Original Article

Systematic Development with Quality by Design Approach of Effervescent Floating Multiple Unit Minitablets of Metoprolol Succinate using Hydrophobic Grade of Gelucire

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ABSTRACT

Objective: The objective of this study was to systematically develop with Quality by Design (QbD) approach of Effervescent Floating Multiple unit Minitablets (EFMM) of metoprolol succinate (MS) for once-a-day dosing using hydrophobic grade of gelucire in order to increase gastric residence time. **Methods:** Risk assessment using Failure Mode Effect Analysis (FMEA) was conducted and further screened using taguchi design. A Box-Behnken Design (BBD) was adopted for the process of optimization. The dissolution profile of optimised formulation was compared with the marketed formulation. Drug compatibility study and stability study were also conducted. **Results:** After conducting risk assessment and screening amount of gelucire 43/01(G 43/01), HPMC K15 M (HM) and $NaHCO_3$ (SB) were found to be as significant factor. The process of optimisation results the single dose of EFMM MS consisting of 125 mg of G 43/01, 72 mg of HM and 28 mg of SB which shows an average of Floating Lag Time (FLT) within 3 min, Floating Time (FT) of 19 hr 36 min, time to release 50% of drug (t50) of 6 hr 38 min and time to release 90% of drug (t90) of 19 hr 12 min. The optimised formulation found to have better dissolution profile as compared to the marketed formulation. The stability study revealed no significant change in various parameters before and after storage. **Conclusion:** It can be concluded that an optimum combination of various excipient can be used to increase the gastric residence time, sustaining the drug release and ultimately achieve the desired objective of once-a-day dosing of MS.

Key words: Risk assessment, Failure mode effect analysis, Taguchi design, Box-Behnken design, Stability study.

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INTRODUCTION

Since a long time, oral Controlled Release (CR) formulations are popularly applied as drug reservoirs for controlling the release of drugs over a defined period of time,[1] Gastric Retention Time (GRT) in transit of the dosage forms has the major importance for drugs which are having site of absorption in different part of Gastro Intestinal Tract (GIT).[2] Short transit time of drug with absorption window in stomach causes release of drug in non-absorbing distal segment of GIT leading to poor bioavailability. These aspects lead to the development gastro retentive drug delivery systems.[3] GRDDS have been categorised into different system like bio-adhesive systems, floating systems, expandable systems and high-density systems.[4] One of the most suitable approaches is the designing of Floating Drug Delivery System (FDDS) using different rate controlling polymer and gas generating agent.[5] Vacuum, air or an inert gas can be incorporated in a floating chamber made up of polymer for formulation of floating drug delivery system.[6,7] Dose-dumping is the main disadvantage associated with

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sustained-release single-unit dosage form due to polymer failure.[8] Like other multiple unit systems, minitablets can be considered as promising approach which releases the drug from the subunits (minitablets) after disintegration of capsule.[9]

The drug having short biological half-life favours development of a Sustained Release (SR) while drug with absorption window in upper GI tract favours for development of floating drug delivery system, respectively.[10] Metoprolol Succinate (MS), a β-*selective adrenergic blocking agent* used to treat patients with hypertension or angina pectoris.[11] Considering the fact of MS having short half-life (3-4 hr) favours for development of a Sustained Release (SR) while absorption window in upper GI tract favours for development of floating drug delivery system.[12,13] Single dose per day is essential to reduce dosage frequency, facilitates patient compliance and decrease the risk of myocardial infarction.[14,15] It has been reported that MS absorption window mainly at duodenum and jejunum and also exhibits a high solubility at gastric pH.[16] These characteristics of MS suggest its high suitability for gastro retentive multiple unit drug delivery system. Hydrophobic polymer can be used in the preparation of sustained and floating formulations. Extreme hydrophobicity (HLB 1) of Gelucire 43/01 is the reason for its release retarding ability.[17] Due to its low melting point (43°C), it can be used for the preparation of sustained released formulations by melt granulation method. Patel *et al*. have reported that only gelucire 43/01 based granules could not achieve the desired sustainability and to sustain the release further release rate modifiers were used.[18] Jamula *et al*. reported that the drug release of gelucire 43/01 based granules was sustained by compressing into minitablets.[19] Thakkar *et al*. have reported that to achieve desirable floating for any gelucire based formulation incorporation of swell able polymer and gas generating agent is essential.[20] Higher concentration of gelucire 43/01 content promote better controlling of the drug release because of the increase of lipid matrix density and large diffusion path length.[21] Hence in the present research work, it is planned to use hydrophobic polymer like gelucire 43/01, release modulator like HPMC K15M, gas generating agent like $NaHCO_3$ in the formulation of Effervescent Floating Multiple unit Minitablets (EFMM) of Metoprolol Succinate (MS).

Quality by Design (QbD) approach is adopted by different researcher for the development floating DDS. Joseph M. Juran was first researcher who published the concept of QbD.[22] Quality by Design (QbD) is defined a systematic approach that starts with some justified objectives, identifying the process parameter with its control, quality risk management, screening of significant factor and its optimisation.[23,24] QbD methodology includes defining the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), risk assessment, screening of significant factor, data analysis using Design of Experiments (DoE) and optimisation using Response Surface Methodology (RSM) to plot the design space.[25,26] The QTPP is a prospective summary of the quality characteristics of a drug product in order to achieve the objective of formulation design of EFMM. The first step in the risk assessment is to identify all possible risk factors which could influence the CQAs of EFMM using the Ishikawa fish-bone diagram.[27] The next step is risk analysis to screen the influential factor. FMEA is a progressive and systematic approach in order to identify the various potential failure mode associated with the product or process design.[28] Design of Experiments (DOE) is a statistical technique which can be used for optimisation of any formulation with the regression analysis methods.[29,30] In recent year many researcher apply quality by design as tool in order to optimise and develop sustained release gastro-retentive dosage form. Chudiwala *et al*. developed sustained release gastro-retentive tablet formulation of nicardipine hydrochloride applying Quality by Design (QbD) approach. He found that the release of drug from the formulation effected by the concentration of variable such as glyceryl behenate (mg/tab) and HPMC K15M (mg/tab) whereas floating lag time influence by the concentration of sodium bicarbonate (mg/tab).[31] Rapoul K. *et al*. 2013 prepared effervescent floating tablets of metronidazole by applying the Box-Behnken design in order to prolong gastric residence time and improve local effect in stomach in the treatment of peptic ulcer.[32] On the basis of these literatures, the present research for the development and characterization of effervescent floating multiple unit minitablets of metoprolol succinate is performed using Quality by Design approach.

