ORIGINAL ARTICLE

Preparation and Evaluation of Extended Release Pellets of Chiral Molecules of s-Metoprolol Succinate by Different Technology

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Abstract

Introduction: The present research was focus on preparation and evaluation of extended pellets of chiral molecule of metoprolol succinate, i.e., s-metoprolol succinate. **Materials and Methods:** For preparation of extended release (ER), drug pellets of s-metoprolol succinate were prepared using two different technology, i.e., extrusion and spheronization and drug layering utilizing Wurster technology. These drug-loaded pellets were further coated with ethyl cellulose as rate controlling polymer, hypromellose as pore former, acetyl tributyl citrate as plasticizer, and talc as anti-adhering agent by fluid bed process to yield ER coated pellets. **Results and Discussion:** ER coating was optimized using center composite design for both drug layered pellets. Higher percentage of ER coating required to control the drug release from pellets prepared by extrusion and spheronization compared to pellets prepared by fluid bed technology. These are due to the wider particle size distribution of the pellets prepared by extrusion and spheronization. Drug release of pellets was comparable to that of reference product. **Conclusion:** ER coated pellets of chiral molecules of metoprolol succinate were successfully prepared by extrusion and spheronization technique and using fluid bed technology. Percentage ER coating required to control the drug release is less in pellets prepared by fluid bed technology compared to ER coated pellets prepared by extrusion and spheronization technique. This may be due to narrower particle size distribution and more sphericity of the pellets prepared by the fluid bed technology.

Key words: Center composite design, extrusion and spheronization, s-metoprolol succinate, Wurster technology

INTRODUCTION

A molecule is considered chiral if there exists another molecule that is of identical composition, but which is arranged in a nonsuper 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 and 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 time greater than that of R-enantiomer.[2,3] Due to its selective beta-1 blocking activity, s-metoprolol 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, biopharmaceutics classification

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system (BCS) Class - I molecule and having short biological half-life makes s-metoprolol succinate ideal molecules for development of the extended release (ER) dosage form.

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 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] For the preparation of the ER coated pellets, drug pellets of s-metoprolol succinate were prepared. Drug pellets were prepared using extrusion and spheronization technique and by drug layering process utilizing Wurster technology.

For the preparation of drug pellets by extrusion and spheronization technique, drug was mixed with suitable diluents (i.e., microcrystalline cellulose and lactose monohydrate) and binder (hypromellose) in different ratio. Granulated mass was then pass through extruder (Dalton MG-55, Fuji Paudal, Japan) to get long extrudes. These extrudes were then cut into smaller pellets using spheronizer (Dalton Marumerizer Q-230T-1, Fuji Paudal, Japan). For the preparation of drug pellets by Wurster technology, drug layering was done on microcrystalline cellulose (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] Drug pellets prepared by both technology were than coated with ethyl cellulose as rate controlling polymer, hypromellose as pore former, acetyl tributyl citrate as plasticizer, and talc as anti-adhering agent. Pellets were evaluated for assay, particle size sieve analysis, process efficiency and drug release was determined as per USP method for metoprolol ER tablets.

MATERIALS AND METHODS

Materials

s-metoprolol succinate (Emcure Pharmaceuticals Ltd.), MCC PH 101 (Avicel PH 101, FMC Biopolymer), lactose monohydrate (Pharmatose 200M, DFE Pharma), hypromellose E5 Premium LV (METHOCEL™ E5, DOW Chemicals), hypromellose E3 premium LV (METHOCEL™ E3, DOW Chemicals), ethyl cellulose 10 cps (Ethocel STD 10 PREM, DOW Chemicals), acetyl tributyl citrate (Citroflex® A-4, Vertellus), talc (Luzenac Pharma, Imerys), and MCC spheres (150-300 µm, Celphere CP-203, AshaiKASEI, Japan) were used as raw materials for formulation development. All reagents and chemicals were of analytical grade and used as received.

Preparation of drug pellets by extrusion and spheronization technique and ER coating

Preliminary trials for drug pellets

s-metoprolol succinate along with MCC, lactose monohydrate, and hypromellose were dry mixed into rapid mixer granulator. These materials than granulated with purified water to get wet granulated mass. These granulated mass was then extruded using 0.5 mm frontal screen. Then, extrudes are cut and made spherical using spheronization. The spheronized pellets are then dried in rapid dryer till desired loss on drying value (NMT 1.5% w/w). Then, this dried pellets were sieve analyzed to find the different fraction of the pellets using sieve shaker [Table 1].

Preliminary trials for ER coating on drug layered pellets prepared by extrusion and spheronization technique

ER coating on drug loaded pellets was done using ethyl cellulose as ER polymer, hydroxypropyl methyl cellulose as pore former and acetyl tributyl citrate as novel hydrophobic plasticizer. ER coating was done in range of 30-60% of ethyl cellulose or 48-96% w/w of weight gain. ER 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 ER coating and drying process and to minimizing agglomeration formation during spraying process.[5] For the preparation of ER 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 ethylcellulose 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 loaded spheronized pellets too get final ER coated micropellets of 250-700 µm. During process, dispersion was continuously stirred to avoid settling of talc [Tables 2 and 3].

