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ORIGINAL ARTICLE

Design and Evaluation of Controlled Release Drug Delivery System of Generic Drug

Dedania Satyenkumar Jamanadas[1], Vishwanath B A[1,*]

[1] *Department of Pharmaceutics, Krupanidhi College of Pharmacy, Krupanidhi College of Pharmacy, Bangalore, 560035, Karnataka, India*

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* *Corresponding author.*
Vishwanath B A

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ABSTRACT

Objective: Metoprolol succinate, an off-patent generic drug, is an ideal model drug for incorporation into an extended-release dosage form owing to its short half-life (3-7 hrs), low plasma protein binding (12%), and high solubility. The main objective of this study was to develop metoprolol succinate extended-release tablets based on the monolithic matrix technology for once-daily administration. The developed formulation has an in vitro release profile similar to the FDA approved target in vitro release profile while conforming to the USP limits.

Methods: Metoprolol succinate matrix tablet formulations were prepared with different compositions employing different excipients, different polymers, and different concentration of polymers. Finally, one optimized formula with optimum hardness and coating parameters for the matrix tablet was selected and studied.

Findings: Drug release from the formulated products was deemed acceptable, matching the release from the marketed formulation and falling within the limits set by the USP.

Novelty: The formulations that were developed remained stable even after undergoing three months of accelerated stability studies. The manufacturing process was found to be consistent, cost-effective, and suitable for large-scale production using conventional tablet machines.

Keywords: Extended release; Metoprolol succinate; Formulation; Physical parameters; Invitro release; Stability

INTRODUCTION

Drug delivery systems, including tablets, injectables, suspensions, creams, ointments, liquids, and aerosols, are used to treat both acute and chronic illnesses. The goal is to deliver a therapeutic dose to the body's proper site, maintain the desired concentration, and minimise adverse effects. Spatial placement and temporal delivery are crucial aspects of drug delivery[1]. Maintaining a once-daily regimen with extended-release dosage forms can be more convenient and patient-friendly, thereby advancing the development of improved drug delivery methods over the past two decades[2]. Oral administration is the safest, easiest, and most economical route of drug administration, with solid forms of oral dosage, such as capsules and tablets, being the preferred class of products[3]. Over the past 20 years, the development of controlled-release drug delivery systems has gained attention due to concerns about drug toxicity and poor efficiency of conventional methods. These systems maintain the drug concentration within the therapeutic window for extended periods, ensuring extended therapeutic action. Conventional drug delivery systems often produce fluctuating drug concentrations and unpredictable absorption[3,4].

Controlled drug delivery systems improve the bioavailability and sustained release of active pharmaceutical ingredients, thereby overcoming the limitations of the conventional systems. Oral delivery is the most frequently employed method, because of its natural, convenient, and safe nature. These systems offer advantages, such as patient compliance, less side effects, reduced drug activity, improved treatment efficiency, and reduced healthcare costs[5].

Hydrophilic matrix systems are used widely in forms of solid oral dosage for controlled drug delivery because of their simplicity, ease of production, and resistance to

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drug dumping. These systems are familiar, proven, and easy to produce, making them suitable for several tablet sizes. Metoprolol, a beta1-selective adrenoreceptor-blocking agent, is well absorbed orally and is suitable for extended-release dosage forms owing to its short half-life, high solubility, and low plasma protein binding[6]. However, they have disadvantages, such as decreased systemic availability, poor in vitro-in vivo correlation, difficulty in drug retrieval due to toxicity, poisoning, or hypersensitivity reactions, and reduced potential for dose adjustment. Considering the factors mentioned above, this study aimed to develop metoprolol succinate extended-release tablets to ensure steady and expected metoprolol release for daily use.

METHODOLOGY

Chemicals Metoprolol succinate USP, Lactose, Microcrystalline cellulose PH 101, hydroxypropyl methyl cellulose, carbopol 971P, Sodium CMC, Colloidal silicon dioxide, sodium stearyl funerated, talc, and PVP K-30 were procured from qualified vendors. All the solvents used were of HPLC grade.

