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Extended Release Micro-pellets of Chiral Molecule of Metoprolol Succinate by Fluid Bed Technology

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ABSTRACT

The objective is to prepare extended release micro-pellets of the s-Metoprolol Succinate which is chirally pure molecules. Commercially Metoprolol Succinate is available the racemic mixture of the s and r isomers. Out of both the isomers s-isomer is predominantly responsible for the cardiac beta blocking activity. So to use the more desirable beta blocking activity of s-Metoprolol Succinate, extended release micro-pellets of the s-Metoprolol Succinate was prepared. Due to pure chiral molecules the dose was also reduced to half to that of the racemic mixture. Extended release micro-pellets of the s-Metoprolol Succinate was prepared by the fluid bed technology, in which s-Metoprolol Succinate along with binder and anti-adherent material was sprayed on the inert core. These drug loaded pellets of the s-Metoprolol Succinate was than coated with ethyl cellulose as extended release polymer, hypromellose as pore former and acetyl tri butyl as novel plasticizer and talc as an anti-adherent. The formulation was further optimized for drug release, as per USP recommended dissolution condition, using central composite design (CC). Results shows that at level of 58-66% w/w extended release coating with any studied concentration of acetyl tri butyl citrate and hypromellose gives desired drug release profile.

Keywords: s-Metoprolol Succinate, Micro-pellets, Fluid bed technology, Acetyl tributyl citrate, Central composite design.

INTRODUCTION

A molecule is considered chiral, if there exists another molecule that is of identical composition, but which is arranged in a non-super imposable mirror image. Human hands are perhaps the most universally recognized example of chirality. The left hand is a non-super imposable mirror image of the right hand; no matter how the two hands are oriented, it is impossible for all the major features of both hands to coincide. [1] Many active pharmaceutical ingredients are marketed as racemate. Some of them need to be separated into single enantiomers or chirally pure components to provide selective effects of enantiomers and also reduces the dosage regimen over racemic mixture. This leads to more attention of the pharma industry to develop different dosage form of chirally pure active ingredients. [1] Metoprolol Succinate is available as racemic mixture of the s and r isomer in 1:1. R-enantiomer has relative stronger activity in blocking beta-2 receptor than beta-1 receptor, which is not required for treatment of hypertension. The beta-1 receptor affinity of the S-enantiomer is about 500 times greater than that of R-enantiomer. [2-3] Due to its selective beta-1 blocking activity, s-Metoprolol

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Succinate can be used at half level of its racemic mixture to produce same beta-1 blocking activity to that of racemate. This half dose reduction advantage, BCS class- I molecule and having short biological half-life makes s-Metoprolol Succinate ideal molecules for development of the extended release micro pellets.

These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. In multiple-unit systems, the total drug dose is divided over many units. Failure of a few units may not be as consequential as failure of a single-unit system. This is apparent in sustained release (SR) single-unit dosage forms, where a failure may lead to dose-dumping of the drug. When multiple-unit systems are taken orally, multi particulates are released into the gastrointestinal tract and are less dependent on gastric emptying than single-unit systems. Their small size allows them to pass through the pyloric sphincter easily. This reduces intra- and inter- subject variation in gastrointestinal transit time. [4]

There are many techniques to prepare extended release micro pellets. Which include extrusion and spheronization technique and fluid bed processing. Extrusion and spheronization technique is less time consuming process over fluid bed processing. But main disadvantage of extrusion and spheronization technique is that it provides irregular size of pellets which leads to variable drug release profile. So to achieve controlled extended release and to get more spherical micro pellets, fluid bed technique is used.

During research work, drug layering was done on microcrystalline (MCC) spheres using different drug to binder ratio to provide maximum process efficiency. MCC sphere is selected as highly spherical and uniform in its particle size distribution, enabling greater accuracy and consistency in drug layering and coating which also exhibits high mechanical strength and low friability allowing it to withstand the rigors of fluidized-bed or wurster coating process. [5] This drug loaded pellets are then coated with ethyl cellulose as extended release coating polymer, hypromellose as pore former, acetyl tributyl citrate as novel plasticizer and talc as anti-adherent to get final micro pellet size of 250-700 micron. During research work formulation was also optimized using central composite design. Pellets were evaluated for assay, particle size sieve analysis, process efficiency and drug release was determined as per USP method for Metoprolol Extended Release Tablets.

