Effect of hydrophilic polymer on bouancy of floating tablet prepared by wet granulation technique using *Musa paradisiaca* starch

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Abstract: The purpose of research was to develop and optimized Floating tablet of Metoprolol succinate using hydrophilic polymer (HPMC & Carbopol) by wet granulation method by using *Musa paradisiaca L.* starch as binding agent. A 3^2 full factorial design was applied to systemically optimize the drug release profile and floating lag time by using Design Expert Software 7.0. As the concentration of HPMC increases in formulation the floating lag time decreases and % drug release is retard as the concentration of Carbopol 971P increases. As per hardness and friability of floating tablet, it was assure *Musa paradisiaca* starch shows good binding property and longer floating time (24 hr.) favourable for sustained drug delivery of active pharmaceutical ingredient. Wet granulation method is useful for preparation of floating tablet that valuable for the buoyancy and gastro retentive drug delivery.

Key words: Floating tablet, *Musa paradisiaca L*., Hydrophilic polymer, Binder, Optimization

INTRODUCTION

Metoprolol succinate, β1- selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. [1] Metoprolol absorption in the duodenum and jejunum is directly proportional to dose availability. The maintenance of a constant plasma level of a cardiovascular drug is vital in ensuring the desired therapeutic response. Since the half-life of Metoprolol is ~3 to 4 hours, multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance.[2-6] It is need to develop sustained release gastro-retentive drug delivery to achieved higher bioavailability for longer period of time. The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time. [7] Indeed, gastric drug retention has received significant interest in the past few decades. Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time. [8] Gastro retentive drug delivery is achieved by maintaining buoyant dosage form on gastric fluid. [9]

In this study the gastro-retentive drug delivery system was achieved by developing floating tablet of Metoprolol succinate using wet granulation method. HPMC K100M was used as swellable polymer as well as release retardant. Carbopol 971P chemically polymer of acrylic acid are cross linked with either allyl sucrose or allyl ethers of pentaerythritol was used as release modifying agent. Carbomer is available in different grade out of this Carbopol 971PNF or Carbopol 974PNF used in oral preparation because of having low residuals of ethyl acetate. Sodium bicarbonate was used as gas generating agent [10] & *Musa paradisiaca* starch obtained from green fruit of *Musa paradisiaca L.* is belonging to family *Musaceae* was used as binder in 5% to 6% concentration. *Musa paradisiaca* starch has smooth surface texture and oval & polygonal shape having 25.95 µm to 27.09 µm × 9.19 µm to 15.28 µm in size. [11]

MATERIAL AND METHOD

Material: Metoprolol succinate was gift sample from Wockhard limited pharmaceutical company, Aurangabad, Maharashtra. Hydroxyl propyl methyl cellulose K100 as swelling polymer, Carbopol 971P as a release retardant, gas forming agent sodium bicarbonate and An. Citric acid, Banana starch as a binder isolated from green fruit of *Musa paradisiaca L.,* Maize starch, Magnesium stearate, talc, lactose and other excipients and chemicals were of analytical grade and purchase from research lab Finechem industries Mumbai, Maharashtra.

Experimental Design: A full factorial 3^2 design was applied for optimization of formula. In this study 2 factors were evaluated, each at 3 levels; 9 experimental trials were performed at all possible combinations as shown in table 01. The amount of HPMC K100M (X1) & Carbopol 971P (X2) were selected as independent variables.

The % drug release at 8 h & floating lag time (s) were selected as dependent variable. The data were fitted into Stat Ease, Design Expert 7.0.0 software and analyzed statistically using analysis of variance (ANOVA). [15] It is appropriate for investigating the quadratic response surfaces and for constructing a second-order polynomial model. The data were subjected for 3-D response surface methodology to determine the impact of HPMC K100M and Carbopol 971P on dependent variables. Tablet weight 315 mg was adjusted using lactose as diluents. [4, 12-14]

Preparation of floating tablet: Floating matrix tablet of metoprolol succinate was prepared by wet granulation method. All the ingredients were shifted through 60 mesh sieve separately. The granules were prepared by mixing required quantities of HPMC K100M, Carbopol 971P, Sodium bicarbonate, and Anhydrous citric acid and form wet mass using aq. *Musa paradisiaca* starch paste as a granulating agent. The granules were prepared by shifting through sieve no 16# before and sieve no 22 # after drying at 60°C for 30 minutes in an oven. Magnesium stearate and talc used as lubricant and glidant. Preformulation parameter were evaluated for granules and then compressed into tablets by using a single punch tablet compression machine (Royal Artist, Mumbai, India) fitted with 09 mm curve-faced punches. Compression was controlled to produce a 5 kg/cm^2 tablet hardness. [8, 15, 16]