Instruments: Vibratory sifter, rapid mixer granulator, peristaltic pump, fluidised bed dryer, Conta blender, weighing balance, hardness testing apparatus, digital vernier callipers, dissolution test apparatus, friability test apparatus, rotary compression machine, halogen moisture analyser, tap density tester, stirrer and HPLC were used for the study

Infrared Spectroscopy study

The infrared spectra of the samples were recorded using an FTIR spectrophotometer with a Perking Elmer spectrum GX FTIR range of 400-4000 cm-1. A pellet of metoprolol succinate and dry potassium bromide was prepared and compared to the working standard.

Melting point determination

Thiel's tube method for melting point determination in liquid paraffin was used in the present study.

Drug- excipients compatibility study

Excipients and API were thoroughly mixed in predetermined ratios according to the compatibility study protocol given in the above table and passed through a 40# sieve. The mixture was placed in clear glass vials and sealed with grey rubber stoppers, followed by aluminium seals. These vials were then placed in chambers subjecting to various testing conditions such as photostability at 60°C and 40°C. Similarly, only API and all excipients without API should be kept under all conditions as samples. The samples were withdrawn for analysis as per the compatibility study protocol.

Physical observation

Physical observation of the samples was performed every week for any colour change, lump formation, or any other visual changes.

Selection of excipients

Qualitative

Excipients for metoprolol succinate extended-release tablets were selected on the basis of the compatibility data collected during preformulation and qualitative composition of the marketed product.

Sourcing

The excipients utilised during the development process were acquired from qualified vendors.

Characterization of metoprolol succinate

Description

Approximately 1 g of the sample was transferred to a white piece of paper. The powder was then spread and examined visually.

Density

Bulk density, tapped density, compressibility index, and Hausner's ratio were determined using the cylinder method, where a fixed volume (V1) of metoprolol succinate was placed in a tarred measuring cylinder, and the weight of this cylinder was noted (W), which was placed on a tap density tester (USP). Volume (V2) was measured after getting constant volume[7]

Matrix tablet formulation

The study aimed to create a formulation with the same dissolution profile as the marketed product, following USP31 limits. The formulation was developed based on polymer type, concentration range, and drug. Various polymers and excipients have been combined to obtain a tablet with a good dissolution profile, meeting the pharmacopoeia requirements[8].

Marketed product characterization

Physical characterization

Physical characterisation of the marketed product, description, label claim, inactive ingredients, dimensions, colour, thickness, average weight, hardness, and disintegration time were determined.

Chemical characterization

Dissolution profile of marketed product extended-release tablet was performed in pH 6.8 phosphate buffer/500 ml/Paddle/50 RPM (As per USP).

Manufacturing process development -Wet granulation

Similar to the dry granulation process, batch-to-batch variation is not observed in wet granulation, and slug formation is a tedious method. So wet granulation approach was used (Figure 1).

