ROLE OF QUALITY BY DESIGN FOR THE OPTIMIZATION OF PUSH PULL OSMOTIC PUMP OF *S*-METOPROLOL SUCCINATE

Bhupendra G. Prajapati[a]*, Dipesh V. Patel[a] and Dignesh M. Khunt[b]

ABSTRACT

The present research was focus on the preparation and evaluation of push pull osmotic pump of *S*-metoprolol succinate based on Quality by Design (QbD) approaches. For preparation of push pull osmotic pump, pull layer of *S*-metoprolol succinate was prepared using low molecular weight Polyox by wet granulation. Push layer containing higher molecular weight polyox and sodium chloride as osmotic agents were prepared by wet granulation. Both layers were compressed to get bilayer tablets and these bilayer tablets were coated with cellulose acetate, which act as a semipermeable membrane, and poly-ethylene glycol, which act as pore former. Extended release coated tablets were laser drilled on drug layer side to allow delivery of drug. The formulation was optimized using a center composite design (CCD). The effect of different drilled diameter on drug release was also evaluated. Extended release coating (%), concentration of sodium chloride (%w/w) and cellulose acetate : PEG 3350 ratio impact on drug release was optimized using center composite design (CCD). 20% Extended release coating. 20% w/w concentration of sodium chloride, and 90:10 cellulose acetate : PEG 3350 ratio gave zero order release (R^2 value greater than 0.9) up to 20 h. Push pull osmotic pump of *S*-metoprolol succinate was successfully developed using low molecular weight polyox in pull layer and higher molecular weight of polyox in push layer.

INTRODUCTION

Metoprolol succinate is a routinely administered cardioselective beta blocker. Like other beta blockers, it is a racemic combination of *S* and *R*-isomers in a 1:1 ratio. In metoprolol succinate, the *S*-isomer selectively blocks the beta-1 receptor, while the *R*-isomer blocks the beta-2 receptor. Beta-1 receptors can be found in abundance in the heart and kidney, whereas beta-2 receptors can be found in the vascular and nonvascular smooth muscle tissues. The selective blockade of the beta-1 receptor is therefore beneficial in the better management of high blood pressure. Compared to the *R*-isomer metoprolol succinate, *S*-isomer residues of metoprolol succinate have a 500-fold greater affinity for the beta-1 receptor[1, 2].

In order to get the same beta-1 blocking activity as its racemate, *S*-metoprolol succinate can be employed at half the concentration of its racemic combination. Despite these benefits, one of the most difficult tasks is to keep *S*-metoprolol succinate in the formulation. Because metoprolol succinate has a shorter half-life (3-4 h), it is swiftly eliminated from the body. Because of this, metoprolol succinate needs to be administered on a regular basis. The controlled release dose formulations of metoprolol succinate are a perfect fit because of this. Drug levels in plasma must be maintained at a constant level in order to treat chronic illnesses such as cardiovascular disease, diabetes, and the like[1,2].

Different types of controlled-release dosage forms of metoprolol succinate were explored by different researchers, such as controlled release matrix type tablet[3], multi-unit particulate formulation[4–7], floating multi-particulates by hot-melt extrusion[8], sandwiched osmotic tablet[9], porosity osmotic tablet[10] etc. Till date, there is little research work done on formulation development of *S*-metoprolol succinate due to difficulties of controlling one isomer in a formulation as well as an analytical method.

a Department of Pharmaceutics and Pharmaceutical Technology, Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana-384 012, Gujarat, India

b Graduate School of Pharmacy, Gujarat Technological University, Gandhinagar-382 028, Gujarat, India

*For Correspondence: E-mail: bhupen27@gmail.com

Keep this in mind, current research focuses on the development of *S*-metoprolol succinate osmotic release osmotic (OROS) tablets by using QbD-based approaches. There are various kinds of OROS technologies available such as elementary osmotic pump, controlled porosity osmotic pump, sandwiched osmotic tablets, push-pull osmotic pump, etc[11]. Out of this, current research work focus on the development of a push pull osmotic pump. Push-pull OROS tablets are bilayer tablets that consist of a pull layer and push layer. Drugs are loaded in the

Table I: QTPP and CQA for OROS tablets

Sr. No.	QTPP element	Target	Is this CQA?	Justification
1	Physical appearance	Pink to light pink film coated tablets	No	Safety and efficacy are not impacted on color and appearance. It only impacts on patient acceptability.
2	Assay	90-110% w/w of label claim	Yes	Assay has directly relationship with the efficacy and safety of drugs and that's why it is very crucial for the optimization of tablets.
3	Uniformity of dosage units	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity may affect safety and efficacy. *S*-metoprolol succinate is mixed with other excipients and granulated using isopropyl alcohol. Wet granulation gives good distribution of the drug. Therefore, there will be no effect of formulation parameters on uniformity of dosage units of *S*-metoprolol succinate. Uniformity of dosage units will be monitored at the time of batch release.
4	Drug dissolution	1h: NMT 20% 4h: 20% - 40% 8h: 40% - 60% 16h: NLT 80% of labeled amount of *S*-metoprolol succinate dissolved in 500 mL of pH 6.8 phosphate buffer in USP apparatus-II (paddle) at 50 RPM	Yes	Bioavailibity and bioequivalence are the prime factor for evaluation of drug release from the formulation. It is directly impact on *in vivo* performance of drug. Failure to meet the dissolution specification may impact bioavailability.
5	Related substance	Imp C : NMT 0.2% Single max Unknown impurities : 0.2% Total impurities : NMT 1.50 %	Yes	Related substance directly impacts on safety of formulation and that's why it must be controlled based on compendial/ICH requirements or RLD characterization to limit patient exposure. Formulation variables may affect degradation of molecule. The limit of related substances is critical to drug product safety. The target for any unknown impurity is set according to the ICH.
6	Water content	NMT 6.0%	No	Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. *S*-metoprolol succinate is non hygroscopic in nature and none of its impurities are generated due to hydrolysis. Therefore, this CQA will not be monitored through out development process.