MATERIALS AND METHODS

Materials

s-Metoprolol Succinate (Emcure Pharmaceuticals Ltd) used as a model drug. MCC spheres (150-300µm, Celphere CP-203, AshaiKASEI, Japan) were selected as inner core. Hypromellose E5 Premium LV (METHOCEL™ E5, DOW Chemicals) was selected as binder during drug layering process and Hypromellose E3 Premium LV (METHOCEL™ E3, DOW Chemicals) was selected as pore former during extended release coating process. Acetyl tributyl citrate (Citroflex® A-4, Vertellus) used as novel plasticizer during extended release coating process. Micronized talc (Luzenac Pharma M, Imerys) was selected as anti-adherent material during drug layering and extended release coating process.

Table 1: Composition of s-Metoprolol Succinate drug layered pellets

Ingredients	SMDL1 (mg)	SMDL2 (mg)	SMDL3 (mg)
Microcrystalline Cellulose Sphere (Celphere CP203)	17.649	17.412	17.174
S-Metoprolol Succinate	11.875	11.875	11.875
Hypromellose E5 cps	0.238	0.475	0.713
Talc Micronized (Luzenac Pharma M)	0.238	0.238	0.238
Purified Water	q.s. to 15% w/w	q.s. to 15% w/w	q.s. to 15% w/w
Total	**30.000**	**30.000**	**30.000**

Table 2: Composition of s-Metoprolol Succinate extended release coated micro pellets

Ingredients	SMDL4 (mg)	SMDL5 (mg)	SMDL6 (mg)	SMDL7 (mg)
Drug pellets	30.000	30.000	30.000	30.000
Ethyl cellulose 10 cps (Ethocel STD 10 PREM)	9.000	12.000	15.000	18.600
Hypromellose E3 cps	3.000	4.000	5.000	6.000
Acetyl tri butyl citrate	1.200	1.600	2.000	2.400
Talc (Luzenac Pharma M)	1.200	1.600	2.000	2.400
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.
Dichloromethane	q.s.	q.s.	q.s.	q.s.
Total	**44.400**	**49.200**	**54.000**	**58.800**
Concentration of extended release dispersion	8%	8%	8%	8%
Total % of extended release coating	48%	64%	80%	96%
% of ethyl cellulose	30%	40%	50%	60%

Manufacturing of Drug-Layered Pellets

Drug layering of s-Metoprolol Succinate was done on MCC sphere (150-300µm, Celphere CP-203, AshaiKASEI, Japan) by applying drug solution of s-Metoprolol Succinate, which is prepared by dissolving s-Metoprolol Succinate into purified water with different binder concentration. Binder concentration selected in a range of 2-6% of active. Talc (2% of active) is added to the solution to avoid any static charge generation and to minimize agglomeration formation during process. [6] Drug layering was done in fluid bed processor (wurster coating process) (ACG Pam Glatt

GPCG 1.1, Gremany). The final drug layered pellets have 11.875 mg of s-Metoprolol Succinate in 30mg of drug pellets.

Manufacturing of Extended Release Coated Micro-pellets

Extended release coating on drug layered pellets were done using ethyl cellulose as extended release polymer, hydroxy propyl methyl cellulose as pore former and acetyl tri butyl citrate as novel hydrophobic plasticizer. Extended release coating was done in range of 30-60% of ethyl cellulose or 48-96%w/w of weight gain. Extended release polymer to pore former ratio was taken as 75:25. Acetyl tributyl citrate and talc concentration selected were 10% of total polymer. Talc in was added to avoid any static charge generation during extended release coating and during drying process and to minimizing agglomeration formation during spraying process. [6] For preparation of extended release coating dispersion (8% w/w), hypromellose E3 cps was dispersed into isopropyl alcohol under stirring. To this dichloromethane was added to gel clear solution. To this ethyl cellulose was added under continuous stirring and stir till clear solution obtained. After dissolving of ethyl cellulose, acetyl tributyl citrate was added followed by talc and stir for 30 min. This dispersion was then sprayed onto drug layered pellets too get final extended release coated micro pellets of 250-700µm. During process dispersion was continuously stirred to avoid settling of talc.