MATERIALS AND METHODS

Metoprolol succinate was received as a gift sample from Aurobindo Pharma (Hyderabad, India). Neusilin US2 was kindly provided as ex-gratis by Gangwal Chemicals Pvt Ltd (Mumbai, India). Gelucire 43/01 was provided as a gift sample from Gattefosse Pvt Ltd (Mumbai, India). All other chemicals and solvent were of analytical grade or highest quality and were used as such as obtained. This article does not contain any studies with human or animal subjects performed by any of the authors.

Methods

Identification and justification of various QTPP and CQAs

The QTPP of the EFMM was identified as an inevitable abstract of desired quality characteristics for the product element of a QbD approach. The QTPP elements were set-up considering the need of sustaining drug release, increasing the gastric retention time and reducing the dosage frequency. CQAs were identified with proper justification to achieve the formulation objective for the development of EFMM once-a-day dosing formulation.[33]

Risk assessment

At first risk factors were identified which could influence the CQAs of EFMM using the Ishikawa fish-bone diagram. Then risk analysis was carried out using FMEA to screen the influential factor. The Failure Mode Effect Analysis (FMEA) method was used as tool in order to conduct the risk analysis. Each factor was assigned a score in terms of Severity (S), Detectability (D) and Occurrence (O). S, D and O scores were multiplied together which gave the "Risk Priority Number" (RPN) for each of the risk factor. We assigned S, D and O of 10 for high risk case, 1 for least risk case and 5 for moderate risk case.[34,35]

Screening of factors using Taguchi design

Screening of factors was carried out employing a 7-factor 2-level Taguchi design in order to identify the influential factor affecting the CQAs. According to the design matrix a series of formulations were prepared by melt granulation method and characterised for the CQAs as described below. For each CQA regression equation were analysed to study the effect of each factor. Pareto charts and half normal were plotted to illustrate the influence of each factor on the CQAs. Significance of each factor was analysed using ANOVA as tool. On the basis of *P* value the significant variable were identified.[36,37]

Preparation of EFMM of MS

Melt granulation technique was adopted for preparing the solid dispersion of MS and gelucire 43/01. Gelucire 43/01 was heated on a water bath in a temperature range of 50-60°C with continuous stirring. To the molten liquid of gelucire 43/01, MS powder was added and stirred for 10 min. The preheated (80°C) neusilin US2 was added to the dispersion with continued mixing for 10 min in order to solidify the molten mass. The required amount of HPMC K15M, MCC and $NaHCO_3$ was added to the mixture and sieved through mesh no. # 40 to get uniform size granules. The resultant granules were compressed into 3 mm circular minitablets each containing 2.5 mg of MS. Twenty minitablets were filled into a gelatine capsule of size '0'.

Measurement of FLT

The floating lag time was determined by conducting vitro buoyancy studies for each of the formulation. Each of the EFMM was placed in a beaker containing 100 mL of 0.1N HCl. Floating Lag Time (FLT) may be defined as the time required for each of the minitablet to start floating on the surface of the dissolution media.

Measurement of FT

EFMM tablets were placed in USP dissolution apparatus- II containing 900mL of 0.1N to determine FT of each formulation. FT is the total time of floating when a dosage form is placed in a dissolution media.

In vitro dissolution studies (Measurement of t50 and t90)

In vitro dissolution studies of different EFMM were conducted in a USP dissolution apparatus- II taking 0.1 N HCl as dissolution medium. 5mL sample was withdrawn at regular time intervals up to 24 hr (1, 2, 4, 6, 8, 12, 16, 20 and 24 hr) and were analysed using UV-spectrophotometer at 270 nm. The time taken to release 50% of drug (t50) and time taken to release 90% of drug (t90) were determined during the dissolution test.

Experimental design, optimisation and analysis

Systematic optimization of EFMM of MS was accomplished employing Box-behnken Design (BBD) with the help of design expert ver. 11.1.01 software (Stat-Ease, Minneapolis, MN). The highly influential factor finalised after screening and risk assessment studies were correlated with the Critical Quality Attributes (CQAs). According to the design matrix a series of formulations were prepared by melt granulation method and characterised for the CQAs as described above. For each CQA regression equation were analysed and by using response surface analysis contour plot and 3D plot were plotted. Optimisation of EFMM of MS were carried out by setting up the upper and lower limit of different CQAs. The overlay plot was constructed to identify the design space.[38,39]

Comparison of drug release kinetics

The drug release pattern of the optimized EFMM, marketed conventional tablet and marketed Sustain Release (SR) tablet were compared. The *in vitro* dissolution study was conducted as prescribed above using a USP dissolution apparatus- II.

Compatibility studies using Differential Scanning Calorimeter (DSC)

The pure MS, physical mixture and optimised EFMM were examined for compatibility study employing DSC (Shimazu Ltd., Japan). The heat capacity of MS, physical mixture and optimised EFMM was analysed and DSC

curve was plotted over a temperature rang in order to predict the thermodynamic compatibility.