Table II: Drug substance attributes for OROS tablets

Low	Broadly acceptable risk. No further investigation is needed.							
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.							
High	Risk is unacceptable. Further investigation is needed to reduce the risk.							
Drug product CQA	**Drug substance attributes**							
Drug product CQA	**Solid state form**	**Particle size distribution (PSD)**	**Hygroscopicity**	**Solubility**	**Moisture Content**	**Residual Solvent**	**Process Impurities**	**Chemical Stability**	**Flow properties**
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
Uniformity of dosage units	Low	Low	Low	Low	Low	Low	Low	Low	Low
Drug dissolution	Low	Low	Low	Low	Low	Low	Low	Low	Low
Related substance	Low	Low	Low	Low	Low	Low	Low	Low	Low

Drug substance attribute	Drug Products CQA	Justification
Solid state form	Assay	Drug substance solid state form doesn't affect tablet assay and uniformity of dosage unit. Hence the risk is low.
	Uniformity of dosage unit	
	Drug dissolution	There is no reported polymorphic form of *S*-metoprolol succinate. Therefore solid state form of API does not have any impact on drug product dissolution and related substances. So risk is low.
	Related substance	
Particle size distribution (PSD)	Assay	*S*-metoprolol is BCS Class-I drug and therefore there is no impact of initial particle size of drug on assay. Hence the risk is low.
	Uniformity of dosage unit	There is no effect of initial particle size of drug on uniformity of dosage unit. Therefore the risk is low.
	Drug dissolution	*S*-metoprolol succinate exhibited very good solubility across the physiological pH range, particle size of API is irrelevant to dissolution. So risk is low.
	Related substance	Drug substance stability has been evaluated by the DMF holder. So the risk is low.
Hygroscopicity	Assay	*S*-Metoprolol succinate is not hygroscopic. The risk is low.
	Uniformity of dosage unit	
	Drug dissolution	
	Related substance	
Solubility	Assay	Solubility does not affect capsule assay and uniformity of dosage unit. Thus, the risk is low.
	Uniformity of dosage unit	
	Drug dissolution	*S*-metoprolol succinate exhibited very good solubility across the physiological pH range. Being a BCS Class-I drug, initial solubility of as such API is irrelevant to dissolution. So risk is low.
	Related substance	Solubility does not affect degradation products. Thus, the risk is low.
Moisture content	Assay	Moisture content is controlled in the drug substance through specification of loss on drying (<0.5 %w/w) and *S*-metoprolol succinate is non hygroscopic in nature. Thus, impact of variable moisture content on assay, uniformity of dosage unit, drug dissolution and degradation product dissolution is low. Hence the risk is low.
	Uniformity of dosage unit	
	Drug dissolution	
	Related substance	
Residual solvent	Assay	Residual solvents are controlled in the drug substance specification and comply with USP requirement. At ppm level, residual solvents are unlikely to impact hence the risk is low.
	Uniformity of dosage unit	
	Drug dissolution	
	Related substance	
Impurities	Assay	Impurities are controlled in the drug substance specification. Impurity limits comply with ICH recommendations. Within this range, process impurities are unlikely to impact and hence the risk is low.
	Uniformity of dosage unit	
	Drug dissolution	
	Related substance	

pull layer while the push layer contains osmogen and swellable polymer. These bilayer tablets are then coated with semipermeable membrane along with pore former which allow entry of fluid into tablets upon solubilization. Extended release coated tablets were than laser drilled on drug layer side to allow delivery of drug from the OROS tablets. There are several excipients available that can act as a semipermeable membrane but out of these excipients, cellulose acetate is widely used.

For OROS tablets, there are many formulation variables that can affect the release of drug from the device, like concentration of the osmotic agent, % extended release coating, and the ratio of semipermeable polymer to pore former[11–13].

To retain the highest possible concentration of S-metoprolol succinate in the formulation, quality by design was used to optimise the parameters that control the drug release. Quality by design (QbD) is a concept that has gained traction in recent years by regulatory agencies such as the FDA, EMEA, MHRA and others as a means of developing higher-quality products through a better understanding of essential process and product parameters based on risk management. The design of experiment (DOE), a component of QbD, plays a crucial role in assessing the impact of a large number of critical process parameters (CPP) on the critical quality attributes (CQA) of the product. By reducing the number of trials, which can be expensive and time-consuming, DOE aids in the production of high-quality products[14,15].

The current research was focussed on the development and optimization of S-metoprolol succinate push pull osmotic tablets using laser drilling on the basis of QbD. Optimized push pull osmotic tablets was characterized for compendial test and non-compendial test of tablet with multimedia dissolution study.

MATERIALS AND METHODS

Materials

S-Metoprolol succinate (Emcure Pharmaceuticals Ltd.), polyethylene oxide (Polyox™ WSR N10Polyox™ WSR N80, Polyox™ WSR Coagulant and Polyox™ WSR 303, Dow Chemicals, USA), polyvinylpyrrolidone (Kollidon® 30, BASF Germany), sodium chloride (Merck, Germany), cellulose acetate (Eastman™ CA-398-10, Eastman Chemical Company, USA), polyethylene glycol 3350 (Clariant, Switzerland), magnesium stearate (Ligamed MF-2-V, Peter Greven, Nederland), iron oxide Red (Koelin/PH- 919, Koel Colours Private Ltd., Gujarat) and iron oxide black (Koelin/PH- 999, Koel Colours Private

Ltd., Gujarat) were used as raw materials for formulation development. All reagents and chemicals were of analytical grade and used as received.