Table 3: Processing parameters

Parameters	Drug Layering	Extended Release Coating
Machine	GPCG 1.1	GPCG 1.1
Air distribution plate	C	C
Spray nozzle diameter (mm)	1.0	1.0
Inlet air temperature (°C)	50 – 60	40 – 50
Product temperature (°C)	40 – 45	32 – 36
Inlet air flow (cfm)	50 – 80	50 – 80
Atomization air pressure (Bar)	1.0 – 1.2	1.0 – 1.2
Spray rate (g/min)	5 – 15	2 – 10
Drying temperature (°C)	60	55
Drying time (min)	30	30

Table 4: Summary of CCD design

Independent Variable	Level	
	-1	+1
% Weight gain	56.00	72.00
% of Hypromellose	28.33	38.33
% of Acetyl tri butyl citrate	5	15
Response to be studied		**Limit**
Drug Release at 1 hour		NMT 25%
Drug Release at 4 hours		20 – 40%
Drug Release at 8 hours		40 – 60 %
Drug Release at 20 hours		NLT 80%

Optimization of the Extended Release Coating

After getting satisfactory results for drug release from the extended release coated micro pellet, % extended release coating, amount of pore former in extended release coating and amount of plasticizer were optimized using central composite design (CCD Design). During optimization study talc concentration was kept constant. As % extended release, amount of pore former and hydrophobic plasticizer plays important role for controlling drug release from micro pellets, these factors were selected as independent parameters during optimized study using CCD design using three center points. The dependent parameters selected were drug release at 1, 4, 8 and at 20 hours.

Evaluation of Pellets [7-9]

Drug layered pellets and extended release coated micro pellets were evaluated for particle size distribution by using a nest of the standard sieve (ASTM). % process efficiency was also determined for both drug layering and extended release coating process using equation (1). Assay of drug pellets and extended release coated micro pellet and in-vitro dissolution study (pH 6.8 phosphate buffer / 500ml / USP Apparatus – II / 50 RPM [10]) of extended release micro pellets was evaluated at specified time interval and measure the concentration release in time profile using HPLC as per USP monograph of metoprolol extended release tablets. Drug release was compared to reference products for similarity factor (F_2) mean dissolution time and mean residence time. An f2 value between 50 ± 100 suggests that the two dissolution profiles are similar and the mean dissolution profiles are assumed to differ by no more than 1 5%at any time point

$$F2 = 50 * \log \{[1 + (1/n) \sum t=1\ n\ (R\ t\tilde{n}\ T\ t)\ 2] - 0.5 \times 100\} \quad \text{……e.q. (1)}$$

Where Rt and Tt are the per cent dissolved at each time point for reference (R) and test (T) products. An f2 value greater than 50 suggests that the two dissolution profiles are similar and the mean dissolution profiles are assumed to differ by no more than 15% at any time point. [11]

$$\text{\% process efficiency} = \frac{(\text{Wt of Final Coated Pellets} - \text{Initial wt of Starter Pellets})}{\text{Amount of Solid in Solution}} \times 100 \quad \text{…e.q.(2)}$$

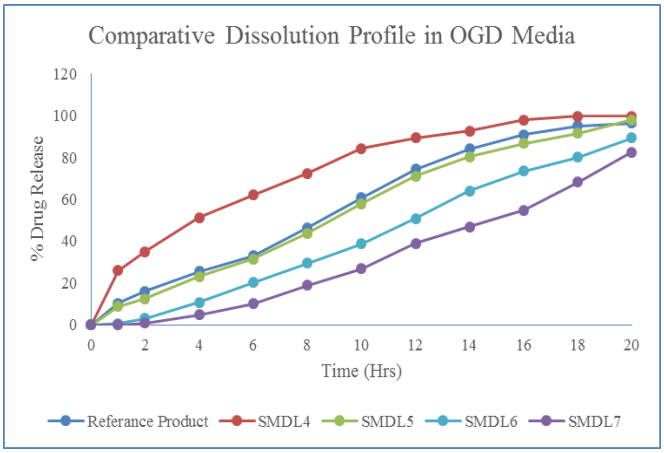

Fig. 1: Comparative dissolution profile % extended release coating on drug release from micro pellets

