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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF METOPROLOL TARTRATE BY SUBLIMATION METHOD

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ABSTRACT

Metoprolol tartrate is effective β-blocker which is having antianginal properties and used in the treatment of myocardial infarction. Oral bioavailability of metoprolol tartrate is around 40%. In present work an attempt has been made to prepare fast dissolving tablets of metoprolol tartrate to enhance the dissolution rate. Sublimation method was used to prepare the fast dissolving tablets by using different concentrations of superdisintegrants like indion-414, crospovidone, sodium starch glycolate, croscarmellose sodium. The blend was examined for the pre-compressional parameters and post-compressional parameters. Drug compatibility with excipients was checked by FTIR and DSC studies. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. In all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 99 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.00-2.90 kg/cm^2. The formulations F1, F8, F9 shows less *in vitro* dispersion time 18, 25, 19 sec respectively with rapid *in vitro* dissolution within 5 min. *In vitro* dispersion time decreases with increase in concentration of indion 414 upto 3% then dispersion time increases. Where as *in vitro* dispersion time decreases with increase in the concentration of croscarmellose sodium. No chemical interaction between drug and excipients was confirmed by DSC and FTIR studies. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. The results concluded that fast dissolving tablets of metoprolol tartrate showing enhanced dissolution will lead to improved bioavailability and effective therapy by using sublimation method.

KEY WORDS

Fast dispersible tablet, metoprolol tartrate, croscarmellose sodium, sodium starch glycolate, crospovidone, Indion 414.

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INTRODUCTION

Metoprolol tartrate is a selective beta1-adrenoreceptor blocking agent. Chemically 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. Oral bioavailability of metoprolol tartrate is around 40% and having half life 3 to 5 hrs.

Orodissolving tablets are those which disintegrate or dissolved in saliva without the need of water. As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. In such cases bioavailability of drug is significantly greater than those observed from conventional dosage form by avoiding first pass metabolism. Many patients express difficulty in swallowing tablets and hard gelatin capsules tending to non compliance and effective therapy. Recent advances in novel drug delivery systems aim to enhance safety and efficacy of the drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance[1,2].One such approach is orodispersible tablets, most pharmaceutical dosage form for oral administration are formulated to be swallowed or chewed in order to deliver the drug. The fast dissolving tablets known as melt-in-mouth tablet, rapimelts and mouth dissolving tablets or rapidly disintegrating tablets are the novel oral formulations aiming at fast disintegration and fast onset of action for required pharmacological action[3,4].

Literature survey revealed that delivery of metoprolol tartrate oral, intranasal route but no systematic previous report available on orodissolving tablet formulation. In present work mouth dissolving tablets of metoprolol tartrate are formulated by sublimation methods that disperse rapidly when placed below tongue. The basis of sublimation technique is to add inert solid ingredients that volatilize readily (eg camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation which generates a porous structure[13,14].Koizumi et al [13] applied the sublimation technique to prepare highly porous compressed tablets that were soluble in saliva. Mannitol and camphor were used as a tablet matrix material and subliming the material respectively. Camphor was iminated by subliming in vaccum at 80^0 C for 30 mins to develop pores in the tablets.

The main objective of present work was to develop fast dissolving metoprolol tartrate tablet by sublimation method and to study the effect of functionality differences of superdisintegrants on the tablet properties.

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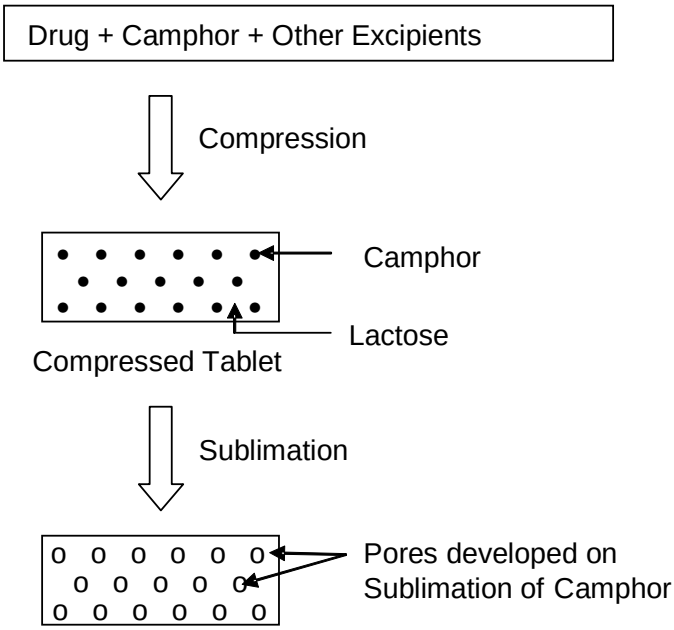

