Formulation and Evaluation of Pulsatile Drug Delivery System of Metoprolol Tartarate Using Core in Cup Tablet

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Abstract   The purpose of this work is to formulate a pulsatile drug delivery system using metoprolol tartarate as model drug. A core in cup (three component tablet) is prepared where in core tablet, an impermeable material surrounding the tablet except the top and soluble hydrophilic polymer layer at the top is designed. The core tablet contains metoprolol tartarate, cellulose acetate propionate is used as impermeable membrane and sodium alginate 500 cps and sodium alginate 2000 cps used as soluble hydrophilic polymer layer .The top cover layer is prepared using 3^2 factorial design. Quantification of water uptake, top layer expansion, in-vitro dissolution studies, radial and axial expansion, stereomicroscopic image, and short term stability studies are performed. The concentration of top layer of hydrophilic polymer is a critical factor governing the release pattern, increase in the concentration increased lag time and delay the release .The T70% and T90 % values are also influenced by the polymer concentration with less polymer concentration of hydrophilic polymer lesser T70% and T90 % values are obtained and as the concentration increased higher values are obtained. It can be concluded from the study that pulsatile drug delivery system useful in chronotherapy of hypertension can be prepared by this technique.

Keywords Pulsatile Release Tablet, Lag Time, Metoprolol Tartarate, Soluble Polymer

1. Introduction

Chronotherapy refers to treatment in which the availability of the drug to the body can be tailored to meet the therapeutic requirement. Earlier the development of the drug delivery system was based on the homeostatic theory according to this theory biological functions are constant over time however chronobiological studies contradict this theory, nearly all functions of the body including those influencing pharmacokinetic parameters display significant variation. Circadian or 24 hrs rhythm exists in blood pressure, blood flow, stroke volume, peripheral resistance, gastric acid secretion, gastro intestinal motility and gastric emptying as in[1]. Common symptoms of allergic rhinitis such as sneezing, nasal rhinorrhea, red itchy eyes were found to occur most frequently in the morning and least frequently in middle of the day as in[2].

Circadian rhythm exists in arthritic pain and patients with rheumatoid arthritis experience great pain in the early morning and patient with osteoarthritis have more pain in the evening hours as in[3]. In cardiovascular diseases capillary resistance and vascular reactivity are higher in the morning and decrease latter in the day, platelet agreeability is increased leading to state of reactive hypercoagulability of the blood because of this reaction the frequency of myocardial infarction and sudden cardiac death are more prone in the morning. Ambulatory blood pressure study also confirmed the presence of circadian rhythm as in[4].

Pulsatile drug delivery system is a controlled drug delivery system where drug is released after a preprogrammed lag time. Various approaches have been used to design a pulsatile release formulation, erodible devices provided with hydrophilic polymer coating are widely used and such a system when exposed to dissolution medium undergo swelling, dissolution and/or erosion. Lag time in such a system can be controlled by using various hydrophilic polymers such as HPMC, polyethylene oxide, sodium alginate, sodium CMC. The concentration and viscosity of these polymers play a significant role in controlling the lag time and release pattern as in[5].

A Capsular system in which the body part coated with impermeable polymer and hydrophilic matrix plug sealing the drug formulation is used to prepare pulsatile drug delivery system. Upon contact with aqueous fluids a rapid dissolution would occur and plug undergoes a gradual swelling and finally expluded from the body thus allowing the drug to release. The lag time in such formulation is

controlled by the time needed for the plug removal and its duration depends on the physical, chemical nature, size and position of the plug. On the other hand an insoluble plug and semi permeable capsule body containing active ingredient is also used, the influx of water into capsule would lead to surge in its internal pressure ultimately resulting in plug expulsion and drug release as in[6]. Osmotic pumps are also used to achieve pulsatile release from the formulation.

Metoprolol tartarate is selective beta adrenoreceptor blocking agent used to treat hypertension, angina and heart attack.

The aim of the present work is to develop a simple one pulse drug delivery system based on dry coated tablet preparation. The system consist of a core tablet containing the drug, an impermeable outer shell and top cover layer barrier that dissolves at predetermined time. Cellulose acetate propionate is used as insoluble material and a blend of sodium alginate 500 cps and sodium alginate 2000 cps used as hydrophilic top layer. The hydrophilic polymers concentration is selected using 3^2 factorial designs to get the desired pulsatile release. The drug is released after removal of top layer of hydrophilic polymers and the lag time being adjusted by properties of the material in top cover, metoprolol tartarate is used as model drug

2. Material and Methods

Metoprolol tartarate is received as gift sample from Torrent research centre Ahmadabad, cellulose acetate propionate is purchased from Arcos Organics New Jersey USA. Sodium alginate 500 cps is purchased from Finar Chemicals Ltd Ahmadabad and Sodium alginate 2000 cps is purchased from loba chemie Mumbai.