RESULTS AND DISCUSSION

Preliminary Trials of Drug Layered Pellets

As the drug layering was done using Wurster coating process the amount of drug layered on to the inner pellets was important which nothing but % process efficiency. This process efficiency ultimately affects the

assay of drug pellets and particle size distribution of the drug pellets. The preliminary trial drug layered pellets were evaluated for said parameters.

Table 5: Results of drug layered pellets

Parameters		Concentration of Binder		
		2%	4%	6%
% Process Efficiency		95.28	98.47	98.49
Assay (%)		95.1	98.9	99.0
Particle Size Distribution (by sieve analysis)	>50#	1.02	1.18	1.25
	50 – 60#	85.62	85.98	86.32
	60 – 80#	10.24	9.95	9.87
	<80#	3.12	2.89	2.56

Table 6: Results of extended release micro pellets

Parameters		% of Ethyl Cellulose Concentration			
		30%	40%	50%	60%
Process Efficiency		96.1	95.8	96.5	95.4
Assay		98.6	98.2	98.2	98.4
Particle Size Distribution (by sieve analysis)	>25#	1.59	1.48	1.67	1.52
	<60#	0.28	0.34	0.31	0.42

Preliminary trials of Extended Release Coating

Preliminary trials of extended release coated micro pellets were evaluated for % process efficiency, assay, particle size distribution and drug release as per USP monograph of Metoprolol Succinate Extended Release Tablets.

Drug Layering

Binder concentration is more critical for good adhesion of drug on the inner core. Less binder concentration may results into poor adhesion and loss of the drug during process which ultimately may results into low assay of the drug pellets. High binder concentration gives good adhesion of the drug onto the inner pellets but may increase chance of agglomeration. Results of feasibility trial of drug layering showed that there is increase in process efficiency with increase in the binder concentration. With hypromellose concentration at 4 & 6% of API gives greater than 98% process efficiency with same particle size distribution of drug layered pellets. So for drug layering, hypromellose concentration is selected as 4% of API. This gave good process feasibility and good adhesion of the drug on to the base pellets. Talc at 2% of API shows better removal of static charge as well as minimize the agglomeration generation during wurster process.

Table 7: Drug release of extended release micro pellets

Time (Hours)	Limit	Reference Product	30% ER Coated	40% ER Coated	50% ER Coated	60% ER Coated
1	NMT 25%	10.2 ± 4.5	25.9 ± 3.8	8.8 ± 3.4	0.5 ± 6.8	0.0 ± 0.0
2		15.9 ± 3.8	34.9 ± 3.0	12.4 ± 2.8	3.1 ± 3.7	0.8 ± 7.6
4	20-40%	25.4 ± 2.2	51.3 ± 2.5	23.0 ± 2.1	10.8 ± 2.4	4.8 ± 4.0
6		33.0 ± 1.0	62.1 ± 2.1	31.4 ± 1.8	20.1 ± 1.8	10.1 ± 3.1
8	40-60%	46.5 ± 1.3	72.3 ± 1.5	43.8 ± 1.3	29.4 ± 1.1	18.9 ± 2.6
10		60.7 ± 1.0	84.3 ± 1.1	57.8 ± 1.0	38.6 ± 1.0	26.8 ± 1.9
12		74.4 ± 0.8	89.3 ± 0.9	71.1 ± 0.7	50.8 ± 0.9	38.9 ± 1.2
14		84.0 ± 0.9	92.6 ± 0.7	80.3 ± 0.4	64.1 ± 0.5	46.8 ± 1.1
16		91.0 ± 0.7	97.9 ± 0.5	86.7 ± 0.6	73.5 ± 0.5	54.8 ± 0.7
18		95.2 ± 0.6	99.7 ± 0.5	91.6 ± 0.3	80.2 ± 0.2	68.3 ± 0.6
20	NLT 80%	96.5 ± 0.4	99.8 ± 0.4	97.9 ± 0.3	89.2 ± 0.2	82.6 ± 0.2
F_2		-	38	76	40	29
MDT (hours)		8.07	5.20	8.80	10.72	12.46
MRT (hours)		5.86	4.62	6.15	7.16	7.91

