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Formulation and Evaluation of Metoprolol Tartrate Fast Dissolving Tablet

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ABSTRACT

Metoprolol Tartrate is effective β-blocker used in the second line treatment for angina and for myocardial infarction. Adult dose as conventional preparations is 25-100 mg daily in single or divided doses, as extended release 100-200 mg once daily. The bioavailability of the drug when formulated as conventional tablets is 40 % due to hepatic metabolism. The present investigation was undertaken with a view to develop a fast dissolving tablet of Metoprolol Tartrate which offers a new range of product having desired characteristics and intended benefits prepared by direct compression method using different concentrations of superdisintegrant. Effect of superdisintegrant on wetting time, drug content, in-vitro drug release, disintegration time has been studied. Disintegration time increased with increase in the level of Croscarmellose sodium while it decreased for Crospovidone, the release was dependent on the aggregate size in the dissolution medium. It is concluded that Metoprolol Tartrate fast dissolving tablets could be prepared using superdisintegrant with improved bioavailability and rapid onset of action.

Keywords: Fast dissolving tablets, Metoprolol Tartrate, Croscarmellose sodium, Crospovidone, disintegration time, in-vitro drug release.

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INTRODUCTION

Fast dissolving tablets (FDT) dissolve rapidly in the mouth and provide an excellent mouth feel. The tablet comprises a compound which melts at about 37°C [1]. Many patients express difficulty in swallowing tablets and hard gelatin capsules, tending to non-compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance [2]. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension, migraine, dysphasia, nausea and vomiting, Parkinson's disease, schizophrenia, pediatric emergency. Most commonly used methods to prepare fast dissolving tablet are; freeze-drying/Lyophilization tablet molding and direct-compression methods [3, 4]. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets [5, 6].

Metoprolol Tartrate (MT) is a selective beta1-adrenoreceptor blocking agent. Metoprolol Tartrate is (±)-1- (isopropyl amino)-3-[p-(2-methoxyethyl) phenoxy]-2- propanol (2:1) dextro-tartrate salt used in essential hypertension, prevention after a myocardial infarction, tachycardia, coronary heart disease (prevention of angina attacks), treatment of heart failure[7].The oral bioavailability is 40%.The concept of formulating FDT of Metoprolol Tartrate is to improve bioavailability and to decrease the disintegration time of the tablets by simple and cost effective direct compression technique.

MATERIAL AND METHODS

Metoprolol Tartrate (MT) from Vaibhav Analytical Laboratories, Ahmedabad, Croscarmellose sodium, Microcrystalline cellulose, Aspartame and Talc (Lesar chemicals, Ahmedabad), Crospovidone (Kawarlal & Co., Chennai), Magnesium stearate from ACME laboratory, Ahmedabad, India.

Preparation of fast dissolving tablets by direct compression method:-

Different formulations of Metoprolol Tartrate FDT were designed to be prepared by direct compression technique using super disintegrant, (Crospovidone, Croscarmellose sodium). Super disintegrant is varied with 3 different concentrations, (3, 5, 7% respectively) keeping all other ingredients constant, there are assigned with formulation codes shown in Table1. All the ingredients were passed through # 60 meshes separately. Then the ingredients were weighed and

mixed in geometrical order and compressed into tablets of 200 mg using 8mm round flat punches on ten station rotary tablet machine (Rimek).

Table 1: Formulation of MT Batch

Ingredient	F1	F2	F3	F4	F5	F6
Drug	25	25	25	25	25	25
CP	6	10	14	-	-	-
CCS	-	-	-	6	10	14
MCC	32	26	16	32	26	16
Mannitol	125	125	125	125	125	125
Aspartame	4	4	4	4	4	4
Talc	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Flavour	q.s	q.s	q.s	q.s	q.s	q.s
Total wt.	200	200	200	200	200	200

Evaluation of blends [8]

Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h) was obtained. Diameter of heap (D) was measured. The response angle (θ) was calculated by formula.

$\tan \theta = 2h/D$

Bulk density

Apparent bulk density was determined by pouring pre-sieved drug excipients blend into a graduated cylinder and measuring the volume and weight "as it is".

Tapped density

It was determined by placing a graduated cylinder containing a known mass of drug, excipients blend on mechanical tapping apparatus, which was operated for a fixed no of taps until the powder bed volume has reached a minimum using the weight of a blend in a cylinder and this minimum volume the tapped density was computed.

Percent compressibility and Hauser ratio

These were calculated by using below equations.