Figure 1: Schematics figure of Sublimation method for design of Mouth dissolving tablets

MATERIALS AND METHODS

Material

Metoprolol tartrate was obtained as a gift sample from Emcure pharma. Ltd., Pune. Directly compressible microcrystalline cellulose (MCC), camphor, crosscarmellose sodium (CCS), crosspovidone (CP), sodium starch glycolate (SSG), Indion 414, aspartame and mannitol (directly compressible) were obtained from Cipla pharma. Ltd. Vikroli, Mumbai. Other reagents were of analytical grade**.**

Methods

Preparation of fast dissolving tablets of metoprolol tartrate by sublimation method

Fast dissolving tablets of metoprolol tartrate were prepared by direct compression. All the ingredients were passed through # 44-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 8mm round flat punches on 10-station rotary tablet machine (Rimek). A batch of 30 tablets of each formulation was prepared for all the designed formulations. The compressed tablets were than subjected to sublimation at 80^0 C for 30 min. Different formulations were prepared by sublimation technique compositions of which are given in Table 1.

Evaluation of Metoprolol tartrate fast dissolving tablets

The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time, drug content, and stability studies. In weight variation[13] test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. The Pfizer

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hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded. Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge. The friability of tablets was determined using Roche friabilator (Cambel Electronics, Mumbai, India). Six tablets were tested from each formulation. For the content uniformity test[14], ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of metoprolol tartrate was extracted into distilled water and liquid was filtered (0.22 µm membrane filter disc (Millipore Corporation). The Metoprolol Tartrate content was determined by measuring the absorbance at 223 nm (using UV-vis spectrophotometer, Shimadzu 1700) after appropriate dilution with distilled water. 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[15] one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5ºC and the time required for complete dispersion was determined.

Wetting time and water absorption ratio (R)[16] were determined by using 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 (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b)/ w_b$$

Where w_b and w_a were tablet weights before and after water absorption, respectively.

In vitro dissolution studies[16] of the fast dissolving tablets of metoprolol tartrate formulation were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 µm membrane filter disc and analyzed for drug content by measuring the absorbance at 223 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates. Stability studies were carried out the tablets of the promising formulations were subjected to accelerated stability studies, by storing in amber colored rubber stopper glass vials at 40ºC/75% RH over a period of 3 months. At intervals of 1 month, the tablets were visually examined for any physical changes and evaluated for changes in drug content and *in vitro* dispersion time.

Characterization of metoprolol tartrate tablets

FTIR Studies: IR spectra for drug, tablets F1, F8 and F9 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC Studies: DSC scan of about 5mg, accurately weighed metoprolol tartrate and formulations were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan) Sealed and perforated aluminum pans were used in the experiments for all the samples. Temperature calibrations were performed using Indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C.

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RESULTS AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property is given in **Table 2**. The data obtained from post-compression parameters in all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 99 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.00-2.90 kg/cm^2. *In vitro* dispersion time, water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 18-48 sec, 48-85% and 37-50 sec respectively is given in **Table 3**. Sublimation techniques use to prepare highly porous compressed tablets (mentioned in Fig 1) that were rapidly soluble in saliva. Mannitol and camphor were used as tablet matrix material and subliming agent respectively. Camphor was removed by subliming in vacuum at 80º C for 30 minutes to develop porous structure. It is observed that *in vitro* dispersion time of tablets 18 sec with Indion 414 upto 3% and then, *in vitro* dispersion time increases. In case of CCS *in vitro* dispersion time of tablets were decreased from 33 sec - 25 sec with increase in concentration of CCS. However with SSG *in vitro* dispersion time increased with increase in concentration of SSG in tablets, at higher level, formation of viscous gel layer by SSG might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. In case of tablet containing CP increasing the level of CP had no much greater effect on in vitro dispersion times of the tablets. The dissolution profiles of formulations are shown in Fig 2 to 6. The stability study for tablets was carried out according ICH guidelines for 3 months. **Table 5** shows the parameters of tablets after stability studies. No appreciable change in physical characteristics of tablets.