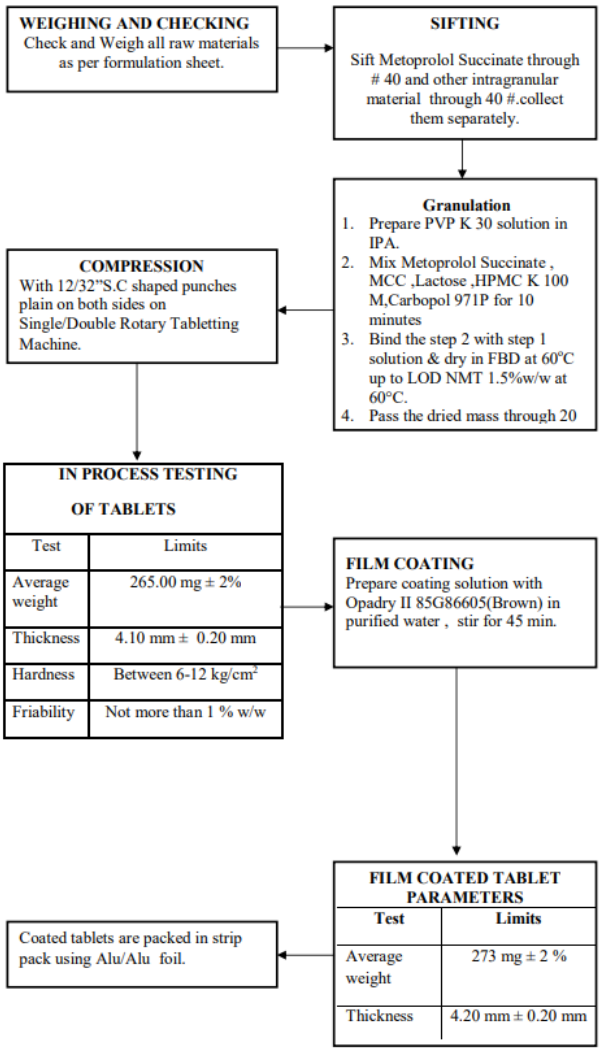

Fig. 1: Process flow diagram

Sifting of Raw Materials

The sifting process involved passing microcrystalline cellulose PH 101 Powder and Metoprolol succinate USP through a 40 # SS sieve, mixing Carbopol 971 P, lactose, and HPMC K100 M through a 40 # SS sieve, and collecting them. Sift extra granular materials, Talc and Sodium stearyl fumarate were filtered through a 60 # SS sieve, and colour ferric oxide red was filtered through a 100 # SS sieve and collected separately.

Preparation of Binder Solution

Isopropyl alcohol in an S.S. vessel was mixed with PVP K-30 under continuous stirring and dissolved until a clear solution was obtained.

Granulation

Previously sifted metoprolol succinate and a mixture of dispensed quantities of Lactose and Carbopol 971 P, HPMC K100 M was loaded in a Rapid Mixer granulator and mixed at a slow impeller speed for 10 min. A binder solution was added in slow motion at slow speed in the RMG mixer and run in the mixer at slow speed, and the duration of binder addition and granulated the wet mass with a high-speed impeller for 3 min. The chopper and impeller were run for 2 min at high speed. Granulation time was recorded, and the granules were unloaded in a fluid bed dryer bowl for drying.

Drying and Dry Screening

The wet mass was dried in Fluid Bed Drier at ambient temperature initially for 5 min and then at inlet temperature of 60 to 65 °C for 1.45 h or LOD of granules at 60°C was NMT 1.5%, whichever was later, and the outlet temperature was recorded. The dried granules were passed through # 24, and the retention of #24 was milled through a multimill using a 1.5 mm screen, knives forward, medium speed, passed through #24, and granules were collected in the SS bin. Make sure that all granules should pass through #24.

Addition of Extra Granular Ingredients

Talc, Sodium stearyl fumarate, and ferric oxide red were added one by one and blended for 8 min in a cage blender at 10 ± 2 RPM. The granules were unloaded in double polythene-lined drum/intermediate product containers and closed tightly. The drums were labelled appropriately, and all details were recorded. These were considered the final lubricated blends for compression.

Compression

The final blended powder was compressed into tablets using 12/32"-mm round SC punches with a plain surface on both sides (D-tooling) using 16 station single rotary compression machine.

Coating

The prepared tablets were coated as films using a Ganscota machine. Opadry II Brown 85G86605 was dispersed in purified water with continuous stirring for 45 min to obtain a homogeneous dispersion. The coating solution was then passed through a #60 mesh filter. The tablets in the coating pan were loaded and pre-warmed at an inlet temperature of 65 ± 5 °C to obtain a bed temperature of 45 ± 5 °C. The average weight of 100 tablets after pre-warming was checked, and spraying of the coating solution was started at the required rate to obtain a uniform coating. After achieving

the required weight gain/build up, the tablets were dried at a product bed temperature of 35-45 °C for 15-30 min (weight gain: 265–273 mg).

Evaluation parameters of extended release

The following examinations were undertaken to evaluate the formulated extended-release tablets of metoprolol succinate:

