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Formulation and Evaluation of Once a Day Regioselective Dual Component Tablet of Atorvastatin Calcium and Metoprolol Succinate

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Abstract: The aim of present investigation was to develop and evaluate Atorvastatin calcium (ATC) & Metoprolol succinate (MP) in same dosage form, so there is no need to take individual dosage form. The regioselective tablets were prepared by direct compression. Polyox WSR N-60K and HPMC K100M was used as hydrophilic polymers. Effervescent was incorporated into the formulations to float the dosage form. The amount of polymer blends was optimized using 3^2 full factorial design. The swellings and in-vitro release were studied. Floating lag time and floating duration of prepared tablets was determined. All formulations floated for more than 18-20 h. More than 90% of Atorvastatin calcium was released within 1 h. HPMC K100M and polyox WSR N-60K sustained the release of Metoprolol succinate from the controlled release layer for more than 20 h. Diffusion exponents (n) were determined for all the formulations (0.45-0.89), so predominant drug release mechanism is non-Fickian (anomalous) transport. The stability study showed no significant change in appearance of tablets, floating characteristics and drug dissolution profile. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets.

Key-words: Regioselective tablet, Dual component, Optimization, Hydrophilic polymers, Gas generating agent.

Introduction

Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment. Hypertension and hypercholesterolemia are major risk factors in the pathogenesis of coronary heart disease (CHD).[1] These two risk factors coexist in patients more frequently than would be expected by chance alone,[2-3] and a syndrome of dyslipidemic hypertension has been identified. The current investigation aims at development of regioselective floating dual component (bilayer) tablets having different release patterns of Atorvastatin calcium (ATC) and Metoprolol succinate (MP) by using a gas generating agent.

Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia.[4] It is reported that the absolute bioavailability (*F*) of atorvastatin is 12% after a 40mg oral dose.[5] In the present study, an attempt was made to improve the dissolution of atorvastatin calcium using poloxamer 188 as a melt binder. Metoprolol succinate is a white crystalline powder with high aqueous solubility and high permeability throughout gastrointestinal tract.[6] The half-life of drug is relatively short approximately 4-6 hrs and in normal course of therapy drug administration is required every 4-6 hrs, thus warrants the use of sustained release formulation for prolong action and to improve patient compliance.[7-8]

Effervescent floating dosage forms prepared with the help of swellable polymers such as HPMC K100M, Polyox WSR N-60K, Polyox WSR 303 and effervescent compounds such as sodium bicarbonate, tartaric acid, and citric acid. When effervescent

compound comes in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The amount of polymer blends was optimized using 3^2 full factorial design.

The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood.

Materials and Methods

Materials

Atorvastatin calcium was kindly gifted by Unison Pharma. Pvt. Ltd. (Ahmedabad, India). Metoprolol succinate was kindly gifted by Lupin Pharma Pvt. Ltd. (Pune, India). Poloxamer 188 was gifted by Signet Chemicals (Mumbai, India). Polyox WSR N-60K, Polyox WSR 303 and HPMC K4M was gifted from The Dow Chemical Company, USA. Starch, sodium starch glycolate, cross carmellose sodium and microcrystalline cellulose were purchased from S.D Fine Chemicals (Mumbai, India). All other ingredients were of laboratory grades.

Methods

Preliminary Screening

Preliminary trial batches of immediate release layer of ATC

Preliminary trial batches of ATC were taken using poloxamer 188 as a melt binder in different ratios of ATC and poloxamer 188. The ratio 1:1, 1:4 and 1:8 were chosen and tablets having final weight of 200 mg were prepared by melt granulation followed by direct compression using Rimek Mini Press II MT (Karnavati Engineering Private Ltd., Kadi).

Preliminary trial batches of sustain release layer of MP

The sustained release layer composed of MP, various hydrophilic polymers such as HPMC K4M, HPMC K100M, Polyox WSR N-60K, Polyox WSR 303 and effervescent compound (sodium bicarbonate : citric acid in 3:1). Each 400mg tablet contains Mg. stearate (2%), Talc (1%) and microcrystalline cellulose q.s.

***Optimization of sustain release layer of MP* using 3^2 full factorial design**

A statistical model incorporating interactive and polynomial term was used to evaluate the response:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \ldots\ldots (1)$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

Polyox WSR 303 (X_1) and HPMC K100M (X_2) were selected as independent variables. The preparation and evaluation method for tablets and amount of MP were kept constant for all trials. The full factorial design layout, coded values for Polyox WSR 303 (X_1) and HPMC K100M (X_2), and composition of factorial batches MP1 to MP9 is shown in Table-1. All the batches contained 95 mg MP, 10% gas generating agent, 2% mag. stearate, 1% talc and MCC (q.s.)