METHODS

Analytical method development

The high-performance liquid chromatography system (HPLC) (E2659, Waters, USA) consists of an ultra-violet (UV) detector. The reverse-phase C8 column (250 mm x 4.6 mm, 5μ) (Thermo) was used at room temperature. The mobile phase consists of the phosphate buffer pH 3.0 and acetonitrile in the proportion of 75:25 (V/V). Flow rate and λ_{max} were 1.0 mL min^{-1} and 280 nm, respectively. The calibration curve was made in the range of 12.5 to 37.5 μg mL^{-1} with the linearity of 0.9984 R^2 value.

Quality target product profile (QTPP) and risk assessment

QTPP is the first step to apply QbD approaches for the development of OROS tablets of S-metoprolol succinate. It is a content summary of the quality parameters of OROS tablets required in finished products[14,15]. QTPP of S-metoprolol succinate OROS tablets with critical quality attributes (CQA) are shown in Table I. Risk assessment was done based on qualitative risk based matrix analysis of drug and finished formulation which are shown in Tables II and III.

Formulation and development of OROS tablets

Preliminary trials for OROS Tablets

OROS tablets are composed of two layers i.e. pull layer and push layer. Polyethylene oxide (polyol) is a widely used polymer for controlled release tables due to its very fast hydration. So, a preliminary trial was performed to screen the grades of Polyox. A preliminary trial was performed with two different grades of Polyox in the drug layer and push layer. During trial, sodium chloride level and extended release coating were kept constant. During the preliminary trial, three different ratios of cellulose acetate and polyethylene glycol were also evaluated at fix percentage of weight gain i.e. 20%. Detailed composition of preliminary trial formulation are given in Table IV.

Pull layer (drug layer blend) preparation

For the preparation of blend of pull layer, S-metoprolol succinate and Polyox were sifted through #20 sieve and Iron oxide red sifted through #80 sieve. Povidone (PVPK-30) was dissolved in isopropyl alcohol with continued

Table III: Formulation variables for OROS tablets

Low	Broadly acceptable risk. No further investigation is needed.		
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.		
High	Risk is unacceptable. Further investigation is needed to reduce the risk.		

Drug product CQA	Formulation variables		
	Concentration of Sodium chloride	% Extended release coating	Concentration of plasticizer / Pore former
Assay	Low	Low	Low
Uniformity of dosage unit	Low	Low	Low
Drug dissolution	Medium	High	High
Related substance	Low	Low	Low

Drug product attribute	Drug products CQA	Justification
Concentration of Sodium chloride	Assay	Sodium chloride is used as osmotic agent. Concentration of sodium chloride does not have any impact on assay and uniformity of *S*-metoprolol succinate in drug product. So risk is low.
	Uniformity of dosage unit	
	Drug dissolution	As sodium chloride act as an osmotic agent in the dosage form and its concentration plays critical role in creating osmotic pressure across the membrane and ultimately water penetrating into the tablets. Therefore, risk of sodium chloride concentration to affect drug dissolution is high.
	Related substance	During preformulation study, drug excipient compatibility study is conducted and found that drug is compatible with all the excipients used during investigation. So risk of microcrystalline cellulose to lactose ratio on related substance is low. Thus risk is low.
Extended release coating	Assay	Extended release coating does have any impact on drug product assay and uniformity of dosage unit. So risk is low.
	Uniformity of dosage unit	
	Drug dissolution	As product is extended release tablets where drug release is controlled by applying semi permeable membrane. % extended release coating may have significant impact of drug release. So risk is high.
	Related substance	During preformulation study, drug excipient compatibility study is conducted and found that drug is compatible with all the excipients used during investigation. Hence, risk of extended release coating on related substance is low. Thus risk is low.
Concentration of plasticizer / pore former	Assay	PEG is used as pore former as well as it acts as plasticizer to give good flexibility to semi permeable membrane to with stand osmotic pressure created into tablets. Concentration of plasticizer / pore former do not affect the assay and uniformity of drug. So risk is low.
	Uniformity of dosage unit	
	Drug dissolution	PEG is used as pore former as well as it acts as plasticizer to give good flexibility to semi permeable membrane to with stand osmotic pressure created into tablets. As a pore former it create channels into semi permeable membrane to allow water to penetrate into tablets and hydrate the swellable polymer. PEG as a plasticizer gives good flexibility to semi permeable membrane to with stand osmotic pressure created inside the tablets and prevent breakage of semi permeable membrane to rupture. Therefore the concentration of pore former / plasticizer may have significant impact of drug release. So risk is high
	Related substance	During preformulation study, drug excipient compatibility study is conducted and found that drug is compatible with all the excipients used during investigation. So risk of %extended release coating on related substance is low. Thus risk is low.

stirring. Sifted *S*-metoprolol succinate and Polyox along with iron oxide red were dry mixed into rapid mixer granulator for 10 min. This dry mix blend was granulated using a binder solution of povidone to get desired consistency of granules. The granulated mass was dried in the rapid dryer at 60°C till the desired LOD limit was achieved (LOD: NMT 1.5%). Dried granules were sifted through #20 sieve. Retained granules over the #20 sieve were collected into separate polybags. Oversized granules were milled through a 1.2 mm screen using the multi mill. Magnesium stearate was passed through #60 sieve and mixed with dried milled granules into the blender.

