RESEARCH ARTICLE

Development and Evaluation of Novel Multi-unit Pellet System Formulation of Metoprolol Succinate for Extended Release

Deepak S. Khobragade[1], K. Vighneshwar[2], Mrunali S . Potbhare[3]

[1]*Datta Meghe College of Pharmacy, Salod (H), Datta Meghe Institute of Medical Sciences, Deemed to be University, Sawangi (Meghe), Wardha, Maharashtra, India*
[2]*Vijaya College of Pharmacy Munagnoor, Hyderabad, Telangana, India*
[3]*School Of Pharmacy, GITAM University, Vishakhapatnam, Andhra Pradesh, India*

Received: 20th July, 2022; Revised: 13th August, 2022; Accepted: 28th August, 2022; Available Online: 25th September, 2022

ABSTRACT

Metaprolol succinate is a highly water-soluble drug with extensive first-pass metabolism. It needs to be administered about 3-4 times a day for optimum therapeutic effect. Conventional extended-release formulations are available but have their own disadvantages. The study was to designed formulate and evaluate the prolonged-release compressed multiple-unit pellet system (MUPS) of Metoprolol succinate. MUPS are novel formulations with benefits of both single and multi unit dosage forms and can provide extended drug delivery release profile and increase the efficiency profile of the drug. Metaprolol succinate pellets were prepared, coated with a different polymer, and compressed into tablets with suitable excipients. The tablet MUPS disintegrates after ingestion into extended-release pellets. MUPS formulations prepared with polymers like ECN50, Surelease, Kollicoat. Pellets formulation with Kollicoat coating (7.5%) was found to be the best formulation. MUPS prepared using this formulation of pellets and lubritab were found to be most promising formulation with acceptable limits of all physicochemical properties, dissolution profile and stability. Thus from the results, it can concluded that multiple-unit pellet systems (MUPS) can be ideal formulations for drugs like Metaprolol succinate.

Keywords: Ethyl Cellulose, Kollicoat, Lubritab, Metaprolol succinate, MUPS, Pellets, Surelease.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.3.49

How to cite this article: Khobragade, DS, Vighneshwar, K, Potbhare, MS. Development and Evaluation of Novel Multi-unit Pellet System Formulation of Metoprolol Succinate for Extended Release. International Journal of Drug Delivery Technology. 2022;12(3):1219-1227.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Metoprolol succinate (MS), a BCS-I class drug, blocks cardiac beta 1-adrenergic receptors and lowers heart rate, a force of contraction and thus the cardiac output.[1] Decreasing the renin secretion, aldosterone secretion, other sympathetic activities, and blood angiotensin II level reduces vaso-constriction.[2-5]

Due to high water solubility and higher permeability, directly – indirectly, it affects the absorption through intestinal tract and undergoes extensive first-pass metabolism and thus only 50% of drug shows bioavailability. After administration in conventional form orally, it shows peak plasma concentration after 1–2 hours and readily eliminated within a 3–4 hours. The frequency of dosing is four times a day and may leads to patient non-compliance.[6,7]

Literature survey reveals that, there are various formulations developed for metoprolol which includes Mucoadhesive extended-release sustained release tablets[8-10] Pellets[11,12] Buccal patches.[13,14] But none of the methods is developed to prepare and evaluate Metoprolol Succinate extended release Multi Unit Particulate System (MUPS) to overcome tablet defects and resolve poor bioavailability.[15,16]

The single unit controlled drug release formulations are avoided as sometimes it shows dose dumping. Multiple unit pellet system (MUPS) are compressed tablets containing small coated pellets of Metoprolol succinate which will disintegrate and distributed uniformly from the stomach to the small intestine, release drug for extended period resulting in less localized irritation, uniformity in drug absorption and more bioavailability.[17-19] It also helps to avoid dose dumping or poor drug release. Also, it improves patient compliance in both paediatric and geriatric patients.[20-25]

Hence, the study's main objective was to formulate and evaluate the prolonged-release compressed multi-unit pellet system (MUPS) of Metoprolol succinate. MUPS-based new drug delivery system that provides extended drug delivery release profile and increases efficiency profile of a drug.

**Author for Correspondence: deepak.pharmacy@dmimsu.edu.in*

MATERIALS AND METHODS

MATERIALS

Metoprolol succinate was gifted as research sample by Sun Pharmaceutical Industries Ltd.India. Sugar pellets (50-60) and Sucrose Blend was procured from Shiva Shakthi Pharma. Aerosil (Aerosil 200 Pharma) procured from Evonik. HPMC 6cps (Hypromellose) procured from ShinEtsu. Ethylcellulose N50 was procured from Aqualon Hercules. Kollicoat SR 30D and Surelease were procured from Colorcon, Stearic acid was procured from Oleo Chemicals, PEG 6000 was procured from Clarient Chemicals and Isopropyl Alcohol from R.A. Chem Pharma Ltd.

METHODS

Evaluation of Metaprolol Succinate

The drug Metoprolol succinate was evaluated for general physicochemical properties like Physical appearance, Solubility, Melting Point, density, flow properties and moisture content.

Drug-Excipients Compatibility

Compatibility studies of drug and excipients were carried out to evaluate both Physical compatibility and Chemical compatibility

Physical compatibility was evaluated by taking the pure drug (API) and excipients in the ratio as used in the formulation and kept at 40°C/75% R.H. and 25°C/60% R.H. for one month in sealed vials.

