India), HPMC (5 cps) as a gift sample from Shinetsu Chemicals (Mumbai India). Eudragit S100 and Eudragit L100-55 were from Degussa (Mumbai India). Empty hard gelatin capsules of size zero from Associated Capsules (Mumbai India).

2.2. Preparation of capsular pulsatile drug delivery system

2.2.1. Capsule size determination

The sugar beads which had to be used for drug loading and polymer coating were filled in the empty hard gelatin capsule of size '0'. Then the quantity was weighed on Shimadzu AY-120 balance. The calculations were done accordingly to decide the required weight gain on the sugar beads to deliver 100 mg of drug [9]. The capsule sizes, volume filled in it and fill weight at powder density of 0.8 gm/cm^2 are as given in Table 1.

2.2.2. Drug loading on sugar beads

Metoprolol tartarate was loaded on sugar beads using 10% (w/v) solution in isopropyl alcohol/water mixture. Four formulations were prepared as F_1, F_2, F_3, F_4 with different proportions of isopropyl alcohol/water mixture as (67:20 w/w, 65:20 w/w, 63:20 w/w, 60:20 w/w) containing 3, 5, 7, 10% HPMC (5 cps), respectively, were used for drug loading in an Instacoat R&D coater. The loading conditions were: batch size 30 g, preheating 10 min., inlet temperature 30 °C, air pressure 0.3 Kg/cm^2, nozzle to bed distance 11cm, pan speed 15 rpm, spray rate 1 ml/min., final drying at 40 °C for 15 min.

The drug loaded sugar beads were evaluated for bulk and tapped density, friability, gastric resistance, drug content and % of drug release.

2.2.3. Procedure for the determination of drug content

Drug loaded sugar beads (0.1 g) were weighed and placed in a 100 ml volumetric flask. Distilled water was added up to 100 ml. One ml was pipetted out from this stock solution and diluted to 10 ml in a volumetric flask. The absorbance of the solution was observed at the λ_{max} of 222 nm. The amount of drug present in 100 ml solution was calculated from the equation of the calibration

Table 1. Metoprolol tartarate capsule size determination.

Size	Volume (ml)	Fill weight at powder density of 0.8 (g/cm^2)
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.140

curve. From this result, the amount of drug loaded on total bed of sugar beads was calculated. The efficiency of drug loading was calculated from the following formula,

$$\% \text{ Drug loading} = \frac{\text{Practical weight gain}}{\text{Theoretical weight gain}} \times 100$$

The optimized drug loaded formulation was then used for enteric coating with Eudragit S-100 and Eudragit L100-55 polymers.

2.2.4. Coating of drug loaded sugar beads with Eudragit L100-55 polymer

Drug loaded sugar beads (23 g) were placed in a 4-inch coating pan of Instacoat R&D coater. They were preheated at 50 °C for 10 min. and sprayed with 11.5% Eudragit L100-55 polymer [10]. The aqueous coating suspension of Eudragit L100-55 polymer was prepared according to the procedure given by Degussa polymers. The coating parameters were set as: pan speed 20 rpm, inlet temperature 40 °C, air pressure 0.3 kg/cm^2, spray rate 1 g/min. The drug loaded sugar beads were evaluated for drug content and percent drug release. Three different formulations as L_1, L_2 and L_3 based on different % total weight gain were separated and evaluated for drug release studies.

2.2.5. Coating of drug loaded sugar beads with Eudragit S-100 polymer

The same quantity of drug loaded sugar beads were placed in a 4-inch coating pan of Instacoat R & D coater. They were preheated at 50 °C for 10 min. and sprayed with 6.5% coating solution of Eudragit S-100 polymer [10]. The coating solution of Eudragit S-100 polymer was prepared as per the procedure given by Degussa polymers. The coating parameters were: pan speed 15 rpm, inlet temperature 30 °C, air pressure 0.3 kg/cm^2, spray rate 1 g/min. Three different formulations as S_1, S_2 and S_3 based on different % total weight gain were separated and evaluated for drug content and drug release studies.