Evaluation of Floating matrices Tablets: As tablets were evaluated for thickness, weight variation, hardness, and drug content. [17-19]

Floating Behaviour: Floating behaviour was determined by placing three tablets in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 ºC. The time interval between insertion of tablet in media and the buoyancy to the surface was taken as floating lag time. Floating time is the time duration for which tablet is float on media. [20]

Swelling Behaviour of Tablets

The swelling behaviour of the tablets was determined and performs in triplicate. In brief, a tablet was weighed (W1) using electronic balance (model: Shimadzu AUX220, Japan) and placed in a glass beaker, containing 200 mL of 0.1 N HCl (pH 1.2), maintained in a water bath at 37 ± 0.5 ºC. At periodic time intervals, the tablet were removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The swelling index (SI) was calculated using the formula;

SI = W2 - W1 / W1 Eq. 01

Table 01 Formulations using Banana starch binder as per 3^2 Full Factorial Design Layouts

Name of ingredient	Bs1	Bs2	Bs3	Bs4	Bs5	Bs6	Bs7	Bs8	Bs9
Metoprolol succinate	100	100	100	100	100	100	100	100	100
HPMC K100M	50	50	50	70	70	70	90	90	90
Carbopol 971P	10	15	20	10	15	20	10	15	20
Banana starch paste	5%	5%	5%	5%	5%	5%	5%	5%	5%
Sodium bicarbonate	75	75	75	75	75	75	75	75	75
Citric acid	20	20	20	20	20	20	20	20	20
Magnesium stearate	05	05	05	05	05	05	05	05	05
Talc	05	05	05	05	05	05	05	05	05
Lactose	50	45	40	30	25	20	10	5	-
Total	315	315	315	315	315	315	315	315	315

***In-Vitro* Dissolution Studies:** The in vitro release rates of Metoprolol succinate from the floating tablets were determined using the USP type II (basket apparatus). [21] The rotation speed and temperature was kept at 75 rpm & 37±0.5 °C. The 900 ml 0.1N HCl (pH 1.2) was selected as dissolution media and sink condition maintained by 10 mL dissolution medium at periodic time interval of 1hr. The samples were filtered through a whatman filter paper and assayed at 222 nm by UV spectrophotometry (UV). Six tablets of each formulation were used in the dissolution test. A linear correlation between the absorbency and Metoprolol succinate concentrations ($r2 > 0.997$) was obtained over the range of 5–50 µg/ml. [22, 23]

Characterization of Tablet by Differential scanning calorimeter (DSC): DSC curves were obtained by Shimadzu 60; Sample 1-5 mg was placed in aluminium pan press sealed with an aluminium cover. An empty sealed in the same way was used as reference. Thermograms were measured by heating the sample from 35 to 300^{0}C at the rate of 10^{0}C /min, under a nitrogen flow of 10 ml /min.

RESULT AND DISCUSSION

Musa paradisiaca starch is good binder for tablet and shows better hardness & friability when used in floating tablet. Gas forming agent sodium bicarbonate & citric acid is helpful for buoyancy of tablet. As the *Musa paradisiaca* starch is good binder and maintains intactness of tablet for longer period of time this property is

useful for the sustained delivery of drug for longer period of time. Preliminary study of granules shows the good flowing property and good compressibility as shown in table 02.

Table 02 Evaluation parameter of granules of Metoprolol succinate

Batches	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner ratio
Bt1	0.3756±0.004	0.4817±0.007	32.28	21.20±0.002	1.26±0.002
Bt2	0.3756±0.003	0.4817±0.005	33.42	22.03±0.004	1.28±0.004
Bt3	0.3949±0.002	0.4928±0.003	28.16	19.85±0.002	1.24±0.002
Bt4	0.4001±0.003	0.4952±0.002	29.30	19.20±0.002	1.23±0.002
Bt5	0.4060±0.003	0.4831±0.001	28.42	15.95±0.002	1.18±0.002
Bt6	0.3948±0.002	0.4933±0.004	31.16	19.97±0.003	1.24±0.003
Bt7	0.4066±0.004	0.4864±0.002	28.42	16.41±0.003	1.19±0.003
Bt8	0.4049±0.002	0.4822±0.003	29.30	16.02±0.002	1.19±0.002
Bt9	0.3938±0.001	0.4837±0.005	31	18.57±0.003	1.22±0.003

Hausner ratio also shows the flow properties as per the shape of particle, coarse spheres - 1.2, flakes greater than 1.6.