Chemical Compatibility

- Digital signature certificates (DSC): DSC was studied by transferring about 3–5 mg of drug was into standard aluminum pan and heating the samples from room temperature to 390°C with scan rates of 10°C/minute. An empty pan was used as a reference. The Obtained DSC curves were recorded with the help of computer scans and evaluated.[20]
- Fourier transform infra-red spectroscopy (FT-IR) Studies: About 2 mg of each sample to be studied was mixed with dried KBr at 120ºC for 30 min. The formed mixture was kept in sample holder and pressed with pressure under 10 tones into a pellet and scanned from 4000 to 400 cm^{-1} in a spectrophotometer and peaks obtained were recorded. Pure, completely dried KBr was used as blank.

Formulation Development of MUPS

Formulation Steps

Sifting and Blending

Metoprolol succinate was sifted with excipients Aerosil and Sucrose Powder through #40 mesh by geometric dilution using vibrosifter. Sifted material was blended for 10 min at 12 RPM.

Binder Solution Preparation

Sucrose and HPMC E5 were added simultaneously to purified water under continuous slow stirring for about 12–15 minutes and formed solution was filtered through # 200 mesh.

Drug Loading

The drug loading was done in a conventional coating pan. The sugar pellets (50#-#60) were added into the coating pan, allowing the beads to rotate and achieve a bed temperature of about 45°C. The drug was loaded by alternate cycles of spraying binder solution and drug powder to achieve the desired loading. Binder solution was sprayed at a compressed air pressure of 1.0–2.0 kg/cm^2 with a peristaltic pump operated at 10–40 rpm and gun distance of 15–20 cm from pellet bed. All parameters were observed and monitored at regular intervals.

Drying

The semi-dry drug-loaded pellets were loaded into trays of tray drier were kept for drying at the inlet temperature of around 50 ± 5°C to get the bed temperature between 40–45°C to get a constant loss on drying

Sifting

The dried pellets were sifted through mesh #24-#30 and were collected into containers lined with double polythene bags for further processing. The composition of the formulation is represented in Table 1.

Coating of Drug Loaded Pellets

Coating Solution Preparations

Preparation of Ethyl Cellulose (E.C.) Coating Solution

Ethyl cellulose was added in Isopropyl alcohol with continuous stirring to get a clear solution. Polyethylene glycol talc and stearic acid were added to E.C. solution, mixed for about 5 minutes, and passed through #200 mesh Nylon cloth.

Preparation of Kollicoat S.R. 30d Coating Solution

Aqueous solution of Kollicoat, Polyethylene glycol was prepared by dissolving in purified water with continuous stirring to form a clear solution. Talc and stearic acid were added to this solution, mixed well and passed through #200 mesh Nylon cloth.

Preparation of Surelease Coating Solution

Surelease and Polyethylene glycol were added in purified water with continuous stirring to form uniformly mixed dispersion. Talc and Stearic acid were added and mixed vigorously and passed through #200 mesh or Nylon cloth.

- **Coating:** Drug pellets were loaded into Fluidised Bed Coater (FBC) bowl, cores are coated with inlet temperature to 45–50°C to maintain the bed temperature at 40–45°C. Coating was applied by bottom spray Wurster with a peristaltic pump with an application rate of 1–3 mL/min and atomizing air pressure of 0.8–1 Kg/cm^2. All the pellets were sub-coated with 1–2% w/w ethyl cellulose to make water resistant. Sub-coated pellets were applied polymer coatings to achieve the desired coating level as shown in Table 1 using the the aforementioned coating parameters.
- **Sifting:** The sifted pellets (#24-#30) are collected into HDPE containers lined with double polythene bags.

Table 1: Formulation trials for pellets

Development trials for metoprolol succinate pellets												
Ingredients	*Batch*											
Drug loading	F1	F2	F3	F4	F 5	F6	F 7	F 8	F 9	F 10	F 11	F 12
Metoprolol Succinate	66	66	66	66	66	66	66	66	66	66	66	66
Sugar spheres (#50 - #60)	13	13	13	13	13	13	13	13	11.5	13	13	13
Aerosil	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Sucrose	0	4	7.8	4.8	1.8	7.05	3.8	0.55	0	7.05	3.8	0.55
Binder solution												
Sugar	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
HPMC E5	2	2	2	2	2	2	2	2	2	2	2	2
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Coating												
Surelase			7.5	10	12.5							
Ethyl cellulose						7.5	10	12.5	15			
Kollicoat SR 30D										7.5	10	12.5
Stearic acid			1.5	2	2.5	1.5	2.0	2.5	2.5	1.5	2.0	2.5
PEG 6000			0.9	0.9	0.9	0.75	1.0	1.25	1.25	0.75	1.0	1.25
Talc			Nil	Nil	Nil	0.9	0.9	0.9	0.9	0.9	0.9	0.9
IPA			Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Nil	Nil	Nil
Purified water			Q.S	Q.S	Q.S	NIL	NIL	NIL	NIL	Q.S	Q.S	Q.S

Table 2: Formulation development trials for tablets

S. no	*Ingredients*	*T1 (mg/ tablet)*	*T2 (mg/ tablet)*	*T3 (mg/ tablet)*	*T4 (mg/ tablet)*
1	Metoprolol succinate E.R. Coated pellets	151.50	151.50	151.50	151.50
2	MCC pH 102	244.50	234.50	229.50	224.50
3	Aerosil	2.00	2.00	2.00	2.00
4	Lubritab	0.00	10.00	15.00	20.00
5	Magnesium stearate	2.00	2.00	2.00	2.00

Preparation of Metoprolol Succinate (MUPS) Tablets

Direct Compression Method

All the excipients (MCC pH102, Aerosil, Magnesium stearate, Lubritab) were passed through #40. Metoprolol succinate pellets (24#-#30) were mixed with all excipients and the mixture was blended properly with Double cone blender for about 2–4 minutes.