% Compressibility: $\{(\rho t-\rho b)/ \rho t\} * 100$

Where, ρt= Tapped density. ρb= Bulk density

Hauser Ratio: ρt/ρb

Evaluation of MT fast dissolving tablets

The prepared tablets were evaluated for weight variation, hardness, friability, in vitro dispersion time, wetting time, drug content, in vitro release study, FTIR and DSC studies.

Weight variation [9]

Twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance. The individual weights were compared with the average weight for the weight variation.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a vernier caliper.

Hardness and Friability [10]

Hardness of the tablets was measured using the Monsanto hardness tester. The friability of a sample of twenty tablets was measured using a USP type Roche friabilator. Preweighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

Drug content uniformity [2]

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 200 mg of Metoprolol Tartrate was added to 100 ml of 6.8 pH phosphate buffer and liquid was filtered. Again 1ml of above solution was diluted with 10ml of 6.8 pH phosphate buffer to obtain 25µg/ml concentration. The MT content was determined by measuring the absorbance at 222 nm (using UV Spectrophotometer, Shimadzu 1700) .The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

In vitro dispersion time [11]

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5°C and the time required for complete dispersion was determined.

Wetting time[12, 13]

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time.

Water Absorption Ratio[12, 14]

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed. Water absorption ratio, R was determined using following equation;

R = 100 (Wa−Wb)/Wb, Where, Wa = weight of tablet after water absorption & Wb = weight of tablet before water absorption.

FTIR Studies

FTIR studies were performed on drug, excipients and the optimized formulation using (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm.

Dissolution study [15]

In vitro release of MT from tablets was monitored by using 500ml of USP phosphate buffer solution, (pH 6.8) at 37±0.5° and 50 rpm using [Paddle type, model TDT-08L, Electro lab, (USP), India]. Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed Spectrophotometrically (UV-1700, Shimadzu, Japan) at 222 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three

Comparison of dissolution profiles of optimum batch [16]

The similarity factor (f_2) was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profile of products were compared using a f_2 which is calculated from following formula,

$$f_2 = 50 \mathrm{X} \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \mathrm{x}\,100\right\}$$

Where, n is the dissolution time, Rt and Tt are the reference and test dissolution value at time t.

Accelerated stability study of optimized batch

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established.ICH specifies the length of study and storage conditions, Long term testing 25±20°C/60% ±5%RH for 12 months, Accelerated testing 40±20°C / 75% ±5%RH for 6 months. The prepared tablets were subjected to short term stability study for a period of one month as per ICH guidelines. In the present study, stability studies were carried out at 25°C/60% RH and 40°C/75% RH for a specific time period up to one month for all formulations. Samples were evaluated at 1 month time for drug content, in-vitro drug release study, weight variation, hardness, thickness and friability.

Statistical Analysis

Each tablet formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variable release parameter were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel 2002. Difference was considered significant when P <0.05.

RESULT AND DISCUSSION

Evaluation of blends

Physical properties such as bulk density, tapped density, percent compressibility index, Hausner's ratio, angle of repose are determined (Table-2) for the prepared tablet blend.

Table 2: Evaluation of blends

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hauser's ratio
F1	0.51 ± 0.007	0.65 ± 0.01	31.56±1.47	12 ± 1.21	1.21 ± 0.02
F2	0.52± 0.007	0.62 ± 0.01	31.00±0.20	15± 1.05	1.25 ± 0.02
F3	0.50± 0.007	0.63± 0.03	32.17±1.35	13 ± 1.24	1.20 ± 0.03
F4	0.55± 0.007	0.63 ± 0.04	32.05±1.27	17 ± 1.35	1.16 ± 0.02
F5	0.51± 0.007	0.64 ± 0.04	30.12±0.29	14 ± 1.25	1.22 ± 0.02
F6	0.56± 0.007	0.65± 0.05	31.16±1.18	16 ± 1.00	1.28 ± 0.04

Table 2A: Evaluation tests of prepared tablets

Formulation	Thickness (mm)±SD, n=3	Hardness (Kg/cm²)± SD, n=3	Friability (%)	Wt. Variation (mg)±SD, n=3	Wetting Time(secs) ±SD, n=3
F1	3.18±0.009	4±0.03	0.162	193.6±9.2	54.1± 0.88
F2	3.19±0.008	4±0.07	0.198	195.0±9.3	47.3± 0.24
F3	3.20±0.002	3±0.02	0.190	195.6±9.4	52.0± 0.45
F4	3.36±0.124	4±0.07	0.12	192.2±13.	76.3± 0.54
F5	3.36±0.125	4±0.04	0.105	194.2±13.	72.3± 0.56
F6	3.36±0.124	5±0.05	0.107	197.2±13.	78.4± 0.45