Table 1. Formulation Chart

Formulation code	Sodium alginate 500 cps (X1)	Sodium alginate 2000 cps (X2)
SA1	-1	-1
SA2	-1	1
SA3	-1	+1
SA4	1	-1
SA5	1	1
SA6	1	+1
SA7	+1	-1
SA8	+1	1
SA9	+1	+1
C1	-0.5	-0.5
C2	+0.5	+0.5

Sodium alginate 500 cps (X1)   Sodium alginate 2000 cps (X2)
- 1 = 55 mg   -1 = 30 mg
1=65 mg   1 = 40 mg
+1= 7   +1 = 50 mg

The tablets are prepared based on 3^2 factorial design, concentration of Sodium alginate 500cps and Sodium alginate 2000 cps are selected as two independent variable .Three level determined from preliminary studies of each variable are selected and totally 9 batches are prepared

Table 1. The tablets are compressed using Karnavati minipress and the system consists of core in cup tablet. The core tablet is prepared with 100 mg of metoprolol tartarate using 7 mm punches further 9 mm punches are used to prepare core in cup tablet. Cellulose acetate propionate 100 mg is placed at the bottom and gently compacted to make powder bed, core tablet is placed at the centre and impermeable cellulose acetate propionate 65 mg is placed at the sides of the tablet so that surrounding surface of core tablet was fully covered. On the top a blend of hydrophilic soluble polymer material (sodium alginate 500 cps and sodium alginate 2000 cps) is placed and finally compressed to get a core in cup table.

3. Evaluation

3.1. FTIR and DSC Studies

The formulation is subjected to FTIR and DSC studies to determine the compatibility of drug and excipients.

3.2. Pre Compression Parameters

The pre compression parameters evaluated include bulk density, tapped density, hausner's ratio,carr's index and angle of repose.

3.3. Post Compression Parameters

Post compression parameters evaluated are thickness, hardness, friability, weight variation of the tablets. Further the tablets are subjected to the following evaluation parameters.

3.4. Drug Content Estimation

Five tablets are taken and crushed, drug equivalent to 100 mg is placed in a stoppered 100 ml conical flask and drug is extracted with 25 ml of phosphate buffer PH 7.4 and filtered into 100 ml volumetric flask through Whatman No.1 filter paper (Mean pore diameter 1.5 µm) and volume is made up to 100 ml. Aliquots of the solution are filtered and analyzed for drug content by measuring the absorbance at 225 nm.

3.5. Quantification of Water Uptake

For studying the water uptake the dissolution beakers are marked with time points 0.5, 1, 1.5 up to 6.5 hours. One tablet is placed in each of the marked dissolution beakers containing Phosphate buffer PH 7.4 maintained at 37±0.5℃ and stirred at 50 rpm. The tablets are removed from the beaker after completion of the respective time and the excess water present on the surface is removed with the help of the filter paper the tablets are weighed on shimadzu digital balance. The increase in weight of the tablet reflects the water uptake. It is estimated by equation

Q=100 (Ww-Wi)/Ww

Where Q = the percentage of liquid uptake and Ww and Wi are the mass of the hydrated sample and initial starting dry weight respectively.

Prashant A. Borgaonkar *et al.*: Formulation and Evaluation of Pulsatile Drug Delivery System of
Metoprolol Tartarate Using Core in Cup Tablet

116

3.6. Top Cover Layer Expansion

The purpose of this study is to observe the top cover layer expansion and correlate with the lag time and drug release of the formulation. The tablet is attached to microscopic slide with adhesive and edges of the microscopic slides are tied with a thread and placed in a dissolution beaker (dissolution apparatus) containing 900ml of phosphate buffer PH 7.4 maintained at 37±0.5℃ and stirred at 50 rpm. At every 30 min interval the microscopic slide is withdrawn from the dissolution beaker with the help of the thread tied to the slides. The tablet is photographed using Samsung digital camera (NV 20) to study the top cover layer expansion and observe the influence of hydrophilic polymers on the lag time and release pattern.

3.7. In-Vitro Drug Release

Dissolution studies of metoprolol tartarate is carried out in phosphate buffer PH 7.4 maintained at 37±0.5℃ using USP XXIII tablet dissolution test apparatus-II (Campbell electronics DR-6 dissolution apparatus) at 50 rpm. 5ml samples are withdrawn every 30 minutes filtered and analyzed at 225 nm using PG instruments UV-Visible spectrophotometer, equal volume of dissolution medium is replaced immediately.

