

FORMULATION AND EVALUATION OF IMMEDIATE RELEASE PELLETS USING EXTRUSION SPHERONIZATION**Ms. Shramika A. Chore*¹, Dr. Sachin J. Dighade², Ms. Sanjeevani S. Deshkar³ and Mr. Abhijit Patil⁴**¹Department of Pharmaceutics, Institute of Pharmacy and Research, Badnera-Amravati.²Department of Pharmaceutical Chemistry, Institute of Pharmacy and Research, Badnera-Amravati.³Department of Pharmaceutics, Dr. D. Y. Patil Institute of Pharmaceutical Science & Research, Pimpri, Pune.⁴Department of Pharmaceutics, Dr. D. Y. Patil Institute of Pharmaceutical Science & Research, Pimpri, Pune.***Corresponding Author: Ms. Shramika A. Chore**

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ABSTRACT

Drug delivery systems (DDS) are a strategic tool for expanding markets/ indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Tablet/Pellets are the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing, however in many cases immediate onset of action is required than conventional therapy. Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which $\geq 85\%$ of labelled amount dissolves within 30 min. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug. Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. The general term "granulation" and "pelletization" are sometimes used synonymously, the unit obtained are referred to as granules, pellets, agglomerates or spheroids without making any clear distinction among them. Generally, if a size-enlargement process produces agglomerates of a size distribution within the range of 0.1 mm to 2.0 mm and a high porosity (about 20-50%), the process may be called "granulates". "pelletization" is often referred to as a size-enlargement process that involves the manufacture of agglomerates with a relatively narrow size range, usually with mean size from 0.25 to 2.0 mm, named "pellets". Pellets have free-flowing properties and a low porosity (about 10%).

KEYWORDS: Spheronization, Metoprolol Succinate, Box-behnken etc.**INTRODUCTION**

Hypertension sometimes called arterial hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Normal blood pressure at rest is within the range of 100-140 mmHg for systolic and 60-90mmHg for diastolic. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg. Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries, peripheral arterial disease and is a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy.

β_1 - Selective blockers are presently considered an important class of drugs for hypertension and angina pectoris. Metoprolol Succinate is used in Hypertension, Angina pectoris and stable, symptomatic heart failure of ischemic, hypertensive, or cardiomyopathic origin. Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta (1)-adrenergic receptors in the heart. Beta (1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure. Metoprolol Succinate is BCS Class-I drug, the absolute oral bioavailability is 12% and biological half-life is 3-7 hrs.^[39,40]

Since last decade, multiparticulate systems like pellets have gained lot of attention for oral drug delivery and are

preferred over single unit dosage form for various reasons like uniform distribution in the gastrointestinal tract, better *in vitro* and *in vivo* release of the drug substances with reproducible release characteristics, increase in the bioavailability, reduced risk of dose dumping and flexibility to modify the drug release. In addition, due to the spherical shape and low surface area to volume ratio, pellets provide ease for the coating.

Pelletization is an agglomeration process of converting fine powder particles into spherical units that is pellets. Various techniques are employed in the manufacture of pellets, such as extrusion-spheronization, solution/suspension layering, powder layering etc. Out of these techniques, extrusion/spheronization is a simple, cost effective technique allowing formation of pellets with high drug loading and strength. Various processing and formulation parameters need to be identified and controlled during processing of pellets by extrusion spheronization technique.^[15]

Thus, the aim of present study was to formulate and evaluate immediate release pellets of Metoprolol by extrusion spheronization technique. The effect of formulation variables on Metoprolol pellets was also studied.

MATERIALS AND METHOD

Materials: Metoprolol was obtained as a gift sample from IPCA Laboratories, Mumbai. India. Iso-propyl alcohol was received as a gift from Loba chemical,

Mumbai India. Sodium starch glycolate was a gift sample from Loba chem, Mumbai. HPMC was purchased from Colorcon Asia Pvt. Ltd. India. Microcrystalline cellulose was received as a gift from Loba chem, Mumbai.

Method

API was accurately weighed and sifted through 12 # and transferred in 100 ml graduated cylinder. The cylinder was placed on the tapped density tester and was mechanically tapped, allowing it to drop under its own weight that provides a fixed drop from 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and the tapped volume (V_1) was measured to the nearest graduated units. The tapping was repeated for additional 750 times and the tapped volume (V_2) nearest to graduated units was noted. The tapped density was calculated by the formula.

$$TD = M/V_2$$

Where,

M = Weight of powder

V_2 = Tapped Volume (after 500+750 taps)

1. FORMULATION AND DEVELOPMENT

The following pharmaceutical development report summarizes the development of Metoprolol pellets, (For the reference, the SR marketed metoprolol 25 mg Tablet was taken). The metoprolol 25 is an immediate release (IR) tablet indicated for Mild to moderate essential hypertension.

2. Component & Composition of Metoprolol pellets

Table 1 : Composition of Metoprolol pellet.

Sr. No.	Ingredient	Function
1	Metoprolol	Active
2	HPMC K4M	Binder
3	Microcrystalline cellulose	Filler
4	Sodium starch glycolate	Disintegrate
5	Iso-propyl alcohol	Filler

3. PRELIMINARY STUDY

Table 2 : Preliminary Study.

Sr. No.	Ingredient	F1 (gm)	F2 (gm)	F3 (gm)	F4 (gm)	F5 (gm)	F6 (gm)
1	Metoprolol	2	2	2	2	2	2
2	HPMC K4M	2	-	-	-	1	-
3	HPMC K15	-	-	2	1	-	-
4	HPMC K100	-	1.5	-	-	-	1
5	Microcrystalline cellulose	16	14.5	14	14	16	16
6	Lactose	-	2	2	-	-	-
7	Sodium Starch Glycolate	-	-	-	3	1	1
7	Iso-propyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

4. MANUFACTURING PROCEDURE FOR PELLETS BY EXTRUSION SPHERONIZATION TECHNIQUE

1. Metoprolol, Avicel PH 101, HPMC, SSG were weighed and sifted through 40# sieve.
2. All the ingredients were triturated in mortar for proper formation of powder mass and mixed properly.
3. Isopropyl alcohol was slowly added in sufficient amount to form wet mass.
4. The wet blend was extruded through 16# sieve in one direction.
5. The extrudates were dried at room temperature as wet extrudates stick to each other during spheronization.
6. This extrude was spheronized into the lab spheronizer using 5 mm plate at the 1200 rpm for 2 min to get desired size and shape .
7. The wet pellets were dried into the R & D Coater / Oven.

5. APPLICATION OF DESIGN OF EXPERIMENTS FOR FORMULATION OPTIMIZATION:

Design of experiments (DOE):^[52]

A Box-behnken design was used with 17 trial runs to study the impact of three factors on the two key response

variables. In this design 3 factors were evaluated, each at 3 levels, and experimental trials were performed at all 3 possible combinations. The speed of spheronization (S-X1), Binder Hydroxypropylmethyl cellulose (HPMC-X2) and amount of superdisintegrant sodium starch glycolate (SSG-X3) were selected as independent variables and disintegration time (DT) and dissolution (% release of drug in 30 mins), were selected as dependent variables. The resulting data were fitted into design expert software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of speed (S-X1), Binder hydroxypropylmethyl cellulose (HPMC-X2), superdisintegrant sodium starch glycolate (SSG-X3) on dependent variables. The probable trial runs using 3³Box behnken designs are as shown in following table.

Table 3: Design used for DOE experimentation.

Design Used	Box-Behnken Design
Factors	03
Replicates	01
Run	17
Block	01
Center points(total):	05

Table 4. Factors/Variables studied in DOE Trial.