A quantity of sugar beads showing 50 mg drug content coated with each polymer was weighed and filled into the body of empty hard gelatin capsule. These capsules were then used for studying percentage drug release.

2.2.6. Gastric resistance

The drug loaded sugar beads coated with Eudragit S100 (6%, 8% and 10%) and Eudragit L100-55 (5%, 10% and 15%) were subjected to gastric resistance study [11, 12]. HCl (900 ml of 0.1 N) was placed in the vessel of USP dissolution tester (Electrolab, TDT -08L). The medium was allowed to equilibrate to a temperature of 37±0.5 °C. A weighed quantity of sugar beads equivalent to 50 mg of metoprolol tartrate was transferred (calculated on the basis of the assay of batch to be tested) in the dissolution vessel and the apparatus was operated for exactly specified time. At the end of two hours, the medium was slowly drained without loosing the sugar beads, transferred to a filter paper and the sugar beads were dried by blotting with filter paper. They were assayed for drug content. The parameters used were as: Dissolution test apparatus: USP type-II apparatus; medium: 0.1 M HCl, 900 ml; stirrer speed: 75 rpm; temperature 37±0.5 °C; dissolution time: 2 h.

Table 2. Physical properties of drug and excipients.

Material	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
Metoprolol tartrate	0.3300	0.4081	18.328	1.2244
Sugar beads	0.8696	0.8696	0.0000	1.0000
Microcrystalline cellulose	0.2940	0.4540	35.295	1.5454
Crosscarmellose sodium	0.2200	0.2460	19.240	1.2100

2.2.7. In vitro dissolution of pulsatile capsule containing drug loaded and both polymer coated sugar beads

Drug release studies were performed using USP dissolution rate test apparatus (Apparatus 1, 100 rpm, 37±0.5 ºC) for the first 2 h in 0.1 N HCl (750 ml). The dissolution medium was changed with 250 ml of 0.2 M trisodium phosphate and the pH adjusted to phosphate buffer (pH 6.8), dissolution was continued for 1 h. Then entire medium was replaced with 900 ml fresh phosphate buffer of pH 6.8 for the next 3 h, which is considered as the intestinal transit time. Then the pH was adjusted to 7.2 by the addition of 0.1 N NaOH for further hours. At predetermined time intervals 5 ml samples were withdrawn and replaced by an equal volume of fresh medium and test were continued in phosphate buffer (pH 7.2) for 2 h. Samples were filtered, diluted and assayed at each interval for metoprolol tartarate content released at λ_{max} of 222 nm using a Double Beam UV-Spectroph otometer (JASCO V-550 UV/VIS Spectrophotometer) [12].

2.2.8. Capsule filling with polymer coated sugar beads

Eudragit L100-55 and Eudragit S-100 polymer coated sugar beads (265 mg of each) were filled in a hard gelatin capsule of size '0'. Then they were evaluated for percentage of drug release.

2.3. Design and evaluation of enteric and compression coated pulsatile DDS

2.3.1. Formulation of enteric and compression coated pulsatile tablet

The MT immediate release core tablets were prepared according to the composition given in Table 2.

They were evaluated for weight variation, hardness, friability, disintegration and drug content as per I.P. 1996. The formulation showing the least disintegration time was used for further study.