Bulk density

The bulk density of the powder sample was calculated by measuring the volume occupied by a known mass of powder M, which had been sieved through a screen and placed in a graduated cylinder. The powder was carefully levelled, ensuring that it was not compacted, and the unsettled apparent volume V_0 was read to the nearest graduated unit. The formula used to calculate the bulk density in gm/ml is:

$$Bulk\ Density = \frac{M}{V_0}$$

Tapped density

Achieving tapped density involves mechanical tapping of a measuring cylinder containing a powder sample. A measured quantity of the powdered sample was added to a graduated glass cylinder. The powder was carefully levelled, ensuring that it was not compacted, and the unsettled apparent volume V_0 was read to the nearest graduated unit. Mechanical tapping of the cylinder was performed using a suitable tester that allowed for a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute by raising and then dropping the cylinder under its own weight. The cylinder was initially tapped 500 times, and the volume tapped, V_a, was subsequently measured. The tapped volume, V_b, was measured after repeating the tapping 750 times. If the variance between the two volumes is < 2 percent, V_b is the final tapped volume, which is denoted as V_f. The tapping process was carried out in increments of 1250 taps as required until the variation between successive measurements was < 2percent. The formula used to calculate the tapped density (gm/ml) is as follows:

$$Tapped\ density = \frac{M}{V_f}$$

Loss on drying

The substance to be tested was mixed and weighed accurately, and the determination was conducted on 1–2 g. If the test specimen was in the form of large crystals, the particle size was reduced to approximately 2 mm by rapid crushing. The test specimen was dried at this temperature for the time specified in the monograph. This technique is used to ascertain the quantity of any type of volatile substance that can evaporate under specified conditions.

Mechanical sieving is particularly well-suited for particles that are primarily larger

Particle size distribution

Sieving is a traditional technique for categorizing powders and granules based on their distribution of particle size than approximately 75 μm. Each test sieve was tared, an accurately weighed quantity of the test specimen was placed on the top sieve, and the lid was replaced. The nests of the sieves were agitated for 5 min. Each sieve was then carefully removed from the nest without material loss. Each sieve was re-weighed, and the weight of the material on each sieve was determined. After performing the analysis, the weights of the materials were compared and reconciled. It is essential that the total losses do not exceed five percent of the original test specimen's weight.

Compression parameters

Average weight

The weight variation of the tablets was determined by taking the average weight of the 10 tablets. The acceptable weight variation range is 9-110 mg (±10%).

Thickness

The tablet's thickness was calculated with the help of digital vernier scale and Erweka Hardness Tester. The thickness is expressed in millimetres.

Hardness (tablet breaking force

The breaking load was applied through the action of a small motorised hydraulic pump.

Friability

If a unit weight for tablets weighed <650 mg, a sample of whole tablets equivalent to 6.5 gm was taken. Conversely, if a unit weight for tablets weighed > 650 mg, a sample consisting of 10 tablets was taken. The tablets were de-dusted, weighed, and placed in a drum. The drum was rotated 100 times, and any loose dust was removed. If broken, cleaved, or cracked tablets were detected, the sample was counted to have failed the test. If irregular tumbling occurs due to the tablet shape or size, the drum base should be adjusted to form an angle of approximately 10° with the horizontal, preventing tablets from falling freely.

Standard preparation

The process involved weighing and transferring 50 mg of Metoprolol Succinate working/reference standard into a 100 ml volumetric flask, adding 60 ml of mobile phase, and mixing thoroughly. A tablet was crushed and weighed, and then the tablet powder was added, sonicated, and mixed with 30 ml of methanol and 0.1 N hydrochloric acid. The solution was filtered through a 0.45 μm filter, and the first 10 ml was discarded. The solution was then diluted with the mobile phase and mixed thoroughly. System suitability involves

injecting duplicate injections of the standard preparation, with a column efficiency of at least 1500 theoretical plates, a tailing factor of not > 2.0, and a relative standard deviation of not > 2.0%. The procedure involved introducing equal volumes of the standard and test solutions into a chromatograph, recording chromatograms, and measuring the responses for major peaks.

The calculation of the metoprolol succinate percentage in each tablet was determined using the following formula.

$$\%\ Metoprolol\ succinate = \frac{Au}{As} \times \frac{W}{50} \times \frac{5}{50} \times \frac{100}{LC} \times \frac{50}{5} \times \frac{P}{100} \times 100$$

Where, Au = Area of Metoprolol peak in the chromatogram obtained with Sample preparation

As = Average area of Metoprolol peak in the chromatogram obtained with standard preparation

W = Weight of Metoprolol succinate working/reference standard in mg

LC = Label claim of Metoprolol succinate in mg

P = Potency of Metoprolol succinate working/reference standard in percentage on as is basis

Assay[9]

The mean value of the quantity (in mg) of metoprolol succinate in the tablets analysed for content uniformity was determined.