Factors/ variables	Low level	Medium Level	High Level
Speed (X1)	1000 rpm	1200 rpm	1400 rpm
Binder Conc (HPMC-K4M) (X2)	2 %	3.5 %	5 %
Disintegrating agent (SSG) conc (X3)	2 %	5 %	8 %

Table 5 : Box behnken designs.

Run Order	RPM of S-X1	% of HPMC-X2	% of SSG-X3
1	1000	2	5
2	1400	2	5
3	1000	5	5
4	1400	5	5
5	1000	3.5	2
6	1400	3.5	2
7	1000	3.5	8
8	1400	3.5	8
9	1200	2	2
10	1200	5	2
11	1200	5	2
12	1200	2	8
13	1200	5	8
14	1200	3.5	5
15	1200	3.5	5
16	1200	3.5	5
17	1200	3.5	5

Table 6 : Unit Operations for Pellets preparation.

Sr. No.	Processing Steps	Equipment Used
1	Weighing	Electronic Balance
2	Granulation	Manual
3	Blending	Manual
4	Extrusion	Sieve
5	Spheronization	Spheronizer
6	Drying	R & D Coater/ Oven

Table 7. Compositions of DOE trials.

Sr. No.	Ingredients	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm
	Batch no.	K1	K2	K3	K4	K5	K6	K7	K8
1	Metoprolol	2	2	2	2	2	2	2	2
2	HPMC K4m	0.4	0.4	1	1	0.7	0.7	0.7	1
3	Sodium starch glycolate	1	1	1	1	0.4	0.4	1.6	1
4	Microcrystalline Cellulose (avicel 101)	16.6	16.6	16	16	16.9	16.9	15.7	16
5	Speed	1000	1400	1000	1400	1000	1400	1000	1000
6	Iso-propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 8 : Compositions of DOE trials.

Sr.No.	Ingredients	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm
	Batch no.	K9	K10	K11	K12	K13	K14	K15	K16	K17
1	Metoprolol	2	2	2	2	2	2	2	2	2
2	HPMC K4m	0.7	0.4	1	1	0.4	1	0.7	0.7	0.7
3	Sodium starch glycolate	1.6	0.4	1	0.4	1.6	1.6	1	1	1
4	Microcrystalline Cellulose (avicel 101)	15.7	17.2	16	16.6	16	15.4	16.3	16.3	16.3
5	Speed	1400	1200	1400	1200	1200	1200	1200	1200	1200
6	Iso-propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 9. Factors/Variables studied in DOE Trial.

Factors/ variables	Low level	Medium Level	High Level
Speed (X1)	1000 rpm	1200 rpm	1400 rpm
Binder Conc. HPMC-K4M (X2)	2 %	3.5 %	5 %
Disintegrating agent (X3)	2 %	5 %	8 %

6. EVALUATION OF FORMULATION^[53,54]

6.1 Physical characterization of Pellets

All physical tests of pellets were performed like Bulk density, Tapped density, Compressibility index, Hausner's ratio and Loss on drying.

6.2 Pellets evaluation

The Pellets were evaluated for the following tests:

- **% Yield:**

Formulated batch were taken randomly and weighed accurately and the average weight of each batch was calculated.

% yield = Actual wt. of batch – Theoretical wt. of batch × 100

- **Hardness/Crushing strength**

The term hardness indicates the ability of a pellets to withstand mechanical shocks while handling. It is generally expressed in Kg/cm² or in Newton(N). Hardness of a pellets was measured using digital hardness tester.

- **Thickness**

2-3 pellets were selected randomly and sphericity was measured using digital microscope and thickness was measured by using vernier caliper.

- **Disintegration test**

100 mg pellets were selected from each batch for Disintegration test. This test was performed in tablet disintegration apparatus USP without disc in water at $37 \pm 0.5^\circ\text{C}$ temperature at speed of 30 dips. Disintegration test was carried out three times for each formulation and result were expressed in standard deviation. (\pm SD; $n = 3$).

- **Friability**

To achieve % friability within limits for pellets is a challenge to the formulator. Friability test is performed to assess the effect of friction and mechanical shock, which may often causes pellets to chip, cap, laminate or break.

Method

About 10gm pellets were taken . Pellets were de-dusted prior to testing. Pellets samples were accurately weighed and placed in the drum of friability tester. Drum was

rotated for 100 revolutions. Pellets were deducted and reweighed.

6.3 Assay

The pellets equivalent to the dose of drug were weighed and powdered. The powdered pellets were transferred to the volumetric flask. About 75ml methanol was added and shaken for 15 min. the volume was made with methanol and sonicated for 20 min. The solution was filtered and further appropriate dilutions were made with methanol. The absorbance was measured at 276 nm on a UV-Visible spectrophotometer using methanol as blank. The content of Metoprolol was determined from the calibration curve.

7. *In vitro* Dissolution Study:^[52]

The formulated Metoprolol pellets and marketed tablet were subjected to the dissolution study. Following parameters were used for the dissolution study.

Table 10: Dissolution test details for dissolution study.

Apparatus(Basket) apparatus type II	USP dissolution
Speed of the basket	100 rpm
Temperature	$37 \pm 0.5^\circ\text{C}$
Dissolution medium	0.1 N HCL
5. Volume of fluid	900 ml
6. Sample withdrawn interval	5,10,15,20,25,30 mins

Samples of 5 ml were withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of

medium. The filtered samples were analyzed spectrophotometrically at 276 nm.

RESULTS AND DISCUSSION

1. Differential Scanning Calorimetry (DSC)

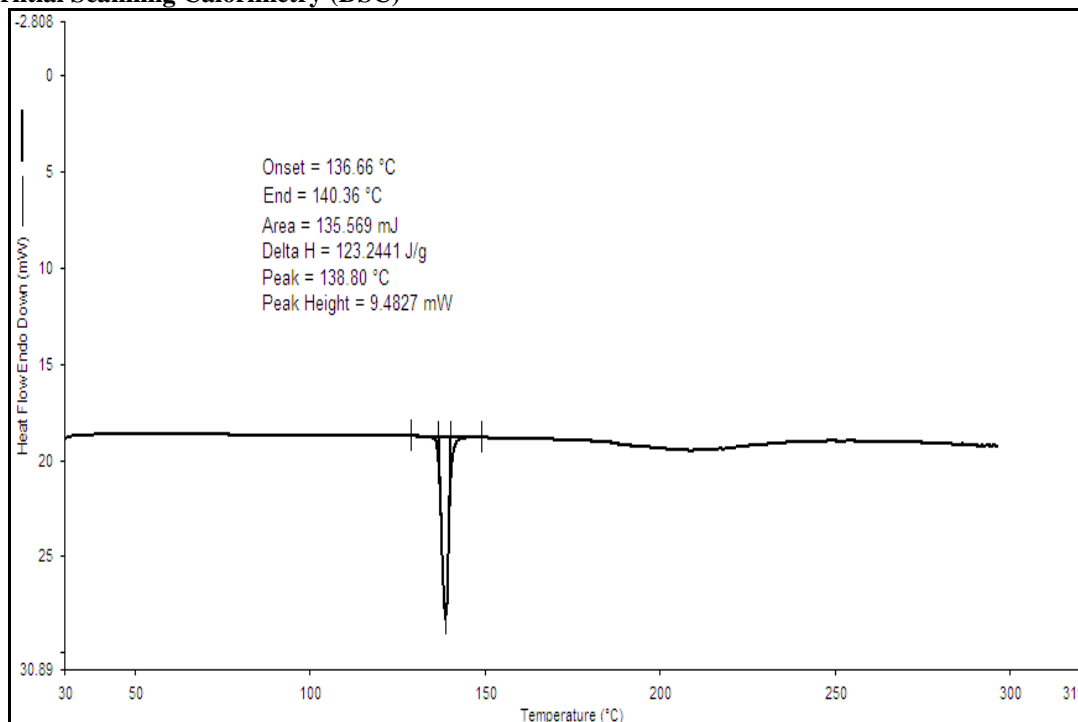


Figure 1 : DSC Spectrum of Metoprolol.