The core tablet was then enteric coated with Eudragit S-100 polymer. The coating was performed in 4 inch pan of an Instacoat R&D coater. The coating parameters were: pan speed: 30 rpm; inlet temp: 60 °C; air pressure: 0.5 kg/cm^2; Pump rpm: 1 rpm; nozzle to bed distance: 11cm. The tablet bed was preheated for 10 min. Then it was sprayed with Eudragit S-100 coating solution at a rate of 1 ml/min (1 rpm). Tablets were checked for % of total weight gain (TWG) intermittently. Then, tablets of different % TWG as 2%, 4%, 6%, 8%, 10% were separated. They were checked for release profile and the % TWG showing <10% drug release in 4 h in pH 6.8 phosphate buffer and rapid and complete release within 1 h after changing pH to 7.2 was selected for the final formulation. The coating solution was prepared as per the formula given by Degussa Pharma Polymers. The optimized tablets were evaluated for physical appearance and coating thickness by Scanning Electron Microscopy (SEM) and % of drug release study. The % of drug release studies were conducted for all the different % TWG tablets using dissolution apparatus. Drug release studies were performed using USP dissolution test (Apparatus 1, 100 rpm, 37±0.5 ºC) for the first 3 h in 900 ml of fresh phosphate buffer of pH 6.8 which is considered as the intestinal transit time. Then the pH was adjusted to 7.2 by the addition of 0.1N NaOH for further h. At predetermined time intervals 5 ml samples

Table 3. Composition of formulation of metoprolol tartrate immediate release core tablet.

Formulation (mg / tablet)	A_1	A_2	A_3	A_4	A_5	A_6
Drug	50	50	50	50	50	50
MCC	15	15	15	15	15	15
PVP	5	5	5	5	5	5
Croscarmellose sodium	-	1	2	3	4	5
Talc	1	1	1	1	1	1
Lactose	29	28	27	26	25	24
Total	100	100	100	100	100	100

were withdrawn and replaced by an equal volume of fresh medium and test were continued in (pH 7.2) for 2 h. Samples were filtered, diluted and assayed at each interval for metoprolol tartarate content released at λ_{max} of 222 nm using double beam ultra violet (UV)-Spectrophotometer (JASCO V-550 UV/VIS spectrophotometer).

2.3.2. Formulation of compression coated tablets

As the composition of blend used for the compression coat was the same as that of core tablet, the blend containing 5% cross-carmellose sodium was used for the compression coating of Eudragit S100 coated core tablet. The composition of this blend was as given in Table 3. The blend (250 mg) was kept at the bottom of 12.5 mm die with standard concave punches. The Eudragit S100 polymer coated core tablet was placed manually at the center of it. Remaining 250 mg of blend was added over it and compressed to form a compression coated pulsatile tablet. The compression force was adjusted in such a way that the polymer coat on core tablet will not get broken.

2.3.3. Barrier layer coating of compression coated pulsatile tablet with HPMC (5 cps)

The compression coated tablets were barrier layer coated with non-aqueous HPMC (5 cps) solution as given in Table 4. This barrier layer coated tablets were then coated with Eudragit L100-55 polymer and the coating level which gave the total lag time of 2 h was selected as optimum coating level.

2.3.4. Enteric coating of barrier layer coated tablets with Eudragit L100-55

The barrier layer coated tablets were finally coated with aqueous dispersion of Eudragit L100-55 polymer. The coating solution was prepared as per the procedure given by Degussa (Evonik) polymers.

2.3.5. In-vitro dissolution study of Eudragit L100-55 enteric polymer coated final tablets

Drug release studies were performed using USP dissolution test (Apparatus 1, 100 rpm, 37±0.5 ºC) for all of the different % TWG tablets using dissolution test. The test was conducted in 0.1 N HCl for the first 2 h. Then the pH was changed *in situ* to 6.8 by the addition of 250 ml of trisodium phosphate buffer solution. The whole medium was replaced with fresh 900 ml of phosphate buffer pH 6.8 for 3 h which is considered as intestinal transit time. The pH was then increased to 7.2 for the next 1 h by the addition of 0.1 N NaOH. Aliquots (5 ml) were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically (JASCO V-550 UV/VIS Spectrophotometer) at 222 nm.

3. Results and discussion

3.1. Physical properties of drug and excipients

The micromeritic parameters were evaluated for the drug and other excipients as shown in Table 5.

3.2. Capsule dosage form

3.2.1. Capsule size determination

The quantity of neutral sugar beads filled

Table 4. Composition of metoprolol tartrate immediate release compression coat (500 mg).

Ingredients	Quantity (mg)
Drug	50
PVP	50
Crosscarmellose sodium	25
Talc	10
Lactose	365

Table 5. Formula for the barrier layer coating solution of HPMC.