Evaluation of Floating Tablets

Physical Parameters: Formulations shows the hardness in between 4.66 to 5.33 Kg/cm^2, thickness in the range 4.32 - 4.4mm and % friability in between 0.22 to 0.33%, where as above all parameter are within the pharmacopoeias limit. The content uniformity test was also carried out as per literature and it was found that all batches show poor content uniformity. It was found that all batches show percent drug content within the range 82.82 – 91.73 %.

In-vitro buoyancy study: The all 9 batches shows the buoyancy, as the floating lag time is vary from 21 ± 1 s to 71 ± 1 s given in table 03. The generated CO_2 is trapped and protected with the gel formed by HPMC K100M and density of tablet is decreases below 1gm/ml. The both gas generating agent and swelling polymer HPMC K100M has positive effect on floating lag time. Floating time of tablet is extended to 24 hr. because of inter particle attraction of excipients due to binding property of *Musa paradisiaca* starch.

In Fig.1 shows floated tablet in beaker containing 0.1N HCl, the former photo was taken at 1 hr and later at 8 hr both of tablet have differ in size, as the time goes on tablet become swelled.

Table 03 Floating Lag Time of Formulation Bt1-Bt9

Formulation	Bt1	Bt2	Bt3	Bt4	Bt5	Bt6	Bt7	Bt8	Bt9
Floating Lag Time (s)	70.66±1.15	71±1	63.3±2.08	42±1	47.66±1.52	46.33±1.52	28±1	37±1	21±1

* Mean± S.D., n=3

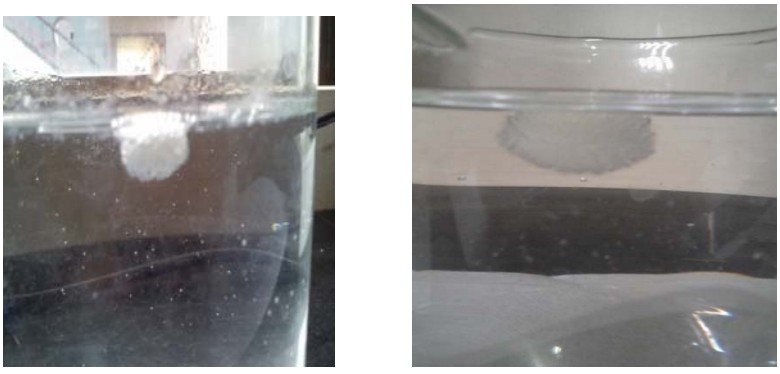

Fig. 1: A) Floating tablet after 1 hr. B) Floating tablet after 8 hr.

Swelling Behaviour of Tablets: From the swelling index study of all the batches, it was observed that the increase in the concentration of polymer increases the swelling property of the tablets as shown in fig 02. From the formulation batches, it was observed that the formulations batch 9 (Bt9) showed maximum swelling index. The swelling index is resembles to % water uptake, it enhanced with increased concentration of HPMC K100M as cellulose derivative and have a more tendency to attract water. Drug release is markedly influenced by the diffusion path length as drug release inversely proportional to diffusion path length. The diffusion path length

proportionally depends on hydration volume of the system as it expands swelling get increased that leads to increase in diffusion path length. Expansion of tablet dimension is due to more flexibility, mobility and expansion of the polymer chains which leads to marked swelling.

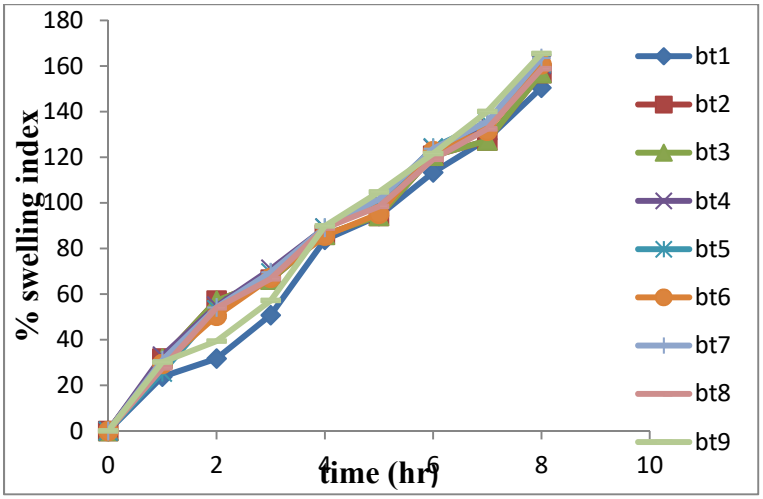

Fig. 02 % Swelling of Optimized Formulations (batch 1-9)