The DSC Spectrum of the Metoprolol clearly depicts the melting point close to the 132.26°C which is nearly equal

to pharmacopoeial specification. So it was Concluded that the given sample of drug was pure.

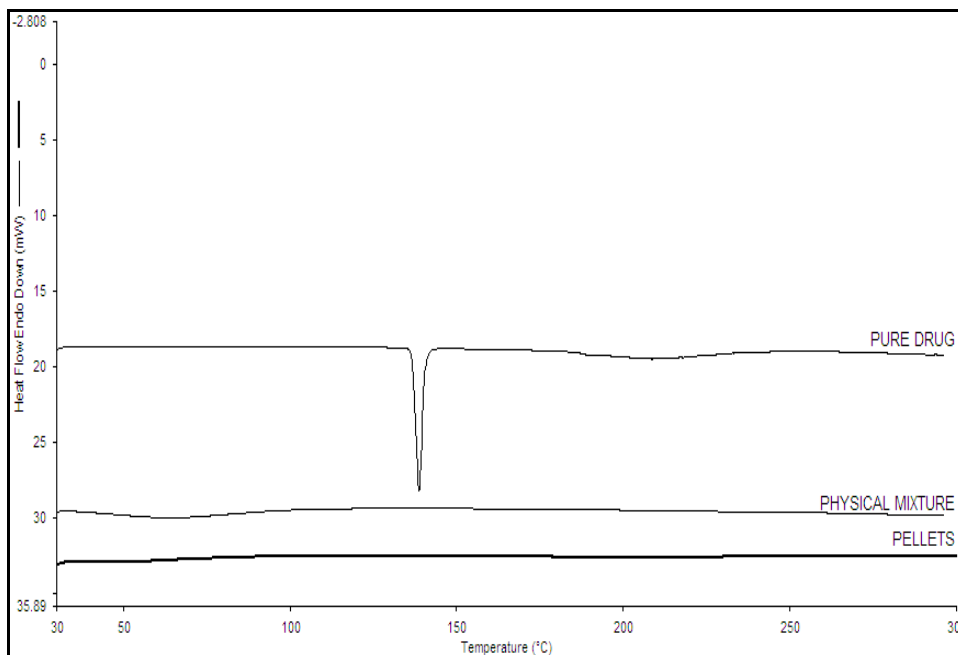


Figure 2 : DSC Spectra of drug & optimized Formulation.

2. Compatibility Study

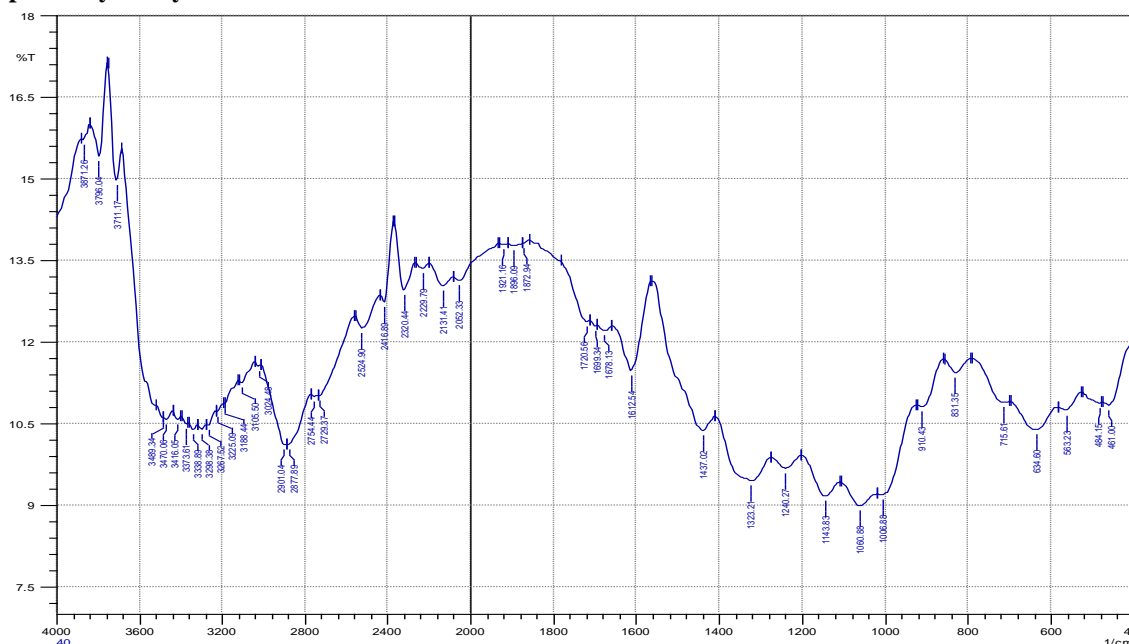


Figure 3 : IR Spectrum of Metoprolol and Excipients (1:1) at 40°C±2°C After 1 Month.

Table 11 : IR spectrum interpretation of Metoprolol and Excipient at 40 ±2°C.

Sr. No	Functional Group	Wave No. (cm ⁻¹)
1	-OH	3600
2	-NH	3400
3	-CH(un)	3100
4	-CH	2900
5	-CN	1200
6	-CO	1100

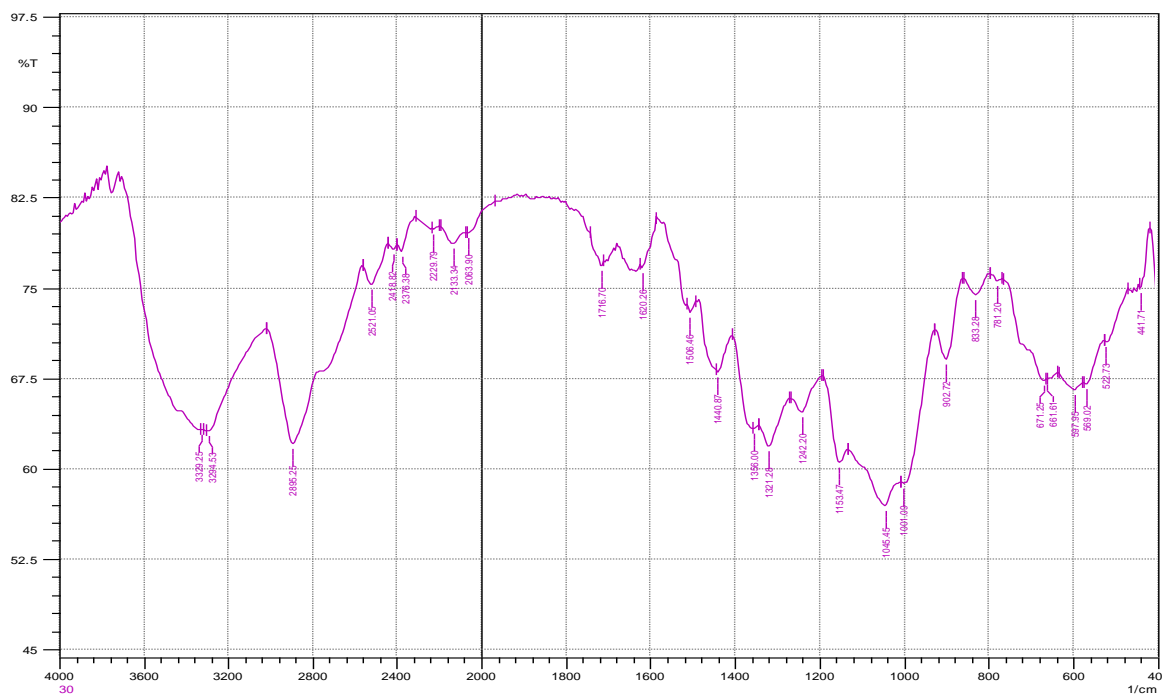


Figure 4 : IR Spectrum of Metoprolol and Excipients (1:1) at $30\pm 2^{\circ}\text{C}$ After 1 Month.