Ingredients	Quantity (%)
HPMC (5 cps)	04 %
Propylene glycol	01%
Ethyl alcohol	45%
Methylene chloride	*q.s.* to 100%

in a capsule was 530 mg. The drug loading was performed accordingly, so that 530 mg of sugar beads will contain 100 mg of drug and the enteric coats [9].

3.2.2. Evaluation of drug loaded sugar beads

The drug loaded sugar beads were evaluated for bulk density, tapped density, friability and drug content. From the results (Table 6), it was observed that the bulk density of F_1 was 0.921 g/ml which increased gradually to 0.934, 0.945 and 0.952 g/ml for F_2, F_3, and F_4 formulations. Similarly, the tapped density was ranged from 0.958 for F_1 to 0.971, 0.984 and 0.998 g/ml for F_2, F_3 and F_4 formulations which might be due to increase in the concentration of binder HPMC. As the concentration of binder increased, the loading of drug on the sugar beads also increased that may be accounted for the gradual increase in the densities. The friability of F_1 was found 0.125% which was found to decrease gradually to 0.114, 0.097 and 0.027 % for F_2, F_3 and F_4 formulations, which was due to increase in binder concentration that led to stronger binding between drug and neutral sugar beads. Consequently, the drug release was also found to increase from 67% for F_1, 74.6%, 79.8% and 86.4 % for F_2, F_3 and F_4 formulations, respectively.

3.2.3. Evaluation of sugar beads coated with enteric Eudragit L100-55 & Eudragit S100 polymers

The previously drug loaded beads were coated with Eudragit L100-55 coating solution and the coated beads of different % total weight gain (TWG) were separated out and evaluated for drug content, gastric resistance, coating uniformity SEM and percent drug release. The drug content of sugar beads coated with Eudragit L100-55 and Eudragit S100 polymer after residing in gastric media for 2 h is as given in Table 7. The gastric resistance study showed that all the three coating levels L_1, L_2, L_3 and S_1, S_2, S_3 released less than 1% drug in the gastric media. All the six formulations showed similar drug content after 2 h. This indicated that all the three levels were sufficient to protect the drug form releasing in stomach *i.e.* in gastric environment.

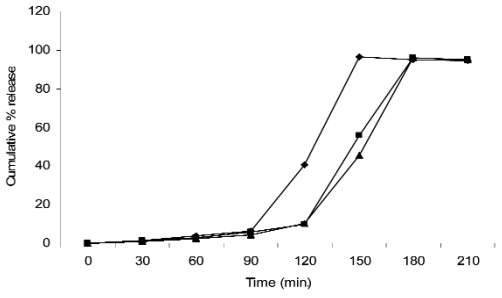

Figure 1. Dissolution profile of Eudragit L100-55 polymer coated sugar beads. ◆ L_1, ■ L_2, ▲ L_3.

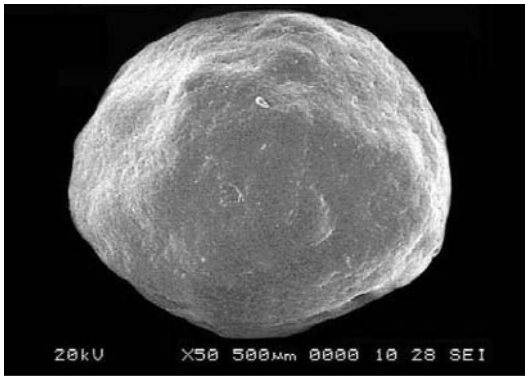

Figure 2. SEM photomicrograph of eudragit L100-55 coated sugar bead as revealed by ccanning electron microscopy (SEM).

Table 6. Evaluation of metoprolol tartarate loaded sugar beads.