As the amount of HPMC K100 increased in the formulation it showed greater swelling value.

***In-vitro* Dissolution study:**

Hydrophilic polymer shows hydration of tablet matrix when come in contact with water, leading to swelling. Water decreases the glass transition temperature of the polymers to the experimental temperature and transfer the polymer from glassy state to rubbery state. At rubbery state polymeric chain become more flexible and mobile, favors the transport of water into the tablet and dissolved drug get diffuse out from the tablet core to the dissolution medium. Banana starch binds the particle that affects the release mechanism and diffusion of medium into the tablet and swellability of polymer. Banana starch adversely retards the drug release and prolongs the release of drug in medium. Percent cumulative drug release from different formulations is mentioned in table 04.

Optimization data analysis: Floating formulation of Metoprolol succinate using Banana starch (binder) was optimized by Response Surface methodology

Analysis of variance and model equations: Significance of this influence was statistically confirmed by ANOVA Test. In design expert software 7.0.0 a model equation was obtained to get the fit result for % drug release.

drug release coded factor = +81.31 - 4.33 * A - 2.78 * B + 1.80 * A * B + 1.55 * A^2 + 2.20 *B^2 Eq. 02

Table 04 Cumulative drug release of formulation(Bt1to Bt9)

Time (hr.)	Bt1	Bt2	Bt3	Bt4	Bt5	Bt6	Bt7	Bt8	Bt9
1	13.06± 0.65	12.56± 0.27	12.59± 0.66	12.41± 0.8	11.64± 0.11	11.87± 0.04	11.85± 0.09	11.23± 0.8	11.26± 1.8
2	21.60± 0.47	20.93± 1.05	20.82± 0.95	20.94± 0.9	19.19± 0.13	19.92± 3	21.05± 2.7	20.41± 3.2	21.1±5. 3
3	30.10± 1.5	29.53± 2.0	28.29± 1.0	29.92± 1.1	27.74± 1.5	28.68± 4.1	29.52± 2.8	28.53± 3	29.36± 6.1
4	43.34± 0.66	42.04± 2.2	39.82± 4.6	39.92± 2.4	33.98± 2.6	39.28± 2.2	41.34± 1.3	38.69± 2.5	37.94± 8.1
5	53.85± 0.37	51.28± 3.2	48.39± 5.7	51.69± 2	45.37± 2.5	48.89± 2.5	49.26± 2.1	47.94± 2.6	46.67± 3.6
6	62.42± 0.65	59.79± 4.4	60.20± 3.3	61.12± 1.5	56.49± 3	57.47± 2.9	58.12± 1.3	57.79± 1	55.5±3. 7
7	77.56± 3.34	73.19± 6.3	70.85± 2.1	73.72± 1.2	65.42± 5.1	68.50± 4.4	71.43± 1.6	68.22± 0.9	68.36± 6.4
8	94.29± 0.99	87.05± 7.2	84.74± 4.4	86.13± 3	81.29± 6.5	81.58± 2.2	81.83± 6.6	79.37± 3.4	79.41± 8.4

Mean±S.D. (n=3)

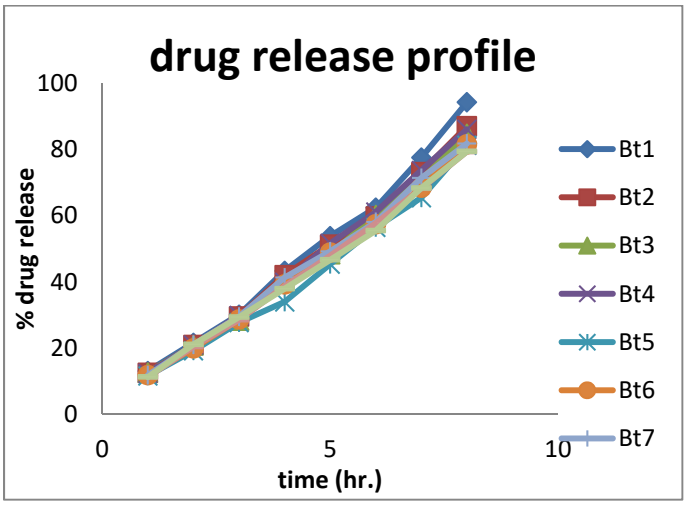

Fig. 03 The dissolution profile of floating tablets (Bt1-Bt9) of Metoprolol Succinate