Table 12 : IR spectrum interpretation of Metoprolol and Excipient at 30°C .

Sr. No	Functional Group	Wave No.(cm^{-1})
1	-OH	3319
2	-NH	3294
3	-CH(un)	2896
4	-CH	2521
5	-CN	1321
6	-CO	1153

From the IR spectrum of drug and excipient physical mixture, it was evident that there was no interaction between the drug and the excipients.



Figure 5: Formulated pellets.

2. Preliminary studies for optimization of pelletization process

Preliminary studies were carried out to select the binder and optimize the process.

Batch F1 : Formulation F1 was difficult to extrude and

proper blend was not formed. The pellets were of uneven size and as the disintegrating agent was not added, the hardness of pellets was greater. The dissolution of resulting pellets was not complying with the pharmacopoeal limit.

Batch F2 : In F2 batch, HPMC K100 was used as binder in powdered form without making slurry. The mass was hard and difficult to extrudate and resulting pellets were hard.

Batch F3: In F3 batch the binder HPMC K 15 and lactose were directly added in powder form without making the slurry. Resulting pellets were found to be robust and possessing desired hardness and sphericity.

Batch F4: In F4 batch, SSG was added as superdisintegrant in higher concentration . The pellets were found to be friable and showing fast disintegration.

Batch F5: In F5 batch the concentration of

superdisintegrant was decreased. Resulting pellets were good in size and shape, less friable and disintegrated slowly as compared to F4 batch.

Batch F6: In F6 batch, the binder grade was change (HPMC K100) & superdisintegrant was used as same quantity use in F5 and the resulting pellets showed the proper sphericity with no friability and disintegration as per limit.

3: Physical characterization of Pellets

The results of Bulk Density, Tapped Density, Carr's index, Hausner ratio and Angle of Repose are illustrated in Table No. 13

Table 13 : Evaluation of pellets.

Batch No.	K1	K2	K3	K4	K5	K6
BD(gm/ml)	0.55±1.2	0.50±1.1	0.44±1.1	0.50±1.4	0.57±1.6	0.51±2.1
TD(gm/ml)	0.58±0.8	0.55±1.2	0.49±1.4	0.55±1.1	0.61±1.8	0.54±1.6
CI (%)	5.17±1.1	9.09±0.8	10.20±1.6	9.09±1.6	6.66±1.8	3.55±2.2
HR	1.05±1.2	1.11±0.9	1.110±1.4	1.12±1.2	1.07±1.4	1.05±2.6

Batch No.	K7	K8	K9	K10	K11	K12
BD(gm/ml)	0.60±1.8	0.47±1.7	0.53±1.4	0.45±0.8	0.54±1.1	0.52±1.6
TD(gm/ml)	0.64±1.4	0.53±1.1	0.61±1.6	0.49±0.9	0.52±1.2	0.59±2.1
CI (%)	6.35±1.5	11.3±1.4	13.11±1.8	8.16±1.4	9.09±0.8	11.86±2.4
HR	1.06±2.1	1.12±1.4	1.47±2.0	0.07±1.8	1.12±0.9	1.11±2.1

Batch No.	K13	K14	K15	K16	K17
BD(gm/ml)	0.48±1.7	0.61±1.8	0.65±2.0	0.65±1.5	0.60±2.3
TD(gm/ml)	0.50±1.1	0.68±2.0	0.73±1.6	0.70±1.3	0.64±1.5
CI (%)	11.8±1.4	10.29±1.0	10.95±1.4	7.14±1.7	6.25±1.4
HR	1.02±1.4	1.14±1.7	1.12±1.8	1.07±1.1	1.06±1.6

For bulk density & Tapped density, 10gm pellets were taken and the test was performed. All DOE batches

showed results within the standard limit. The results of the formulations indicated good flow properties.

Table 14. Evaluation of DOE Batches.

Batch	Angle of repose	Hardness (Kg/cm ²)	Disintegration Test(min:sec)	Drug content (%)
K1	18.92°	0.79±0.8	00:57±0.8	84.51±1.8
K2	19.44°	0.6±0.7	00:51±1.2	89.03±2.6
K3	26.56°	0.4±0.5	00:53±0.6	82.58±1.6
K4	21.25°	0.4±0.5	00:52±0.8	90.32±1.0
K5	25.0°	0.7±0.6	00:57±1.0	84.51±2.0
K6	25.20°	1.0±0.8	00:59±0.7	94.19±0.8
K7	30.96°	0.6±0.2	00:58±0.9	89.03±1.6
K8	14.74°	0.6±0.7	00:59±1.2	89.03±1.2
K9	26.56°	0.6±0.5	00:48±1.1	91.61±0.6
K10	21.20°	0.4±0.5	00:53±0.4	92.24±1.6
K11	29.90°	0.9±0.96	00:51±1.4	83.22±2.6
K12	34.56°	1.0±0.5	00:52±0.9	86.46±1.4
K13	15.06°	0.6±0.5	00:48±1.1	89.03±1.6
K14	30.96°	0.9±0.4	00:56±1.0	92.90±0.8
K15	17.35°	1.1±0.9	00:52±0.6	91.61±1.0
K16	26.56°	1.2±0.8	00:54±0.8	94.19±0.8
K17	32.75°	1.2±1.0	00:51±0.4	95.48±0.6

The results in the table showed good flow properties and quick disintegration of the pellets within one minute.

4. DOE Specification

In order to evaluate the effect of variables on disintegration and dissolution of pellets, DOE was applied. But, it was observed that there was no significant effect of variables on the performance of immediate release pellets. The pellet formulations showed almost similar results.

$$\text{Disintegration Time (Y1)} = 52.40 - 0.12X_1 + 0.25X_2 - 0.88X_3 + 1.75X_1X_2 - 0.16X_1X_3 - 0.75X_2X_3 + 2.80X_1^2 - 1.45X_2^2 - 0.20X_3^2 \dots\dots\dots (1)$$

$$\text{Average release (Y2)} = 92.64 - 0.12X_1 + 0.89X_2 + 0.21X_3 + 3.30X_1X_2 + 0.25X_1X_3 + 1.32X_2X_3 - 2.81X_1^2 - 3.53X_2^2 - 1.03X_3^2 \dots\dots\dots (2)$$

5. Effect on Disintegration Time

a) Influence of binder concentration and Speed on disintegration time of formulation.