Accelerated stability study

Accelerated stability study of the optimised EFMM of MS was conducted for a period of 6 months as prescribed in ICH guidelines. The formulations were examined at the time points of 0, 3 and 6 months for the different CQAs. ANOVA study was conducted in order to find any significant differences within the response obtained at different time point.

RESULTS AND DISCUSSION

Identification and justification of various QTPP and CQAs

On the basis of the objective to prepare sustain release gastro retentive system various QTPP elements such as dosage form, dosage type, dosage strength, route of administration, drug release profile and stability were set-up. The quality characteristics of the Effervescent Floating Multiple unit Minitablets (EFMM) of Metoprolol Sccinate (MS) along with justification have been discussed in Table 1. Various Qualities Attribute (QAs) such as physical attributes, the times required for 50% of the cumulative drug release(t50), the times required for 90 % the cumulative drug release (t90), Floating Leg Time (FLT), Floating Time (FT), bouncy percentage, drug content. The justifications for selection of CQAs affecting the EFMM of MS were depicted in Table 2. The times required for 50% of the cumulative drug release (t50),

Table 1: Quality Target Product Profile (QTPP) for Effervescent Floating Multiple unit Minitablets (EFMM) of Metoprolol Succinate (MS).

Product profile	Quality target	Justification
Dosage form	Multiple unit minitablets	In case of sustained-release single-unit dosage form a failure may lead to dose-dumping of the drug.
Dosage type	Gastroretentive dosage form	MS having short biological half-life and absorption window in upper part of GI tract which justify development of gastroretentive dosage form
Dosage strength	50 mg	Unit dose of MS
Route of administration	Oral	Recommended route for delivery of MS to reduce the hypertension like conditions
Drug release profile	Drug release in a controlled manner up to 24 hr	Helps in maintaining the therapeutic effect of drug for prolonged periods of time
Stability	6 months of Accelerated stability testing	To study the significant change of various CQAs during storage period

Table 2: Identification of Critical Quality Attributes (CQAs) of EFMM of MS.

Quality attributes of the drug product	Target	Is this a CQA?	Justification
Physical attributes	Acceptable to patients	No	Colour, odour and appearance were not considered as critical since efficacy of dosage form is not affected.
The times required for 50% of the cumulative drug release (t50)	In the range of 6 hr to 7 hr	Yes	Whether the release of the drug is slow enough which result in sustaining the release of the drug for at least 24 hr; hence was regarded as highly critical.
The times required for 90% the cumulative drug release (t90)	In the range of 18 hr to 20 hr	Yes	Cumulative drug release of 90% for a period in the range of 18 hr to 20 hr for a dosage form can fulfil the objective of sustain the drug release for 24 hr; hence was regarded as highly critical.
Floating lag time (FLT)	0-3 min	Yes	Minimum floating leg time required in order achieve better gastric retention; hence was taken up as highly critical.
Floating time (FT)	Floating time in between 18 to 24 hr	Yes	Gastric Retention Time (GRT) has the predominant role in overall transit of the dosage forms which must be adequate for the controlled release system; hence was regarded as highly critical.
Bouncy percentage	100%	No	Since all the minitablets in one capsule are expected to float with less variability hence considered as noncritical

the times required for 90% the cumulative drug release (t90), floating leg time and floating time were identified as the potential CQAs.

Risk assessment

Fish-bone diagram of different factor affecting CQAs of MS EFMM formulation was constructed for the identification of potential risk factors (failure modes) on the basis of literature and previous research experiences. Figure 1 portrays the resultant fish-bone diagram depicting the effect of man, material, measurement, process, equipment, environment on CQAs for the development of EFMM of MS. Based on the risk identification the risk analysis was carried out by assigning ordinal scores to each factor in terms of Severity (S), Detectability (D) and Occurrence (O) using FMEA tool. Table 3 illustrates the RPN scores obtained for potential risk factors (failure modes) using risk analysis tool FMEA. The calculated RPN scores represent their effect on drug product CQAs. A value of RPN above 250 was considered as the high-risk factors against the low-risk factors. High RPN scores (i.e. above 250) were observed in case of amount of gelucire 43/01(G 43/01), amount of HPMC K15 M (HM), amount of $NaHCO_3$ (SB), amount of Neusilin US2 (N US2), Compression Force (CF), Stirring Time (ST) and Melting Temperature (MT) respectively. These factors were further screened using teguchi design and other factors with a lower RPN were eliminated from further study.

Screening of factors using Taguchi design

Taguchi design was employed to screen factors shortlisted using FMEA analysis. Table 4 represents the

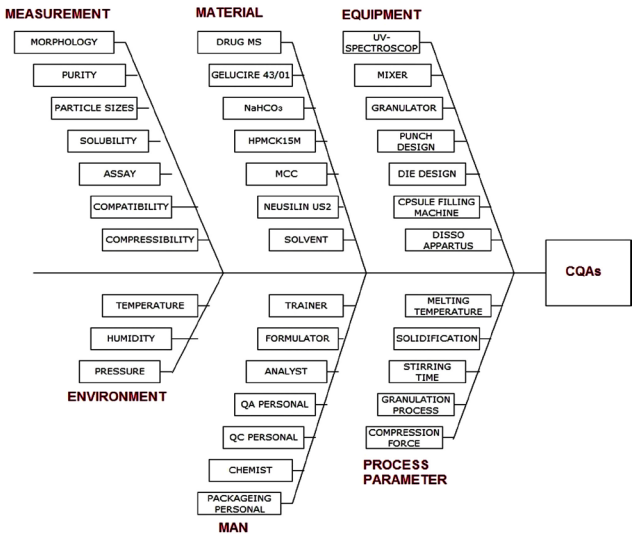

Figure 1: Fish-bone diagram depicting the factors identification that may have impact on CQAs such as Floating Lag Time (FLT), Floating Time (FT), time taken to release 50% of drug (t50) and time taken to release 90% of drug (t90).