Optimization of the ER coating for drug layered prepared by extrusion and spheronization

After getting satisfactory results for drug release from the ER coated micro pellet, % ER coating, amount of pore former in ER coating and amount of plasticizer were optimized using central composite design (CCD design). During

Table 1: Formulation details for preliminary trials of drug loaded pellets

Ingredients	SME1 (mg)	SME2 (mg)	SME3 (mg)	SME4 (mg)	SME5 (mg)
S-metoprolol succinate	11.875	11.875	11.875	11.875	11.875
MCC pH 101 (Avicel pH 101)	16.625	-	8.313	12.469	4.156
Lactose monohydrate (pharmatose 200 M)	-	16.625	8.312	4.156	12.469
Hypromellose E5 cps	1.500	1.500	1.500	1.500	1.500
Purified water	q.s	q.s	q.s	q.s	q.s
Total	30.000	30.000	30.000	30.000	30.000

MCC: Microcrystalline cellulose, SME: s-Metoprolol succinate extrusion

Table 2: Formulation details of preliminary trial of ER coating for drug pellets prepared by extrusion and spheronization technique

Ingredients	30% of ethyl cellulose	40% of ethyl cellulose	50% of ethyl cellulose	60% of ethyl cellulose
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 tributyl 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 solution ER dispersion	8%			
Percentage of talc (on basis of total polymer)	5%			
Total percentage of ER coating	48	64	80	96

ER: Extended release

Table 3: Processing parameters for ER coating

Parameters	ER coating
Machine	GPCG 1.1
Air distribution plate	C
Spray nozzle diameter (mm)	1.0
Inlet air temperature (°C)	40-50
Product temperature (°C)	32-36
Inlet air flow (cfm)	50-80
Atomization air pressure (bar)	1.0-1.2
Spray rate (g/min)	2-10
Drying temperature (°C)	55
Drying time (min)	30

ER: Extended release

optimization study, talc concentration was kept constant. As % ER, amount of pore former and hydrophobic plasticizer plays important role for controlling drug release from micro pellets; this factors were selected as independent parameters during optimized study using CCD design using three center point. The dependent parameters selected was drug release at 1, 4, 8 and 20 h [Table 4].

Preparation of drug pellets by fluid bed technique and ER coating

Preliminary trial of drug pellets by fluid bed technique

Drug layering of s-metoprolol succinate was done on MCC sphere (150-300 µm, 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, Germany). The final drug layered pellets have 11.875 mg of s-metoprolol succinate in 30 mg of drug pellets [Table 5].

Preliminary trials for ER coating on drug pellets prepared by fluid bed technique

ER coating on drug layered pellets was done using ethyl cellulose as ER polymer, hydroxypropyl methyl cellulose as pore former and acetyl tributyl citrate as novel hydrophobic

plasticizer. ER coating was done in range of 30-60% of ethyl cellulose or 48-96% w/w of weight gain. ER 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 ER coating and drying process and to minimizing agglomeration formation during spraying process[6]. For the preparation of ER 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 ethylcellulose 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 ER coated micropellets of 250-700 µm. During process, dispersion was continuously stirred to avoid settling of talc [Tables 6 and 7].

Table 4: Summary of CCD design for ER coating for drug layered pellets prepared by extrusion and spheronization technology

Independent variable	Level	
	−1	+1
Percentage weight gain	72.00	88.00
Percentage of hypromellose concentration	28.33	38.33
Percentage of acetyl tributyl citrate	5	15
Response to be studied		**Limit**
Drug release at 1 h		NMT 25%
Drug release at 4 h		20-40%
Drug release at 8 h		40-60%
Drug release at 20 h		NLT 80%

CCD: Central composite design, NMT: Not more than, NLT: Not less than, ER: Extended release

Optimization of the ER coating for drug pellets prepared by fluid bed processing

After getting satisfactory results for drug release from the ER coated micro pellet, % ER coating, amount of pore former in ER coating and amount of plasticizer were optimized using CCD (design). During optimization study, talc concentration was kept constant. As % ER, amount of pore former and hydrophobic plasticizer plays an important role for controlling drug release from micro pellets; this factors were selected as independent parameters during optimized study using CCD design using three center point. The dependent parameters selected was drug release at 1, 4, 8 and 20 h [Table 8].