Parameters	F_1	F_2	F_3	F_4
Bulk density	0.921	0.934	0.915	0.952
Tapped density	0.988	0.991	0.959	0.999
Carr's index	4.38	4.96	5.21	5.47
Friability	0.125	0.114	0.097	0.027
Drug content (%)	67.0	74.6	79.82	86.4

3.3.4. In vitro release studies of Eudragit L100-55 coated sugar beads

Three different formulations with varying % TWG were formulated and evaluated for drug release. The *in vitro* profile is given in Figure 1. From this, it can be observed that L_1 shows rapid release in 2.5 h with a lag time of 1.5 h which might be attributed to the insufficient coating of Eudragit L100-55 polymer on the sugar beads. Due to the insufficient coating, easy access of acidic medium to the drug layer on the sugar bead took place leading to the rapid release without sufficient protection. L_2 and L_3 showed the lag time of 2 h and gave complete release within 1 h in alkaline media of pH 6.8, so the formulation L_2 was used for further study. The protection in acidic environment by Eudragit L100-55 may be due to the presence of methacrylic acid and ethyl acrylate in 1:1 ratio which dissolves at above pH 5.5; forming salts with alkalis, thus coatings remain insoluble in acidic media but dissolves in alkaline medium. The dissolution profile of Eudragit L100-55 coated sugar beads is showed in Figure 1. The coating uniformity of formulation L_2 was studied with the help of SEM. The photomicrograph of a Eudragit L100-55 coated sugar bead by SEM revealed that the film was homogeneous with a uniform enteric film coating as shown in Figure 2.

3.2.5. In vitro release studies of Eudragit S100 coated sugar beads

Different formulations with varying %TWG were formulated and evaluated for drug release. The *in vitro* release profile is given in Figure 3. It can be observed that the beads coated with 6% TWG of Eudragit S100 (S_1) showed lag time of 3.5 h followed by the release for further 2 h. 8% TWG beads (S_2) showed the lag time of 4.5 h followed by the release for further 2.5 h, whereas 10% TWG beads (S_3) showed the lag time of 5.5 h followed by the release for nearly 8 h after the pulse release. The difference in the release time may be due to the varying thickness of Eudragit S100 polymer coat. So, the formulation S_3 was used for further study. The mechanism by which the polymer gives the lag time is the presence of methacrylic acid and ethyl acrylate in 1:2 ratio. The methacrylic acid groups get converted to methacrylate

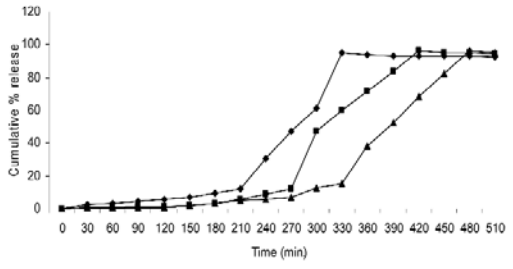

Figure 3. Dissolution profile of Eudragit S100 coated sugar beads loaded with drug. ◆ S_1, ■ S_2, ▲ S_3.

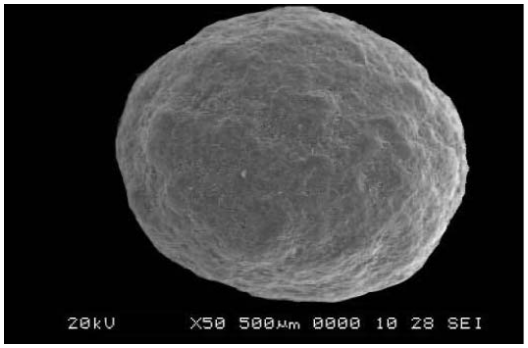

Figure 4. SEM photomicrograph of eudragit S100 coated sugar beads.

Table 7. Gastric resistance study of beads coated with Eudragit L100-55 and Eudragit S100 polymer.

Enteric polymer coated sugar beads (%TWG)	Drug content (%)
L_1 (5%)	82.11
L_2 (10%)	82.24
L_3 (15%)	82.97
S_1 (6%)	81.23
S_2 (8%)	81.45
S_3 (10%)	81.84

L_1, L_2, L_3- Eudragit L100-55; S_1, S_2, S_3- Eudragit S-100.

ions which rapidly dissolve above pH 7. Thus the beads showing the lag time of 5.5 h followed by the release for another 3 h were used for further study.