Model assessment of the dependent variables:

Model for % release: It is shown that both of the process input variables have a significant effect on the percentage drug release. It is demonstrated that the percentage drug release of Metoprolol Succinate depends on the HPMC and Carbopol meanwhile these are most significant factors. HPMC K100 and Carbopol971p can showed the highest percentage drug release at their lower value. 3D response surface plot of the experimental model were drawn to show the effect of the variables on the percentage drug release. It is predicted that in between the range of concentration Carbopol 971p 10 – 13mg and HPMC K100M 50 – 60mg formulation shows the better drug release from the floating tablet. Hence optimized formulation is found in this range of polymer concentration.

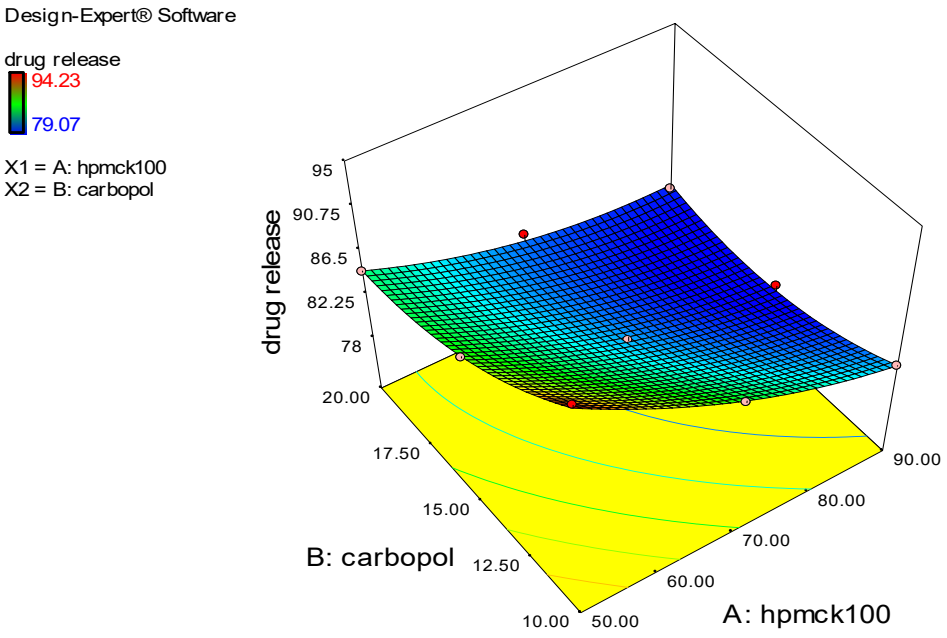

Fig. 04 3-D surface plot Three of Percentage Drug Release with Respect to HPMC K100 and Carbopol 971p

Model for floating lag time: 3D response surface plot of the experimental model were drawn to show the effect of the variables on the floating lag time. Fig. 05 shows the 3 D plot which illustrates the effect of HPMC K100 and Carbopol 971p on the floating lag time. It is shown that only HPMC K100M process input variable has a significant effect on the floating lag time. It is demonstrated that the floating lag time of Metoprolol Succinate

floating tablet depends on the HPMC. HPMC K100 shows lower floating lag time at their high value and Carbopol 971p does not show any significant effect on the floating lag time.

Optimization: The optimized solution obtained from the model was formulated and the results are performed in the triplicates for determination of %CDR, FLT, hardness, friability thickness and contain uniformity.