Evaluation of pellets[6-8]

Drug loaded pellets and ER coated micropellets were evaluated for particle size distribution using a nest of

Table 5: Composition of preliminary trials 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 6: Formulation details for preliminary trial of ER coating for drug pellets prepared by fluid bed process

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 ER dispersion	8%	8%	8%	8%
Total percentage of ER coating	48	64	80	96
Percentage of ethyl cellulose	30	40	50	60

SMDL: s-Metoprolol succinate drug layering, ER: Extended release

Table 7: Processing parameters

Parameters	Drug layering	ER 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

ER: Extended release

Table 8: Summary of CCD design for ER coating for drug layered pellets prepared by fluid bed technology

Independent variable	Level	
	−1	+1
Percentage weight gain	56.00	72.00
Percentage of hypromellose	28.33	38.33
Percentage of acetyl tributyl citrate	5	15
Response to be studied		**Limit**
Drug release at 1 h		NMT 25%
Drug release at 4 h		20-40%
Drug release at 8 h		40-60%
Drug release at 20 h		NLT 80%

CCD: Central composite design, NMT: Not more than, NLT: Not less than, ER: Extended release

the standard sieve (ASTM). % process efficiency for ER coating was determined using equation (1). Assay of drug pellets and ER coated micro pellet and *in-vitro* dissolution study (pH 6.8 phosphate buffer/500 ml/USP Apparatus – II/50 rpm[9]) of ER micropellets was evaluated at specified time interval and measure the concentration release in time profile using high performance liquid chromatography as per USP monograph of metoprolol ER tablets. Drug release was compared to reference products for similarity factor (F_2) mean dissolution time (MDT) and mean residence time (MRT). An F2 value between 50 and 100 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.

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

Where, *Rt* and *Tt* are the percent dissolved at each time point for reference (*R*) and test (*T*) products. An F2 value >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.[10]

$$\% \text{ process efficiency} = \frac{\left(\begin{array}{c}\text{Weight of final coated pellets} - \\ \text{Initial weight of starter pellets}\end{array}\right)}{\text{Amount of solid in solution}} * 100 \quad (2)$$

RESULTS AND DISCUSSION

Results of preliminary trials of drug pellets prepared by extrusion and spheronization technique

Results of feasibility trial of drug loaded pellets show that drug loaded prepared using 1:1 ratio of MCC and lactose monohydrate gives good fractions between the #30 and 60 sieve while drug loaded pellets prepared using either alone MCC or lactose monohydrate gives more fines. Hence, 1:1 ratio of MCC or lactose monohydrate is selected for preparation of drug loaded pellets [Table 9].

Results of preliminary trials of ER coating drug pellets prepared by extrusion and spheronization technique

Preliminary trials of ER coated micropellets were evaluated for % process efficiency, assay, particle size distribution and drug release as per USP monograph of metoprolol succinate extended-release tablets. 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% to 60% of ethyl cellulose drug release profile significantly decreases [Figure 1]. With 80% of weight gain or 50% of ethyl cellulose give comparable drug release to that of brand product with F2 value of 82. MDT and MRT of pellets is comparable to that of brand product. 80% 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 [Tables 10 and 11].

Results of optimization of ER coating for drug pellets prepared by extrusion and spheronization technique

Based on the preliminary trial results, optimization of the ER 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 h. Results of optimization of the ER coating were summarized in Table 12.

Fit summary of various investigated dependent parameters[11] was summarized in Table 13.

Table 9: Results of preliminary trial of drug pellets prepared by extrusion and spheronization technique

Parameters	SME1	SME2	SME3	SME4	SME5
Bulk density	0.72	0.74	0.78	0.75	0.75
Assay (%)	93.5	94.1	98.7	97.5	98.2
Particle size distribution (by sieve analysis)					
>30#	2.5	2.9	2.0	2.6	3.5
30-60#	84	84.3	93.7	89.5	88.4
<60#	13.5	12.8	4.3	7.9	8.1

SME: s-Metoprolol succinate extrusion

Table 10: Results of preliminary trial of ER coating for drug pellets prepared by extrusion and spheronization

Parameters	Percentage of ethyl cellulose concentration			
	30%	40%	50%	60%
Process efficiency	95.8	96.4	96.0	96.2
Assay	98.4±0.4	98.7±0.3	98.6±0.2	98.8±0.4
Particle size distribution (by sieve analysis)				
>25#	1.28	1.34	1.16	1.24
<60#	0.37	0.32	0.21	0.28