3.8. Radial and Axial Measurement

The aim of the study is to measure the radial and axial expansion because of swelling. A tablet is attached on a microscopic slide with adhesive and both ends of slides are tied with thread and further it is placed in the dissolution beaker which contained phosphate buffer PH 7.4 maintained at 37±0.5℃. The slide is removed from the dissolution beaker at every 30 min with the help of thread and increase in diameter and thickness is measured with the help of scale

3.9. Statistical Analysis

Response surface modeling and statistical analysis are performed using (PCP disso 200 V3 software designed by Bharati vidyapeeth Poona college of Pharmacy). 3D plots and contour plots are constructed using the same software

3.10. Stereomicroscopic Studies

The prepared tablet contains three component insoluble polymer layer at the bottom and surrounding the core tablet, core tablet at the centre and hydrophilic swellable polymer at the top. To study the inner arrangement of the assembly the tablet is cut vertically at the centre and photographed using stereomicroscope.

3.11. Stability Studies

Short term stability studies are performed at a temp of 40±2℃ and 75±5 % RH over a period of three months(90 days).The tablets of the best formulation are placed in stability chamber(Thermal instruments and equipments) and samples are withdrawn every month visually examined and

evaluated for drug content and in-vitro dissolution studies.

4. Results and Discussion

4.1. FTIR and DSC Studies

In the present study the drug used is metoprolol tartarate, since the drug contain tartaric acid salt it gives a broad absorption peak around 3450 cm^{-1} corresponding to hydroxyl group of the drug as well as hydroxyl group of tartaric acid residue. It also contains aromatic C-C-H and aliphatic C-C-H which is indicated by the absorption peak at 2980 cm^{-1} and 2872 cm^{-1}. The N-H absorption peak of the drug as merged with the hump is observed at 3150 cm^{-1}, the IR of this compound also exhibited peak at 1690 cm^{-1} and 1632 cm^{-1} corresponding to the carboxylic acid residue of tartaric acid. All the data obtained from the IR spectrum are in agreement with the known structure of the metoprolol tartarate. The above drug is subjected to formulation with different excipients. In cellulose acetate propionate a weak absorption is noticed at 3497 cm^{-1} probably because of free hydroxyl group present in the moiety. The C-C-H of the type which is part of the ring structure of the sugar or C-C-H of the alkyl residue attached to the hydroxyl group are noticed at 2982 cm^{-1} and 2944 cm^{-1} respectively. The ester moiety of acetate as well as propionate have exhibited strong absorption peak at 1743 cm^{-1} which is the normal place of absorption of carboxyl esters.

Sodium alginate contains number of hydroxyl group of primary and secondary nature and hence IR spectrum of this compound gave a broad hump at 3400 cm^{-1} where in primary as well as secondary hydroxyl group absorption peak have been merged to give rise to a hump. It is noticed that only aliphatic C-C-H absorption peak are noticed in the IR spectrum suggesting that it has no aromatic residue. The sodium salt of carboxylic acid residue present in the molecule has also exhibited a broad peak at 1610 cm^{-1} these are the characteristics peak noticed for sodium alginate

A core in cup pulsatile drug delivery system of metoprolol tartarate is formulated and the formulation obtained is taken for IR measurement. The formulation contains metoprolol tartarate, cellulose acetate propionate and sodium alginate, the IR spectrum of the formulation exhibited a weak absorption peak at 3480 cm^{-1} and a peak at 3150 cm^{-1} due to the O-H and N-H of the drug moiety. The presence of C-H due to the aromatic C-H and aliphatic C-H observed at 2980 cm^{-1} and 2872 cm^{-1}, the strong peak are observed at 1739 cm^{-1} and 1632 cm^{-1} due to the ester group of the cellulose acetate propionate. The data obtained suggests that all the characteristic functionalities of the drug and the excipients have remained unchanged during the process of formulation, confirming that no chemical reaction has taken place.

The drug metoprolol tartarate is subjected to DSC measurements in which it starts melting at 121.23℃ giving rise to melting peak at 124.26℃ this is because pure drug is not used its salt is used and because of this broad melting

range is observed but not the Sharpe.

The formulation is subjected to DSC studies, the melting range is obtained at 123.14 ℃ and 66.58 ℃ thereby suggesting that drug and excipients have given rise to melting range 123.14℃ and 66.58℃. The reduction in melting range of the drug by 1℃ is due to the preparation of physical mixture during the formulation. This strongly suggests that drug has remained intact and not under gone any chemical change during the formulation process

A core in cup tablet for Pulsatile release of metoprolol tartarate is prepared. A total of 9 formulations are prepared by keeping the concentration of drug and impermeable layer constant, soluble hydrophilic polymer concentration is selected by using 3^2 factorial design.