Push layer (drug layer blend) preparation

Sodium chloride was milled using a 0.25 mm screen using the multi mill. Milled sodium chloride along with polyol was sifted through #20 sieve. Iron oxide black was sifted through #80 sieve. Povidone (PVPK-30) solution was prepared in isopropyl alcohol and taken as the binding solution. Sodium chloride, Polyox and iron oxide black were dry mixed using a rapid mixer granulator for 10 min. The dry mix blend was granulated using a binder solution of povidone to get desired consistency of granules. The granulated mass was then dried in the rapid dryer at 60°C till the desired LOD limit was achieved (LOD: NMT 1.5%). Dried granules were sifted through #20 sieve and passed and #20 sieve retained granules were collected into separate polybags. Oversized granules were milled through a 1.2 mm screen using the multi mill. Magnesium stearate was passed through #60 sieve and mixed with dried milled granules into a blender.

Bilayer compression of pull layer (drug layer) and pull layer blends

Firstly, pull layer and push payer blends were evaluated for loss on drying, bulk density, tapped density, Hausner's ratio and Carr's index. After that, drug layer and push layer blends were compressed using Cadmach Machinery Co. Pvt. Ltd., India machine.

Extended release coating of bilayer tablets

For the extended release coating (semi permeable coating), acetone and purified water were selected as the solvents in the 85:15 V/V ratio. Polyethylene glycol (PEG 3350) was dissolved in purified water. Cellulose acetate was dissolved in acetone by continue stirring. Detailed formula is shown in Table IV. A solution of PEG was slowly added to the cellulose acetate solution under continued stirring for 30 min. Bilayer tablets were charged into an auto coater and preheated at 45°C till the bed temperature reaches to 30°C. Spraying of the extended release

coating solution was started till the 15-20% weight gain was achieved. The coated tablets were dried at 50 °C for 30 min, after the completion of the extended release coating.

Laser drilling

Extended release-coated tablets were laser drilled onto the drug layer side using a laser drilling machine (TLDM-150, Scantech, India).

Film coating of extended release coated tablets

Opadry pink 03B540159 was dispersed into purified water under continuous stirring to get 10% w/w dispersion. Stirring was continued for 45 min. The dispersion was then filtered through #60 sieve. Laser drilled extended release coated tablets were loaded into auto coater pre-warmed at 55°C till the required bed temperature of 40°C was reached. Once the required bed temperature was reached, the spray of the coating dispersion was started and the spraying is continued till desired weight gain was achieved (~2.7%w/w). After completion of the coating, tablets were dried at 50°C for 15 min. Film-coated tablets were evaluated for the different parameters.

Optimization of the OROS tablets

Based on preliminary screening, Polyox grade was selected. Also, level of cellulose acetate to PEG 3350 ratio was screened. Based on the screening trial, a central composite design (CCD) with three center points was employed for the optimization of OROS tablets formulation. Percentage of extended release coating, concentration of sodium chloride and cellulose to PEG3350 ratio were selected as formulation variable and their effect on drug release profile were investigated. The dependent parameters were drug release at 1, 4, 8 and 20 h (Table V). Preparation of OROS tablets was done as per the preliminary batch procedure.

Confirmatory batches for design space

Confirmatory batches were taken within the design space to evaluate the limits of the design space. Confirmatory batches in these range were taken and observed results of the dependent parameter, i.e. drug release at 1, 4, 8 and 20 h, were compared with predicted results. Formulation details of the confirmatory batches are described in Table V.

Evaluation of extended release coated tablets

Drilled diameter and depth: Drilled diameter and depth were measured using calibrated eyepiece provided

Table IV: Formulation details for preliminary trials of OROS tablets

Ingredients	Trial 1	Trial 2
Pull Layer		
S-metoprolol succinate	11.875	11.875
Iron oxide red (Koelin/PH- 919)	0.100	0.100
Polyvinyl pyrrolidone (PVPK-30) (Kollidon® 30)	5.000	5.000
Isopropyl alcohol	q.s.	q.s.
Magnesium stearate (Ligamed MF-2-V)	1.000	1.000
Push Layer		
Polyethylene oxide (Polyox™ WSR Coagulant)	36.950	-
Polyethylene oxide (Polyox™ WSR 303)	-	36.950
Sodium chloride	10.000	10.000
Polyvinyl pyrrolidone (PVPK-30) (Kollidon® 30)	2.500	2.500
Iron oxide black (Koelin/PH- 999)	0.050	0.050
Isopropyl alcohol	q.s.	q.s.
Magnesium stearate (Ligamed MF-2-V)	0.500	0.500
Total weight of bilayer layer tablet	**150.00**	**150.00**
Extended release coating (Semipermeable coating)		
Cellulose acetate (Eastman™ CA-398-10)	25.500	25.500
Polyethylene glycol 3350	4.500	4.500
Acetone	q.s.	q.s.
Purified water	q.s.	q.s.
Total extended release coated tablets weight	**180.00**	**180.00**
Film coating		
Opadry 03B540159 Pink	5.000	5.000
Film coated tablets weight	**185.00**	**185.00**
Sodium chloride concentration	**20%**	
Cellulose acetate : PEG 3350 ratio	**85.15**	
% of Extended release coating	**20%**	
Drug release profile of trail 1 to trial 2 batches		