In vitro drug release[9]

Dissolution Parameters

Dissolution medium preparation (pH 6.8 phosphate buffer preparation) was prepared with 6.8 g of potassium dihydrogen orthophosphate (KH2PO4) transferred into a 1 litre volumetric flask and dissolved in 900 ml water. The pH was adjusted to 6.8±1 with 2N sodium hydroxide (8%w/v). The volume was made up of water and mixed thoroughly.

HPLC parameters

5.0 ml of the standard stock solution was diluted to 25.0 ml with dissolution medium and mixed properly.

Dissolution procedure

Instrument parameters were set as described above and the medium was degassed prior to use. One tablet was placed in each of the six different vessels using 500 ml of pH 6.8 Phosphate buffer. The apparatus was operated for 20 hours. At the end of 1, 4, 8, and 20 h, samples were withdrawn and replaced with the same amount of dissolution medium.

Sample preparation

Samples withdrawn at the end of 1, 4, 8, and 20 h were filtered through a 0.45 μm filter discarding the first few millilitres of the filtrate and used as the sample solutions. System suitability:

The standard preparation was administered through replicate injections. The column efficiency was no < 1500 theoretical plates, the tailing factor was no greater than 2.0, and the relative standard deviation for the replicate injections was no greater than 2.0%. Equal volumes of 20 microliters of the standard solution and test solution were injected separately into the chromatograph, and chromatograms were recorded. The responses for the major peaks were then measured.

The actual percentage of metoprolol succinate dissolved in 4 h after considering drug loss by sampling 10 ml solution at the end of 1 h, the content of metoprolol succinate dissolved at the end of 20 h in percentage in each tablet, and the actual percentage of metoprolol succinate dissolved in 20 h after considering drug loss in sampling 10 ml solution at the end of 1 h, 4 h, and 8 h was calculated using the formula:

$$\%Metoprolol\ succinate\ (M_1) = \frac{Au1}{As} \times \frac{W}{50} \times \frac{10}{50} \times \frac{500}{LC} \times \frac{P}{100} \times 100$$

Analysis of the release mechanism

The in vitro dissolution data were fitted to zero order, first order, Higuchi release model, Korsemeyer and Peppas model, and Hixson Crowell model to analyse the mechanism of drug release from the matrix tablets[10].

Formulation development and optimisation

Formulation development was initiated with the aim of matching the dissolution profile of metoprolol succinate extended-release tablets with the marketed product formulation as per the limits prescribed by USP32[9]. Eighteen formulations were developed (F1 to F18).

Stability studies

The stability study was conducted for the optimised formulation under the following conditions and time periods at 30 °C / 65% RH for up to 3 months (real-time stability study). At 40°C / 75%RH for up to four months (accelerated stability study), Batche no. F18 was packed in 10's PVC/PVDC blisters and 10's Alu/Alu blisters and loaded in a stability chamber. After completion of the specified time period, the samples were collected, and analysis were performed[11].

RESULTS AND DISCUSSION

Oral drug delivery systems offer patient compliance advantages and controlled release rates based on polymer concentration[12]. The generic market offers opportunities for developing countries, such as India, where low production costs and quality manpower are available. Indian pharmaceutical companies file Abbreviated New Drug Applications (ANDAs) in the US, focusing on pipeline drugs that are either gone off patent or out of patent cover[13]. This study aimed to develop extended-release tablets of metoprolol succinate, a generic antihypertensive drug, using wet granulation and trial and error methods.

Formulation development involves pre-formulation studies, which involve selecting suitable polymers and excipients compatible with drugs. These studies standardised the analytical procedures for drug content estimation and in vitro drug release. In this study, matrix tablets were prepared by a wet granulation technique using metoprolol succinate, diluents, and release-controlling polymers[14]. The tablets were then compressed using a 16-station compression machine. Different polymers and excipients have been used to achieve sustained drug release, mimicking the marketed formulation and meeting the USP criteria for in vitro drug release.