4.2. Pre Compression Parameters

The bulk density is in the range of 0.64 g/cc to 0.68 g/cc and tapped density in the range of 0.75g/cc and 0.79 g/cc, carr's index in the range of 12.80 % to 15.18 %, hausner's ratio in the range of 1.14 to 1.17 and angle of repose in the range of 24.18 to 26.24 degree as shown in Table 2. It can be concluded from the study that formulation has good flow property and can be compressed into a tablet which meets all the requirements.

Table 2. Pre-compression studies

Formula tion code	Bulk densit y	Tapped density	Carr's index(%)	Hausner' s ratio	Angle of repose(de grees)
SA1	0.67	0.79	15.18	1.17	24.18
SA2	0.67	0.78	14.01	1.16	25.21
SA3	0.64	0.75	14.66	1.17	25.42
SA4	0.65	0.76	14.47	1.16	25.18
SA5	0.68	0.78	12.8	1.14	25.62
SA6	0.67	0.79	15.18	1.17	26.12
SA7	0.64	0.75	14.66	1.17	25.14
SA8	0.67	0.79	15.18	1.17	25.69
SA9	0.68	0.79	13.92	1.16	26.42

4.3. Post Compression Parameters

The appearance of the tablets is smooth and uniform, hardness of the tablets is in the range of 5.5 to7.0 kg/cm^2, thickness in the range of 5.5 to 6.5 mm, weight variation in the range of 3 to 4 % and drug content in the range of 98.40 to 99.82 %.

The prepared pulsatile drug delivery system has three parts a core tablet, impermeable layer and soluble hydrophilic top layer consisting of sodium alginate 500 cps and sodium alginate 2000 cps used in 3^2 factorial design .The top hydrophilic layer in the formulation is designed to absorb water and swell when it gets in contact with liquid, after swelling a gel layer is formed around the tablet which acts as a barrier that prevents the liquid from reaching the core surface. In total 9 formulations are prepared and the tablet with less amount of polymer on top layer achieved less swelling when compared to tablets having higher

concentration of polymer on top layer. Visual observation shows a greater swelling for SA9 formulation with polymer ration (+1,+1). Thus from the study it is observed that the top cover layer swelling and lag time are influenced by polymer concentration and viscosities.

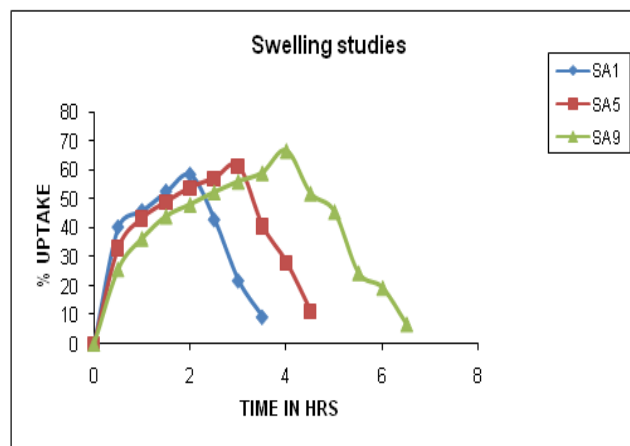**Figure 1.** Quantification of water uptake studies of SA9 formulation

Figure 2. Quantification of water uptake studies of SA9 formulation

Swelling of the polymer is an critical aspect governing the release pattern, the process starts immediately when the tablet gets in contact with liquid as shown in Figure 1/Figure 2 three formulation are selected to understand the swelling process and its influence on lag time and release pattern. SA1 with low concentration of polymer (-1,-1), SA 5 with medium concentration of polymer (1,1) and SA 9 with high concentration (+1,+1) are selected. Visual observation indicates formation of a gel layer at the top of the tablet when exposed to liquid, formulation SA9 exhibited higher extent of swelling in comparison of other two formulations.

In SA1 maximum swelling is obtained at 2.0 hrs and after reaching maximum swelling a gradual reduction in swelling is observed, the swelling process is terminated at 3.5 hrs. In SA5 maximum swelling is observed at 3 hrs and the process is terminated at 4.5 hrs and in case of SA9 maximum swelling is observed at 4.0 hrs and the swelling process is terminated at 6.5 hrs.

SA1 achieved maximum swelling of 58.31%, SA5

achieved maximum swelling of 61.34 % and SA9 achieved maximum swelling of 66.69 % respectively. Reduction of swelling is faster in case of SA1 followed by SA5 and SA9.