The blend was loaded in to hopper and compressed using 8 station tablet compression machine (Karnavati Mini Press II). The composition of the formulation represented in Table 2.

Evaluation of Pellets

Pre-formulation Study

Evaluation of physical and chemical properties of a drug substance alone and in combination with excipients is main aim of pre-formulation testing which serves as the first step in the logical development of dosage forms. The properties like organoleptic evaluation, solubility studies, bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose were evaluated as per requirement of pre-formulation study.

Water Content by K.F. Titration

30 mL Methyl alcohol was taken in a clean and dried Karl Fischer titration flask and titrated with K.F. reagent to neutralize the free water. Accurately weighed 0.5 gm of sample was transferred to the titration flask, dissolved and titrated with KF reagent. Percentage water content was determined using the following formula.[26]

$$\% \text{ Water Content} = \frac{V \times F \times 100}{W}$$

Where,
V = Volume of K.F. reagent consumed by the sample
F = Factor for K.F. reagent
W = Weight of sample in grams.

Evaluation of Tablets

To design tablets and get optimized tablet formulation, the quality of tablet production, quantitative evaluation, and physicochemical evolution and bioavailability properties of tablet must be evaluated. The tablet evaluation parameters are divided into physical and chemical parameters.[27] The evaluated physical parameter includes Physical appearance, Tablet size and Thickness, Hardness test, friability and Weight variation of Tablets.

Disintegration Test

In-vitro disintegration time is a critical parameter to achieve a correlation between *in-vitro* and *in-vivo* disintegration time. The test was carried out by placing one tablet into each tube of the disintegration test apparatus and the assembly was suspended into the 1000 mL beaker containing 0.1N HCL, maintained at 37 ± 0.5˚C and operated. The assembly was removed from the liquid and the tablets were observed.[28,29]

Chemical Evaluation

Dissolution Test

The *in-vitro* dissolution test was carried out to evaluate drug release profile of MUPS. Tablets were taken in 500 mL pH 6.8 phosphate buffer in USP type II (Paddle type) dissolution apparatus (Electrolab Tablet Dissolution Apparatus, Edt08lx) rotated at 50 rpm at a temperature of 37 ± 0.5°C. The 5 mL samples were withdrawn at 1st, 4th, 8th, 12th, 20th hours and were analyzed by UV Spectrophotometric method at a wavelength of 223 nm.

Data Analysis

The mechanism of release and release rate kinetics of the dosage form was analysed for Zero order, First order, Higuchi matrix, Peppas model by fitting obtained dissolution data in these models. Based on the r-value, the best-fit model was selected for drug release mechanism and pattern.[30-32]

Assessment of Dissolution Profiles by Model Independent Approach

As per US FDA guidance, Model independent approach involves the estimation of similarity factor (f2) and dissimilarity factor (f1). It helps to compare the dissolution data of various batches and find out the similarity in drug release rate and extent.

Stability Studies

Stability testing conditions of 40 ± 2°C/75% R.H. ± 5% R.H. for 6 months for accelerated testing and of 25 ± 2°C/60% R.H. ± 5% R.H. for long term stability testing are specified by F.D.A. and ICH. The stability testing should be carried out by storing samples at specified temperature and humidity conditions for specified period.

The formulation were kept in closed vials and stored in stability chambers maintained at i) 25°C and 60% RH, ii) 40°C and 75% R.H. The tablets were periodically checked and evaluated for physicochemical changes such as friability, colour, thickness, hardness, drug content and *in-vitro* drug release.

RESULTS AND DISCUSSION

The multi-particulate dosage forms greatly increase the tmax (peak time) and C_{max} (peak plasma concentration). MUPS are therefore important to achieve desired drug release and subsequent therapeutic activity as minimum 10 pellets are displaced from the stomach into small intestine and helps in the enhancement of dissolution rate in the GIT as smaller particles provide larger surface area for drug absorption and thus 100% pharmacological effects. The feeling of capsule dosage form

Table 3: Physicochemical characterisation of metoprolol succinate (API)

S.no	*Physical properties*	*Result*
1.	Physical appearance of drug	A pale white to white coloured Crystalline powder
2.	Solubility	Highly soluble in water, soluble in methanol, slightly soluble in ethanol
3.	Melting Point	135˚C
4.	Bulk density (gm/mL)	0.61 gm/mL
5.	Tapped density (gm/mL)	0.7 gm/mL
6.	Compressibility index (%)	12.7%