The study involved the preparation of extended-release tablets using a trial-and-error method. Initial trials used HPMC K4M and HPMC K100M polymers, but their in vitro drug release profiles did not match those of the marketed product. To control drug release, Carbopol 971P was added intragranularly. In subsequent trials, HPMC K4M was removed, and an extra granular carbopol was introduced. However, the drug release was still higher than that of the marketed formulation and outside the USP limits. The next trial used HPMC K100M and sodium carboxymethyl cellulose (CMC).

The study used lactose for granulation and talc as a lubricant to improve the flow during compression. The drug release profile was within the USP limits but at the higher side. The next trial focused on adjusting the extra granular polymers to improve flow and drug release. A hydroalcoholic binder solution was used; however, the flow properties remained poor. The next two trials were designed to achieve the desired control over drug release with varying polymer combinations and binder quantities. The results showed moderate flow properties and unmatched drug release with marketed formulations.

The melting points were found to be 121 °C for Trial 1, 121 °C for Trial 2, and 122°C for Trial 3. The results of the drug-excipient compatibility studies are shown in Tables 1 and 2.

The Bulk density (BD) and tapped density of the drug were 0.271 and 0.459 gm/ml. Carr's compressibility index (CI) was 40.91%. Hausner's ratio (HR) was found to be 1.692, indicating poor flow properties. The granule size parameters are listed in Tables 3 and 4 , respectively.

The drug release profile of trial F8 did not match the marketed formulation's lower limits prescribed by USP. Trial F9 was within the prescribed range but was near the higher side. To improve this, trials F10, F11, F12, and F13 were developed. Trial F12 achieved the desired drug release profile, matching the marketed formulation and pharmacopoeia limits. Trial F13 had moderate flow properties but was considered the final formula for uncoated tablets.

The formula from trial F13 was used in trials F14 and F15 for the aqueous film coating. Trial F14 used 2% weight gain with Opadry II Brown 85G86605 coating material, whereas trial F15 used 3% weight gain. In-vitro drug release studies showed no significant changes. Trial F16 optimised the formula by compressing tablets with three different hardness values. The optimum hardness was 6-8 kg/cm2, which was considered as the final optimised formula.

Batch-to-batch uniformity is crucial to obtain reproducible results. Reproducibility batch F17 of the final optimised formulation was prepared. In vitro drug release studies showed first-order kinetics and Higuchi's model, with super case II transport indicated by Korsmeyer-Peppas plots. (Table 5).

The Infrared spectrum of metoprolol succinate USP and a comparison of metoprolol succinate with the working standard are shown in Figure 2.

Trial F18 was used as the stability batch and was conducted according to ICH guidelines, focusing on real-time stability at 30°C/65% RH for 3 months in the Alu-Alu Blister and PVC-PVDC Blister, and accelerated stability at 40°C/75% RH for 3 months. Real-time stability data are shown in Figures 3 and 4 . The surfaces remained unaltered in colour, appearance, microbial growth, and odour, and the tablets' smoothness remained unchanged. The in vitro drug release and assay results were similar to those at zero days, indicating that the design and evaluation of a controlled-release drug delivery system for generic drugs in the form of extended-release tablets of metoprolol succinate was successfully achieved.

CONCLUSION

Preformulation studies showed good compatibility between API and excipients, resulting in a successful once-daily extended-release tablet dosage form of metoprolol succinate. Batch F13 was identified as the final formulation, while batch F17 had optimized process parameters for film coated tablets. The manufacturing procedure was standardised and reproducible, and the optimised formulations were comparable to those of the marketed products.