ER: Extended release

Table 11: Drug release profile from ER coated pellets

Time (h)	Limit	Reference product	30% of ethyl cellulose	40% of ethyl cellulose	50% of ethyl cellulose	60% of ethyl cellulose
1	NMT 25%	10.2±4.5	51.3±7.7	28.8±6.2	11.2±6.8	2.9±7.1
2		15.9±3.8	59.8±6.5	42.2±4.1	14.8±4.6	5.8±5.6
4	20-40%	25.4±2.2	71.1±3.0	58.3±2.1	23.5±2.8	10.6±3.4
6		33.0±1.0	81.4±1.6	67.2±1.3	31.2±1.7	18.3±1.5
8	40-60%	46.5±1.3	86.1±1.0	75.6±1.1	44.2±1.1	24.3±1.2
10		60.7±1.0	97.9±0.9	82.4±0.9	58.1±0.8	38.9±1.0
12		74.4±0.8	98.9±0.8	94.2±0.9	72.1±0.8	56.3±0.9
14		84.0±0.9	99.4±0.7	97.9±0.7	81.6±0.6	67.8±0.6
16		91.0±0.7	99.8±0.2	98.6±0.6	88.2±0.6	72.8±0.5
18		95.2±0.6	99.8±0.2	99.7±0.6	92.3±0.4	80.9±0.4
20	NLT 80%	96.5±0.4	99.9±0.2	100.3±0.3	97.8±0.4	82.6±0.4
F_2		-	25	34	82	41
MDT (h)		8.07	2.89	4.66	8.61	9.90
MRT (h)		5.86	3.26	4.26	6.09	7.17

MDT: Mean dissolution time, MRT: Mean residence time, NMT: Not more than, NLT: Not less than, ER: Extended release

In Table 14, ANOVA results show that model *F* value is 128.52 which is more than 0.05, which show that selected model is significant. Here % weight gain, concentration of the hypromellose and concentration of acetyl tributyl citrate are more significant formulation parameter to impact drug release at 1 h. All remaining terms are not significant. The value of adequate precision is 33.870 which means 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*C13.22 − 9.8*A+1.76*B − 0.83*C − 0.60 *A*B − 0.13*A*C − 0.50*B*C + 3.46*A2 + 0.86*B2 − 0.89*C2

In Table 15, ANOVA results show that model F value is 79.00 which is more than 0.05, which show that selected model is significant. Here % weight gain, concentration of the Hypromellose and quadratic term of the % weight gain has more significant impact of drug release at 4 h. All remaining terms are not significant. The value of adequate precision is 25.567 which means that model can be used to navigate the design space. Final equation for the response Y_2 is: 25.2 − 18.69*A + 2.36*B − 1.54*C − 0.51*A*B − 0.41*A*C − 1.24*B*C + 6.19*A2 + 0.54*B2 + 0.44*C2

Table 12: Results of trials for ER coating optimization for drug layered pellets prepared by extrusion and spheronization technology using CCD design

Standard run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
% weight gain	72.00	88.00	72.00	88.00	72.00	88.00	72.00	88.00	72.00	88.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00
% 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	98.90	98.56	99.12	98.45	98.87	98.26	98.59	99.52	99.03	98.75	98.56	99.24	99.18	98.87	99.40	99.32	99.14
Efficiency	95.26	96.12	95.87	96.02	95.56	95.87	96.10	95.40	95.29	95.87	96.03	95.78	95.26	95.39	96.16	96.15	95.98
Time	**% drug release**																
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	23.9	6.5	29.9	8.6	24.6	5.2	27.1	6.8	26.8	7.2	11.6	17.2	14.2	11.1	12.5	13.1	12.8
4	47.9	13.2	56.8	18.9	48.5	11	51.3	12.9	52.9	14.5	25.9	30.2	29.1	26.8	24.3	22.6	23.8
8	66.8	30.8	78.9	34.9	67.1	28.9	75.9	29.5	71.1	32.8	48.2	55.8	50.2	47.9	46.1	44.3	45.3
20	99.8	92.5	101.2	93.4	98.6	94.5	98.1	94.1	98.6	92.8	96.3	96.2	97.6	95.2	98.1	99.1	98.3

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate, CCD: Central composite design, ER: Extended release

Table 13: Fits summary of dependent parameters for CCD design of ER coating optimization for drug pellets prepared by extrusion and spheronization technology

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Response Y_1: Drug release at 1 h						
Mean versus total	3948.99	1	3948.99			
Linear versus mean	998.97	3	332.99	68.33	<0.0001	
2FI versus linear	5.00	3	1.67	0.29	0.8345	
Quadratic versus 2FI	51.95	3	17.32	18.97	0.0010	Suggested
Cubic versus quadratic	5.02	4	1.26	2.75	0.2159	Aliased
Response Y_2: Drug release at 4 h						
Mean versus total	15336.02	1	15336.02			
Linear versus mean	3572.57	3	1190.86	64.75	<0.0001	
2FI versus linear	15.71	3	5.24	0.23	0.8703	
Quadratic versus 2FI	186.23	3	62.08	11.69	0.0041	Suggested
Cubic versus quadratic	1.80	4	0.45	0.038	0.9957	Aliased
Response Y_3: Drug release at 8 h						
Mean versus total	42951.19	1	42951.19			
Linear versus mean	4242.19	3	1414.06	121.29	<0.0001	Suggested
2FI versus linear	41.23	3	13.74	1.25	0.3444	
Quadratic versus 2FI	64.46	3	21.49	3.28	0.0887	
Cubic versus quadratic	3.85	4	0.96	0.069	0.9872	Aliased
Response Y_4: Drug release at 20 h						
Mean versus total	1.591E+005	1	1.591E+005			
Linear versus mean	85.87	3	28.62	16.73	<0.0001	Suggested
2FI versus linear	7.43	3	2.48	1.67	0.2358	
Quadratic versus 2FI	3.48	3	1.16	0.72	0.5727	
Cubic versus quadratic	1.73	4	0.43	0.13	0.9588	Aliased