Formulation of regioselective dual component tablet

For the preparation of the dual component formulation, the die of the tablet machine was filled manually with the weighed amounts of the sustain release component (MP). The sustain release component is compressed lightly and the fast release powder (ATC) was added to precompressed sustain release component. The dual component compressed tablet systems were prepared by direct compression, Rimek Mini Press II MT (Karnavati Engineering Private Ltd., Kadi). The formulation of dual component system is shown in Table-2

Physicotechnical parameter of regioselective tablet

Standard physical tests were performed for bilayer matrix tablets and average values were calculated. Mass variation was determined by weighing 20 tablets individually. Resistance to crushing was determined by taking 6 tablets from each formulation using a Pfizer hardness tester (Electrolab Pvt. Ltd., India). Thickness was determined by vernier calipers. Friability was determined by weighing 10 tablets after dusting and placing them in a Roche friabilator (Campbell Electronics, Mumbai, India).

Drug content

UV spectrophotometric method was developed and validated for simultaneous estimation of Atorvastatin calcium and Metoprolol succinate from the prepared formulations as per Ajit Kulkarni et al.[10]

Swelling study [1,12]

The swelling behavior of tablet described as the water absorbing capacity. The tablets were weighed individually (W_0) and placed separately in petridish containing cellophane membrane and incubated at 37 ± 1'C. At regular time intervals until 18 hours, the tablet was removed carefully. The swollen tablet was then

reweighed (Wt) and the % swelling were calculated using the following formula:

% swelling = {(Wt-W_0)/W_0} × 100 …..(2)

Where Wt is the weight of tablet at time t and W_0 is the initial weight of tablet. The swelling was calculated and then graph was plotted.

Floating lag time and floating duration of prepared tablets

Floating lag time and floating duration of all the batches were determined by putting the tablet in a beaker containing 0.1 N HCL.

In vitro drug release study of regioselective dual component tablet

The dual component tablet formulated as per the formula of optimized batches of ATC and MP was subjected for in vitro dissolution study. The dissolution (n=3) was carried out under sink condition using USP XXIV apparatus II (paddle) equipped with an auto sampler. The dissolution media was 0.1 N HCL. During dissolution, the dissolution media were maintained at 37±0.5 ºC and paddle speed was 75 rpm. Samples through a 40µ filter were taken automatically at each sampling time point.

The release of ATC and MP from dual component tablet was detected by applying simultaneous spectrophotometric estimation method developed and validated for estimation of ATC and MP in single dosage form. All dissolution tests were performed in triplicate. Pictures were taken at different intervals during dissolution for swelling, floating observations and physical changes associated with the delivery system.

The surface response plot [13]

The surface response plots were drawn using Sigma plot software (Jandel Scientific, San Rafael, CA).

Kinetic modeling of drug release [14]

To analyze the mechanism of drug release from the tablet, the dissolution data were fitted to the Zero-order equation; First order equation**;** Higuchi's equation and Korsmeyer-peppas equation equations.

Accelerated stability study of regioselective dual component tablet [15,16]

In order to determine the change in in-vitro release profile and floating behavior on storage, accelerated stability study of dual component tablet was carried out according to ICH guidelines. The formulation (n=3) were sealed in aluminium packaging and kept at 40 ºC in a humidity chamber having 75% RH for 3 months. At the end of the period, samples were analyzed for drug content, floating characteristics, hardness values, and in vitro dissolution studies.

Results and Discussion

Preliminary screening

Floating lag time and floating duration of prepared tablets

The floating lag time and floating duration of tablets were determined using a beaker containing 0.1 N HCL. It was shown that the floating lag time is directly proportional to the concentration of gas generating agent. Moreover the molecular weight of polymer also plays significant role on floating behavior; as the molecular weight of polymer increases, the time required to float the tablet also increases. The results of floating lag time for all the batches are presented in Figure-1.

The tablets of the batches F1-F8 remain float for 12-16 hours whereas formulation F9-F16 had floating duration of more than 21 hours. It was shown that the concentration of gas generating agent has effect on floating duration as high concentration of the gas generating agent affect the matrix formed by polymer.

Swelling study of factorial design batches

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water this gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored.[17]

The % swelling of the entire batch after 18 hours was in the range of 25.9-42.5 which may be because of high viscosity and high water retention property of HPMC K100M and Polyox WSR 303 (Figure-2). It was shown that the swelling property is directly dependent on polymer concentration and the formulations having 40% Polyox WSR 303 showed maximum swelling.

In vitro Dissolution study of factorial batches

Based on the data obtained from release profile of metoprolol from preliminary trial batches, the factorial design was applied to screen the optimum batch. All the factorial batches showed drug release upto 15-24 hrs. depending on the ratio of Polyox WSR 303 and HPMC K100M (Figure-3). The results shown that there is little effect of HPMC K100M as compared to polyox WSR 303 on the release of MP. At the initial stage, swelling occurs very rapidly due to entry of water via metastable pores in the tablet containing HPMC K100M and Polyox WSR 303. The Polyox WSR 303 performed better swelleng property

compared to HPMC K100M. So, more sustain release effectwas observed.

Formulations MP1-MP3 shows rapid disintegration, more erodibility and complete drug release within 15-18 hrs. Here, drug release was observed faster than the required release for once a day formulation.

Formulations MP7-MP9 shows drug release in a controlled manner for more than 24 hrs. The percentage drug release after 24 hrs. was 99.7%, 97.9% and 95.6% for Fomulations MP7, MP8 and MP9 respectively which was not sufficient to achieve 100% drug release.