Table 3: Factor analysis of material and process variables using FMEA as tool.

Failure Mode	RPN	S	O	D
UV-SPECTROSCOPY	36	3	4	3
MIXER	48	4	3	4
GRANULATOR	32	4	2	4
PUNCH DESIGN	16	2	4	2
DIE DESIGN	18	2	3	3
DISSO APPARTUS	36	3	4	3
CAPSULE FILLING	16	2	4	2
MELTING	72	4	6	3
SOLIDIFICATION	18	3	2	3
STIRRING TIME	280	8	7	5
GRANULATION PROCESS	36	3	4	3
COMP. FORCE	315	9	7	5
DRUG MS	12	3	2	2
GELUCIRE 43/01	378	9	7	6
$NaHCO_3$	336	8	6	7
HPMCK15M	288	8	6	6
NEUSILIN US2	294	7	7	6
MCC	60	5	4	3
SOLVENT	36	4	3	3
TRAINER	18	3	3	2
FORMULATOR	27	3	3	3
ANALYST	24	3	4	2
QA PERSONAL	36	4	3	3
QC PERSONAL	24	4	3	2
CHEMIST	18	2	3	3
PACKAGEING PERSONAL	24	3	4	2
MORPHOLOGY	40	5	4	2
PARTICLE SIZE	30	5	3	2
PURITY	60	5	4	3
SOLUBILITY	48	4	4	3
ASSAY	80	4	5	4
COMPATIBILITY	180	6	6	5
COMRESSIBILITY	40	5	4	2
MELTING TEMP.	288	8	6	6
HUMIDITY	24	2	3	4
PRESSURE	12	3	2	2

different formulation with coded value and actual value of each factor which was formulated and characterized for the various CQAs. The effect of various factor such as amount of gelucire 43/01(A-G 43/01), amount of HPMC K15 M (B-HM), amount of $NaHCO_3$ (C-SB), amount of Neusilin US2 (D-N US2), Compression force (E-CF), Stirring Time (F-ST) and Melting Temperature (G-MT) were studied. The equation in terms of coded factors for each of the responses was determined. The relative impact of each factor can be predicted by comparing the factor coefficients. Following are the polynomial equation obtained after a regression analysis for each CQA.

FLT=227.13+11.87A-50.37B-84.38C+12.12E+2.38G
FT=1068.13+31.13A+98.63B-44.62C+8.38E-4.87G
t50=302.50+62.00A+90.25B-31.75C+9.50E+3.25G
t90=987.50+92.00A+148.75B-30.25C+9.75E-4.50G

The influence of each factor on various CQAs was represented in terms of half-normal plots and Pareto charts as depicted in Figure 2. The influence of factors such as amount of gelucire 43/01(A-G 43/01), amount of HPMC K15 M (B-HM) and amount of $NaHCO_3$

Table 4: Design matrix for factor screening as per Taguchi design with seven factors at two levels along with actual and coded values.

RUN	A	B	C	D	E	F	G
1	2	1	2	2	1	2	1
2	1	1	1	1	1	1	1
3	1	2	2	1	1	2	2
4	1	2	2	2	2	1	1
5	2	2	1	2	1	1	2
6	2	2	1	1	2	2	1
7	1	1	1	2	2	2	2
8	2	1	2	1	2	1	2

FACTOR	CODE	LOW LEVEL (1)	HIGH LEVEL (2)
Gelucire 43/01 (G 43/01)	A	75 mg	150 mg
HPMC K15M (HM)	B	25 mg	75 mg
$NaHCO_3$ (SB)	C	2.5 %	7.5 %
Neusilin US2 (N US2)	D	1:1	1:2
STIRRING TIME (ST)	E	10 min	20 min
COMPERSSION FORCE (CF)	F	1N	2N
Melting Temperature (MT)	G	333 K	353 K

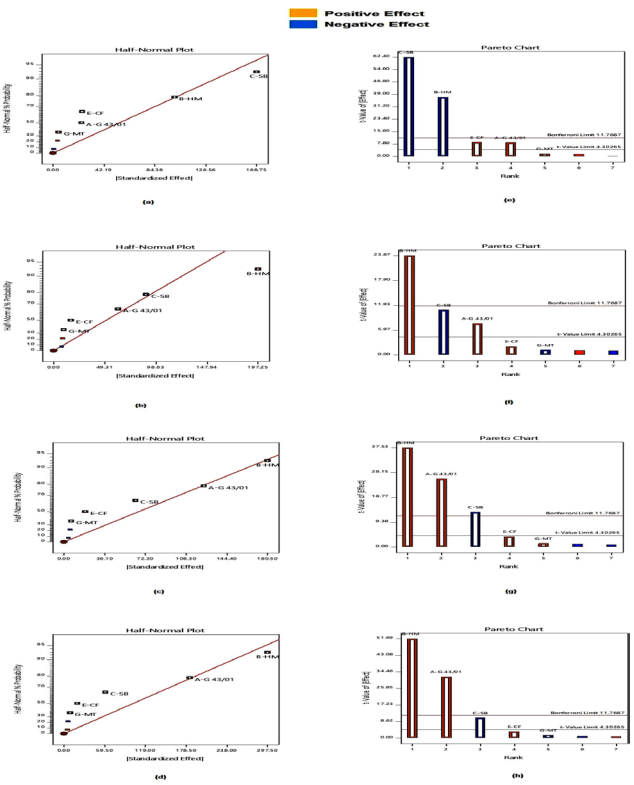

Figure 2: Half-normal plots (a, b, c, d) and Pareto charts (e, f, g, h) for screening of influential factors as per Taguchi design such as A: G 43/010, B: HM, C: SB, D: N US2, E: CF, F: S, G: MT.