Table 8: Results of optimization of extended release coating using CCD design

Std Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
% Wt gain	56.00	72.00	56.00	72.00	56.00	72.00	56.00	72.00	56.00	72.00	64.00	64.00	64.00	64.00	64.00	64.00	64.00
HPMC	28.33	28.33	38.33	38.33	28.33	28.33	38.33	38.33	33.33	33.33	28.33	38.33	33.33	33.33	33.33	33.33	33.33
ATBC	5.00	5.00	5.00	5.00	15.00	15.00	15.00	15.00	10.00	10.00	10.00	10.00	5.00	15.00	10.00	10.00	10.00
Talc	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Assay of ER Coated Pellets	97.5	98.3	99.1	98.4	98.8	98.2	98.5	99.5	99.0	98.7	98.5	99.2	99.1	98.8	99.4	99.3	99.1
Efficiency	96.4	95.6	96.4	95.3	96.4	96.7	95.1	95.6	96.3	96.0	96.1	95.7	96.8	95.7	95.8	96.1	96.0
Time	% Drug Release																
1	17.2	1.8	22.8	5.8	18.3	1.8	20.1	2.1	19.7	4.8	7.3	14.3	10.2	7.4	8.6	7.8	8.1
4	38.1	13.4	47.2	18.6	39.5	10.4	41.6	12.7	42.8	15.6	21.4	28.3	26.7	22.8	22.8	21.2	21.9
8	53.8	31.7	61.2	37.1	55.9	28.1	58.4	30.8	59.6	34.9	41.8	52.6	48.6	44.3	43.8	44.8	43.9
20	98.4	91.7	100.8	94.1	98.0	94.8	97.8	94.8	99.0	93.1	96.8	96.4	97.1	94.9	97.8	99.8	99.0

Extended Release Coating

Extended release coating plays important role in controlling drug release from the micro pellets. Due to micro size of the pellets, surface area increases. Due to increase in the surface area, more % of extended release coating required. The preliminary trials were taken by applying different % of weight gain or by varying different % of ethyl cellulose. As the % coating increases from 48-96% or from 30-60% of Ethyl cellulose drug release profile significantly decreases. With 64% of weight gain or 40% of ethyl cellulose give comparable drug release to that of brand product with f 2 value of 76. Mean dissolution time (MDT) and mean residence time (MRT) of pellets is comparable to that of

brand product. 64% of weight gain gives comparable drug release to that of brand product. This much of higher % weight gain is required due to micro size of pellets.

Optimization of Extended Release Coating

Optimization of the extended release coating for micro pellets is done using CCD design with three center point. Four dependent parameters were investigated which are drug release at 1, 4, 8 and 20 hours. Fit summary of various investigated dependent parameters were summarized in below table.