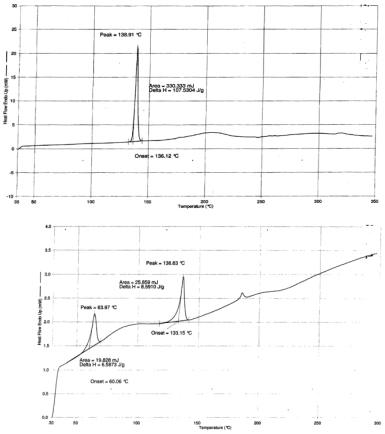


Figure 1: D.S.C. Thermograms (A) Metoprolol succinate (B) Metoprolol succinate-Excipient

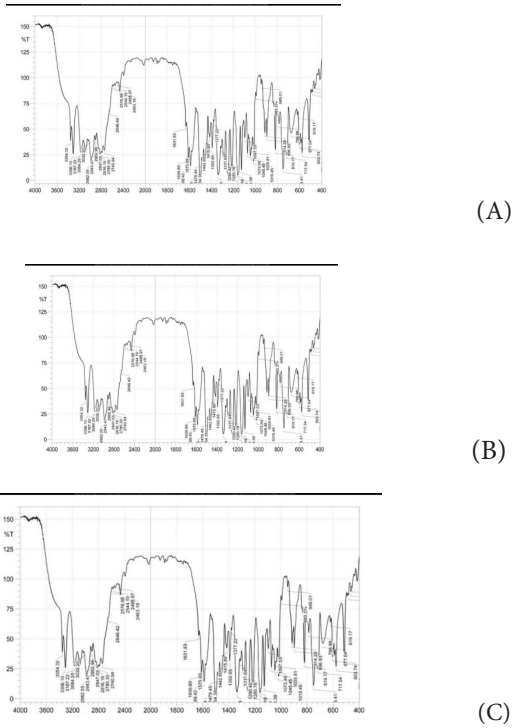


Figure 2: FT-IR spectra (A) MS (B) MS+EC N50 (C) MS +KSR 30 D

by using MUPS dosage form is greater than the conventional pellet, which helps reduce inter- and intra-subject variation in bioavailability and clinical activities. These factors make MUPS a good novel drug delivery system giving increased research potential.

Pre-Formulation Studies

API Characterization

Physicochemical evaluation of Metaprolol Succinate was performed as per the standard procedure. The results were shown in Table 3.

Drug-excipients Compatibility Studies

Suitable quantities of the drug and excipients were weighed, mixed and transferred to glass vials and sealed. The sealed vials were stored at 25°C/60% RH and 40°C/75% RH for a period of 1 month and tested for physical and chemical compatibility. The analysis of the drug-excipients blend and API after 30 day's storage under accelerated and real time conditions showed that the drug was stable and there was no evidence of incompatibility.

Chemical Compatibility

DSC Studies

The DSC thermograms of API, and drug-excipients mixture are shown in Figure 1.

The DSC thermograms show no change in peaks of Metoprolol succinate indicating that there was no interaction between the API and excipients and they can be used in the formulation.

FT-IR Studies

FT-IR studies were carried out to evaluate the physicochemical compatibility of the drug and excipients. The FT-IR spectra of drug and different excipients are illustrated in the Figure 2.

FT-IR Spectral analysis of Metoprolol succinate, physical mixture of Metoprolol succinate with Ethyl cellulose N50 and physical mixture of Metoprolol succinate with Kollicoat SR30D are given in Figure 2. Peaks for primary functional groups are given in Table 4. The FT-IR spectra show the typical peaks confirming the purity of drug. No interactions or instability in the drug and excipients were observed from the peaks and respective functional groups. Major peaks for functional groups in all samples show no significant change.

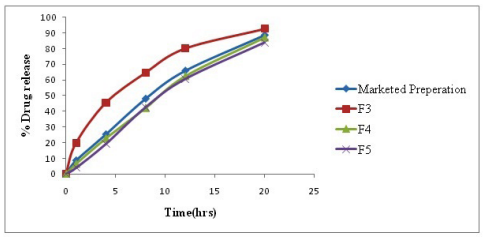


Figure 3: *In-vitro* dissolution studies of the formulations F3, F4, F5 and innovator in pH 6.8 Phosphate buffer

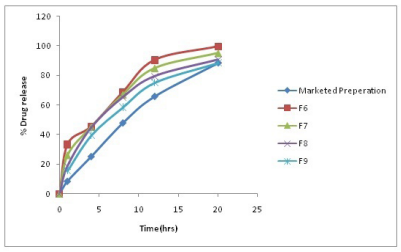


Figure 4: *In-vitro* dissolution studies of the formulations F6, F7, F7, F9 and innovator in pH6.8 Phosphate Buffer.