Formulations MP4, MP5 and MP6 shows good release profile compare to other formulations and exactly fit in the criteria for drug release. (More than 95% drug release within 21 hrs. for once a day formulation). Among all the factorial batches, the Formulation MP7 containing 40% of Polyox WSR 303 and 10% of HPMC K100 M was considered as the optimum formulation.

Results of full factorial design batches

The t_{80}, Q_{15} and % swelling values of the nine batches showed wide variation. The results depicted in Table-3 clearly indicate that all the dependent variables are strongly dependent on the selected independent variables.

Statistical analysis of factorial design batches

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel 2003. The results are shown in Table-4. The data clearly indicate that the values of t_{80}, Q_{15} and % swelling are strongly dependent on the independent variables. The fitted equations (full and reduced) relating the responses t_{80}, Q_{15} and % swelling to the transformed factors are shown in Table-4.

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and mathematical sign it carries (i.e. positive or negative). Table-5 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.

The high value of correlation coefficient for t_{80}, Q_{15} and % swelling indicates good fit i.e., good agreement between dependent and independent variables. The equations may be used to obtain estimates of the responses as small error of variance was noticed in the replicates. The significant test for regression coefficients was performed by applying student *F* test. A coefficient is significant if the calculated *F* value is greater than the critical value of *F*.

Full and reduced model for t_{80}

The significant level of coefficient b_{11}, b_{22} and b_{12} was found to be *p=0.415, p=0.507 and p=0.730 respectively* hence it was omitted from full model to generate reduced model. The coefficients b_1 and b_2 were found to be significant at $p < 0.05$; hence they were retained in reduced model. The results for testing the model in portion are shown in Table-5.14. The critical value of F for $\alpha = 0.05$ is equal to 9.28 (DF = 3, 3). Since the calculated value (F = 0.0039) is less than critical value (F = 9.28), it may be concluded that the polynomial term b_{11}, b_{22} and b_{12} do not contribute significantly to the prediction of t_{80} and therefore can be omitted from the full model. The fitted equation for full and reduced model relating the response was given below.

Full model (t_{80})

$$Y = 14.97 + 2.53X_1 + 0.53X_2 + 0.04X_1X_2 + 0.12X_1^2 + 0.09X_2^2 \quad \text{……..….. (7)}$$

Reduced model (t_{80})

$$Y = 15.10 + 2.56X_1 + 0.56X_2 \quad \text{..... .....(8)}$$

Full and reduced model for Q_{15}

The significant level of coefficient b_{11}, b_{22} and b_{12} was found to be $p = 0.09$, $p = 0.42$ and $p = 0.13$ respectively, hence it was omitted from full model to generate reduced model. The coefficients $b_1$and b_2 were found to be significant at $p < 0.05$; hence they were retained in reduced model. The critical value of F for $\alpha = 0.05$ is equal to 9.28 (DF = 3, 3). Since the calculated value (F = 0.0039) is less than critical value (F = 9.28), it may be concluded that the interaction term and polynomial terms b_{11}, b_{22} and b_{12} do not contribute significantly to the prediction of Q_{15} and therefore can be omitted from the full model. The fitted equation for full and reduced model relating the response was given below.

Full model (*Q_{15})*

$$Y = 81.73 - 9.57X_1 - 2.87X_2 + 1.03X_1X_2 + 1.36X_1^2 - 0.43X_2^2 \quad \text{…….(9)}$$

Reduced model (*Q_{15})*

$$Y = 82.08 - 9.17X_1 - 2.47X_2 \quad \text{……(10)}$$

Full and reduced model for % swelling

The significant level of coefficient b_{11}, b_{22} and b_{12} was found to be $p = 0.19$, $p = 0.69$ and $p = 0.62$ respectively, hence it was omitted from full model to generate reduced model. The coefficients b_1 and b_{11} were found to be significant at $p < 0.05$; hence they were retained in reduced model. The critical value of F for $\alpha = 0.05$ is equal to 9.28 (DF = 3, 3). Since the

calculated value (F = 0.0040) is less than critical value (F = 9.28), it may be concluded that the interaction term and polynomial terms b_{11}, b_{22} and b_{12} do not contribute significantly to the prediction of % swelling and therefore can be omitted from the full model. The fitted equation for full and reduced model relating the response was given below.

Full model (% swelling)

$$Y = 34.54+4.96X_1 +3.41X_2+0.25X_1X_2 -1.06X_1^2 +0.28X_2^2 \quad \text{.....(11)}$$

Reduced model (% swelling)

$$Y = 34.02+4.966X_1+3.41X_1^2 \text{..... (12)}$$

The response surface plot

For drawing the conclusions, contour plot and response surface plot was used (Figure-4 a-f show the plot of amount of Polyox WSR 303 (X_1) and amount of HPMC K100M (X_2) versus t_{80}, Q_{15} and % swelling value respectively. The plots were drawn using Sigma plot software (Jandel Scientific, San Rafael, CA).

The plots demonstrate that X_1 and X_2 affect the t_{80}, Q_{15} and % swelling. Based on the results obtained for t_{80}, Q_{15} and % swelling, batch MP7 was selected as best batch. It was arbitrarily decided to select a batch of tablets that gives moderate floating behaviour and drug release in a control manner. The final selection is done after considering some aspects such as drug release profile % swelling and t_{80}.