Table 9: Fits summary of dependent parameters

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Response Y1: Drug release at 1 hour						
Mean vs Total	157.97	1	157.97			
Linear vs Mean	**19.14**	**3**	**6.38**	**83.82**	**< 0.0001**	**Suggested**
2FI vs Linear	0.33	3	0.11	1.69	0.2319	
Quadratic vs 2FI	0.15	3	0.048	0.66	0.6006	
Cubic vs Quadratic	0.30	4	0.075	1.07	0.4984	Aliased
Response Y2: Drug release at 4 hours						
Mean vs Total	11648.53	1	11648.53			
Linear vs Mean	2012.66	3	670.89	72.86	< 0.0001	
2FI vs Linear	16.72	3	5.57	0.54	0.6648	
Quadratic vs 2FI	**79.88**	**3**	**26.63**	**8.07**	**0.0113**	**Suggested**
Cubic vs Quadratic	4.39	4	1.10	0.18	0.9366	Aliased
Response Y3: Drug release at 8 hours						
Mean vs Total	34994.33	1	34994.33			
Linear vs Mean	**1700.31**	**3**	**566.77**	**119.88**	**< 0.0001**	**Suggested**
2FI vs Linear	18.20	3	6.07	1.40	0.2986	
Quadratic vs 2FI	3.56	3	1.19	0.21	0.8867	
Cubic vs Quadratic	17.77	4	4.44	0.61	0.6862	Aliased
Response Y4: Drug release at 20 hours						
Mean vs Total	1.590E+005	1	1.590E+005			
Linear vs Mean	**67.11**	**3**	**22.37**	**9.00**	**0.0017**	**Suggested**
2FI vs Linear	9.61	3	3.20	1.41	0.2965	
Quadratic vs 2FI	7.40	3	2.47	1.13	0.4007	
Cubic vs Quadratic	3.48	4	0.87	0.22	0.9107	Aliased

Table 10: ANOVA result of dependent parameters (Y_1: drug release at 1hr)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	19.14	3	6.38	83.82	< 0.0001	Significant
A-% wt gain	17.93	1	17.93	235.61	< 0.0001	Significant
B-Conc of HPMC	0.95	1	0.95	12.52	0.0036	Significant
C-Conc of ATBC	0.25	1	0.25	3.34	0.0908	
Residual	0.99	13	0.076			
Lack of Fit	0.98	11	0.089	17.90	0.0541	Not significant
Pure Error	9.947E-003	2	4.973E-003			
Cor Total	20.13	16				Significant

Above ANOVA results shows that model F value is 83.82 which is more than 0.05, which shows that selected model is significant. Here % weight gain and concentration of the hypromellose are more significant formulation parameter to impact drug release at 1hrs. All remaining term are not significant. The value of adequate precision is 27.009 which mean that model can be used to navigate the design space. Final equation for the response Y_1 is: 3.05 – 1.34*A + 0.31*B – 0.16*C.

Table 11: ANOVA result of dependent parameters (Y_2: drug release at 4 hours)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	2109.27	9	234.36	71.01	< 0.0001	Significant
A-% wt gain	1918.22	1	1918.22	581.21	< 0.0001	Significant
B-Conc of HPMC	65.54	1	65.54	19.86	0.0029	Significant
C-Conc of ATBC	28.90	1	28.90	8.76	0.0211	Significant
AB	1.71	1	1.71	0.52	0.4948	
AC	2.76	1	2.76	0.84	0.3908	
BC	12.25	1	12.25	3.71	0.0954	
A^2	51.92	1	51.92	15.73	0.0054	Significant
B^2	7.276E-003	1	7.276E-003	2.205E-003	0.9639	
C^2	6.144E-003	1	6.144E-003	1.862E-003	0.9668	
Residual	23.10	7	3.30			
Lack of Fit	21.82	5	4.36	6.78	0.1335	Not significant
Pure Error	1.29	2	0.64			
Cor Total	2132.37	16				

Above ANOVA results shows that model F value is 71.01 which is more than 0.05, which shows that selected model is significant. Here % weight gain, concentration of the hypromellose and concentration of

acetyl tributyl citrate are more significant formulation parameters to impact drug release at 4hrs. The value of adequate precision is 25.995 which mean that model can be used to navigate the design space. Final equation for the response Y_2 is: 23.58 – 13.85*A + 2.56*B – 1.70*C – 0.46 *A*B – 0.59*A*C – 1.24*B*C + 4.40*A2 + 0.052*B2 + 0.048*C2.