The coating uniformity of formulation S_3 was studied with the help of SEM. The photomicrograph of a Eudragit S100 coated sugar bead by SEM revealed that the Eudragit S100 coated sugar bead showed a homogeneous and uniform film coating as shown in Figure 4.

From Figure 5, it was observed that all the three capsules C_1, C_2 and C_3 showed a lag time of 2 h in 0.1 N HCl followed by a rapid release after changing the pH to 6.8. Again a second lag time of 4.5 h followed by a complete release after changing the pH to 7.2.

3.3. Tablet dosage form

3.3.1. Weight variation, thickness, hardness, friability, disintegration time tests

The compressed tablets were subjected to the tests like weight variation, thickness, hardness, friability, disintegration time and percentage of drug content. The results were as showed in Table 8.

According to this data, all the formulations showed uniform thickness. In weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of less than 130 mg is ±10%. Good uniformity of drug content was found among different batches of the tablets, and the percentage of drug content was between 95-105. The percentage of friability of all the formulations was below 1% indicating that the friability is within the prescribed limits. The disintegration time of A_1 formulation was 10.23 min., and it was found to decrease as the concentration of crosscarmellose sodium increased. Formulation A_6 showed DT of 4.23 min. which was the lowest and attributed to the highest concentration of superdisintegrant. This formulation was used for further study in which it was coated with Eudragit S100 polymer and evaluated for drug release. From the dissolution profile of Eudragit S100 coated core tablet formulations (2-10%) as shown in Figure 6, it was observed that as the %TWG increased; i.e. increase in the coating level (or thickness of coat) further caused increase in the lag time. The increase in the lag time along with the increase in the thickness of the coat was due to presence of free carboxyl groups and ester in 1:2 ratios in Eudragit S-100 polymer. Thus along with increase in the thickness, the concentration of these groups also increases which takes more time to dissolve in alkaline pH. So it can be said that by changing the thickness of the coat, we can control the lag time as desired.

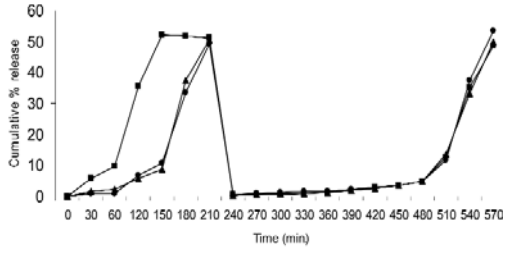

Figure 5. Dissolution profile of Pulsatile capsules containing 50% each of Eudragit S100 and Eudragit L100-55 coated sugar beads. ◆ C_1, ■ C_2, ▲ C_3.

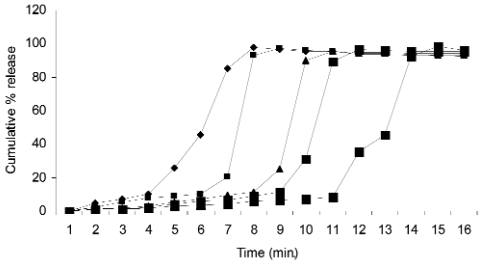

Figure 6. Dissolution profile of Eudragit S100 coated core tablets.

Table 8. Tablet properties of metoprolol tartrate immediate release core tablet.

Formulations	Weight variation	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (min.)	Drug content (%)
A_1	0.1±0.030	3.4±0.3	4-5	0.01	10.23	98.13±0.49
A_2	0.1±0.010	3.4±0.5	4-5	0.03	9.12	98.57±0.47
A_3	0.1±0.050	3.4±0.1	4-5	0.01	8.05	99.23±1.70
A_4	0.1±0.021	3.4±0.4	4-5	0.00	6.45	101.67±0.57
A_5	0.1±0.035	3.4±0.3	4-5	0.02	5.14	101.23±0.25
A_6	0.1±0.026	3.4±0.1	4-5	0.03	4.23	99.45±0.15

The SEM study of Eudragit S-100 polymer coated core tablet was performed to see the uniformity of the film and to find out the thickness of polymer. From Figure 7, it was observed that the film thickness was homogenous with average coating thickness of 27.6 µm.