CCD: Central composite design, ER: Extended release

Table 14: ANOVA result of dependent parameters (Y_1: Drug release at 1 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	1055.93	9	117.33	128.52	<0.0001	Significant
A - % weight gain	960.40	1	960.40	1052.02	<0.0001	Significant
B - Concentration of HPMC	31.68	1	31.68	34.71	0.0006	Significant
C - Concentration of ATBC	6.89	1	6.89	7.55	0.0286	Significant
AB	2.88	1	2.88	3.15	0.1190	
AC	0.13	1	0.13	0.14	0.7223	
BC	2.00	1	2.00	2.19	0.1824	
A^2	32.09	1	32.09	35.15	0.0006	Significant
B^2	1.98	1	1.98	2.17	0.1839	
C^2	2.12	1	2.12	2.32	0.1714	
Residual	6.39	7	0.91			
Lack of fit	6.21	5	1.24	13.80	0.0689	Not significant
Pure error	0.18	2	0.090			
Correlation total	1062.32	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

Table 15: ANOVA result of dependent parameters (Y_2: Drug release at 4 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	3774.52	9	419.39	79.00	<0.0001	Significant
A - % weight gain	3493.16	1	3493.16	658.03	<0.0001	Significant
B - Concentration of HPMC	55.70	1	55.70	10.49	0.0143	Significant
C - Concentration of ATBC	23.72	1	23.72	4.47	0.0724	
AB	2.10	1	2.10	0.40	0.5492	
AC	1.36	1	1.36	0.26	0.6281	
BC	12.25	1	12.25	2.31	0.1725	
A^2	102.59	1	102.59	19.33	0.0032	Significant
B^2	0.78	1	0.78	0.15	0.7136	
C^2	0.51	1	0.51	0.097	0.7647	
Residual	37.16	7	5.31			
Lack of fit	35.63	5	7.13	9.34	0.0996	Not significant
Pure error	1.53	2	0.76			
Correlation total	3811.68	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

In Table 16, ANOVA results show that model *F* value is 121.29 which is more than 0.05, which show that selected model is significant. Here % weight gain and concentration of the hypromellose have more significant impact of drug release at 8 h. All remaining terms are not significant. The value of adequate precision is 29.995 which means that model can be used to navigate the design space. Final equation for the response Y_3 is: $50.26 - 20.29*A + 3.32*B - 1.23*C$

In Table 17, ANOVA results show that model *F* value is 16.73 which is more than 0.05, which show that selected model is significant. Here % weight gain and concentration of the Hypromellose have more significant impact of drug release at 8 h. All remaining terms are not significant. The value of adequate precision is 10.811 which means that model can be used to navigate the design space. Final equation for the response Y_4 is: $96.73 - 2.90*A + 0.13*B - 0.40*C$

For all the response the model $P < 0.05$, which shows that selected model can effectively use to predict the response. ANOVA results of all dependent parameters show that % weight gain and concentration of hypromellose are more significant formulation parameters.

Yellow color zone in overlay plot shows the design space, which shows in any concentration selected for independent

Table 16: ANOVA result of dependent parameters (Y_3: Drug release at 8 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	4242.19	3	1414.06	121.29	<0.0001	Significant
A - % weight gain	4116.84	1	4116.84	353.11	<0.0001	Significant
B - Concentration of HPMC	110.22	1	110.22	9.45	0.0089	Significant
C - Concentration of ATBC	15.13	1	15.13	1.30	0.2752	
Residual	151.56	13	11.66			
Lack of fit	149.94	11	13.63	16.76	0.0576	Not significant
Pure error	1.63	2	0.81			
Correlation total	4393.76	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

Table 17: ANOVA result of dependent parameters (Y_4: Drug release at 20 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	85.87	3	28.62	16.73	<0.0001	Significant
A - % weight gain	84.10	1	84.10	49.15	<0.0001	Significant
B - Concentration of HPMC	0.17	1	0.17	0.099		
C - Concentration of ATBC	1.60	1	1.60	0.93		
Residual	22.25	13	1.71			
Lack of fit	21.69	11	1.97	7.04	0.1308	Not significant
Pure error	0.56	2	0.28			
Correlation total	108.12	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

variable in the design space gives the desired results. As shown in all results for DoE study for ER coating, % weight gain has more significant effect on drug release. Even all center point lies in design space. Overlay plot shows that any concentration of hypromellose and acetyl tributyl citrate (ATBC) will give desired drug release if weight gain is done in range of approximately 77.4-82.0%. Final selected formula was also lies in this range (% weight gain of final formulation was 80%) [Figures 2 and 3].