Table 12: ANOVA result of dependent parameters (Y_3: drug release at 8 hours)

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	Comments
Model	1700.31	3	566.77	119.88	< 0.0001	Significant
A-% wt gain	1595.17	1	1595.17	337.40	< 0.0001	Significant
B-Conc of HPMC	82.94	1	82.94	17.54	0.0011	Significant
C-Conc of ATBC	22.20	1	22.20	4.70	0.0494	
Residual	61.46	13	4.73			
Lack of Fit	60.85	11	5.53	18.24	0.0531	Not Significant
Pure Error	0.61	2	0.30			
Cor Total	1761.78	16				

Above ANOVA results shows that model F value is 119.88 which is more than 0.05, which shows that selected model is significant. Here % weight gain and concentration of the hypromellose are more significant formulation parameters to impact drug release at 8hrs. The value of adequate precision is 32.236 which mean that model can be used to navigate the design space. Final equation for the response Y_3 is: 45.37 – 12.63*A + 2.88*B – 1.49*C.

Table 13: ANOVA result of dependent parameters (Y_4: drug release at 24 hours)

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	Comments
Model	67.11	3	22.37	9.00	0.0017	Significant
A-% wt gain	65.02	1	65.02	26.16	0.0002	Significant
B-Conc of HPMC	1.76	1	1.76	0.71	0.4148	
C-Conc of ATBC	0.32	1	0.32	0.13	0.7239	
Residual	32.32	13	2.49			
Lack of Fit	30.29	11	2.75	2.72	0.2997	Not Significant
Pure Error	2.03	2	1.01			
Cor Total	99.43	16				

Above ANOVA results shows that model F value is 9.00 which is more than 0.05, which shows that selected model is significant. Here % weight gain and concentration of the hypromellose are more significant formulation parameters to impact drug release at 24hrs. The value of adequate precision is 8.237 which mean that model can be used to navigate the design space. Final equation for the response Y_4 is: 96.72 – 2.55*A + 0.42*B – 0.18*C.

Overall conclusion of ANOVA results reveal that % weight gain, concentration of hypromellose and concentration of the acetyl tributyl citrate are more significant parameters which affect the release of the drug from the micro pellets at initial stage of the drug release profile. While on later stage the drug release was controlled by the %weight gain (extended release coating) and concentration of the hypromellose (pore former).