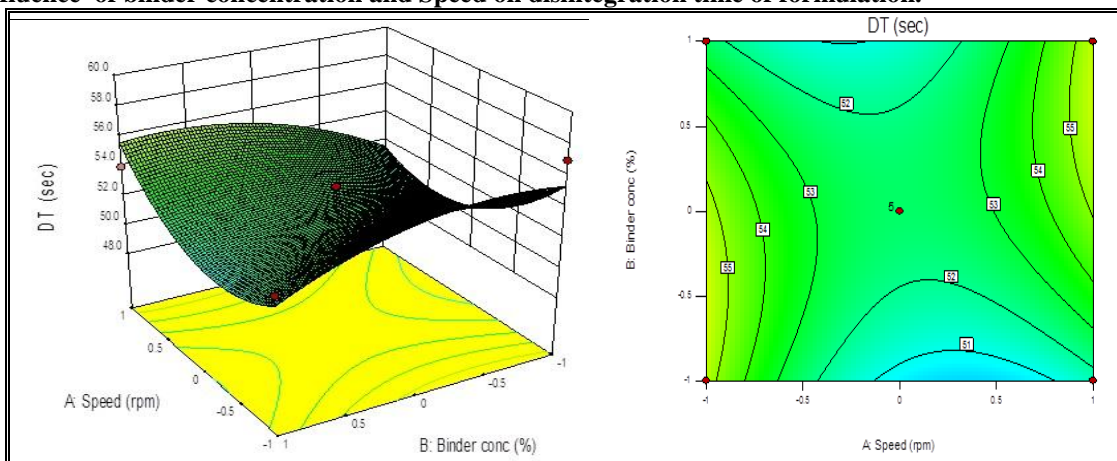


Figure 6: (a) Counter plot (b) Response surface area showing influence of binder concentration and Speed on disintegration time of formulation.

The response plots and counter plots in figure 6 indicate a relative effect of increase in speed and binder concentration on disintegration time of pellets.

At a higher level of binder concentration, when speed of spheronizer was increased, disintegration time of pellets was found to be increased whereas at lower ratio of binder concentration with decreased in speed, there was decreased in disintegration time of pellets.

b) Influence of binder concentration and concentration of disintegrant on disintegration time of formulation.

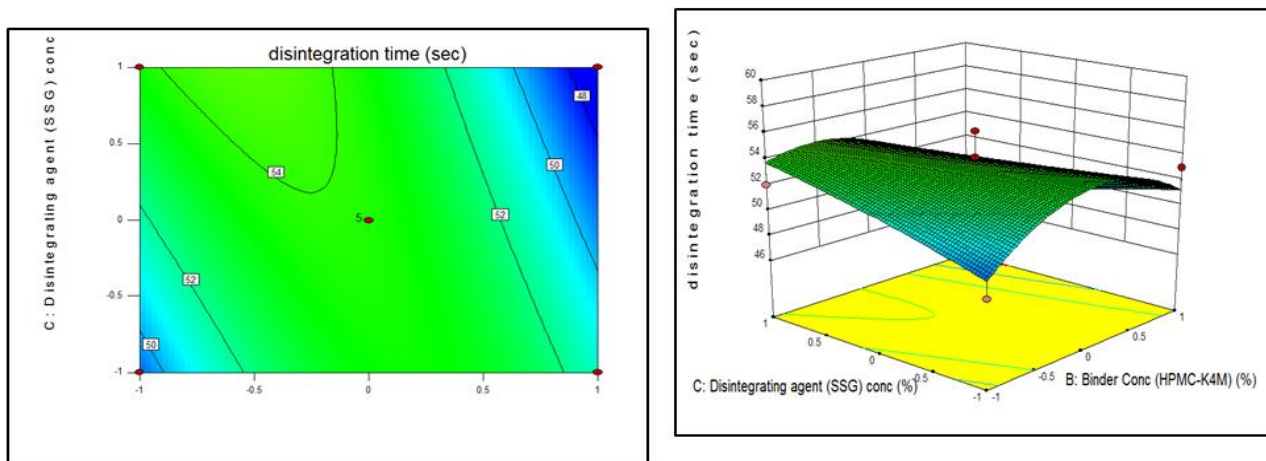


Figure 7: (a) Counter plot (b) Response surface area showing influence of binder concentration and concentration of superdisintegrant on disintegration time of formulation.

The response plots and counter plots in figure. 7 indicate a relative effect of increase in superdisintegrant concentration and binder concentration on disintegration time.

At a lower level of superdisintegrant concentration, when binder concentration was increased, disintegration time of pellets was found to be increased. This might be due to increase in hardness of pellets due to addition of high

amount of binder which lead to increase in disintegration time. At higher concentration of superdisintegrant, though binder concentration was increased disintegration time decreased. Thus, increase in binder concentration does not have any effect on disintegration in presence of high concentration of superdisintegrant.

Similarly, at higher concentration of binder with increase in superdisintegrant, there was decrease in disintegration time.

b) Influence of concentration of disintegrating agent and Speed on disintegration time of formulation

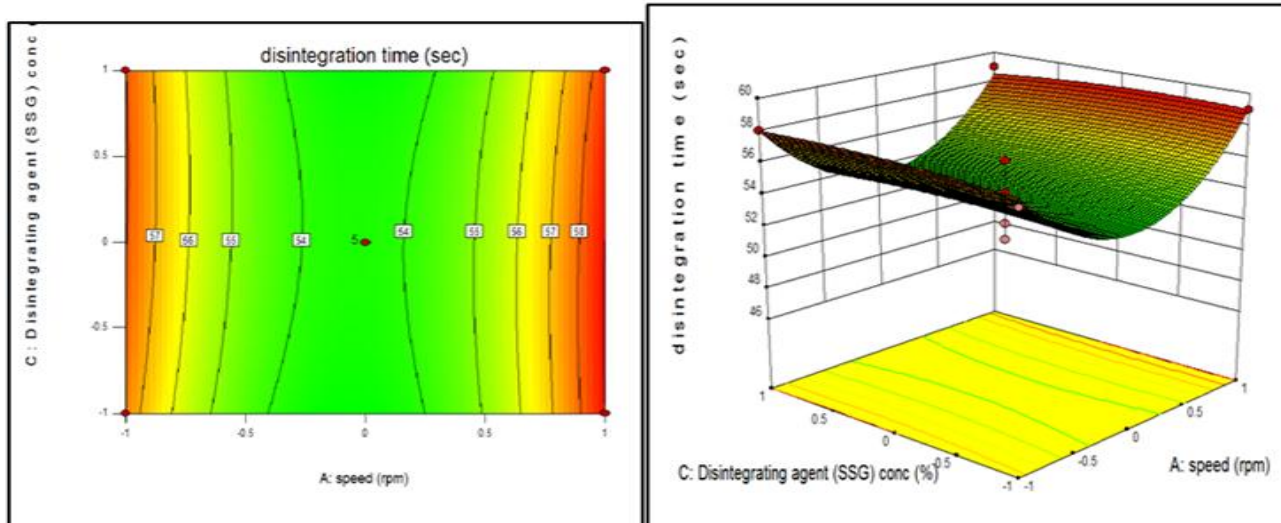


Figure 8 :a) Counter plot (b)Response surface area showing influence of concentration of disintegrating agent and Speed on disintegration time of formulation.

The response plots and counter plots in figure. 8 indicates a relative effect of increase in superdisintegrant concentration and speed on disintegration time.

At all levels of disintegrating agent concentration, when speed was increased from lower level to middle level, disintegration time was decreased. With further increase in speed disintegration time was found to be increased. Thus, at middle level, faster disintegration of pellets was obtained.

It is evident from the figure that at all the levels of speed, when concentration of disintegrating agent was increased, there was no significant change in Disintegration time.