Table 3: Evaluation tests of prepared tablets

Formulation	Drug content	D.T (secs)	In-vitro-drug release (%)	Water absorption ratio (%)
F1	97.45	65	76.85	54.1± 0.88
F2	104.4	54	90.22	47.3± 0.24
F3	94.5	72	94.41	52.0± 0.45
F4	96.4	89	97.83	76.3± 0.54
F5	102.2	46	99.36	72.3± 0.56
F6	96.08	33	101.64	78.4± 0.45

Evaluation of prepared Metoprolol Tartrate FDT

Prepared tablets were evaluated for parametric tests (Table2A & 3). The drug content in various formulations varied between 97.45% to 102.96%. Maximum diameter and thickness of prepared tablets were 8.00 mm and 8.02 mm respectively. Hardness values of formulated tablets were

ranging between 3±0.02 and 5±0.05kg/cm2. Friability of prepared tablets ranges between 0.105 to 0.198%.

The wetting time was determined for all the formulations prepared. The wetting time for the optimized formulations is below one minute; this indicates quicker disintegration of the tablet.

Water absorption ratio, 'R,' of formulations containing CCS were greater than that of CP containing formulations demonstrated greater 'R' values compared to CCS. Water absorption ratio 'R' increased with an increase in superdisintegrants' concentrations from 3-7 % .A linear relationship was observed for each of the superdisintegrant types. The increase in 'R' was most likely due to increased water uptake capacity of the superdisintegrants at higher concentrations. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration.

Fourier transforms infrared spectroscopy (FTIR)

IR (KBR) cm-1: Aliphatic C-H of CH3and OCH3 at 2445. The C-O absorption is found at 1572 merged with C=C of aromatic. One of the C=O has undergone hydrogen bonding with the drug to give rise to adduct which is not a chemical reaction product. This hydrogen bond can undergo cleavage during metabolic process. The same drug Metoprolol Tartrate is taken with CCS is subjected for IR reading. It has shown presence of all the absorption peaks of drug along with a strong C=O of carboxylic cluster peak at 1755. It is clear from these observations that tablet that we obtain is containing -H bonding between drug and the CCS. There is no interaction between drug and polymer.