Time (H)	Limit	Condition: Phosphate buffer (pH 6.8) / 500 mL / USP-II / 50 RPM	
		Trial 1	**Trial 2**
1	NMT 25%	10.8 ± 5.3	8.6 ± 5.8
2	-	21.4 ± 4.2	18.2 ± 5.1
4	20-40%	41.8 ± 3.2	35.2 ± 4.2
6	-	61.4 ± 1.8	52.4 ± 3.1
8	40-60%	79.1 ± 1.1	70.3 ± 1.8
10	-	97.2 ± 0.8	84.3 ± 1.1
12	-	99.1 ± 0.5	95.2 ± 0.9
14	-	99.6 ± 0.2	98.5 ± 0.7
16	-	99.9 ± 0.2	99.9 ± 0.4
18	-	100.1 ± 0.3	100 ± 0.2
20	NLT 80%	100.1 ± 0.2	100.1 ± 0.3
Mean Residence Time (MRT) (h)		3.35	4.01
Mean Dissolution Time (MDT) (h)		5.02	5.94

Table V:Summary of central composite design for OROS tablets

Independent variable	Level	
	-1	**+1**
Extended release coating (%)	15	25
Concentration of sodium chloride (w/w%)	15	25
Cellulose acetate : PEG 3350 ratio	85:15	95:5
Response to be studied		**Limit**
Y1 : Drug release at 1 h		NMT 25%
Y2 : Drug release at 4 h		20 – 40%
Y3 : Drug release at 8 h		40 – 60 %
Y4 : Drug release at 20 h		NLT 80%

Confirmatory batches				
Weight gain (%)	15.00	15.00	21.0	21.0
Concentration of sodium chloride (%)	15.00	25.00	15.00	25.00
Cellulose acetate : PEG 3350 ratio	85.00	95.00	85.00	95.00

Results of the CCD for OROS Tablets

Batch No.	Weight gain (%)	Concentration of sodium chloride (%)	Cellulose acetate : PEG 3350 ratio	% Drug release			
				1 h	**4 h**	**8 h**	**20 h**
1	15	15	85:15	9.3 ± 4.1	29.8 ± 3.4	57.8 ± 1.9	98.7 ± 0.9
2	25	15	85:15	5.3 ± 4.9	21.5 ± 3.5	44.9± 2.1	95.6 ± 1.0
3	15	25	85:15	14.9 ± 4.8	34.5 ± 3.7	60.3 ± 2.7	99.9 ± 1.2
4	25	25	85:15	8.2 ± 4.4	28.5 ± 3.3	52.6 ± 2.2	99.2 ± 0.7
5	15	15	95:5	8.4 ± 4.9	27.9 ± 3.2	54.2 ± 1.8	97.8 ± 0.7
6	25	15	95:5	1.2 ± 6.7	12.6 ± 5.1	29.6 ± 3.7	90.5 ± 1.1
7	15	25	95:5	11.1 ± 4.1	30.4 ± 3.3	58.9 ± 2.4	98.9 ± 1.0
8	25	25	95:5	2.5 ± 6.2	15.6 ± 4.9	32.5 ± 2.4	96.2 ± 1.2
9	15	20	90:10	10.2 ± 5.1	29.3 ± 3.9	51.5 ± 1.7	98.9 ± 0.9
10	25	20	90:10	3.1 ± 5.9	18.9 ± 4.1	38.5 ± 2.9	96.8 ± 1.1
11	20	15	90:10	4.6 ± 5.5	21.1 ± 3.9	43.5 ± 2.4	95.6 ± 1.2
12	20	25	90:10	8.5 ± 4.7	25.4 ± 3.1	48.9 ± 2.3	98.5 ± 1.0
13	20	20	85:15	9.5 ± 4.3	26.5 ± 2.9	49.7 ± 1.7	99.5 ± 0.8
14	20	20	95:5	3.5 ± 5.8	19.2 ± 3.8	39.2 ± 2.2	97.9 ± 1.1
15	20	20	90:10	6.1 ± 5.2	24.5 ± 4.0	46.9 ± 2.4	101.3 ± 1.1
16	20	20	90:10	5.9 ± 5.9	25.1 ± 4.3	48.2 ± 3.0	99.5 ± 1.3
17	20	20	90:10	6.3 ± 5.7	24.7 ± 4.4	47.2 ± 2.9	100.1 ± 0.9

Table VI: Model statistical summary for OROS tablets

Response	Source	Sum of squares	df	Mean square	F value	p-value Prob> F	
Drug release at 1 h	Mean vs Total	827.409	1	827.409			
	Linear vs Mean	179.077	3	59.69	38.65	< 0.0001	Suggested
	2FI vs Linear	7.88	3	2.62	2.15	0.1565	
	Quadratic vs 2FI	3.27	3	1.09	0.856	0.5065	
	Cubic vs Quadratic	5.53	4	1.38	1.22	0.4507	aliased
Drug release at 4 h	Mean vs Total	10155.31	1	10155.31			
	Linear vs Mean	441.79	3	147.2651	24.64	< 0.0001	Suggested
	2FI vs Linear	36.99	3	12.33	3.02	0.0800	
	Quadratic vs 2FI	1.79	3	0.59	0.107	0.9530	
	Cubic vs Quadratic	28.58	4	7.14	2.07	0.2872	aliased
Drug release at 8 h	Mean vs Total	38062.32	1	38062.32			
	Linear vs Mean	939.370	3	313.123	14.92	0.0002	Suggested
	2FI vs Linear	117.81	3	39.27	2.53	0.1158	
	Quadratic vs 2FI	3.26	3	1.08	0.05	0.9839	
	Cubic vs Quadratic	105.40	4	26.35	1.71	0.3435	aliased
Drug release at 20 h	Mean vs Total	163052.5	1	163052.5			
	Linear vs Mean	53.66	3	17.88	5.05	0.0154	
	2FI vs Linear	11.43	3	3.81	1.10	0.3928	
	Quadratic vs 2FI	23.88	3	7.96	5.23	0.0331	Suggested
	Cubic vs Quadratic	7.75	4	1.93	2.00	0.2973	aliased