Table 1: Physical observation in different conditions after 1 month

Sl. No.	Sample Name	Physical Observation (Description)		
		Initial	1 Month	
			40°C/75% RH (Open)	40°C/75%RH (Closed)
1	Metoprolol succinate	White to off white powder	White to off white powder	White to off white powder
2	Metoprolol succinate+ Microcrystalline Cellulose	White to off white powder	White to off white powder	White to off white powder
3	Metoprolol succinate+ Lactose	Free flowing , White to off white colored powder	Free flowing , White to off white colored powder	Free flowing , White to off white colored powder
4	Metoprolol succinate+ PVP	White to off white powder	White to off white powder	White to off white powder
5	Metoprolol succinate+ Talc	Free flowing, White to off white powder	Free flowing, White to off white powder	Free flowing, White to off white powder
6	Metoprolol succinate+ Colloidal Silicon Dioxide (Aerosol)	White to off white powder	White to off white powder	White to off white powder
7	Metoprolol succinate+Sodium Stearyl Fumerate	Free flowing, White to off white powder	Free flowing, White to off white powder	Free flowing, White to off white powder
8	Metoprolol succinate+ HPMC K4M	White to off- white powder	White to off- white powder	White to off- white powder
9	Metoprolol succinate+ HPMC K15M	White to off- white powder	White to off- white powder	White to off- white powder
10	Metoprolol succinate+ HPMC K100M	White to off- white powder	White to off- white powder	White to off- white powder
12	Metoprolol succinate+ Carbopol	White to off- white powder	White to off- white powder	White to off- white powder
13	Metoprolol succinate+ Sodium CMC	White to off- white powder	White to off- white powder	White to off- white powder
14	Metoprolol succinate+ All Excipients	White to off- white powder	White to off- white powder	White to off- white powder
15	All Excipients	White to off- white powder	White to off- white powder	White to off- white powder

Table 2: Physical observation in different conditions after 1 month

Sl. No.	Sample Name	Physical Observation (Description)		
		Initial	1 Month	
			60°C (Closed)	Photostability (Closed)
1	Metoprolol succinate	White to off white powder	White to off white powder	White to off white powder
2	Metoprolol succinate+ Microcrystallin e Cellulose	White to off white powder	White to off white powder	White to off white powder
3	Metoprolol succinate+ Lactose	Free flowing , White to off white colored powder	Free flowing , White to off white colored powder	Free flowing , White to off white colored powder
4	Metoprolol succinate+ PVP	White to off white powder	White to off white powder	White to off white powder
5	Metoprolol succinate+ Talc	Free flowing, White to off white powder	Free flowing, White to off white powder	Free flowing, White to off white powder
6	Metoprolol succinate+ Colloidal Silicon Dioxide (Aerosol)	White to off white powder	White to off white powder	White to off white powder
7	Metoprolol succinate+Sodium Stearyl Fumarate	Free flowing, White to off white powder	Free flowing, White to off white powder	Free flowing, White to off white powder
8	Metoprolol succinate+ HPMC K4M	White to off- white powder	White to off- white powder	White to off- white powder
9	Metoprolol succinate+ HPMC K15M	White to off- white powder	White to off- white powder	White to off- white powder
10	Metoprolol succinate+ HPMC K100M	White to off- white powder	White to off- white powder	White to off- white powder
11	Metoprolol succinate+ Carbopol	White to off- white powder	White to off- white powder	White to off- white powder

Table 4: Values of R^2 and K for Zero-order, first-order and Hixon-Crowell

Form. No.	First order		Zero order		Hixon-Crowell	
	R2	K	R2	K	R2	K
F13	0.996	-0.044	0.935	4.075	0.576	0.160
F14	0.996	-0.046	0.941	4.149	0.593	0.163
F15	0.998	-0.042	0.939	4.059	0.591	0.162
F16	0.996	-0.045	0.936	4.113	0.584	0.162
F17	0.995	-0.049	0.939	4.204	0.587	0.163
F18	0.997	-0.047	0.924	4.142	0.567	0.161

Note: R^2 = Coefficient of determination, K= Release rate constant, n = Diffusion exponent

Table 5: Values of R^2 and K for Higuchi and Korsemayer-Peppas model and comparison of the in vitro dissolution profile of the final batch with marketed product

Form No.	Higuchi		Korsemeyer Peppas	
	R2	K	R2	n
F13	0.996	19.88	0.999	1.158
F14	0.994	20.15	0.999	1.301
F15	0.994	19.74	0.998	1.238
F16	0.995	20.05	0.999	1.267
F17	0.994	20.44	0.998	1.236
F18	0.997	20.33	0.999	1.186

Time (min)	Marketed Product(% CDR)	F15 (% CDR)
0	0	0
5	11.4	13.7
10	33.1	33.7
15	58.2	52.7
30	95.3	86.5