(C-SB) were found to be above the *t*-value limit and/or Bonferroni's limits for all the CQAs hence considered as significant. Table 5 represents the summary of ANOVA for the factor screening and its significance as per teguchi design. The *P* values of the regression coefficients were determined to evaluate the significance of each factor on each of the response. The model factor such as amount of gelucire 43/01(A-G 43/01), amount of HPMC K15 M (B-HM) and amount of $NaHCO_3$ (C-SB) are significant science the *P*- value is less than standard α value (i.e. 0.05) and other factor having *P* values greater than 0.1000 indicate the model terms are not significant. Thus, from the factor screening study the factors amount of Gelucire 43/01(A-G 43/01), amount of HPMC K15 M (B-HM) and amount of $NaHCO_3$ (C-SB) were finally selected for further optimization.

Experimental design, optimisation and analysis

Regression equation analysis

Table 6 depicts a set of 15 experimental runs which are prepare as explained earlier in method section using a 3-factor at 3-level BBD. Each formulation were further characterised to study the effect of various factor such as amount of gelucire 43/01(A-G 43/01), amount

Table 5: Summary of ANOVA for factor screening and its significance as per Taguchi design.

Source	FLT	FT	t50	t90	Significance (YES/NO)
	P-values				
A-G 43/01	0.0127	0.0172	0.0015	0.0010	YES
B-HM	0.0007	0.0018	0.0007	0.0004	YES
C-SB	0.0003	0.0085	0.0057	0.0089	YES
D-N US2	>0.1000	>0.1000	>0.1000	>0.1000	NO
E-ST	>0.1000	>0.1000	>0.1000	>0.1000	NO
F-CF	0.0122	>0.1000	>0.0500	>0.0500	Only for one response
G- MT	>0.1000	>0.1000	>0.1000	>0.1000	NO

of HPMC K15 M (B-HM) and amount of $NaHCO_3$ (C-SB) on each of the CQAs. The equation in terms of coded factors for each of the responses was determined. The relative impact of each factor can be predicted by comparing the factor coefficients. Following are the polynomial equation obtained after a regression analysis for each CQA.

$$FLT=213.67+2.87A-38.13B-90.25C+1.50AB+11.75BC-5.33A^2+12.42C^2$$

$$FT=1011.33+70.50A+134.37B+31.38C+36.75AB+27.00BC+21.83A^2-+29.58C^2$$

$$t50=332.00+23.87A+47.00B+11.38C+10.25AB+10.75BC+7.75A^2+10.75C^2$$

$$t90=1001.00+68.12A+134.87B+29.25C+35.25AB+29.00BC+22.13A^2-+27.88C^2$$

Response surface analysis of contour plot and 3D plot

Response surface analysis of contour plot and 3D plot was carried out to evaluate the interaction effect of gelucire 43/01(A-G 43/01), amount of HPMC K15 M (B-HM) and amount of $NaHCO_3$ (C-SB). Figure 3 represents the contour plot and 3D plot of the various CQAs by observing the plot it can be predicted that at low level of B-HM also the prevalence of blue region i.e. low FLT was high only when the concentration of C-SB was on higher side. A comparative study among these formulations showed run no 12 have the minimum value of FLT i.e. 122 sec while run no 5 have maximum FLT value i.e. 368 sec. In case of FT, it was observed that at high level of both A-G 43/01 and B-HM the prevalence of red region i.e. high value of FT achieved while C-SB has negative influence on this CQA. The value of FT found to be in the range of 837 min (run 8) to 1272 min (run 9). Contour plot and 3D plot indicating that the value of t50 and t90 gradually increases with

Table 6: Composition of various EFMM of metoprolol succinate (MS) using Box-Behnken design with actual and coded values.

Run	Gelucire 43/01	HPMC K15M	$NaHCO_3$	FLT	FT	t50	t90
1	0	1	1	125	1216	403	1206
2	1	0	1	138	1168	386	1151
3	0	0	0	212	1015	337	1004
4	0	0	0	218	1012	332	1002
5	0	-1	-1	368	889	295	882
6	1	0	-1	311	1085	356	1071
7	-1	1	0	169	1044	347	1037
8	-1	-1	0	261	837	269	829
9	1	1	0	176	1272	422	1260
10	0	1	-1	281	1092	363	1085
11	0	0	0	211	1007	327	997
12	-1	0	1	122	1013	342	1005
13	-1	0	-1	312	985	318	977
14	0	-1	1	165	905	292	887
15	1	-1	0	262	918	303	911

FACTOR	CODE (-1)	CODE (0)	CODE (1)	
Gelucire 43/01	50 mg	100 mg	150 mg	
HPMC K15M	25 mg	50 mg	75 mg	
$NaHCO_3$	2.5%	5%	7.5 %	

increment in A-G 43/01 and B-HM and reverse with increment in C-SB. The results showed that an increase amount of SB did not affect much to FLT but decrease the t50 and t90. Both G 43/01 and HM has significant role for increasing value of t50 and t90.

ANOVA of the experimental design

Table 7 represents the summary of ANOVA for different factor and its significance with respect to quadratic model. After conducting the design matrix, the resultant model F-value for FLT, FT, t50 and t90 calculated as 120.43, 147.86, 63.50 and 151.57 respectively. These values imply the model is significant. *P*-values less than 0.0500 indicate model terms are significant. For the CQA FLT the model term such as B, C, BC, C^2 are significant. The lack of fit F-value for different CQAs was calculated as 7.75, 15.22, 2.24 and 18.51. It is not significant relative to the pure error which is desirable. *P*-values less than 0.0500 indicate model terms are significant. For the CQA FLT the model term such as B, C, BC, C^2 are significant. A, B, C, AB, BC, A^2, C^2 are significant model terms in case of FT. In case of t50 as CQA the model term such as A, B, C, AB, BC, C^2 are

significant. For t90 the ANOVA table suggest A, B, C, AB, BC, A^2, C^2 are significant model terms.