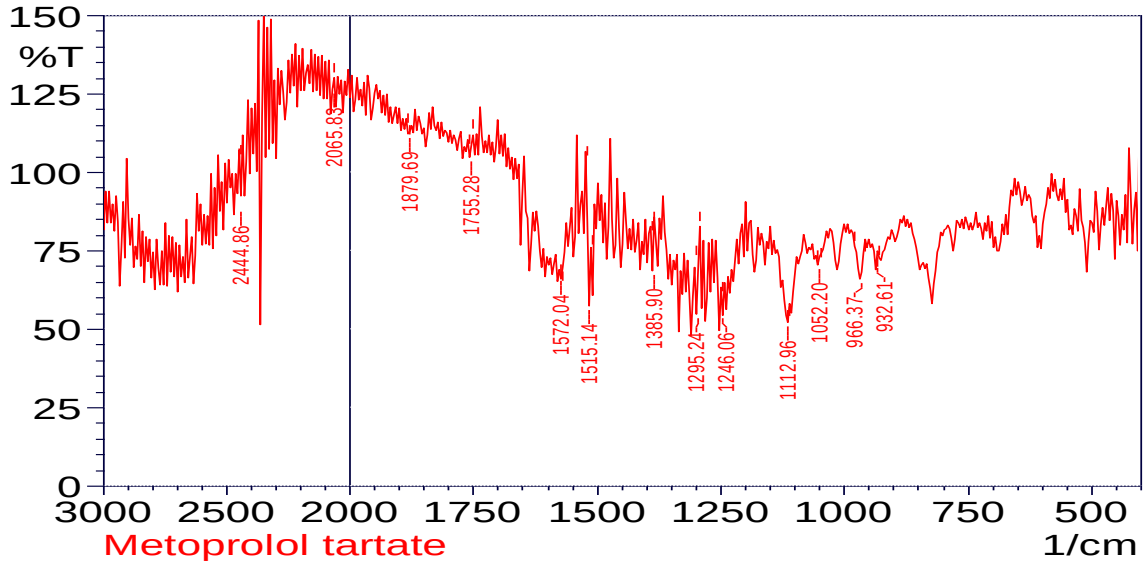

Figure.1: FTIR spectra of pure drug

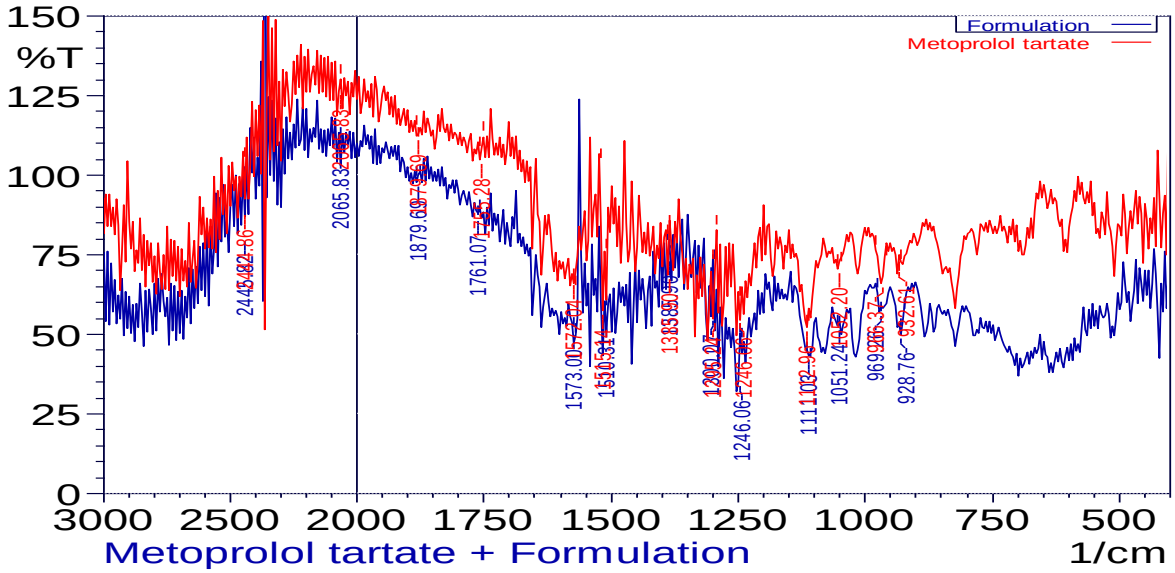

Figure. 2: FTIR spectra of Optimized formulation and drug

In-vitro drug release studies

In the development of fast dissolving tablets of MT the most important parameter that needs to be optimized is the disintegration time of tablets. The DT should be <3min according to official requirements, which all the tablets of MT fulfilled, they were <90secs.It is observed that the disintegration time of the tablets decreased with increase in the level of Croscarmellose sodium ($p \leq 0.05$). In case of tablets containing Crospovidone, increasing level of Crospovidone ($p \geq 0.05$) had no effect on the disintegration times of the tablets because it has excellent wicking nature though it swells only to a small extent. Crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, Crospovidone swells rapidly in water without gelling[17]. The mechanism involved in Croscarmellose sodium is when it comes into contact with water it swells to a large extent to disintegrate the tablets. Also it has fibrous nature that allows intra-particulate as well as extra particulate wicking of water even at low concentration levels.

From figure 3, the in-vitro drug release also increase with increase in the level of Croscarmellose sodium. While drug release didn't increased with increase in the level of Crospovidone. The rapid increase in dissolution of MT with the increase in Croscarmellose sodium may be attributed to rapid swelling and disintegration of tablet into apparently primary particles [18]. Crospovidone exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly but into larger masses of aggregated particles[18]. Thus, the differences in the size distribution generated and differences in surface area

exposed to the dissolution medium with different superdisintegrants rather than speed of disintegration of tablets may be attributed to the differences in *invitro* drug release with the same amount of superdisintegrants in the tablets. Thus, although the disintegration times were lower in Crospovidone containing tablets, were observed due to larger masses of aggregates[18].