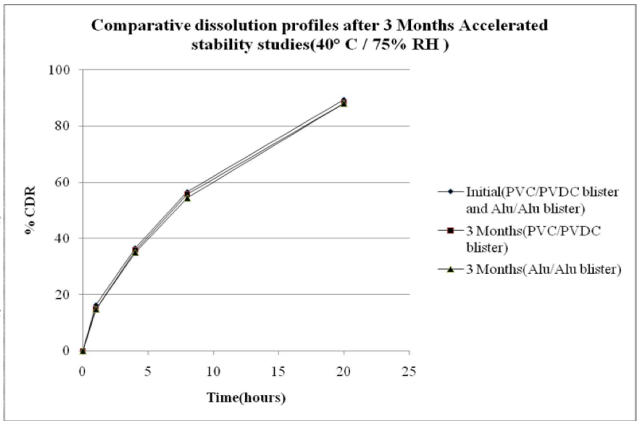

Fig. 4: *In vitro* dissolution profile of stability batch after 3 months accelerated stability studies at 40 °C / 75% RH

Table 3: Sized granules parameters of the formulations F1 to F18

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density (gm/ml)	0.260	0.311	0.334	0.325	0.359	0.389	0.378	0.474	0.447
Tapped Density (gm/ml)	0.361	0.403	0.412	0.411	0.583	0.566	0.573	0.608	0.564
Compre ssibility index (%)	27.97	22.82	18.93	20.92	38.42	31.27	34.03	22.03	20.74
Hausner 's ratio	1.388	1.295	1.233	1.264	1.623	1.455	1.378	1.282	1.26
Parameters	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Bulk Density (gm/ml)	0.458	0.447	0.431	0.521	0.530	0.541	0.528	0.522	0.527
Tapped Density (gm/ml)	0.581	0.564	0.549	0.603	0.597	0.611	0.610	0.592	0.601
Compressi bility index (%)	21.17	20.74	21.49	13.59	11.22	11.45	13.44	11.82	12.31
Hausner's ratio	1.26	1.26	1.27	1.15	1.12	1.12	1.15	1.13	1.14

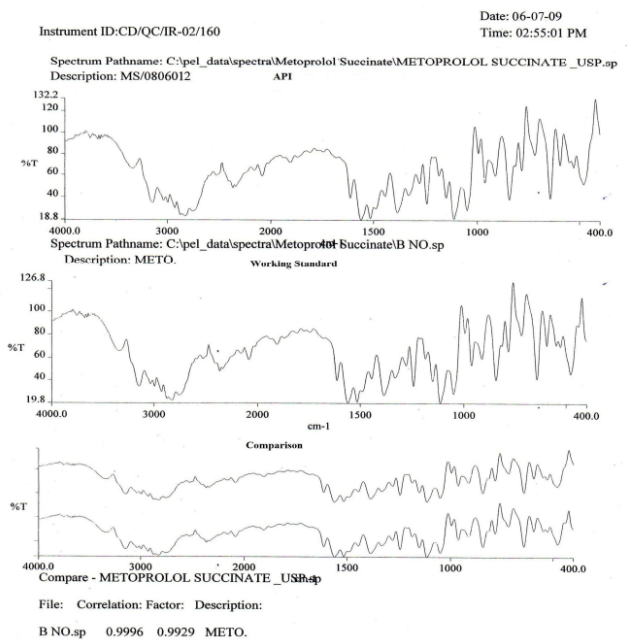

Fig. 2: IR Spectrum of Metoprolol succinate USP, Metoprolol succinate Working standard and comparison

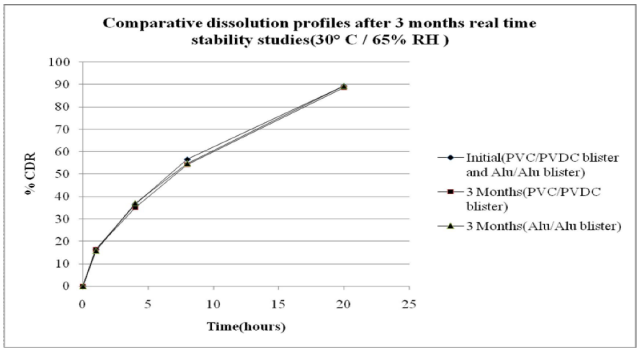

Fig. 3: *In vitro* dissolution profile of stabilitybatch after 3 months real time stability studies at 30° C / 65% RH

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