Summary of BBD quadratic model

Figure 4 illustrates the normal plot of residual and linear correlation plots between the predicted and observed responses for different CQAs. It can be predicted from the graph that there is a high level of correlation between actual and predicted value. The residual plot indicates high level of significance of BBD approach. Table 8 represents the summary of the BBD quadratic model in the process of optimization of the EFMM.

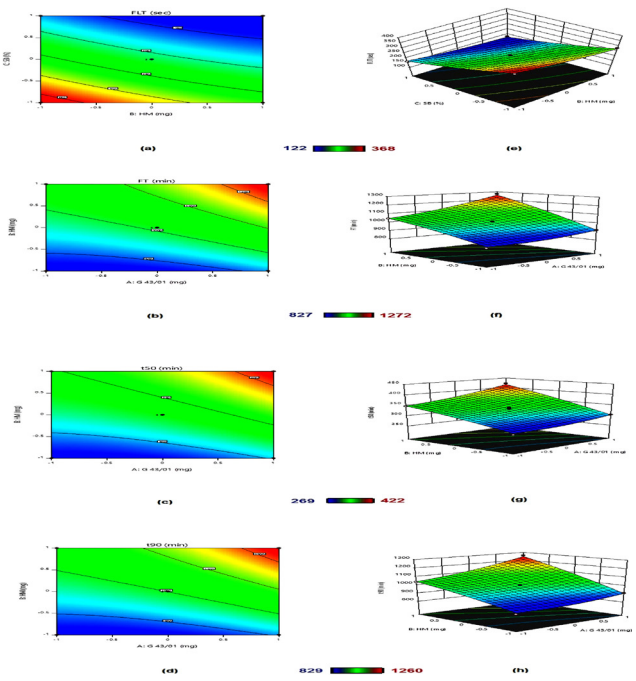

Figure 3: Contour plots (a, b, c, d) and 3D-Response surface plot (e, f, g, h) showing the influence of A: G 43/010, B: HM, C: SB on various CQAs.

For the CQA FLT the predicted R^2 value 0.9315 is very close to the adjusted R^2 value 0.9871. Precision ratio of 36.960 measures a good signal to noise ratio. Similarly, in case of FT the predicted R^2 of 0.9423 is in reasonable closer with the value of adjusted R^2 of 0.9895. A high value of precision ratio 40.220 indicates an adequate signal. For t50 the predicted R^2 of 0.8886 is in narrow gape with the adjusted R^2 of 0.9757. The precision ratio of 26.307 indicates an adequate signal. For t90 the predicted R^2 of 0.9433 is in reasonable agreement with the adjusted R^2 of 0.9898 and also a high value of precision ratio of 40.661 indicates an adequate signal.

Optimisation of EFMM of MS and construction of overlay plot to identify the design space

For obtimistion the desirable goal was fixed for variour responses. On the basis of the QTPP requirement the range of various CQAs were fixed with appropriate weightage which were then processed for optimisation. The summary of the optimisation process along with predicted and experimental value of responses of the optimised formulation are expressed in Table 9. The optimised single dose of EFMM of MS consisting of 125 mg of G 43/01, 72 mg of HM, 28 mg of SB, 125 mg of N US2, 100 mg of MCC and 50 mg of MS which showed an average of FLT within 3 min, FT of 19 hr 36 min, t50 of 6 hr 38 min and t90 of 19 hr 12min. The said optimized run exhibited process of controlled release and gastro retentive for one day and was found to be dependent on a particular pair and ratio of G 43/01, HM and SB. Figure 5 portray the overlay plot with design space and also depicts the selected optimised EFMM composition.

Comparison of drug release kinetics

Table 7: Summary of ANOVA for different factor and its significance with respect to quadratic model.

Source	FLT		FT		t50		t90	
	F value	*P* value	F value	*P* value	F value	*P* value	F value	*P* value
Model	120.43	< 0.0001	147.86	< 0.0001	63.50	0.0001	151.57	< 0.0001
A-G 43/01	0.9135	0.3831	255.40	< 0.0001	104.71	0.0002	248.27	< 0.0001
B-HM	160.65	< 0.0001	927.87	< 0.0001	405.79	< 0.0001	973.12	< 0.0001
C-SB	900.21	< 0.0001	50.58	0.0009	23.77	0.0046	45.77	0.0011
AB	0.1243	0.7388	34.70	0.0020	9.65	0.0267	33.23	0.0022
AC	0.9982	0.3636	4.86	0.0787	0.2067	0.6685	4.52	0.0868
BC	7.63	0.0397	18.73	0.0075	10.61	0.0225	22.49	0.0051
A^2	1.45	0.2823	11.31	0.0201	5.09	0.0737	12.09	0.0177
B^2	3.83	0.1076	5.64	0.0636	1.72	0.2471	4.75	0.0811
C^2	7.86	0.0378	20.76	0.0061	9.80	0.0260	19.18	0.0072
Lack of Fit	7.75	0.1164	15.22	0.0623	2.24	0.3238	18.51	0.0517

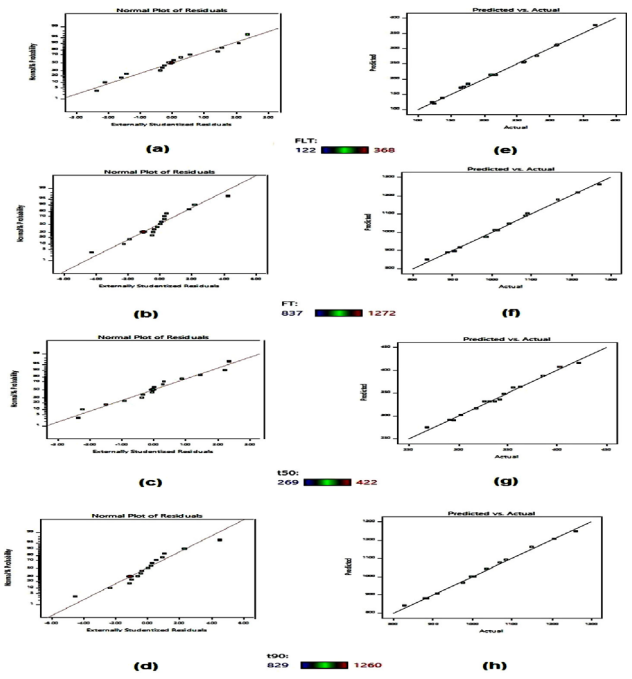

Figure 4: Linear correlation plots (a, b, c, d) and residual plots (e, f, g, h) between the observed and predicted values of various response variables.