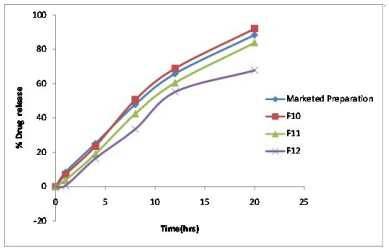


Figure 5: *In-vitro* dissolution studies of the formulations F10, F11, F12 and innovator in pH 6.8 phosphate buffer

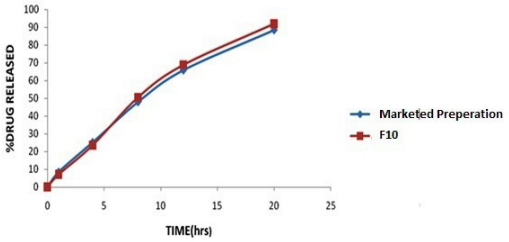


Figure 6: Optimized formulation (F10) comparison graph with the innovator

Table 4: Peaks and functional groups from FTRI of Metoprolol succinate and excipients

S. No	*PEAKS*			*Functional group*
	Metoprolol succinate Figure 2 (A)	*Metoprolol succinate with Ethylcellulose N50 Figure 2 (B)*	*Metoprolol succinate with Kollicoat SR30D Figure 2 (C)*	
1	1215	1219	1217	C-N
2	2847	2850	2850	C-H Alkane
3	1630	1639	1646	N-H Bending
4	1159	1212	1219	OCH_3- stretching
5	3306	3312	3318	C=C

Table 5: Evaluation parameters of pellets.

Parameters	*Formulation*									
	F3	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*
Angle Of Repose (°)	29.2	25.6	29.0	31.7	27.74	27.7	27.4	24.32	29.77	30.2
Bulk Density (gm/mL)	0.703	0.627	0.621	0.614	0.614	0.655	0.694	0.697	0.66	0.621
Tapped Density (gm/mL)	0.792	0.777	0.727	0.712	0.712	0.742	0.775	0.702	0.703	0.727
Compressibility Index (%)	11.1	19.2	14.6	13.7	13.06	11.7	11.5	10.1	6.11	19.2
Hausner's Ratio	1.15	1.23	1.17	1.15	1.15	1.13	1.13	1.11	1.16	1.17
Loss On Drying (%)	1.02	1.25	1.30	1.43	1.24	1.34	1.49	1.32	1.20	1.45
Friability	2.1%	1.2%	1.1%	2.3%	1.8	2%	1.0%	0.6%	0.8%	1.0%
Assay (%)	97.78	99.45	101.4	98.86	97.7	99.6	104.6	99.95	98.65	102.3

Table 6: Evaluation parameters of tablets

F. Code	*Hardness (Kg/cm2)*	*Thickness (mm)*	*Weight (mg)*	*Friability (%)*	*% Drug content (%)*	*Disintegration time (min)*
T1	3.619	5.17	397.6	1.22	98.5	2.3
T2	3.925	5.35	401.2	1.03	989.7	5.30
T3	4.537	5.80	399.9	0.54	100.1	7.45
T4	5.047	5.44	404.5	0.12	99.5	10.20

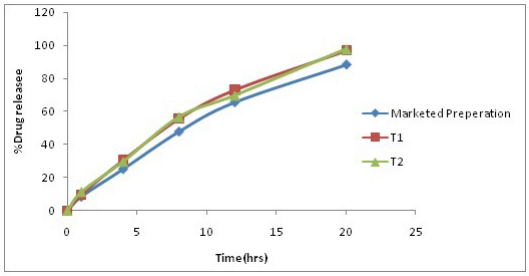


Figure 7: *In-vitro* dissolution studies of the formulations T1, T2 and innovator in pH 6.8 phosphate buffer

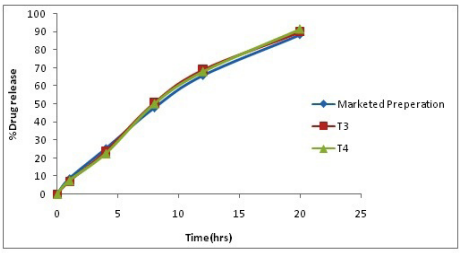


Figure 8: *In-vitro* dissolution studies of the formulations T3, T4 and innovator in pH 6.8 phosphate buffer

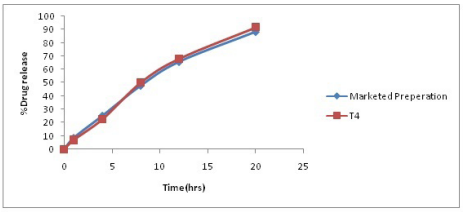
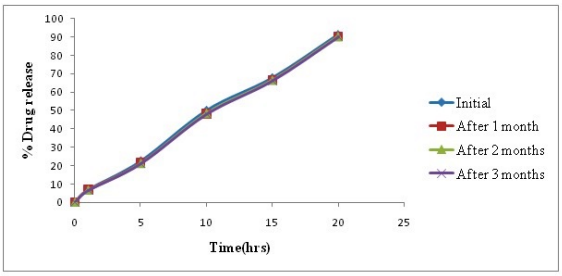


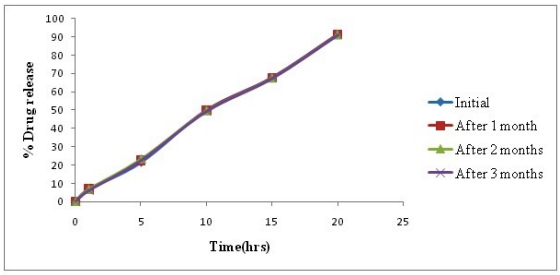
Figure 9: *In-vitro* dissolution studies of the formulations T4 and marketed Preparation (innovator) in pH in 6.8 phosphate buffer

Table 7: Similarity and Dis similarity factor (f1) of the formulations of tablets

Formulation	*T1*	*T2*	*T3*	*T4*
F2 value	59.3	58.9	79.2	87.4
F1 value	12.5	9.8	6.3	2.8



(A)



(B)

Figure 11: Dissolution profiles of metoprolol succinate MUPS during stability studies (A) at 25°c/60% R.H. (B) at 40°c/75% RH

The additional peaks observed in physical mixtures could be attributed to the excipients. The I.R. spectra indicate no chemical interaction between the drug and excipients.