Results of preliminary trials of drug pellets prepared by fluid bed technology

As the drug layering was done using Wurster coating process, the amount of drug layered onto the inner pellets was important, which is 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 18].

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. Highbinder 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% and 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 onto 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 18: Results of preliminary trials of drug pellets prepared by fluid bed technology

Parameters	Concentration of binder		
	2%	4%	6%
Percentage process efficiency	95.28	98.47	98.49
Assay percentage	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

Results of preliminary trials of ER coating drug pellets prepared by fluid bed technology

Preliminary trials of ER coated micropellets were evaluated for % process efficiency, assay, particle size distribution, and drug release as per USP monograph of metoprolol succinate extended-release tablets [Tables 19 and 20].

ER coating plays an 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 percentage of ER coating required. The preliminary trials were taken by applying different percentage of weight gain or by varying different % of ethyl cellulose. As the % coating increases from 48% to 96% or from 30% to 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 [Figure 4]. MDT and 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.

Table 19: Results of preliminary trials of ER coating for drug pellets prepared by fluid bed technology

Parameters	Percentage 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

ER: Extended release

Results of optimization of ER coating for drug pellets prepared by fluid bed technology

Optimization of the ER 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 h. Fit summary of various investigated dependent parameters was summarized in Tables 21 and 22.

In Table 23, ANOVA results show that model F = 83.82 which is more than 0.05, which show that selected model is significant. Here % weight gain and concentration of the hypromellose are more significant formulation parameter to impact drug release at 1 h. All remaining terms are not significant. The value of adequate precision is 27.009 which means 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.

In Table 24, ANOVA results show that model F = 71.01 which is more than 0.05, which show 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 4 h. The value of adequate precision is 25.995 which means 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

In Table 25, ANOVA results show that model F value is 119.88 which is more than 0.05, which show that selected model is

Table 20: Drug release of ER pellets

Time (h)	Limit	Reference product	SMDL4	SMDL5	SMDL6	SMDL7
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
F2		-	38	76	40	29
MDT (h)		8.07	5.20	8.80	10.72	12.46
MRT (h)		5.86	4.62	6.15	7.16	7.91

MDT: Mean dissolution time, MRT: Mean residence time, NMT: Not more than, NLT: Not less than, SMDL: s-Metoprolol succinate drug layering, ER: Extended release

Table 21: Results of trials for ER coating optimization for drug layered pellets prepared by fluid bed technology using CCD design

Standard run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
% weight 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	**Percentage 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

ER: Extended release, HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

Table 22: Fits summary of dependent parametersfor CCD design of ER coating optimization for drug pellets prepared by fluid bed technology

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Response Y_1: Drug release at 1 h						
Mean versus total	157.97	1	157.97			
Linear versus mean	19.14	3	6.38	83.82	<0.0001	Suggested
2FI versus linear	0.33	3	0.11	1.69	0.2319	
Quadratic versus 2FI	0.15	3	0.048	0.66	0.6006	
Cubic versus quadratic	0.30	4	0.075	1.07	0.4984	Aliased
Response Y_2: Drug release at 4 h						
Mean versus total	11648.53	1	11648.53			
Linear versus mean	2012.66	3	670.89	72.86	<0.0001	
2FI versus linear	16.72	3	5.57	0.54	0.6648	
Quadratic versus 2FI	79.88	3	26.63	8.07	0.0113	Suggested
Cubic versus quadratic	4.39	4	1.10	0.18	0.9366	Aliased
Response Y_3: Drug release at 8 h						
Mean versus total	34994.33	1	34994.33			
Linear versus mean	1700.31	3	566.77	119.88	<0.0001	Suggested
2FI versus linear	18.20	3	6.07	1.40	0.2986	
Quadratic versus 2FI	3.56	3	1.19	0.21	0.8867	
Cubic versus quadratic	17.77	4	4.44	0.61	0.6862	Aliased
Response Y_4: Drug release at 20 h						
Mean versus total	1.590E+005	1	1.590E+005			
Linear versus mean	67.11	3	22.37	9.00	0.0017	Suggested
2FI versus linear	9.61	3	3.20	1.41	0.2965	
Quadratic versus 2FI	7.40	3	2.47	1.13	0.4007	
Cubic versus quadratic	3.48	4	0.87	0.22	0.9107	Aliased

CCD: Central composite design, ER: Extended release,

Table 23: ANOVA result of dependent parameters (Y_1: Drug release at 1 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	19.14	3	6.38	83.82	<0.0001	Significant
A - % weight gain	17.93	1	17.93	235.61	<0.0001	Significant
B - Concentration of HPMC	0.95	1	0.95	12.52	0.0036	Significant
C - Concentration 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			
Correlation total	20.13	16				Significant