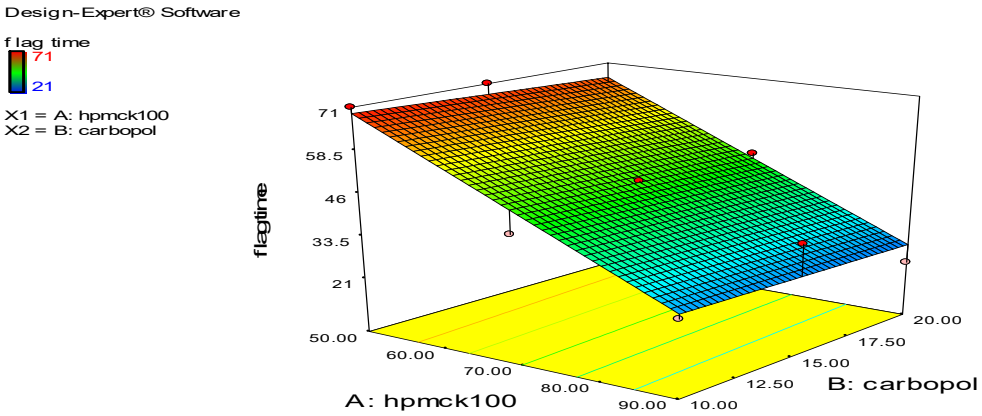

Fig. 05 3-D surface plot for floating lag time

Table 05 Composition of optimized formulation

Metoprolol succinate	HPMC K100M	Carbopol 971p	Banana starch (binder)	Sodium bicarbonate	An. Citric acid	Mg-stearate	Talc	Lactose	Total
100mg	59.40 mg	10.52 mg	5%	75 mg	20 mg	5 mg	5 mg	40.08 mg	315 mg

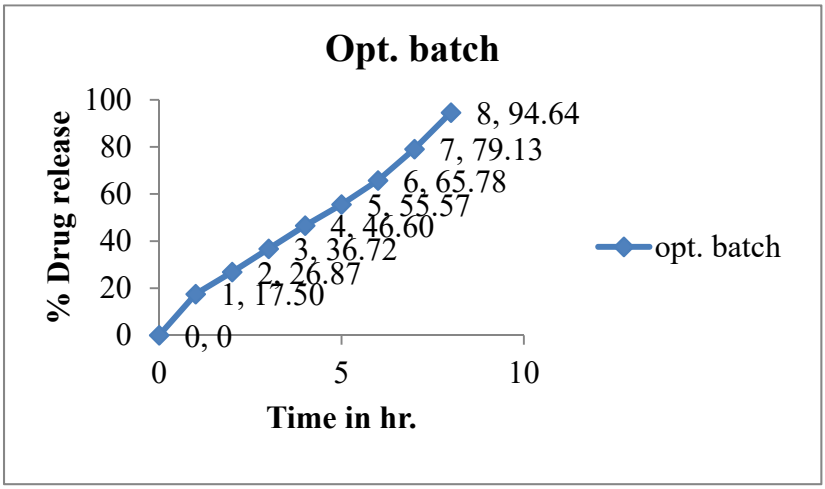

Fig. 06 Dissolution profile of optimized formulation of Metoprolol Succinate

Table 06 comparison of Predicted and experimental values

Responses	Predicted values	Experimental values
% release	89.15	94.63 ± 4.6
Floating lag time	59.51	40.5 ± 7.9

Table 07 the Dissolution Models for Matrix Tablets (O) Of Metoprolol Succinate

batch code	**R2**				**Korsmeyer Peppas (N)**
	Zero order	First order	Higuchi	Korsmeyer Peppas	
O	0.975	0.94	0.93	0.99	0.946

Tablets were compressed with hardness 5 ±0.31 Kg/cm^2 Thickness of tablets was found to be 4.29±0.10mm.Content uniformity was found to be 91.13 ± 0.23.All results obtained were complies with the

official standards. The comparison between predicted values and experimental values was carried out. As per coefficient of correlation the best fitted model for optimized formulation was Zero order and Korsmayer Peppas. This indicate that the drug release is controlled order and super case II transport indicate drug release does not change over time and drug release characterized by zero order.

CONCLUSION

Floating drug delivery of metoprolol succinate by using *Musa paradisiaca* starch as binder was developed. The swelling polymer HPMC K100M and gas forming agent sodium bicarbonate and citric acid was crucial ingredients to achieved buoyancy of tablet. The drug release rate was controlled by Carbopol 971P and binding property of *Musa paradisiaca* starch. The main benefit of *Musa paradisiaca* starch was maintaining the tablet intact for longer period of time and that helpful in extends the drug release for more than 18 hrs. The future scope of this study is extended release floating drug delivery using release retarded polymer and *Musa paradisiaca* starch as a binder in combination with swellable polymer and gas forming agent.

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