The lag time obtained in SA1 is 2.5 hrs which corresponds to time point 2.0 hrs where decline in swelling has started, in SA5 the lag time obtained is 4.0 hrs which corresponds to maximum swelling point 3.0 hrs and finally in SA9 lag time obtained is 5.0 hrs which corresponds to maximum swelling point 4.0 hrs.

4.5. Top Layer Expansion Study
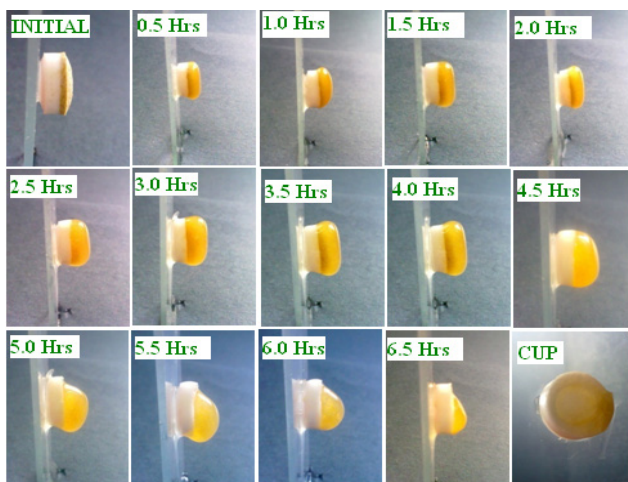
Figure 3. Top cover layer expansion studies of formulation SA9

The formulation SA9 with high concentration of polymer is selected for the study. Figure 3 demonstrate changes in top layer, 30 minutes time interval is selected in order to observe the changes that occur in top hydrophilic layer upon contact with liquid. After contact of tablet with liquid a fast absorption of liquid takes place and the polymer starts to swell as shown in Figure 3 (0.5 hr) as the time proceeds more swelling takes place and after reaching a maximum swelling a gradual decrease of polymer mass is noticed and this is more obvious after 4.5 hrs coinciding with this at 5 hrs the top polymeric layer is dilute enough to initiate the drug release as shown in Figure 3(5.0 hrs) /Figure 4. The polymer after initial swelling retains its intensity for a particular period and then starts reduction in its mass at 6 hrs 20.62 % drug is released and after 6.5 hrs the top layer is completely separated and 39.32 % of drug is released and with time more amount of drug is released and at 10.5 hrs 99.14 % of drug is released

4.6. In-vitro Drug Release

In-vitro dissolution studies of all the formulation confirmed a typical pulsatile release as shown in Figure 4 with a initial lag time (no release period) is observed and as the concentration of the polymer used in top layer increased the lag time is also increased leading to decreased release of the drug. The lag time observed in formulation SA1, SA2, SA3 with polymer concentration of sodium alginate 500 cps and sodium alginate 2000 cps (-1,-1), (-1,1) and (-1,+1) are 2.5 hrs, 3 hrs and 3 hrs, formulation SA4, SA5, SA6 with

polymer concentration of (1,-1), (1,1) and (1,+1) gave a lag time of 3.5 hrs,4.0 hrs and 4 hrs, formulation SA7,SA8, SA9 with polymer concentration of (+1,-1),(+1,1) and (+1,+1) gave lag time of 4.5 hrs,4.5 hrs an 5 hrs respectively. Influence of polymer concentration on drug release was similar to that of lag time, with increase in polymer concentration the release was prolonged. In formulation SA1 (-1,-1) 99.19 % drug is released in 5 hrs, SA2 (-1,1) 98.99 % drug released in 5.5 hrs, SA3 (-1,+1) 99.18 % drug released in 6 hrs, SA4 (1,-1) 99 % drug released in 7hrs, SA5 (1,1) 98.49 % drug released in7.5 hrs SA6 (1,+1) 99.31 % drug released in 8 hrs, SA7 (+1,-1) 99.63 % drug released in 8.5 hrs, SA 8 (+1,1) 99.14 % drug released in 9.5 hrs and finally formulation SA9 (+1,+1) 99.14 % drug released in 10.5 hrs.
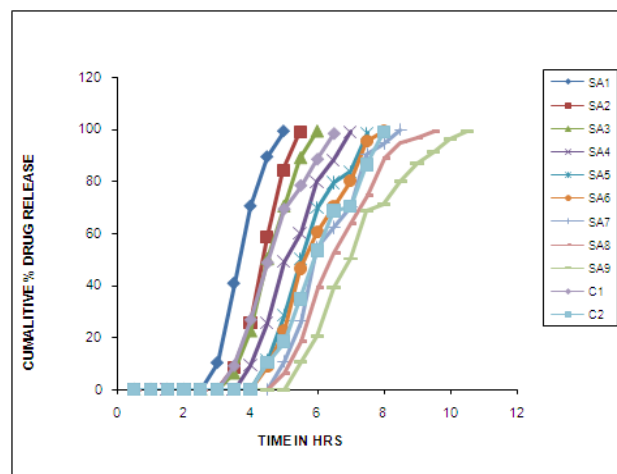