Table 8: Summary of design of experiment with various parameters fitting to quadratic model.

Responses	R^2	Adj. R^2	Pred. R^2	Std. Dev.	Adequate Precision
FLT	0.9954	0.9871	0.9315	8.51	36.96
FL	0.9963	0.9895	0.9493	12.48	40.22
t50	0.9913	0.9757	0.8886	6.60	26.30
t90	0.9963	0.9898	0.9433	12.23	40.66

Table 9: Constraints for the process of optimisation of EFMM of MS using design of experiment.

Name	Goal	Lower Limit	Upper Limit	Coded value of factor with Predicted responses	Actual value of factor with Avg. Experimental responses (n = 6)
A:G 43/01	Range	-1	1	0.492	125 mg
B:HM	Range	-1	1	0.867	72 mg
C:SB	Range	-1	1	0.165	5.5%
FLT (sec)	Range	0	180	175.35	170.02 ± 2.86
FT (min)	Range	1080	1440	1182.87	1177.92 ± 31.82
t50 (%) (min)	Range	360	420	391.19	398.35 ± 11.11
t90 (min)	Range	1080	1200	1172.22	1152.92 ± 33.36

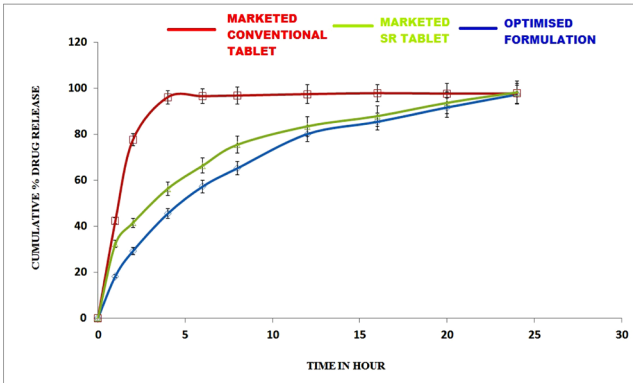

Figure 5: Overlay contour plot depicting the design space and delineate the optimized formulation.

The drug release pattern of the optimized EFMM, marketed conventional tablet and marketed Sustain Release (SR) tablet is illustrated in Figure 6. The optimised EFMM MS showed better dissolution profile than both the marketed formulation. The drug release pattern of the marketed conventional tablet showed more than 96% drug release within 4 h while in case of marketed Sustain Release (SR) tablet more than 30% of drug released at initial 1h only. Hence an optimum combination of gelucire 43/01 and HPMC K 15M provide a better controlled release pattern then the marketed formulation. Applying different kinetic model such as zero-order, first-order and Higuchi model the correlation coefficient (r^2) were calculated. The correlation coefficient (r^2) were found to be 0.979, 0.611 and 0.987 for zero-order in case of optimized EFMM, marketed conventional tablet and marketed Sustain Release (SR) tablet respectively. Similarly, the correlation coefficient (r^2) were found to be 0.987, 0.695 and 0.998 for Higuchi in case of optimized EFMM, marketed conventional tablet and marketed Sustain Release (SR) tablet respectively. The correlation coefficient (r^2) obtained for different kinetic model suggest highest fitness toward zero order and diffusion kinetics for both optimized EFMM and marketed Sustain Release (SR) tablet formulation.

Compatibility studies using Differential Scanning Calorimeter (DSC)

Figure 7 depicts the DSC curve of pure MS, physical mixture and optimised EFMM. The resultant peak is at 137.1°C, 137.8°C and 134.8°C for pure MS, physical mixture and optimised EFMM respectively. It confirms no significant overlapping or shifting of peak in the thermo-gram. These results ratified absence of any

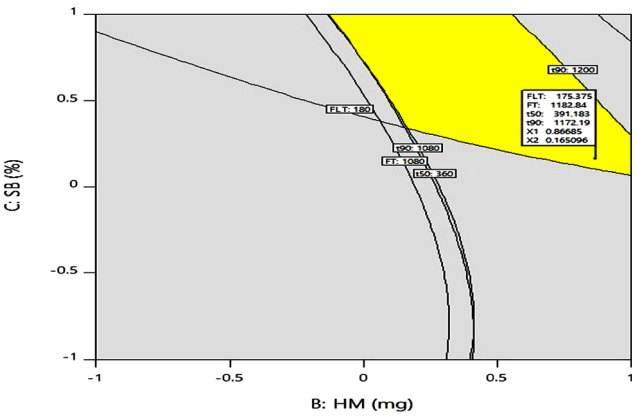

Figure 6: Plot depicting the cumulative drug release profile of optimized EFMM, marketed conventional tablet and marketed sustain release tablet of metoprolol succinate.

Table 10: Similarity study of optimised MS during accelerated stability study using ANOVA.