A checkpoint batch was prepared at $X_1 = 0.7$ level and $X_2 = -0.3$. Table-5.13 indicates that the results of check point batch. From the regression analysis, it is expected that the value of t_{80} of the checkpoint batch should be 18.18; the value of Q_{15} of the checkpoint batch should be 75.95 and % swelling of check point batch should be 36.68. The results obtained with check point batch are very close to predicted values. Thus, we can conclude that the statistical model is mathematically valid.

Kinetic analysis of dissolution data

The in vitro release data obtained were fitted in to various kinetic equations (i.e. zero, first, higuchi and korsmeyer peppas kinetic model).

Batches MP1, MP2, MP4, MP7, MP8 and MP9 showed higher correlation with korsmeyer kinetic, while batches MP3, MP5 and MP6 showed higher correlation with zero order kinetics. The correlation coefficient of the optimized formulation MP7 is 0.9997. In the entire batches exponent 'n' was in between 0.45 and 0.89, so predominant drug release mechanism is non-Fickian (anomalous) transport.

Selection of best batch

It was arbitrarily decided to select a batch of tablets that gives good floating behaviour. The final selection was done after considering some aspects such as drug release profile, % swelling and t_{80}. On the basis of floating behaviour and dissolution release studies MP7 comprising Polyox WSR 303 (40%), HPMC K100M (10%) and amount of effervescent (10%) was considered a good candidate. The aim of study was, tablet should release more than 90% drug within 20-24 hrs and tablet should have satisfactory floating lag time and duration as well. Batch MP7 shows good release profile which exactly fit in our objective.

Physicochemical characterization of regioselective dual component tablets

The average weight (n=20), diameter (n=3), thickness (n=3) and hardness (n=3) of prepared dual component tablets were found to be 597.81±2.92 mg, 12.34±0.06 mm, 4.25±0.025 mm and 7.1±0.35 kg/cm^2 respectively. The drug content of prepared dual component tablets (n=3) was found to be 100.4 ± 1 % (MP) and 99.9 ± 1.62 % (ATC).

In vitro dissolution study for dual component tablet

More than 99% ATC released within 2 hours whereas MP releases in a sequential manner upto 21 hours as shown in figure-5. After the initial phase tablet swells very quickly when in contact with water figure-6. The release was dependent on the composition of the sustained release matrix tablet, particularly, the type and concentration of the polymers. The sustained release tablet kept the metoclopramide release slow for more than 20 hours.

Accelerated stability study of regioselective dual component tablet

The effect of aging was studied for the optimized formulation containing 30 mg of the drug. The data revealed no marked change in resistance to crushing, drug content and *in vitro* drug release. The constant *n* value (1.008 to 1.000 after 6 months) reveals that the release from the dual component mucoadhesive system is not affected by storage.

Table-1: Full factorial design layout				
Batch code	**Variable level in coded form**		**Actual value**	
	X_1	**X_2**	**X_1**	**X_2**
MP1	-1	-1	25	10
MP2	-1	0	25	15
MP3	-1	1	25	20
MP4	0	-1	33	10
MP5	0	0	33	15
MP6	0	1	33	20
MP7	1	-1	40	10
MP8	1	0	40	15
MP9	1	1	40	20
Check point	0.7	-0.3	37	13.5

- *X_1 code for Polyox WSR 303 and X_2 code for HPMC K100M.*

Table-2: Composition of regioselective dual component tablet	
Composition	**Quantity (mg)**
I.R. layer	
ATC	20
Poloxamer 188	120
Starch (3%)	6
SSG (3%)	6
Mg. stearate (2%)	4
Talc (2%)	4
Lactose (q.s. to 200 mg)	40
S.R. layer	
MP	95
Polyox WSR 303	160
HPMC K100M	40
Gas generating agent (10%)	40
Colorant (sunset yellow) (3%)	12
Mg. stearate (2%)	8
Talc (1%)	4
MCC (q.s. to 400 mg)	41

Table-3: Characterization of factorial design batches			
Batch code	**t_{80}**	**Q_{15}**	**% Swelling**
MP1	10.93	99	25.9
MP2	12.49	93.1	27.6
MP3	13.26	88	32.6
MP4	14.59	84.2	31.4
MP5	15.07	81.44	35.3
MP6	15.48	78.9	37.5
MP7	17.11	75.1	34.8
MP8	17.63	73.5	38.6
MP9	18.36	71.1	42.5
Check point	18.14	75.93	36.45

Table-4: Summary of regression analysis

Model	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
Coefficients for t_{80}							
FM	14.9795	2.5262	0.5330	0.1273	0.0998	0.0465	0.9992
RM	15.1065	2.5629	0.5697	-	-	-	0.9986
Coefficients for Q_{15}							
FM	81.7390	-9.5747	-2.8747	1.3614	-0.4385	1.0371	0.9992
RM	82.0853	-9.1713	-2.4713	-	-	-	0.9926
Coefficients for % Swelling							
FM	34.5444	4.9666	3.4166	-1.0666	0.2833	0.25	0.988
RM	34.0222	4.9666	3.4166	-	-	-	0.9765