Figure 4. In-Vitro Release Profile of Formulation SA1 TO SA9

The T70 % and T90 % as shown in Table 3/ Figure 5 (time required for 70% and 90 % of drug to release from the formulation) is also influenced by the amount of polymer incorporated in the top layer. The T70 % and T90 % of SA1 (-1,-1) with low concentration of sodium alginate 500 cps and sodium alginate 2000 cps are 3.97 hrs and 4.53 hrs, SA5 (1,1) with medium concentration of polymer gave T70 % and T90 % values of 5.71 hrs and 6.85 hrs, SA9 (+1,+1) with high concentration of polymer gave T70 % and T90 % values of 7.85 hrs and 9.38 hrs. The concentration of polymer influences the extent of swelling and gel barrier layer formed on the top of the tablet higher T70 % and T90 % values formulation SA9 could be because of greater swelling and stronger gel layer barrier achieved by this formulation.

Table 3. Dissolution parameters of the formulations

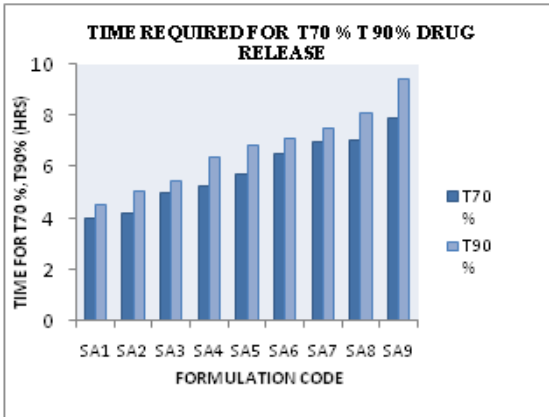| FORMULATION CODE	T70 % (Hrs)	T90 % (Hrs)
SA1	3.97	4.53
SA2	4.15	5
SA3	4.97	5.44
SA4	5.25	6.36
SA5	5.71	6.85
SA6	6.46	7.08
SA7	6.98	7.47
SA8	7.03	8.06
SA9	7.85	9.38

Figure 5. Comparison of dissolution parameters (T70 % and T90 %)

4.7. Radial and Axial Expansion Measurement

SA1, SA5 and SA9 formulations are selected to study radial and axial expansion due to swelling three formulation contained low, medium and high concentration of polymer on top layer.

In SA1 the initial diameter is 9 mm and maximum radial expansion of 10 mm (1.1 fold) is observed at 1 hr time interval followed by a gradual decrease, in SA5 the initial diameter is 9.5mm and maximum radial expansion of 11.5 mm(1.2 fold) is observed at 2.0 hrs and in SA9 the initial diameter is 9 mm and maximum radial expansion of 12.5 mm (1.4 fold) is observed at 2.5 hrs.

The axial (thickness) expansion is also measured in SA1 the initial thickness is 5.5 mm and maximum axial expansion of 12 mm (2.1 fold) is observed at 2.0 hrs, in SA5 the initial thickness is 6.0 mm and maximum axial expansion of 15.5mm (2.6 fold) is observed at 3.0 hrs and in case of SA9 the initial thickness is 6.0 mm and maximum axial expansion of 17.5mm (2.9 fold) is observed at 4.0 hrs respectively. The study confirms the preferential axial expansion, the polymer swells more in axial direction compared to radial direction.

4.8. Statistical Analysis

In order to investigate the factors systematically and to arrive at an optimum formulation a 32 factorial design is employed in the present investigation. A polynomial equation is derived for the lag time and T 70% (time required for 70% of drug release) using PCP disso 2000 V3 software (developed by Bharati vidyapeeth's Poona college of Pharmacy). The studied factors(independent variable) are concentration of sodium alginate 500 cps, sodium alginate 2000cps and the response (dependent variable) studied are lag time and T 70%.

A second order polynomial equation that fitted the data is as follows

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where Y is the independent variable bo is the arithmetic mean response of nine batches, b_1, b_2, b_{11} b_{12} and b_{22} are coefficient computed from the observed experimental values X_1 and X_2 stand for main effect and the polynomial terms X_1^2 and X_2^2 are included to investigate the non linearity.