6. Effect on drug release after 30 min

a) Influence of binder concentration and Speed on drug release after 30 minutes of dissolution.

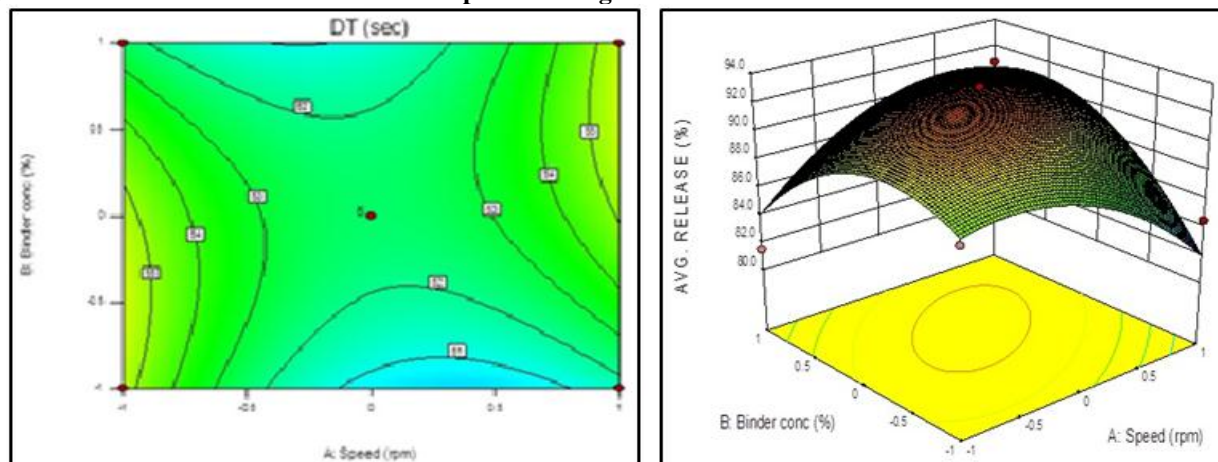


Figure 9: (a) Counter plot (b)Response surface area showing influence of binder concentration and Speed on drug release of formulation.

The response plot and counter plot in figure. 9 indicates a relative effect of increase in Binder conc. and speed on the drug release after 30 min of dissolution from the pellets.

At lower levels of Binder concentration, when speed was increased, percent drug release was found to be slightly

decreased whereas at higher concentration of Binder concentration, with increase in speed, there was increase in percent drug release. This might be due decrease in the size of pellets at higher speed resulting in increased drug release.

b) Influence of binder concentration and concentration of disintegrating agent on drug release of formulation.

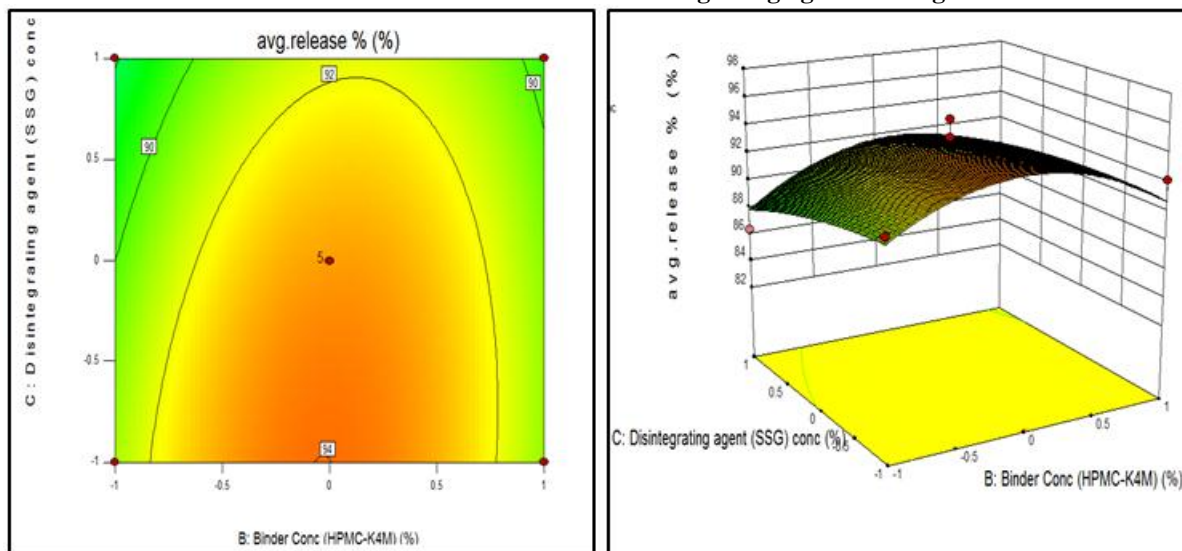


Figure 10:(a) Counter plot (b)Response surface area showing influence of binder concentration and concentration of disintegrating agent on drug release of formulation.

The response plots and counter plots in figure 10 indicate a relative effect of increase in Disintegrating agent concentration and binder concentration on the drug release after 30 min of dissolution from the pellets. It is observed from the figure that there was no significant effect of superdisintegrant concentration on drug release from pellets. In presence of superdisintegrant, when

binder concentration was increased from lower to middle level, there was increase in drug release. This might be due to formation of small and uniform sized pellets giving increase in drug release. With further increase in binder concentration there was slight decrease in the release of drug.

c) Influence of speed and concentration of disintegrating agent on drug release of formulation.

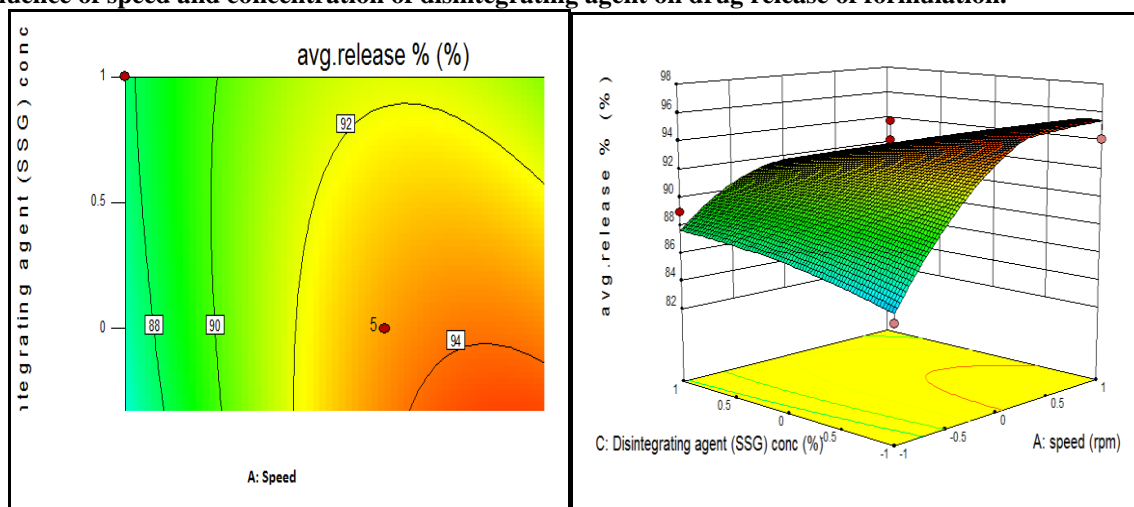


Figure 11:(a) Counter plot (b)Response surface area showing influence of speed and concentration of disintegrating agent on drug release of formulation.