Table-5: Calculation for testing the model in portion (ANOVA)

For t_{80}						
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	
FM	5	30.352	6.070	249.99	0.998	*F*cal=0.0039
RM	2	30.318	15.159	916.53	0.997	*F*tab=9.28
Error						*DF*=(3,3)
FM	2	0.048	0.024	-	-	
RM	5	0.082	0.016	-	-	
For Q_{15}						
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	
FM	5	393.96	78.79	258.44	0.998	*F*cal=0.0038
RM	2	388.82	194.41	169.08	0.985	*F*tab=9.28
Error						*DF*=(3,3)
FM	2	0.609	0.304	-	-	
RM	5	5.748	1.149	-	-	
For % Swelling						
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	
FM	5	220.734	44.146	52.119	0.988	*F*cal=0.0040
RM	2	218.048	109.024	125.142	0.976	*F*tab=9.28
Error						DF=(3,3)
FM	3	2.5411	0.8470	-	-	
RM	6	5.2272	0.8712	-	-	

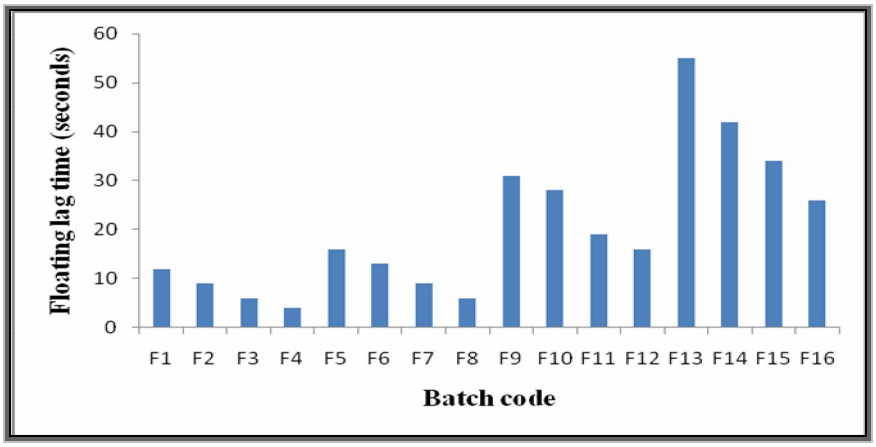

Figure-1: Floating lag time of batch F1-F16

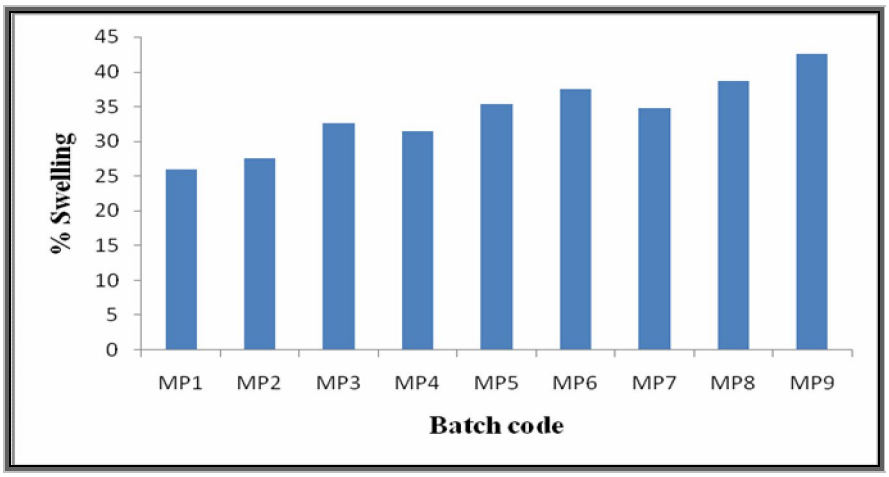

Figure-2: Swelling study of factorial batches

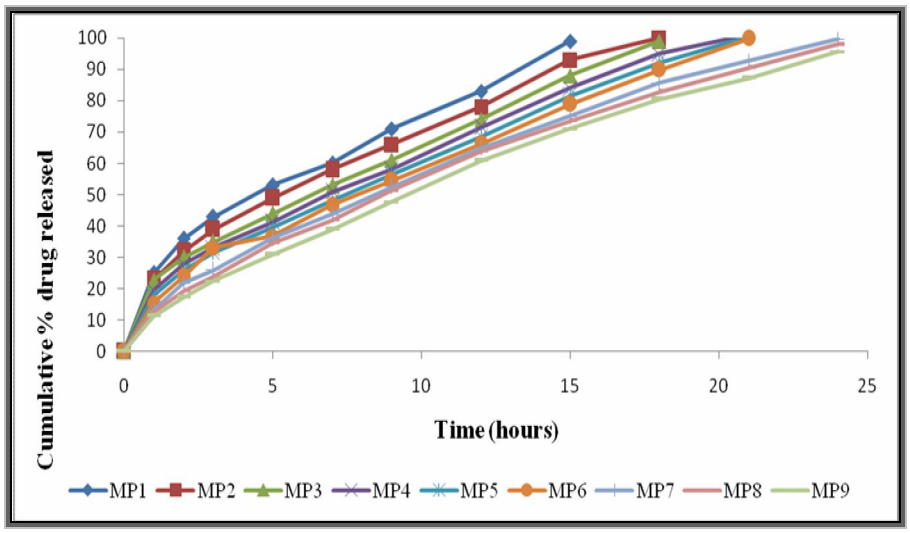

Figure-3: Release profile of MP from factorial batches MP1-MP9

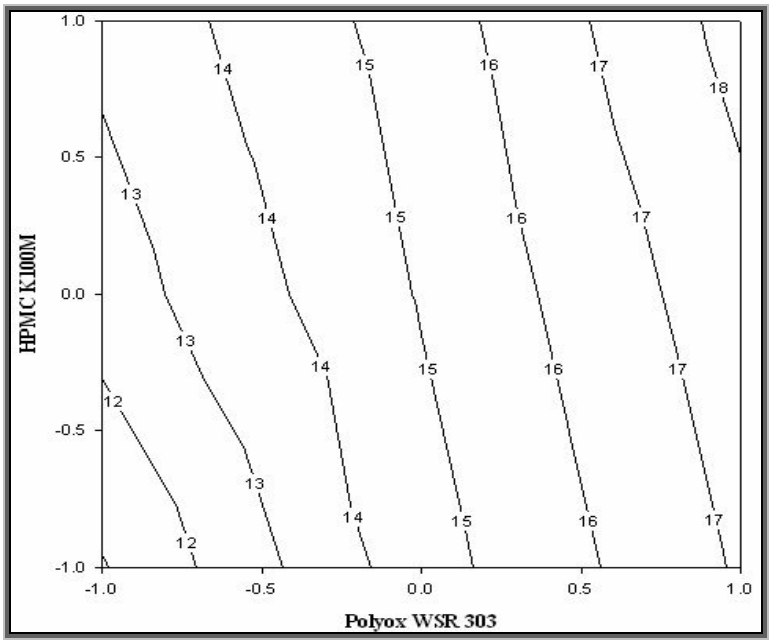

Figure-4a: Contour plot of t_{80}

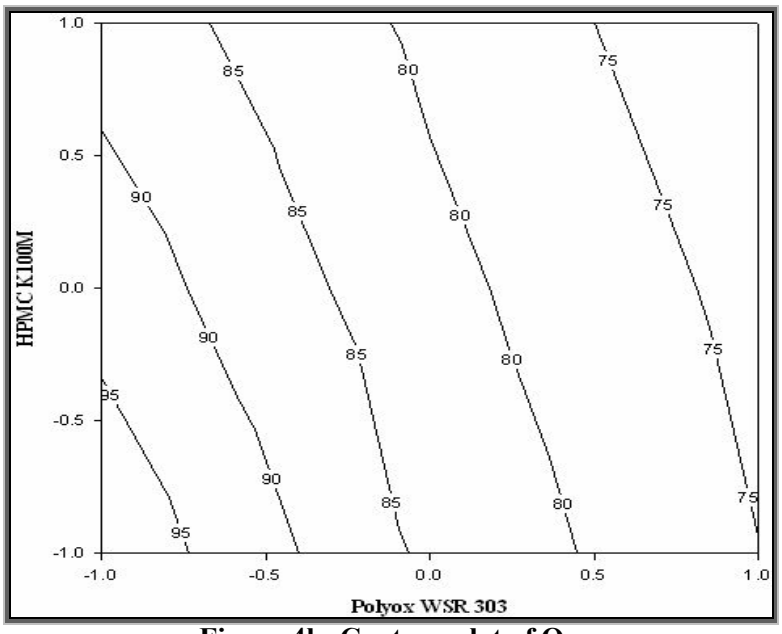

Figure-4b: Contour plot of Q_{15}

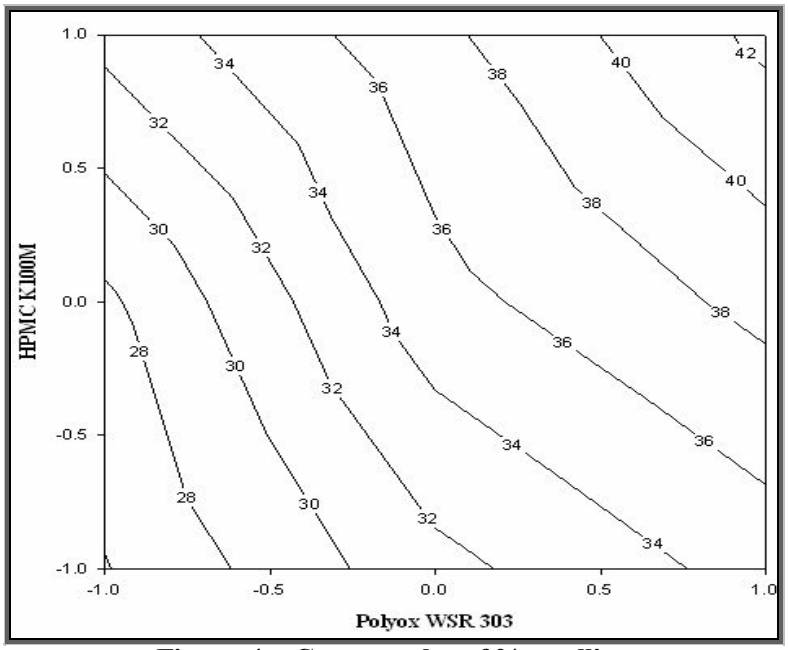

Figure-4c: Contour plot of % swelling

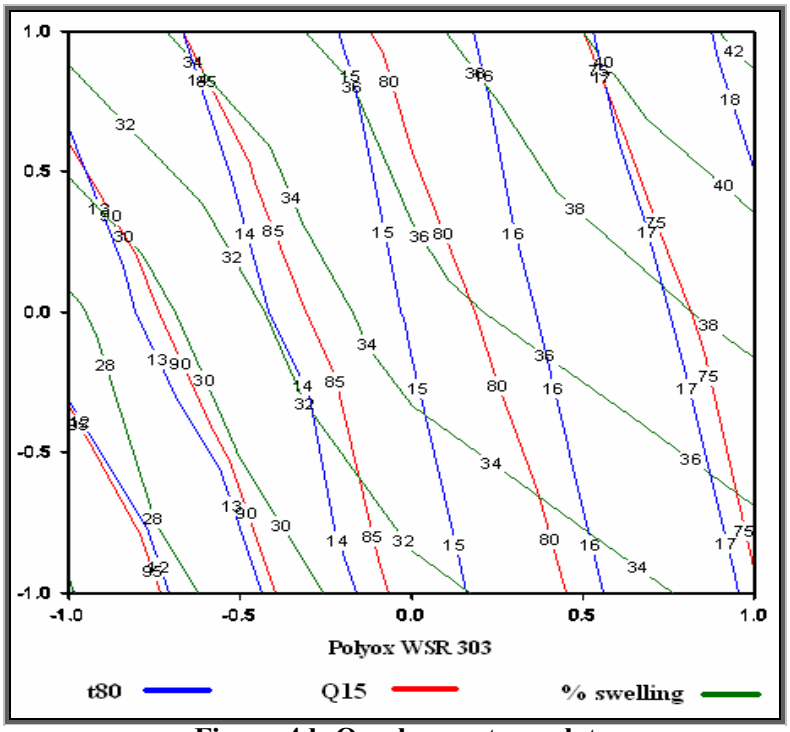

Figure-4d: Overlay contour plot

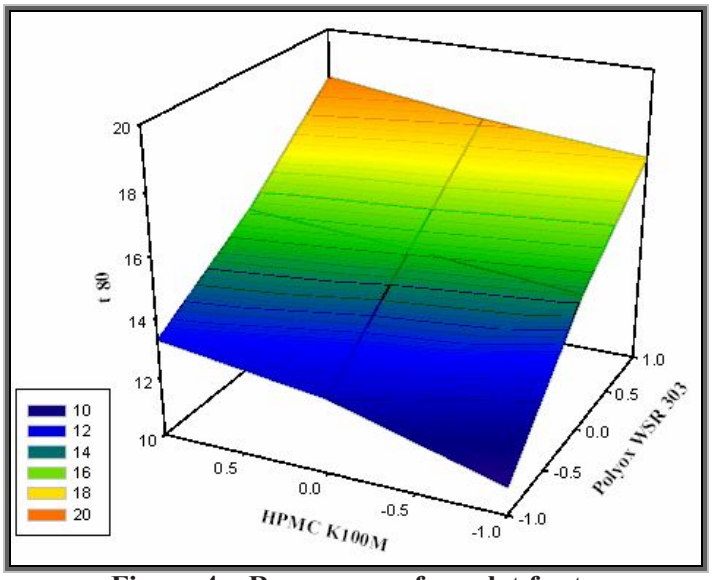

Figure-4e: Response surface plot for t_{80}

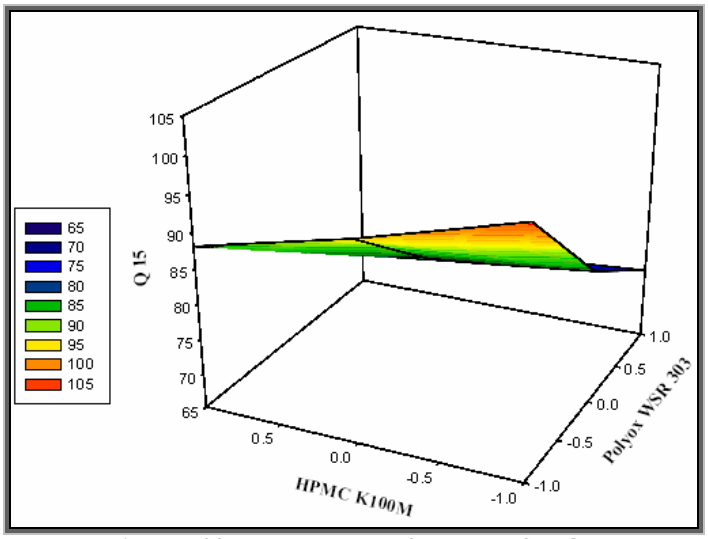

Figure-4f: Response surface plot for Q_{15}