The reduced model with significant values for both the factors are

Lag time Y1 = 3.777 + 0.916 + 0.250
T 70% Y2 = 5.818 + 1.461 + 0.513

Positive sign in front of the term indicate synergistic effect while negative sign indicate antagonist effect of the factor as in[10]. The positive sign observed in the present study indicated synergistic effect and as the concentration of polymer increase the lag time is increased and the time required for T 70% drug release is also is increased, the p value less than 0.05 observed indicant the significance effect.

4.9. Response Surface Analysis

The quadratic models generated by regression analysis are used to construct 3D response surface plots. A linear synergistic effect between two independent variable on response is observed. Figure 6/ Figure 8. The increase in lag time and T70 % with increase in polymer concentration can be attributed to the greater swelling of the polymer with increased concentration.Figure7/Figure9.

Two extra formulation C1 and C2 are designed as check points and evaluated for lag time and T 70 % .The predicted lag time are 3.239 hours and 4.315 and the observed lag time are 3.0 hours and 4.0 hours respectively. Similarly the predicted T70% value for C1 and C2 are 4.832 hours and 6.804 hours and the observed values are 4.911 and 6.986 hours respectively. The nearness of predicted and observed values indicates the validity of the derived equation for dependent variable.
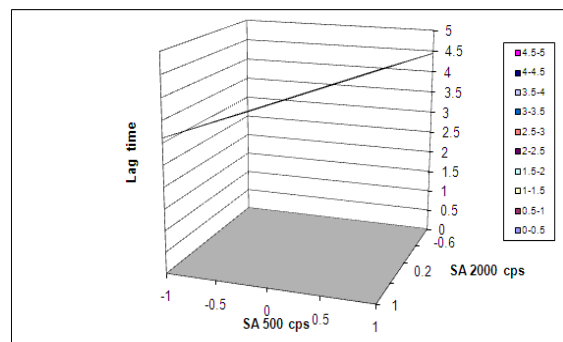

Figure 6. Response surface plots showing the influence of polymer con centration on lag time
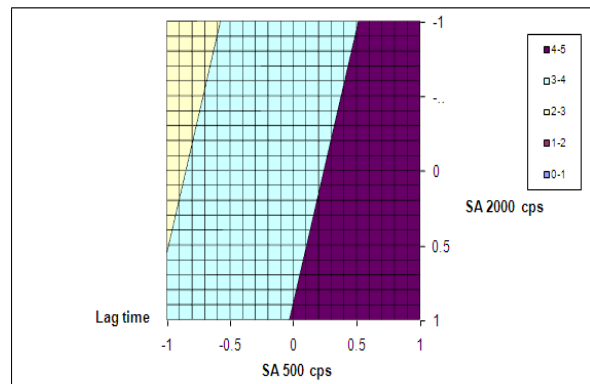

Figure 7. Contour plots showing the influence of polymer concentration on lag time
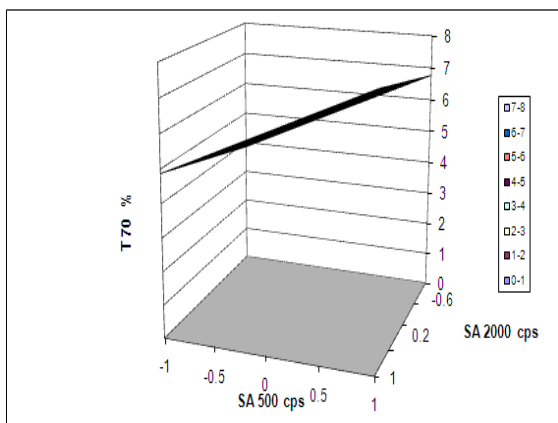
Figure 8.   Response surface plots showing the influence of polymer concentration on T 70% (Time required for 70% of drug release)
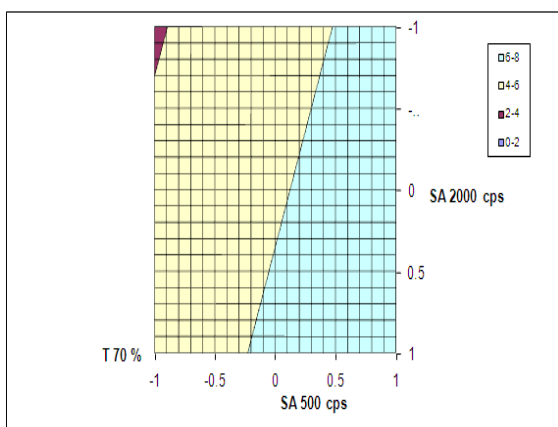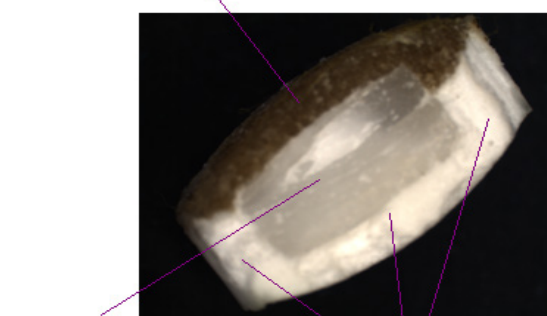