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

Table 24: ANOVA result of dependent parameters (Y_2: Drug release at 4 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	2109.27	9	234.36	71.01	<0.0001	Significant
A - % weight gain	1918.22	1	1918.22	581.21	<0.0001	Significant
B - Concentration of HPMC	65.54	1	65.54	19.86	0.0029	Significant
C - Concentration 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			
Correlation total	2132.37	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

Table 25: ANOVA result of dependent parameters (Y_3: Drug release at 8 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	1700.31	3	566.77	119.88	<0.0001	Significant
A - Percentage weight gain	1595.17	1	1595.17	337.40	<0.0001	Significant
B - Concentration of HPMC	82.94	1	82.94	17.54	0.0011	Significant
C - Concentration 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			
Correlation total	1761.78	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

significant. Here % weight gain and concentration of the hypromellose are more significant formulation parameters to impact drug release at 8 h. The value of adequate precision is 32.236 which means 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

In Table 26, ANOVA results show that model F = 9.00 which is more than 0.05, which show that selected model is significant. Here % weight gain and concentration of the hypromellose are more significant formulation parameters to impact drug release at 24 h. The value of adequate precision is 8.237 which means that model can be used to navigate the

Table 26: ANOVA result of dependent parameters (Y_4: Drug release at 24 h)

Source	Sum of squares	df	Mean square	*F* value	*P* value *P*>*F*	Comments
Model	67.11	3	22.37	9.00	0.0017	Significant
A - % weight gain	65.02	1	65.02	26.16	0.0002	Significant
B - Concentration of HPMC	1.76	1	1.76	0.71	0.4148	
C - Concentration 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			
Correlation total	99.43	16				

HPMC: Hydroxypropyl methylcellulose, ATBC: Acetyl tributyl citrate

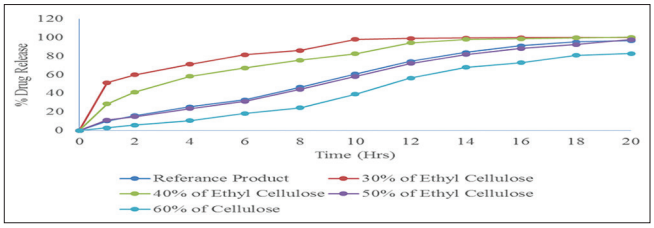

Figure 1: Comparative dissolution profile % extended release coating on drug release from pellets

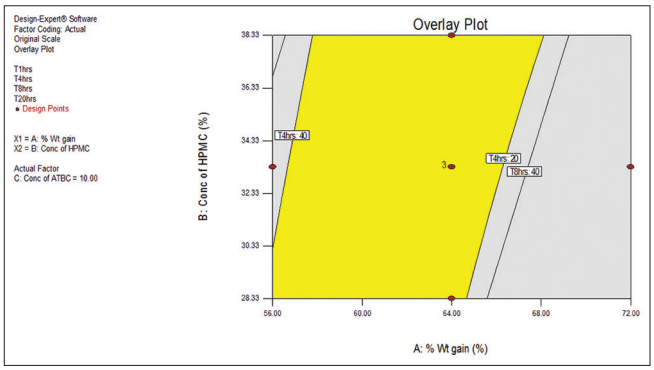

Figure 2: Overlay counter plot of % weight gain versus concentration of hypromellose

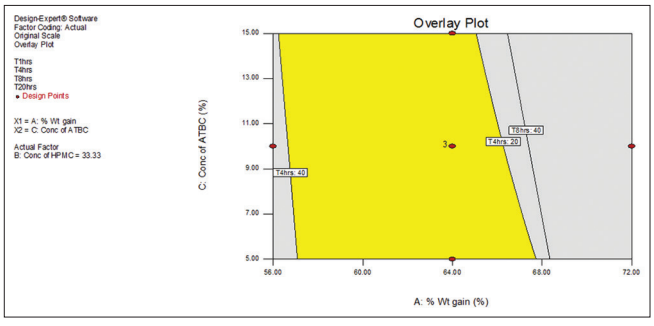

Figure 3: Overlay counter plot of % weight gain versus concentration of acetyl tributyl citrate

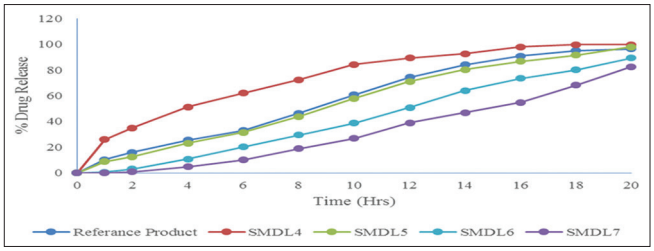

Figure 4: Comparative dissolution profile % extended release coating on drug release from pellets