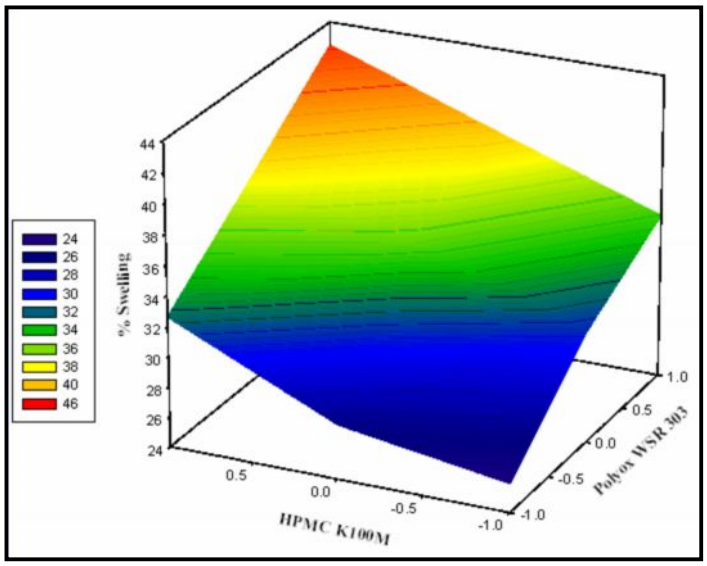

Figure-4g: Response surface plot for % swelling

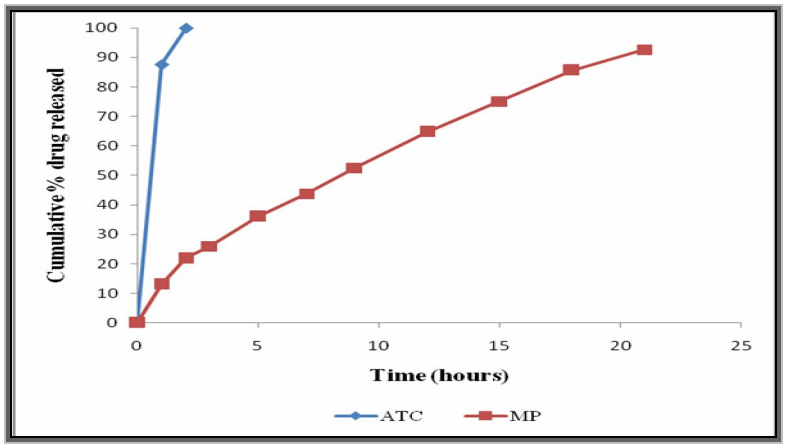

Figure-5: Release profile of ATC and MP from dual component tablet

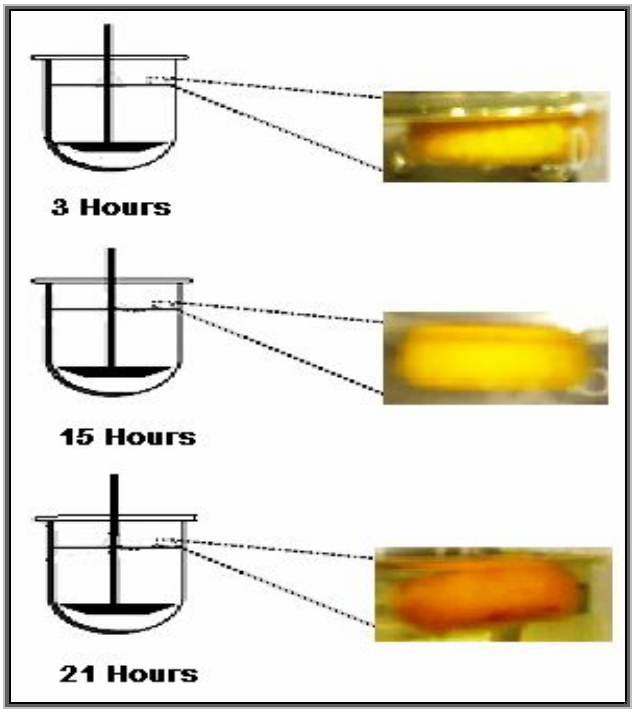

Figure-6: Actual photograph and relative location of swollen tablet in the dissolution vessel during in vitro release study

Conclusion

The design of two different release phases can be easily adjusted in both delivery rate and ratio of the dose fractions, according to the pharmacokinetics and therapeutic needs.

The results obtained with the dissolution test show that the release profile is dependent on both the polymer type and amount in sustain release layer.

The results of 3^2 full factorial design revealed that the polymer type and concentration of polymers significantly affect the responses, floating characteristics, % swelling, Q_{15}, t_{50} and t_{80}. Full and reduced models were derived for the prediction of the response variable, Y. Based on result of multiple linear regression analysis, it was concluded that satisfactory floating duration and good drug release profile of tablet could be obtained when X_1 kept optimum level and X_2 kept at low level. Finally it is concluded that by adopting a systematic formulation approach, delivery of two drugs from, a single dosage form can be obtained which could improve patient compliance and give better disease management.

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