Evaluation of Pellets

The pellets were evaluated for general parameters which indicate the flow properties and compressibility. The results

Table 8: Kinetic data of T4 formulation:

Time (hours)	*√T*	*Log T*	*Cumulative %Drug Release*	*Log Cumulative %Drug Release*	*Log Cumulative %Drug Remaining*
0	0	0	0	0	0
1	1	0.	6.9	0.8388	1.968
4	2.000	0.602	22.5	1.3521	1.889
8	2.828	0.903	50.1	1.6998	1.689
12	3.464	1.0792	67.9	1.8318	0.506
20	4.472	1.301	91.5	1.9614	0.929

Table 9: Kinetic data of T4 formulation

Zero order	*First order*	*Higuchi*	*Korsemeyer-Peppas*	
r^2	r^2	r^2	r^2	N
0.9712	0.9769	0.988	0.9928	0.892

*r2 = Correlational coefficient ; n= Diffusional exponent.

are depicted in Table 5. The formulations F1 and F2 were not evaluated for physicochemical parameters because the pellets were not good enough and formed aggregates or lumps may be due to high binder concentration. Based on these results the best pellet formulation was used for further processing and formulations of tablets (Figure 3 to 5).

Though the parameters for all formulations were satisfactory, formulation F10, having superior properties, was selected as the optimized formulation for further processing (Figure 6).

Dissolution Studies

The rate and extent of drug release is one the most important parameter for any dosage form. The actual therapeutic performance largely depends on drug release profile of drug from the formulation. The results of the *in-vitro* dissolution study in pH 6.8 Phosphate buffer of pellets and marketed formulation are given in the following sections.

The formulations F3, F4 and F5 *in-vitro* %drug release from pellets formed using Surelease with 7.5 , 10 and 12.5% coating, respectively, showed 90.6, 84.2%,80.9% drug release at the end of 20 hours respectively (Figure 7). The marketed preparation released about 88.6% drug in same period.

In F3 fast drug release was observed because of relatively low coating of drug and in F5 slow dissolution characteristics are observed because of increased concentration of coating. In both the formulations drug release is not as desired and doesn't match with the marketed preparation. In the case of F4, desired sustained release characteristics were observed and the dissolution profile was similar to the marketed preparation. The pellets had overall properties in limit and flow properties were equal to that of marketed preparation.

The formulations F6, F7, F8 and F9 pellets were coated with Ethyl cellulose N 50 with 7.5 ,10 ,12.5 and 15% respectively and released 95.6, 93.1, 90.6, 88.6% drug at the end of 20 hours respectively (Figure 8)

In these formulations the rate of drug release is very high which may be due to damage to the coating with agitation in dissolution study. E.C. show low values of punches strength elongation (< 5%) indicating weak mechanical properties and relatively brittle films leading to the loss of the extended release property and faster release especially on smooth and larger surface of pellets.

The formulations F10, F11 and F12 were having pellets coated with 7.5 10 and 12.5% Kollicoat SR 30D, respectively and showed 92.1, 83.9 and 67.8 % drug release at the end of 20 hours, respectively (Figure 9).

In formulation F10 with 7.5 % concentration of Kollicoat SR 30 D, satisfactory and desired release characteristics were observed.

In formulation F11 and F12 drug release was not found to be proper and not as desired because of the high coating thickness.

The drug release from Kollicoat SR 30D coated pellets Compression parameters are found to be satisfactory and within limits with relatively no difference between the drug release profile of the compressed and non-compressed pellets.

The dissolution profile of formulation F10 with 7.5% concentration of Kollicoat SR 30 D, the dissolution profile was most similar to marketed preparation (Figure 10) with high extended release characteristics and also all compression parameters were found to be satisfactory and was selected for further compression in to MUPS.

Evaluation of Tablets

Appearance

The MUPS tablets were uncoated, biconvex, round shaped, white to off white coloured.

Amongst all formulations, T1 and T2 were comparatively of poor quality, not having values within the desired specifications. The reason may be attributed to low concentration of Lubritab in these batches. As the concentration of Lubritab was increased in the formulations, the tablet properties improved and all the parameters were within the specification limits.

The Evaluation parameters of prepared tablets are given in Table 6.

All the tablets formulations showed acceptable values of most of the parameters and found to be satisfactory. The formulation T4 had best values for evaluated parameters and was shortlisted as an optimized formulation, which was finalized after *in-vitro* dissolution studies.