Responses	*F* value	*P* value	F crit	Interpretation	Inference
FLT	2.291	0.135	3.682	*P* value >0.05 *F* value< F crit	No significant difference
FT	0.117	0.889	3.682	*P* value >0.05 *F* value< F crit	No significant difference
t50	0.269	0.767	3.682	*P* value >0.05 *F* value< F crit	No significant difference
t90	0.489	0.622	3.682	*P* value >0.05 *F* value< F crit	No significant difference

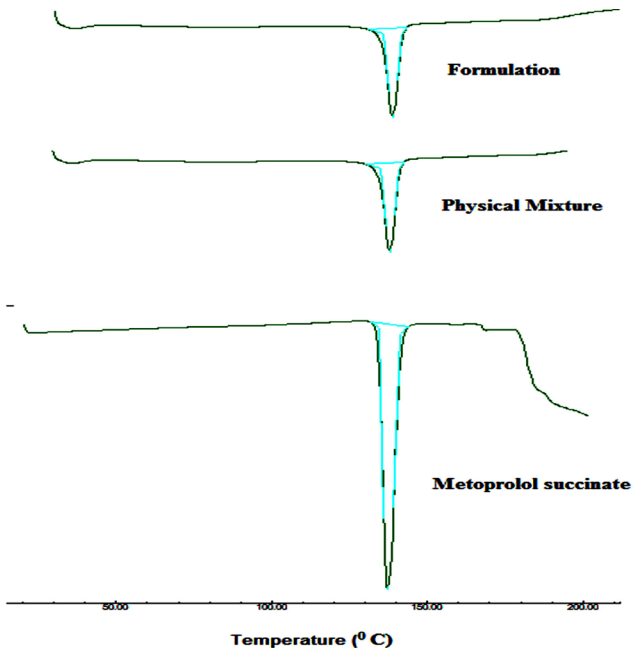

Figure 7: DSC thermo-gram of pure MS, physical mixture and optimised EFMM.

physiochemical incompatibility between the drug and polymer.

Accelerated stability studies

The optimised EFMM of MS was examined for 6 months of accelerated stability study as prescribed in method section. The CQAs of the optimised EFMM at various intervals were subjected to ANOVA for determining any significant difference. The *P* value and F value of the ANOVA during accelerated stability study is shown in Table 10. These values indicate there is no significant difference of the CQAs during the study period. Hence it can be concluded that the optimised EFMM found to satisfy the stability criteria.

CONCLUSION

In this present research work a systematic development of EFMM MS was carried out using QbD approach which result an optimised formulation with desired CQAs. Risk assessment study using FMEA was conducted which identify gelucire 43/01(G 43/01), amount of HPMC K15 M (HM), amount of $NaHCO_3$ (SB), amount of Neusilin US2 (N US2), Compression Force (CF), Stirring Time (ST) and Melting Temperature (MT) as significant factor. Taguchi design was used in order to select the potential factor correspond to the CQAs. After screening 8 run at two level amount of gelucire 43/01(G 43/01), amount of HPMC K15 M (HM) and amount of $NaHCO_3$ (SB) were found to be the influential factors which were further optimised using BBD. The optimised single dose of EFMM of MS consisting of 125mg of G 43/01, 72mg of HM, 28mg of SB, 125mg of N US2, 100mg of MCC and 50 mg of MS which showed an average of FLT within 3 min, FT of 19 hr 36 min, t50 of 6 hr 38 min and t90 of 19 hr 12 min. After experimental study it was confirmed that the said optimized EFMM exhibited process of controlled release and gastro retentive for one day with effective FLT. The optimised formulation found to have better dissolution profile as compared to the marketed formulation. DSC study justifies no interaction of drug with various excipients. Accelerated stability study of the optimised EFMM MS confirms insignificant changes in the CQAs during storage which was evident by conducting ANOVA. The present research concluded that an optimum amount of Gelucire 43/01, HPMC K15M and $NaHCO_3$ in the formulation of EFMM of MS is effective to achieve desired drug release rate and gastric residence time.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

EFMM: Effervescent floating multiple unit minitablets; **UV:** Ultra violet; **HCl:** Hydro choric acid; **GI:** Gastro intestinal; **QbD:** Quality by design; **DSC:** Differential scanning calorimeter; **MS:** Metoprolol succinate; **HPMC:** Hydroxy Propyl Methyl Cellulose; **h:** Hour; **i.e.:** That is; **min:** Minute; **SR:** Sustained release; **λ_{max}:** Absorbance Maximum; **µg:** Microgram; **FMEA:** Failure mode effect analysis; **BBD:** Box-Behnken design; **G 43/01:** Gelucire 43/01; **HM:** HPMC K15 M; **SB:** $NaHCO_3$; **FLT:** Floating lag time; **FT:** Floating time; **t50:** Time to release 50% of drug; **t90**: Time to release 90% of drug; **GRDDS:** Gastro retentive drug delivery system; **FDDS:** Floating drug delivery system; **QTPP:** Quality target product profile; **CQA:** Critical quality attributes; **DOE:** Design of experiments; **RSM:** Response surface methodology.

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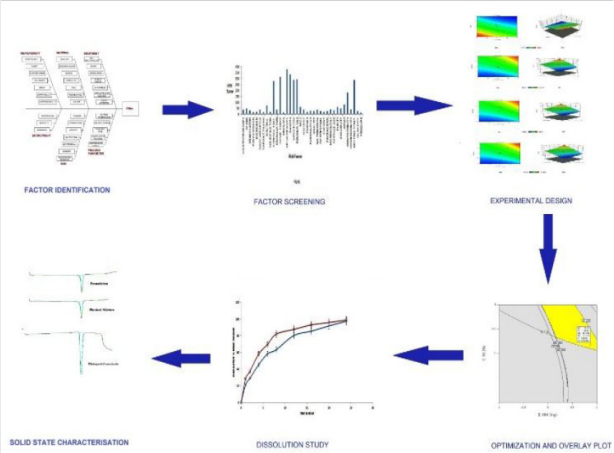
PICTORIAL ABSTRACT



SUMMARY

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