3.3.2. In vitro dissolution study of enteric and compression coated tablets with Eudragit L100-55

These tablets were barrier layer coated with 5% non-aqueous HPMC (5 cps) solution because when the aqueous solution of Eudragit L100-55 was sprayed on the compression coat, it led to swelling because of the presence of superdisintegrant in the compression coat. So, it was applied to prevent swelling and non-uniformity of enteric coat. Finally the barrier layer coated tablets were coated with 11.5% aqueous solution of Eudragit L100-55 polymer so that the tablet will not release the drug at all in the acidic media of the stomach but will release as bipulse in lower part of GIT (small intestine, colon). Six tablets were evaluated for drug release. From Figure 8, it was observed that all of them showed a lag time of 2.5-3 h followed by a rapid release of 50% of the drug that was present in the compression coat. It was followed by a second lag time of 3-3.5 h followed by a rapid and complete release of remaining 50% of the drug contained in the core tablet. The lag times were obtained because of the presence of methacrylic acid and ethyl acrylate present in 1:1 ratio in Eudragit L100-55 which dissolves at above pH 5.5 in the small intestine. The second lag time was due to the presence of same acid and ester but in 1:2 ratio because of which it dissolves at pH 7.

4. Conclusion

The drug release from the pulsatile capsule and tablet dosage form was compared. From the observations of all the formulations, it

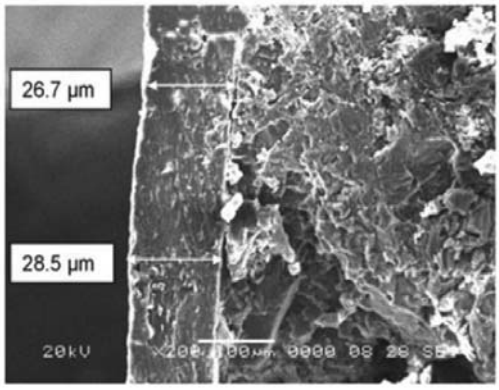

Figure 7. The Scanning electron microscopy (SEM) Photomicrograph of 8% TWG tablet coated with Eudragit S-100 polymer.

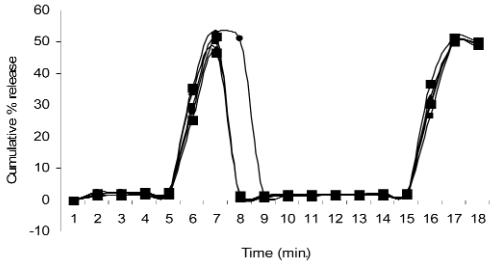

Figure 8. *In-vitro* dissolution profile of enteric and compression coated tablets with Eudragit L100-55 polymer (I-VI). I, II, III, IV, V, VI.

was concluded that capsule dosage form showed a lag time (period of no drug release) followed by better pulsatile release whereas, tablet dosage form showed a lag time in which 10-20% of the drug was released during the lag time followed by a pulsatile release. Also the uniformity of the enteric coated core tablet was dependent on the compression force applied during compression coating. Therefore, getting lag times followed by pulsatile release was more critical in tablet as compared to capsule dosage form. In case of drug loading on sugar beads, when the concentration of binder (i.e. HPMC 5 cps) was increased from 3% to 10%, it led to an increase in the drug content significantly because the binder was responsible for the firm binding between the drug and the neutral sugar beads. As binder concentration increased, it led to the gradual increase in the binding which resulted in higher drug loading, also by applying two different polymers to the different populations of sugar beads, the pulsatile release can be achieved. Since the two different enteric polymers release the drug at different pH in the GIT, the release pattern can also be changed by varying thickness of the polymer coat.

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