***In-vitro* Dissolution Studies of the Formulations**

The dissolution profile is given in the figures given below (Figure 11 and 12) it can be observed that dissolution profiles of T1 and T2 is not super-imposable with marketed preparation. Amongst T4 and T3, T4 had a more similar drug release pattern to that of marketed preparation and was considered optimized

Table 10: Physico chemical parameters of metoprolol succinate tablets from formulation T4 at 25°C/60%

Parameters	*Initial*	*After 1 month*	*After 2 months*	*After 3 months*
Description	White colored tablet	White colored tablet	White colored tablet	White colored tablet
Avg.Weight(mg)	401.5	401.3	401.2	401.2
Hardness(N)	49	47.5	47.5	47.4
Thickness(mm)	5.7	5.67	5.67	5.6
Friability (%)	0.019	0.019	0.018	0.017

Table 11: Physico chemical parameters of metoprolol succinate tablets from formulation T4 at 40°C/75%

Parameter	*Initial*	*After 1 month*	*After 2 months*	*After 3 months*
Description	White colored tablet	White colored tablet	White colored tablet	White colored tablet
Avg.Weight (mg)	402.5	402.3	402.1	401.9
Hardness (N)	51	50.7	50.6	50.6
Thickness (mm)	5.60	5.57	5.55	5.53
Friability (%)	0.019	0.017	0.017	0.017

preparation.

Similarity Factor(f2) and Dis-similarity Factor (f1) of the Formulations of Tablets28-30

The similarity factor f2 was used to compare dissolution data of the test product and reference product (marketed preparation) with respect to the drug release of various batches. These can be applied if more than three or four dissolution time points are available and average difference between Rt and Tt is >100.

The similarity factor was calculated by using following formula.

$$f2 = 50 \times \log \{[1+ (1/n) \sum t=1 \text{ n } (Rt - Tt)2]-0.5 \times 100\}$$

Where,
n = number of full time points
Rt = the reference profile at the time point t
Tt = the test profile at the same point t

Dissimilarity Factor (f1)

Dissimilarity factor express the relative percentage error of two dissolution profiles. If the percent error is zero for test and reference, the profiles are identical, increasing proportionality with the dissimilarity between the two profiles.

$$f1 = \{[\sum t=1 \text{ n } (Rt-Tt)] / \sum t=1 \text{ n } Rt]\} \times 100S$$

The results of Similarity factor (f2) and dis-similarity factor (f1) of the formulations of tablets were illustrated in Table 7.

Based upon these f2 and f1 values of the formulations, the optimized formulation was decided. The f2 values derived from the dissolution profile of all the batches were similar to that of innovator with all formulations having f2 values more than 50. Amongst all formulations, T4 formulation had the highest value of f2 and lowest value of f1 and it was the optimized formulation.

As the T4 formulation was optimized, same formula was used for checking reproducibility at a somewhat higher batch size (scale up) and, dissolution profiles was compared with marketed preparation (TOPROL-XL) again. It showed a similar dissolution profile and concluded that T4 formulation was optimized.

Kinetic Analysis of Dissolution Data

The optimized formulation (T4) had their release kinetics in order to know their mechanism of release. The kinetic data is illustrated in Table 8 and 9.

The drug release data was best explained by Korsmeyer equation, as the plots showed the highest linearity (r2 = 0.992). Based on n value the drug release follows super case-II transport (anomalous diffusion) by erosion and diffusion mechanism.

Results of Stability Study

The optimized formulation T4 was evaluated for stability studies which was stored at 40˚C/75% R.H. and 25ºC/60% RH for month and evaluated for their physical appearance, friability, hardness and % drug release at the end of 3 month. The results were summarized in the Tables 10 and 11

The MUPS kept in stability chambers for stability study were evaluated for any change in dissolution profile under similar dissolution conditions as used during formulation development. From the Figure 11, it can be observed that, there was no significant change in dissolution characteristics of MUPS tested at accelerated stability and long term stability testing conditions.

No significant variations were observed in all the tested stability indicating parameters of MUPS stored at different storage conditions as per stability protocol for 3 months indicating robust and stable MUPS formulation.

CONCLUSION

The results of study show that Metoprolol succinate pellets can be prepared by coating pan method and successfully converted to MUPS. Out of formulations prepared with polymers like ECN50, Surelease, Kollicoat, Formulation, with Kollicoat coating (7.5%) was found to be the best formulation to prepare MUPS. Concentration of lubritab was very crucial for MUPS properties. Formulation of MUPS with 15% lubritab was found to be most promising formulation with acceptable limits of

all physicochemical properties and dissolution profile similar to that of patented marketed formulation. Stability studies indicated that there is no much variation in stability parameters.

CONFLICT OF INTEREST

Authors declare that there is no direct or indirect conflict of interest with this research work.