Multimedia dissolution profile of optimization batch

Condition	500 mL / USP-II (Paddle) / 50 RPM					
Time (H)	0.1N HCl		Acetate buffer (pH 4.5)		Phosphate buffer(pH6.8)	
	Innovator product	SMOT4	Innovator product	SMOT4	Innovator product	SMOT4
1	12.0 ± 3.8	5.9 ± 5.4	10.4 ± 4.7	6.9 ± 6.1	10.2 ± 5.1	6.1 ± 5.3
2	20.5 ± 3.4	12.4 ± 4.1	19.3 ± 3.8	12.1 ± 5.4	15.9 ± 4.2	11.9 ± 4.2
4	41.6 ± 2.4	25.1 ± 3.4	50.2 ± 2.3	23.4 ± 4.1	25.4 ± 2.3	24.5 ± 3.4
6	66.8 ± 2.0	35.8 ± 2.1	71.9 ± 1.7	35.4 ± 3.0	33.0 ± 1.3	36.1 ± 1.9
8	81.3 ± 1.7	47.5 ± 1.8	85.6 ± 1.1	48.5 ± 2.2	46.5 ± 0.8	46.9 ± 1.0
10	92.7 ± 0.4	61.8 ± 1.2	92.4 ± 0.7	61.3 ± 1.3	60.7 ± 0.5	60.3 ± 0.9
12	97.6 ± 0.3	73.1 ± 0.9	96.3 ± 0.4	73.4 ± 0.9	74.4 ± 0.6	72.9 ± 0.8
14	100.0 ± 0.3	86.3 ± 0.7	98.4 ± 0.2	85.9 ± 0.8	84.0 ± 0.7	85.3 ± 0.7
16	101.9 ± 0.2	97.1 ± 0.6	99.7 ± 0.2	97.4 ± 0.6	91.0 ± 0.8	96.5 ± 0.5
18	102.3 ± 0.3	99.4 ± 0.2	100.0 ± 0.1	99.7 ± 0.4	95.2 ± 0.2	98.9 ± 0.5
20	102.4 ± 0.2	99.9 ± 0.2	101.0 ± 0.1	100.1 ± 0.2	96.5 ± 0.2	101.3 ± 0.4

by a laser drilling machine vender. For determination of depth, tablets were cut and depth was measured.

Dissolution profile: Coated tablets were evaluated for drug release profile. Dissolution was carried out as per USP dissolution condition described in Table IV. Samples were collection at the time intervals of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 h. Analysis was done by using HPLC method. Confirmatory batches were evaluated only for drug release profile as per USP monograph.
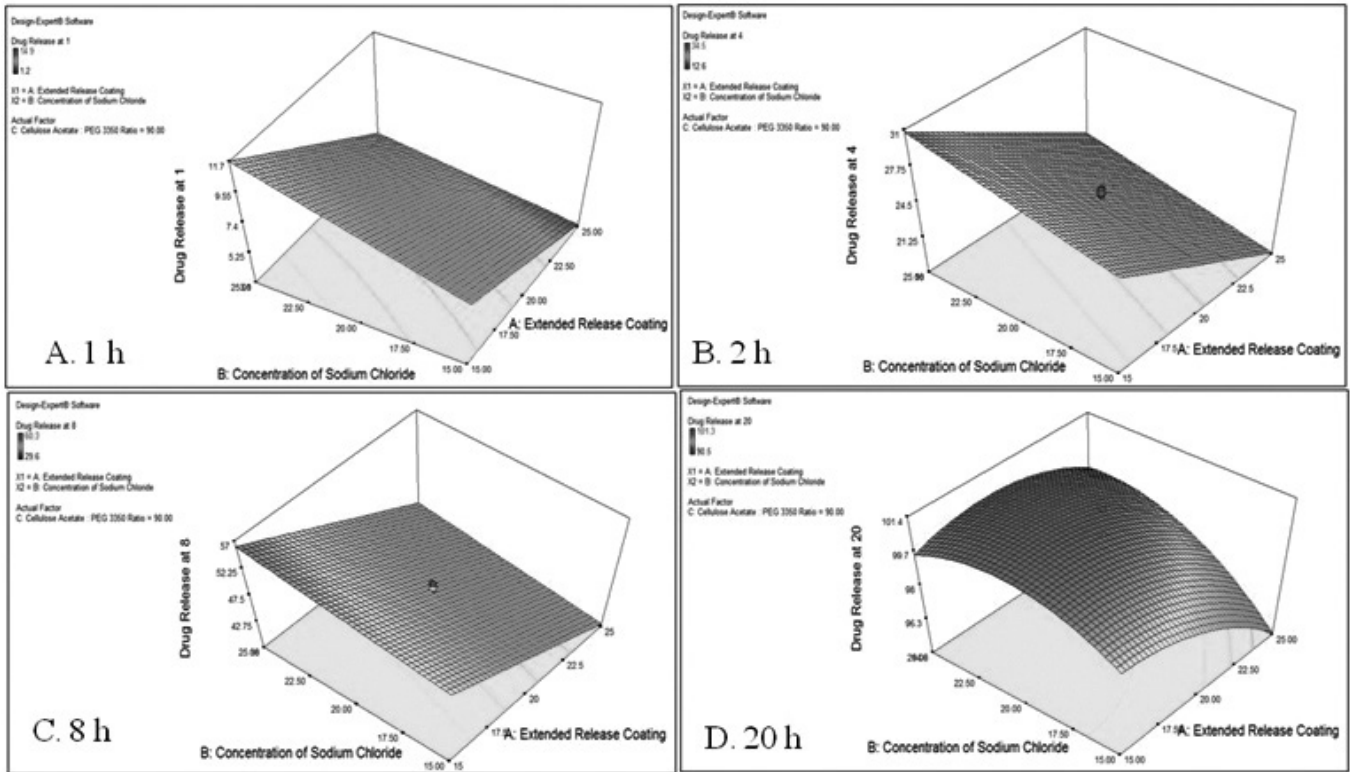