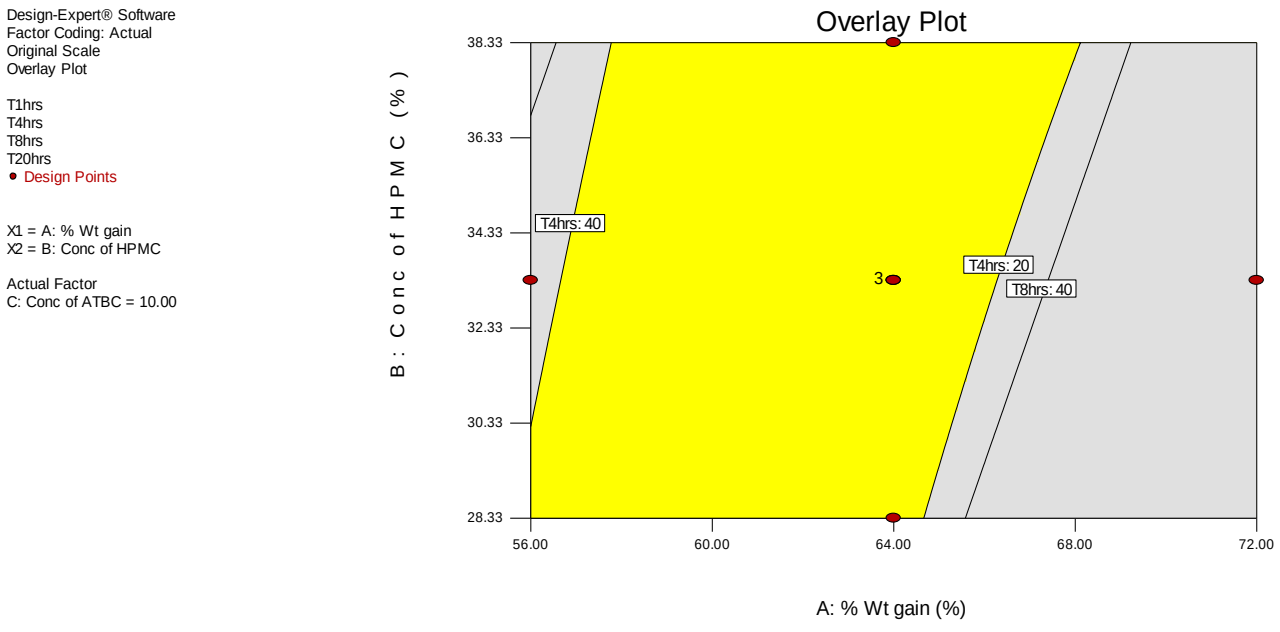

Fig. 2: Overlay Counter Plot of % weight gain vs concentration of hypromellose

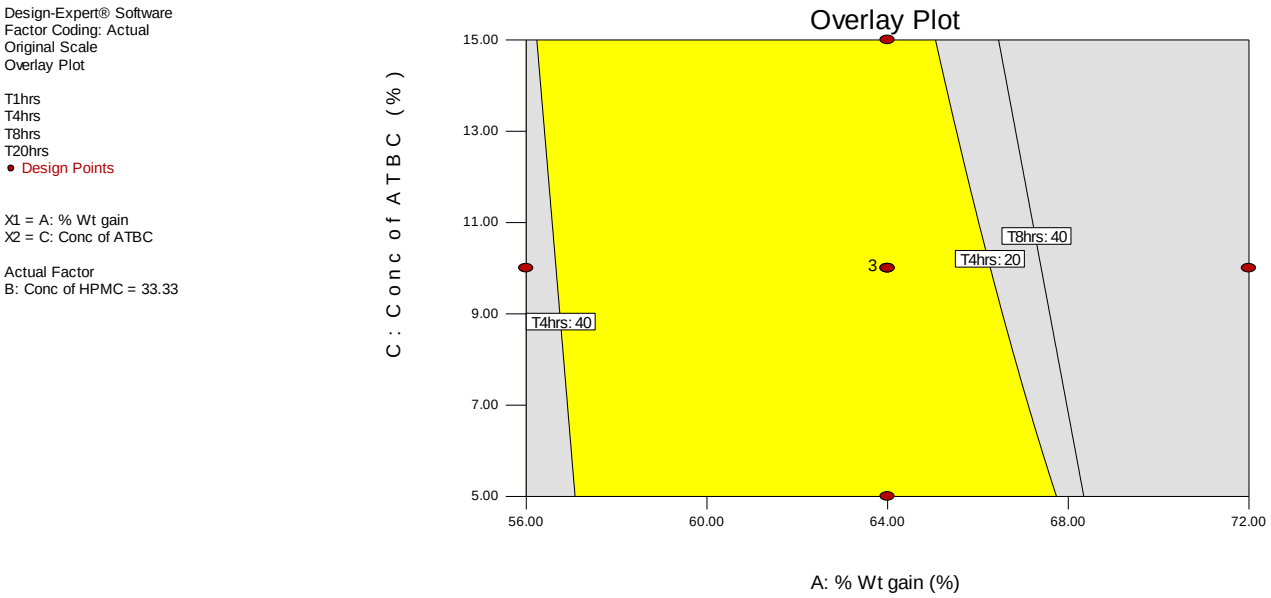

Fig. 3: Overlay Counter Plot of % weight gain vs concentration of acetyl tributyl citrate

Yellow color zone in overlay plot shows the design space. And in any concentration selected for independent variable in the design space gives the desired results. As shown in all results for DoE study for extended release coating, % weight gain has more significant effect on drug release. Even all center point lies in design space.

Based on the research work it was concluded that, micro pellets of s-Metoprolol Succinate was successfully developed using ethyl cellulose coating with hypromellose as pore former and acetyl tributyl citrate as plasticizer. Wurster process gives more uniform micro pellets with narrow particle size distribution. Overlay plot of studied parameters shows that any concentration of hypromellose and acetyl tributyl citrate in studied range will give desired drug release if weight gain is done in range of approx. 58.0 to 66.0%

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