The response plots and counter plots in figure 11 indicate a relative effect of increase in Disintegrating agent concentration and speed of spheronizer on the drug release after 30 min from the pellets. It was observed that there is no significant effect of disintegrating agent on drug release. At all levels of superdisintegrant, with increase in speed of spheronizer there was increase in drug release. This is attributed to small size of pellets formed at a higher speed resulting in higher drug release.

7. IN-VITRO DRUG RELEASE

In vitro dissolution studies of Metoprolol pellets were performed in 0.1N HCL using USP Type II dissolution test apparatus. *In vitro* release experiments were evaluated in order to investigate the effect of binder and disintegrating agent on the drug release from pellets.

Table 15 : % average release of DOE Batches.

Time	K1	K2	K3	K4	K5	K6	K7	K8
5	51.8±1.0	45.0±1.6	48.2±1.4	56.3±2.2	50.3±0.6	52.5±1.6	39.4±1.4	34.9±2.6
10	58.4±1.5	50.9±1.6	52.4±2.0	62.9±2.6	60.3±0.8	59.9±2.7	44.8±1.6	42.9±1.8
15	63.2±1.8	56.4±1.8	58.7±1.6	71.2±1.4	69.6±1.5	69.6±1.5	51.1±1.6	51.4±1.6
20	71.8±0.8	64.6±1.2	67.3±1.8	79.1±1.2	74.1±1.2	76.0±1.8	60.4±1.8	61.1±1.5
25	80.1±1.8	74.7±2.2	74.8±0.8	85.1±1.6	82.0±1.6	83.2±1.6	76.1±2.1	72.3±1.2
30	88.4±2.4	84.5±1.8	81.5±1.2	90.8±1.8	91.5±2.2	87.8±1.0	89.3±1.2	86.6±1.8

Figure 12: Graphical presentation of DOE batches K1-K5.

Time	K9	K10	K11	K12	K13	K14	K15	K16	K17
5	32.6±2.6	48.2±1.4	39.8±1.0	53.3±1.6	52.1±1.5	52.4±1.8	55.5±1.4	50.6±1.5	56.6±2.4
10	41.8±2.2	52.4±2.4	47.1±1.4	59.6±1.8	61.4±2.2	60.8±0.8	61.8±1.6	60.3±1.6	61.8±2.6
15	50.3±1.8	68.0±1.8	55.7±1.6	65.1±1.7	67.4±2.4	68.4±2.0	69.7±2.0	69.2±2.1	69.4±2.0
20	61.8±1.4	74.2±0.8	64.5±1.7	71.5±1.8	77.1±2.8	72.6±1.6	76.0±0.8	77.1±2.4	76.0±1.4
25	73.0±1.0	78.6±1.0	73.9±1.8	79.0±0.8	84.3±1.0	78.6±1.4	83.6±1.6	85.4±2.1	84.0±1.2
30	86.2±0.8	82.4±1.2	87.5±2.4	86.4±1.0	92.6±1.6	84.6±0.8	91.2±2.0	92.2±1.8	93.4±0.8

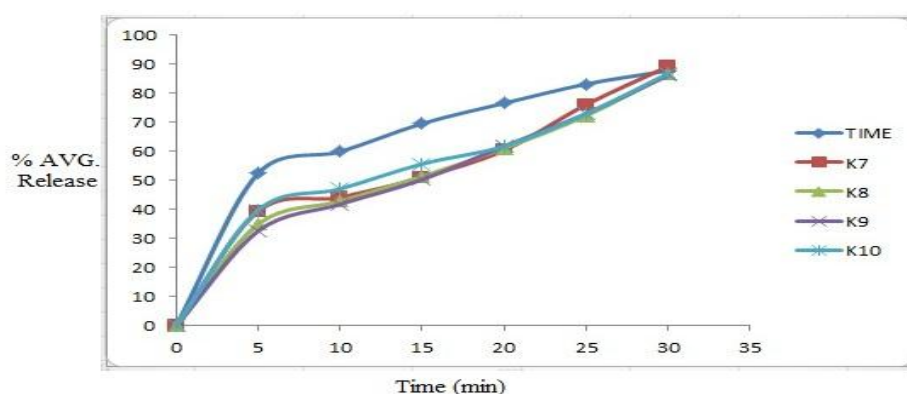
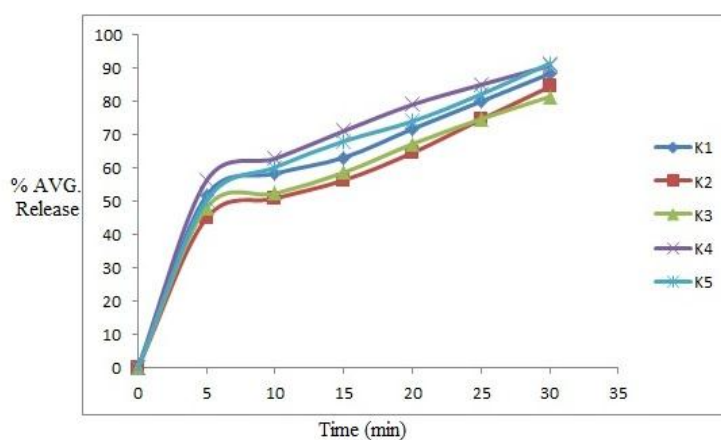


Figure 13: Graphical presentation of DOE batches K6-K10.

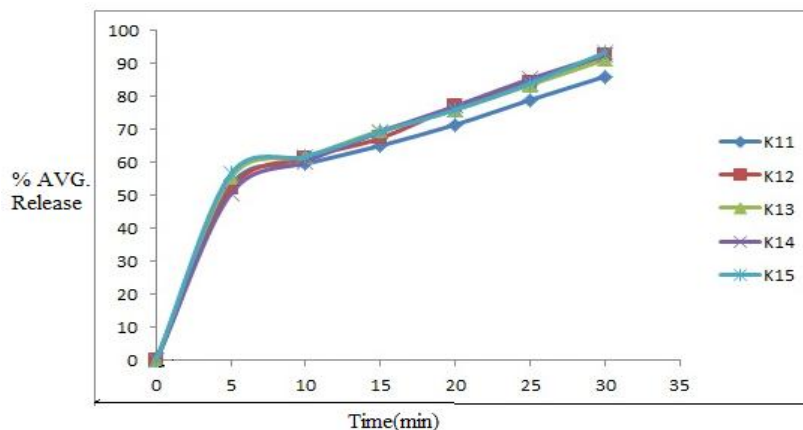


Figure 14: Graphical presentation of DOE batches K11-K17.

As per USP XXIV, the immediate release formulation of Metoprolol should release not less than 80% of the stated amount of drug within 30min. From the dissolution of DOE batches, it is evident that all the batches released more than 80 % of drug within 30 min. Thus, all the formulations comply with the pharmacopoeal limits.

8. *In vitro* dissolution test for marketed tablet

8.1: % Drug release of marketed formulations.

Metoprolol Tablet 25 mg in 0.1N HCL 900 ml, Apparatus: USP II (Paddle), 100 Rpm.

Table 16 : % Average release.

Time (Min)	Average % Drug release (Mean \pm SD)
5	50.67 \pm 0.68
10	61.46 \pm 3.75
15	72.30 \pm 2.59
20	80.57 \pm 3.14
25	87.01 \pm 2.09
30	92.74 \pm 3.17

The percent drug release from the marketed formulations was found to be more than 90 % in 30 min which is as per USP specifications.