Fig. 1: 3D surface plot of dependent variable at A) 1 h, B) 2 h, C) 8 h and D) 20 h
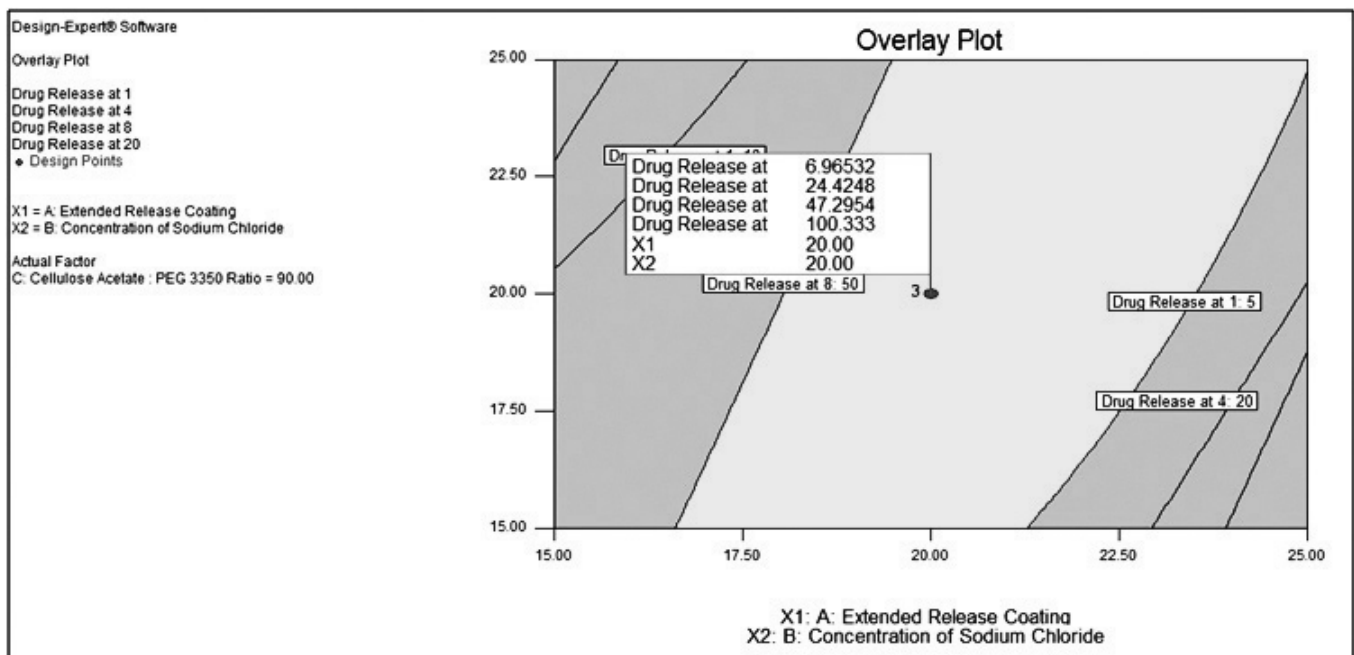
Fig. 2: Overlay plot representing the optimized batch formula

Multimedia dissolution profile: Multimedia dissolving profile of the optimised batch was examined using USP apparatus-II at 50 RPM in 500 mL of 0.1% sodium chloride, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The samples were taken at intervals of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 h. The HPLC technique was utilised for the analysis. To assess the release kinetics of drugs form OROS, dissolution research data was subjected to various kinetic models, such as zero order (cumulative percentage of drug release versus time), first order (log cumulative of drug remaining versus time), and Higuchi model (cumulative percentage of drug release versus square root of time)[14,16].

RESULTS AND DISCUSSION

Quality target product profile (QTPP) and risk assessment

QTPP of developed OROS tablets is shown Table I, which was decided based on the quality necessary in finished products. From the QTPP, CQA was decided. After that, qualitative risk analysis was run to assess the risk or threat involved in finished product. Here, risk analysis matrix was performed to evaluate the possible impact of drug substances and drug products on CQA (Table II and III). The risk from drug substances was control from initially so there was low risk on CQA (Table II). Table III indicated that the concentration of sodium chloride, % extended release coating and concentration of plasticizer was a possible treat on CQA. DoE is run to evaluate the possible impact of above parameter on CQA.

Results of preliminary batches

Bulk density and tapped density of pull layers were in between 0.48-0.52 g mL^{-1} and 0.57-0.61 g mL^{-1}, respectively. Bulk density and tapped density of push layer was between 0.58-0.62 g mL^{-1} and 0.68-0.70 g mL^{-1}, respectively[17].

Carr's index value of pull layer and push layers were between 12-16, which indicate that all lubricated blend of pull layer and push layers have good flow properties. Values of Hausner's ratio were in a range of 1.14 to 1.20, which indicates that all the lubricated blend of pull layer and push layer has good compressibility.