REFERENCES

1. Bhatia A, Bhagwat A, Acharya S, Bhawane A, Acharya N. Postpartum Haemolytic Uremic Syndrome (PHUS) with Posterior Reversible Encephalopathy Syndrome (PRES) Complicating Pregnancy: A Rare Case Report. Journal of Clinical and Diagnostic Research. 2019 Apr 1;13(4).
2. European Pharmacopoeia (Ph. Eur.) European Pharmacopoeia Commission, 2017;8(4); p. 4785. Strasbourg, France.
3. https://go.drugbank.com/salts/DBSALT000863 assessed on 20/07/21 at 6 am.
4. Bains SK et al. Syndrome (GBS) with respiratory and autonomic involvement in pregnancy. A Rare Case Report. International Journal Medical Sciences and Clinical Investigation. 2018;5(05): 3768-3770. https://doi.org/10.18535/ijmsci/v5i5.01
5. Acharya S, et al. S. Subclinical hypothyroidism presenting as cardiac syndrome x . Indian Journal of Medical Case Reports . 2013; 2 (1) :15-17.
6. Federal Register, Food and Drug Administration. Volume 60, No. 230, 61642.
7. United States Pharmacopeia–National Formulary (USP42-NF37). Metoprolol Succinate.United States Pharmacopeia Commission, Rockville, USA (2018)
8. Sakthikumar T, Rajendran NN, Natarajan R. Formulation and in vitro Release Characterization of Metoprolol Succinate Extended Release Tablets. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2011;4(4):1537-43.
9. K. Shakir Ahmad et al, formulation and evaluation of metoprolol succinate extended release tablets. 2015; International Journal of Chemistry and Pharmaceutical Sciences , 3(2): 1509–1512.
10. Shimizu T et al. Orally disintegrating tablets. US 6328994 B1, 2001. doi: 10.1016/j.ejpb.2006.04.004
11. Nadendla Rama Rao. Design and in-vitro evaluation of sustained release pellets of Metoprolol Succinate. Journal of Pharmaceutical Research. 2011; 4(4):1157-1160.
12. Hu LD et al. Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. European Journal of Pharmaceutics and Biopharmaceutics. 2006; 64(2):185-92.
13. Verma, N.et al.. Preparation and evaluation of mucoadhesive buccal patches containing metoprolol succinate. International Journal of Pharmaceutical Sciences. 2011;, 3: 1075-1078.
14. Verma, N.et al. Preparation of Mucoadhesive Patches for Buccal Administration of Metoprolol Succinate: In Vitro and In Vivo Drug Release and Bioadhesion. Tropical Journal of Pharmaceutical Research, 2012 February;11 (1):9-17. http://dx.doi.org/10.4314/tjpr.v11i1.2.
15. Nrupa G. Patel et al. Multiple unit pellet system (mups technology) for development ofmodified release fast disintegrating tablets: a review. Journal of Pharmaceutical and Scientific Innovation. 2017; 6(3) DOI: 10.7897/2277-4572.06352.
16. Majeed S.M. et al., Multiple Unite Pellet Systems (MUPS) as Drug Delivery model, Journal of Drug Delivery and Therapeutics., 2020; 10(6):231-23. http://dx.doi.org/10.22270/jddt.v10i6.4389.
17. Kanweerpreet Singh Bakshi , et al. Investigation on the impact of core and barrier layer composition on the drug release from a triple layer tablet International Journal of Pharmaceutical Research. 2012;3(7):2168-2179. http://dx.doi.org/10.13040/IJPSR.0975-8232.3(7).2168-79
18. Khobragade, D. S. et al. Conception and Evaluation of Sustained Release Polymeric Matrix Beads for Enhanced Gastric Retention. Current Drug Delivery. 2009; 6(3):249-254. 10.2174/156720109788680831
19. D. S. Khobragade et al, A Novel Practical Approach for Enhancement of Bioavailability of A Poorly Water Soluble Drug By Hot Melt Coating Technique. International Journal of Pharmaceutical Science Review and Research. 2014; 26(1): 258-263.
20. Johansson B et al.The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose. European Journal of Pharmaceutics and Biopharmaceutics.2001; 52(3):347-357. 10.1016/s0939-6411(01)00186-2
21. Clarke GM et al.Comparative gastrointestinal transit of pellet system of varying density. Int J Pharm. 1995; 114(1):1-11. https://doi.org/10.1016/0378-5173(94)00200-O
22. Marvola M. et al. Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery system. European Journal of Pharmaceutical Sciences. 1999;7(3):259-267. DOI: 10.1016/s0928-0987(98)00032-3
23. Jitendra Kumar Putikam et al. Formulation and Evaluation of Metoprolol Succinate Extended Release Tablet. Research Journal of Pharmacy and Technology. 2012; 5(1): 75-78. DOI: 10.5958/0974-360X
24. Mariyam Akter et al. In-vitro evaluation of oral extended release drug delivery system for Metoprolol Succinate using Kollidon SR. Journal of Applied Pharmaceutical Sciences. 2012; 2(05):188-192. DOI:10.7324/JAPS.2012.2539
25. Ashish Budhrani et al., Nanosuspension: A Modern Approach In Drug Delivery System- A Review .International Journal of Research in Pharmaceutical Sciences. 2020; 11(SPL4):1526-1530. : https://doi.org/10.26452/ijrps.v11iSPL4.4333
26. United States Pharmacopoeia .2002. 2082-2083.
27. Merck Index. 2001. Francis and Taylor.13th edition,2619;(1),5712,2082-2083
28. United States Pharmacopoeia. 2002. 2010-2013. 2082-2083.2159-2161.
29. United States Pharmacopoeia and National Formulary. 2003. The United States Pharmacopoeial Convention Inc Rockville MD. USP26-NF 21.
30. Alfred Martin., Physical Pharmacy;Oral Dosage Forms. 6th Edition.300-318.
31. Leon Shaegel et al.. Applied Biopharm And Pharmacokinetics. Conventional And Modified Release Drug Products. 5th Edition. 2009; 495-515.
32. Korsemeyer R.W. et al..Mechanisms Of Solute Release. International Journal of Pharmaceutics. 1983;15.(1):23-35. http://dx.doi.org/10.1016/0378-5173(83)90064-9.