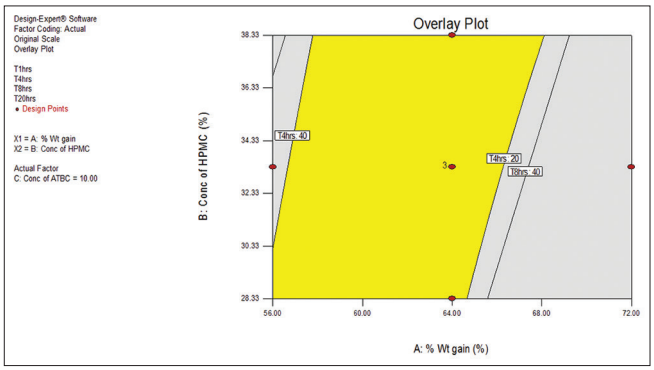

Figure 5: Overlay counter plot of % weight gain versus concentration of hypromellose

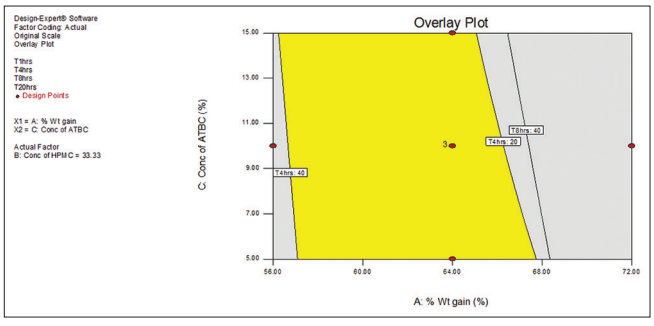

Figure 6: Overlay counter plot of % weight gain versus concentration of acetyl tributyl citrate

design space. Final equation for the response Y_4 is: 96.72 − 2.55*A + 0.42*B − 0.18*C.

The overall conclusion of ANOVA results reveals 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 and concentration of the hypromellose.

Yellow color zone in overlay plot shows the design space [Figures 5 and 6]. 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 ER coating, % weight gain has more significant effect on drug release. Even all center point lies in design space. Overlay plot shows that any concentration of hypromellose and ATBC will give desired drug release if weight gain is done in range of approximately 58.0-66.0%. Final selected formula was also lies in this range (% weight gain of final formulation was 64%).

CONCLUSION

ER pellets of chiral molecules of metoprolol succinate were efficiently prepared by both extrusion and spheronization and fluid bed technology. ER pellets prepared by coating drug pellets prepared by extrusion and spheronization technique gives wider particles size distribution and less sphericity. While in case of ER pellets prepared by coating drug pellets prepared by fluid bed process gives very narrow particle size distribution and more sphericity. Due to narrow particle size distribution and more sphericity comparative less ER coating weight gain is require in case of drug pellets prepared by fluid bed process. So to control drug release from drug pellets prepared by extrusion and spheronization technique, 80% ER coating weight gain is required. While 64% of ER coating weight gain is required to control drug release from drug pellets prepared by fluid bed technology.

REFERENCES

1. Gurjar MK. The future lies in chiral purity: A perspective. J Indian Med Assoc 2007;105:177-8.
2. Gulati V. Different properties of enantiomers of commercially available racemate. J Indian Med Assoc 2007;105:173-4, 176.
3. Dasbiswas A, Dasbiswas D. Chirally pure S-metoprolol - place in therapy. Indian Heart J 2010;62:143-5.
4. Kandukuri JM, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization techniques for oral drug delivery. Int J Pharm Sci Drug Res 2009;1:63-70.
5. Available from: http://www.signetchem.com/signet-the-complete-excipients-company-product-celphere.
6. Rowe RC, Sheskey PJ, Weller PJ. Handbook of Pharmaceutical Excipients. 4th ed. London: Pharmaceutical Press; 2003. p. 641-3.
7. Laicher A, Lorck C, Tobin J, Stanilaus F. Process optimization of pellet coating and drying using fluid-bed production units. Pharm Technol Eur 1994;8:41-8.
8. El-Mahrouk G, Al-Meshal MA, Al-Anagary A, Mahrous G. Preparation and evaluation of sustained-release indomethacin nonpareil seeds. Drug Dev Ind Pharm 1993;19:1903-16.
9. Hosny EA, El-Mahrouk GM, Gouda MW. Formulation and *in vitro* and *in vivo* availability of diclofenac sodium enteric-coated beads. Drug Dev Ind Pharm 1998;24:661-6.
10. United State Pharmacopoeia. Available from: http://www.usp.org.
11. Tang Y, Gan K. Statistical evaluation of *in vitro* dissolution of different brands of ciprofloxacin hydrochloride tablets and capsules. Drug Dev Ind Pharm 1998;24:549-52.

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