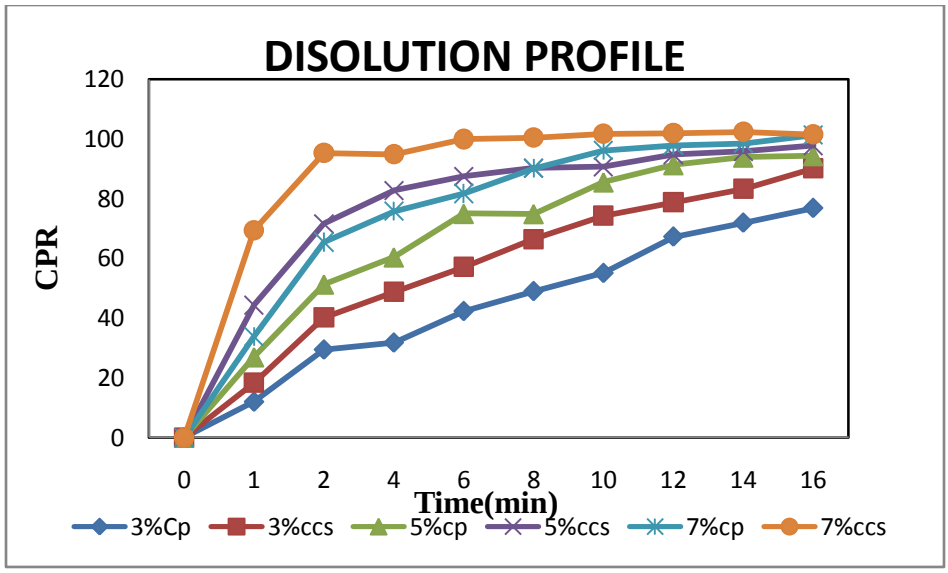

Figure 3: *In-vitro* drug release of MT formulations

Comparison of dissolution profiles of optimized batch in different media.

Figure 4 shows dissolution behavior of MT formulation F6 in phosphate buffer (pH 6.8), 0.1 N HCl for 21min.A basic drug undergoes better solubility/ionization in an acidic medium than a basic medium. An initial burst release of Metoprolol tartrate was observed more in 0.1 N HCl within 1 min. But after 2 mins drug Release was higher in 6.8 pH buffer than 0.1 N HCl. The values of similarity factor (f2) for the batch F6 showed f_2=52.57, f_1=14.09. The value indicates similar profiles for optimized batch in both the media.

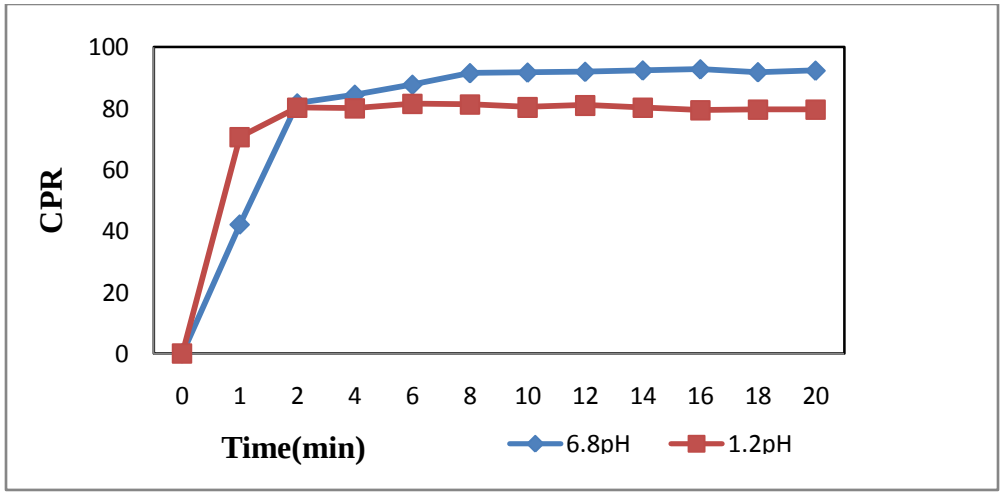

Figure 4: Comparison of dissolution profiles in two different media

Stability study

The stability study for all the formulations were carried according to ICH guidelines by storing the tablets in a stability chamber at 40° C± 20°C, 75 ± 5% RH for one month. There was no significant change in drug content, friability, hardness, cumulative drug release concluded from similarity factor and students t-test.

Table 4: *In vitro* Dissolution Data of Batch F6 after Accelerated Stability Study

Time (mins)	CPR (Initial)	CPR (After 1month)
1	69.49	65.49
2	95.39	90.21
4	94.88	92.42
6	99.97	96.15
8	100.59	99.28
10	101.73	99.01
12	102.08	100.49
14	102.42	101.89
16	101.63	100.15

Table 4 A: Parameters of Batch F6 after Accelerated Stability Study

Parameters	Zero time	After 1 month
Assay (%)	96.08	92.21
Friability (%)	0.107	0.043
Hardness (kg/cm^2)	4	3.8
Similarity Factor (f_2)	-	81.87
T calculated value	-	0.312
T table value	-	1.745

CONCLUSION

The popularity of FDTs has increased tremendously over the last decade. The key to FDT formulations is fast disintegration, dissolution, or melting in the mouth and this can be achieved by producing the porous structure of the tablet matrix or adding superdisintegrant and/or effervescent excipients. Overall, the results suggest that FDT of Metoprolol Tartrate containing superdisintegrants Croscarmellose sodium can be successfully formulated, the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.MT tablets containing Croscarmellose 7% superdisintegrant exhibit quick disintegration and improved drug dissolution was optimized.

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