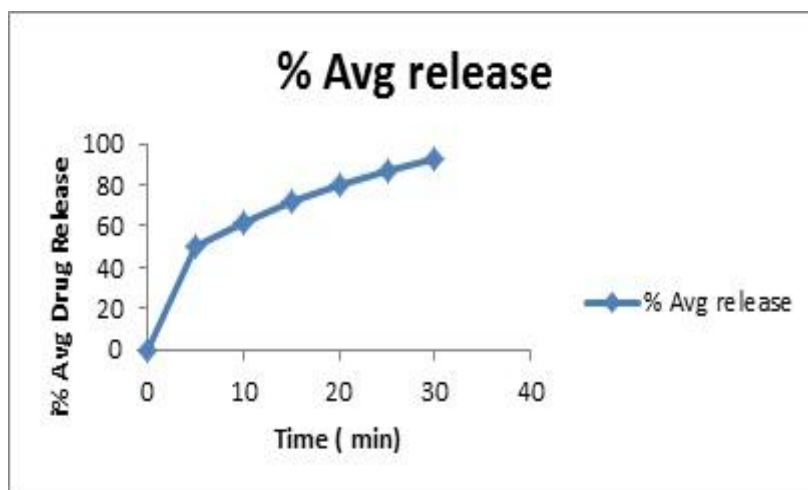


Figure 15: Graph of Time (in min) vs average % drug release of Metolar 25 mg Tablet.

9. % Drug release of optimized formulations: Formulations K15, K16 and K17 were selected as

optimized considering their drug release of more than 90 % in 30 minutes of dissolution.

Table 17. % Average release.

Time	K15	K16	K17
5	55.5±1.4	50.6±1.5	56.6±2.4
10	61.8±1.6	60.3±1.6	61.8±2.6
15	69.7±2.0	69.2±2.1	69.4±2.0
20	76.0±0.8	77.1±2.4	76.0±1.4
25	83.6±1.6	85.4±2.1	84.0±1.2
30	91.2±2.0	92.2±1.8	93.4±0.8

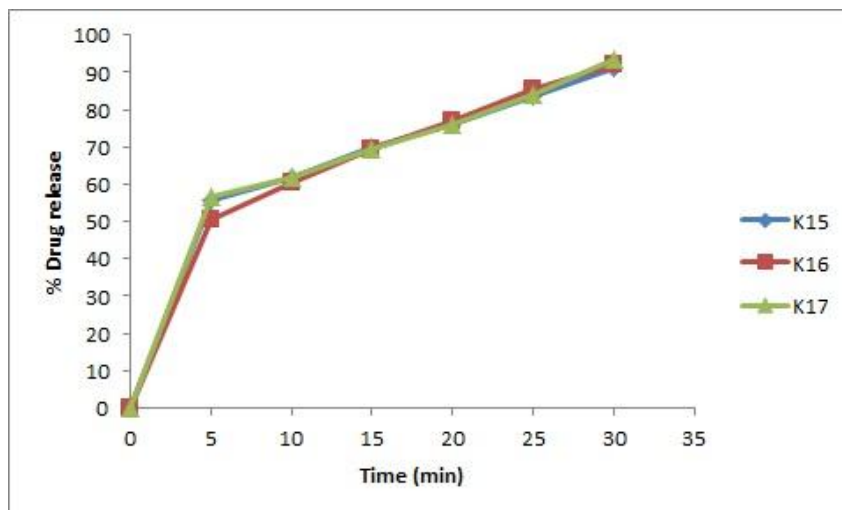


Figure 16: Graph of Time (in min) vs average % drug release optimized batch K15, K16, K17.

10. RESULT FOR SIMILARITY FACTOR

In order to assess the similarity between marketed and the optimized formulations, the similarity factor was calculated for K15, K16 and K17 batches.

Table 18. : Similarity Factor.

Sr. No.	Batch No.	Similarity factor(f_2)
1	K15	71.16
2	K16	81.96
3	K17	71.79

From the table No.18, it was found that the similarity factor (f_2) was found to be in acceptable range (50-100) which indicated that the marketed formulation and the designed formulation were similar in their release pattern.

11. Stability Study

Stability studies were carried out as per ICH guidelines at $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \pm 5\% \text{RH}$ for the selected formulation (DOE) for 3 month. After specified time intervals, parameters like hardness, disintegration time and *in-vitro* dissolution were evaluated.

Table No.19 : Evaluation parameters of stability study.

Batch No.	Hardness (Kg/cm^2)	Disintegration Test(min:sec)	Drug content (%)
K15	1.1±0.6	00:52±0.8	91.61±1.0
K16	1.2±0.8	00:54±1.0	94.19±0.8
K17	1.2±0.6	00:51±0.4	95.48±0.6

*Mean ± SD, n=3

Table No. 20 : % drug release after 3 month.

Time (min)	% AVERAGE DRUG RELEASE		
	After 3 Month		
	K15	K16	K17
10	54.55± 0.4	54.61± 0.8	52.68± 0.6
20	58.14± 0.2	62.20± 0.6	56.85± 1.2
30	66.50± 1.0	70.35± 1.0	68.07± 1.4
45	74.32± 1.1	86.29± 1.2	78.37± 0.9
60	86.22± 0.8	91.11± 0.8	89.13± 0.2

*Mean ± SD, n=3

The optimized batches were further studied for stability. After 3 months, the results found were, hardness ($1.1 \pm 0.6 - 1.2 \pm 0.8 \text{ kg/cm}^2$), Disintegration Test ($00.51 \pm 0.4 - 00.54 \pm 1.0$ (min:sec) and Drug content ($91.61 \pm 1.0 - 95.48 \pm 0.6 \%$).

SUMMARY AND CONCLUSION

Pellets containing the active ingredient are administered in the form of suspensions, capsules, or disintegrating tablets and offer significant therapeutic advantages over single unit dosage forms. Because pellets disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability.

Metoprolol belongs to the Class of organic compounds known as Benzonoids and derivatives. It is a cardioselective β_1 -adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. Metoprolol was administered once or twice in a day as tablet dosage form in dose regimen of 25 to 100 mg.

In the present study, immediate release pellets of Metoprolol were formulated by Extrusion-Spheronization technique and evaluated for *in vitro* characteristics. The preliminary studies were performed in order to optimize various process parameters. In the preliminary studies, various batches were prepared using different grades of HPMC as binders (HPMC K4M, HPMC K15, HPMC K100). HPMC K4 M was selected as binder after evaluating these formulations, and Sodium starch glycolate was used as a superdisintegrants. For further optimization of pellet formulations, a Box Behnkan design was applied. The design consisted of 3 variables at 3 levels. One variable was speed of spheronizer at different rpm (1000, 1200, 1400), second variable was binder (HPMC K4 M) concentration at 2%, 3.5%, 5% w/w and third variable was Concentration of superdisintegrating agent at 2%, 5%, 8% w/w. The dependent variables (responses) like disintegrating time and percent drug release after 30 minutes were used to generate polynomial equation from "Design Expert 9" software. The surface response and counter plot were drawn to facilitate an understanding of the contribution of the variables and their interaction.

On the basis of the evaluation, K15, K16, K17 (spheronizer Speed 1200 rpm, HPMC K4M 3.5%, Sodium starch glycolate 5% ratio batch were selected for further study. The % drug release of these formulation were found to be more than 80% within 30min of dissolution which complied with the USP limits.

Stability studies were carried out as per ICH guidelines at $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \pm 5\% \text{ RH}$ for the selected formulation (DOE) for 3 month. After specified time intervals, parameters like hardness, disintegration time and *in-vitro* dissolution were evaluated. The optimized formulations were found to be stable after three months of stability study.

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