Friability values of all batches were found to be below 0.1%. Percentage weight gain of extended release coating was in a range of 19.9 to 20.2%w/w for all batches. All physical parameters of the extended release coated tablets are similar[18].

Drug release profile of Trial 1 and Trial 2 shows that about 90% of the drug was released within 12 h (Table IV). From the result, polyethylene oxide (Polyox™ WSR 303) was taken as a polymer for push layer due to higher mean residence time (MRT) and mean dissolution time (MDT).

RESULTS OF OPTIMIZATION BATCHES

Based on the preliminary trial results, the results of Trial 2 were found satisfactory. So, based on that further evaluation was carried out to investigate the effect of percentage weight gain, the concentration of sodium chloride in push layer and ratio of cellulose acetate: PEG 3350 in extended release coating on the drug release profile. So for that central composite design (CCD) with 3 center point was selected. Four dependent parameters were investigated which are drug release at 1, 4, 8 and 20 h (Table V). Results of optimization of the extended-release coating are summarized in Table V. The model statistical summary is shown in Table VI.

Drug release at 1 h, 4 h and 8 h were following the linear relationship with percentage weight gain, concentration of sodium chloride and ratio of cellulose acetate and polyethylene glycol 3350, while drug release at 20 h was follow the quadratic response. These result were also revealed by the 3D graph (Fig. 1).

The final equation for the response Y1 in terms of coded value is given below.

Y1: 2.55 − 0.67*A+0.31*B − 0.44*C − 0.025 *A*B − 0.23*A*C − 0.057*B*C   …………..1

Y2: 24.44 − 5.48*A + 2.15*B − 3.51*C + 0.35 *A*B − 1.98*A*C − 0.78*B*C   …………...2

Y3: 47.32 − 8.46*A+2.32*B − 5.09*C + 0.43 *A*B − 3.80*A*C − 0.33*B*C   …………….3

Y4: 99.38 − 1.59*A+1.45*B − 1.16*C + 0.87 *A*B − 0.78*A*C + 0.25*B*C − 0.83*A2 − 1.63 *B2 + 0.017*C2   ………………4

As per the equation % coating of extended release polymer and drug release are negative in a relationship[19]. It is a fact that increasing the concentration of cellulose acetate retards the drug dissolution. A similar result was also found with the ratio of cellulose acetate: PEG. PEG increased the drug release and cellulose acetate decreased the drug release. As sodium chloride concentration increased, drug dissolution increased due to their osmotic nature[13, 20].

For all the responses, the model p-value is < 0.05. This shows that the selected model can be effectively used to predict the response. ANOVA results of all dependent parameters show that % weight gain and concentration of hypromellose are the more significant formulation parameters.

The yellow colour zone in the overlay plot indicates the design space (Fig. 2) where all responses meet the predefined criteria. As discussed during the evaluation of results of DoE study, percentage weight gain, the concentration of sodium chloride and cellulose acetate to PEG3350 ratio have a more significant effect on drug release. Even all center points lie in design space. The overlay plot shows that any studied concentration of sodium chloride and CA: PEG ratio can give desired drug release if weight gain was done in a range of approx. 15.0 to 21.0 %. Confirmatory batches were taken in this range, predicted and actual results were compared.

Results of confirmatory batches

As discussed during the optimization study, any studied concentration of sodium chloride and CA: PEG ratio can give desired drug release if weight gain was done in a range of approx. 15.0 to 21.0 %. Therefore confirmatory batches in this range were taken and observed results of the dependent parameter i.e. % release at 1, 4, 8, and 20 h were compared with predicted results.

Results of confirmatory batches showed that there was no significant difference between the predicted and actual results. Hence design space selected was successfully evaluated.

Results of optimized formula

As discussed during confirmatory batches, Batch 15 falls in the design space. So based on all the outcomes of development and optimization trails, batch 15 was selected as the optimized formulation. It was evaluated for multimedia dissolution profile and the results were mentioned in Table VI. Results of drug release were mean of 6 units (Mean ± %RSD).

The drug release profile of batch 15 in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer followed the zero-order drug release (R^2 value greater than 0.9). Also, K-Peppas Release exponent(n)value was found to be 1.004, which also indicates zero order drug release[16,21].

Risk mitigation and control strategy

CCD was used to study the multidimensional interaction of input factors rated as high risk in the initial risk assessment for establishing a design space. The design space is the allowable range within which the product's quality can be built. The risk mitigation and control strategy is a combination of how quality is determined based on product knowledge and current process.Fig. 2 was showing the design space in the yellow color where the CQA are in control. Impact of concentration of sodium chloride, % extended release coating and concentration of plasticizer on CQA have been described in the section of Results of optimization batches.

CONCLUSION

Osmotically regulated orifice system of *S*-metoprolol succinate has been successfully developed. For OROS tablets, Polyox N80 in the drug layer and Polyox 303 in the push layer part with 20% w/w extended release coating gave desired drug release profile. Cellulose: PEG 3350 in the ratio of 90:10 gave desired drug release profile.Optimization study revealed that percentage weight gain, the concentration of the sodium chloride, and cellulose acetate to PEG ratio were significant formulation variablesthataffect the drug release profile. Optimization study showed that any concentration of sodium chloride and cellulose acetate to PEG ratio in the studied range, gave desired drug release profile if weight gain was done in a range of approximately 15-21%w/w. And this was confirmed by taking confirmatory batches. Studies showed that there was no significant difference in drug release with different drilled diameters.

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