Figure 9. Contour plots showing the influence of polymer concentration on T 70% (Time required for 70% of drug release)

4.10. Stereomicroscopic Studies

Figure 10.   Stereomicroscopic images of SA9 formulation

To study the inner assembly of the three components, the tablet is cut vertically at the centre and photographed using stereomicroscopy. The images Figure 10 clearly shows three components a insoluble polymer at the bottom and surrounding the tablet except the top, core tablet at the centre and soluble hydrophilic polymer at the top of the core tablet.

The images confirm the proper positioning of the core tablet in the assembly.

4.11. Drug Release Kinetics

Table 4.   Regression coefficient R values

Formulation code	Zero order	First order	Higuchi	Peppa
SA1	0.869	0.537	0.765	0.974
SA2	0.810	0.304	0.697	0.954
SA3	0.840	0.510	0.715	0.946
SA4	0.877	0.210	0.811	0.967
SA5	0.896	0.309	0.755	0.967
SA6	0.878	0.254	0.751	0.960
SA7	0.873	0.225	0.755	0.962
SA8	0.889	0.052	0.755	0.940
SA9	0.906	0.083	0.762	0.967

Further the formulations are subjected to goodness of fit test by linear regression analysis according to zero order, first order, higuchi and peppas model. R values of all the formulation were in the range of 0.810 to 0.906 indicating a zero order release as shown in Table 4.

4.12. Stability Studies

The formulation SA9 is subjected to short time stability studies for 3 months (90 days) at $40 \pm 2\,^{\circ}\text{C}$ and 75 ± 5 % RH. Samples are withdrawn every month and analyzed for drug content and invitro release. The drug content and dissolution data of the stability studies does not show any significant variation as shown in table 5/Figure 11.

Table 5.   Drug content estimation of stability formulation SA9

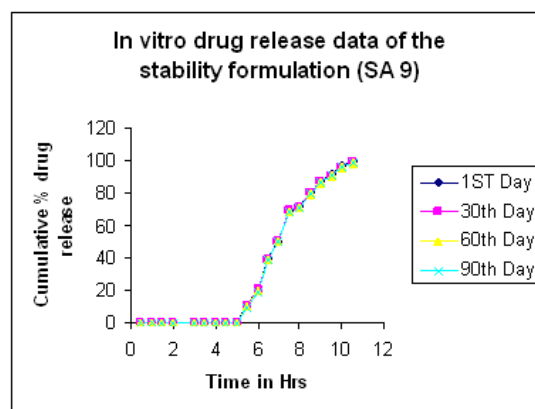| Sl. No.	Trial No.	1st day (%)	30th day (%)	60th day (%)	90th day (%)
1.	I	99.01	98.65	98.23	97.00
2.	II	98.80	98.50	98.21	97.01
3.	III	98.72	98.41	98.00	97.21
4.	Mean (X)	98.84	98.52	98.14	97.07
5.	S.D	±0.14	±0.12	±0.12	±0.11

Figure 11.   In-Vitro drug release studies of formulation SA

5. Conclusions

Core In cup pulsatile drug delivery system of metoprolol tartarate is formulated to increase the therapeutic effectiveness of the drug. The formulation contains three components a core table, impermeable layer and soluble hydrophilic polymer layer. The in-vitro dissolution studies indicates drug release after lag time and the lag time is controlled by the soluble hydrophilic polymer concentration and its properties. The lag time is increased by increasing the concentration of polymer. The formulation SA 9 with (+1,+1) concentration of sodium alginate 500 cps and sodium alginate 2000 cps gave a lag time of 5hrs and 99.14% of drug release in 10.5 hrs. Thus the drug release from the tablet can be tailored to meet the therapeutic requirement of the patients.

The formulation with greater concentration of soluble hydrophilic polymer swells to a greater extent and hence the swelling rate is directly proportional to the polymer concentration. Formulation SA9 shows a greater swelling compared to other formulation.

FTIR and DSC studies confirm that the drug and polymer are compatible with each other.

Short term stability studies indicate no significant changes in drug content and dissolution rates.

Thus with this system a pulsatile drug delivery system can be prepared to increase the therapeutic effectiveness of the drug.

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Prashant A. Borgaonkar *et al.*:   Formulation and Evaluation of Pulsatile Drug Delivery System of
Metoprolol Tartarate Using Core in Cup Tablet

122

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