In Fig 7 shows the IR spectrum of the pure drug metoprolol tartrate and formulations. Metoprolol tartrate has exhibited IR spectrum a broad band around 3454^{-1}cm which is the normal range of absorption for aliphatic hydroxyl group. Secondary imine (NH) has given a weak absorption in the form of a hump. Merged with aromatic C-H at 3030^{-1} cm and aliphatic C-H of CH_3 and OCH_3 at 2980^{-1} cm. The C-O absorption is found at 1589^{-1}cm. merged with C=C of aromatic. These data are in support of the structure of the drug taken for study.

The FTIR of F9 formulation (drug with CP) suggested there is no chemical reactions between the constituents present in the formulation by showing additional peaks in FTIR corresponding to various constituents a strong and broad peak as appear at 3402^{-1} cm due to the number of hydroxyl group present in the components of the formulation. So also very broad peak has been noticed at 2909^{-1}cm because of the number of aliphatic and aromatic C-H systems are present. The strong C=O is noticed near 1700 $^{-1}$cm and 1650^{-1}cm due to the C-O of the ketones and cyclic ketones. This indicates that during the formulation the components have not undergone any chemical reaction during any stage of tablet formulation.

The IR peak of F8 formulation (drug with CCS) is very similar to one obtain during the previous experiment. In this case also broad peaks were obtained around 3400 $^{-1}$cm and 2950 $^{-1}$cm and number of peaks around 1700 $^{-1}$cm suggesting that it is the IR of mixtures but not of any reaction product. In the F1 formulation (Drug with Indion 414), IR spectrum revealed that changes were not at all noticed suggesting that formulation process has not lead to any chemical reaction by changing their proportions. The pure drug characteristic absorption bands and formulations have shown all most same range. As there is no variation and shift in the position of

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characteristic absorption bands it can be justified there is no interaction between drug and polymer.

When the drug metoprolol tartrate is taken to study its properties at higher temperature it has exhibited melting shown in Fig 8 the peak at 123^0C with very little variation with the literature reported temperature. This is probably due to the error in experimental determination.

The F1 formulation was taken for DSC studies to understand its behavior, the mixture started melting at 163°C taking longer time to complete the process of melting at 165°C but the process of softening starts at 160°C suggesting that it takes almost 5°C to melt completely, so these slow melting process suggested it is mixture of the products but not the reaction product. During the formulation chemical reaction has not taken place to result into a single product.

The DSC studies of F9 formulation also suggested that it has not given sharp melting range but very broad range of melting process. These observations again support of idea that the tablet contains the constituents in an unreacted form not in a reaction product. The identical observation is also made in next experiment were croscarmellose sodium 12% is added instead of crospovidone suggesting that in all these formulations no chemical constituents has not undergone to give any reaction product.

Table 1.

The composition of metoprolol tartrate fast dissolving tablets.

Ingredient (mg)	Formulation code															
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Metoprolol tartrate	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Indion 414	6	12	18	24	-	-	-	-	-	-	-	-	-	-	-	-
CCS	-	-	-	-	6	12	18	24	-	-	-	-	-	-	-	-
CP	-	-	-	-	-	-	-	-	6	12	18	24	-	-	-	-
SSG	-	-	-	-	-	-	-	-	-	-	-	-	6	12	18	24
Camphor	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
MCC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
DC Mannitol	74	68	62	56	74	68	62	56	74	68	62	56	74	68	62	56

**** All the formulations contain 3 mg of MC, 15 mg of Aspartame, 2 mg of magnesium stearate, and 5mg of talc.**

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Table 2.
Pre-compression parameters of powder blend

Formulation code	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Angle of repose ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's Ratio ± SD, n=3
F1	0.49 ± 0.007	0.65 ± 0.01	31.25 ± 1.56	17 ± 1	1.30 ± 0.03
F2	0.52 ± 0.007	0.62 ± 0.01	32.02 ± 1.20	16 ± 1.51	1.19± 0.04
F3	0.53 ± 0.007	0.61 ± 0.02	33.1 ± 1.70	13 ± 1.20	1.15 ± 0.03
F4	0.53 ± 0.007	0.64 ± 0.01	32.20 ± 0.88	17 ± 2.51	1.20 ± 0.03
F5	0.50 ± 0.007	0.63 ± 0.01	32.43 ± 1.48	20 ± 1.58	1.26 ± 0.03
F6	0.54 ± 0.007	0.65 ± 0.02	32.72 ± 1.22	16 ± 1.55	1.20 ± 0.04
F7	0.52 ± 0.007	0.63 ± 0.38	34.87 ± 1.32	17 ± 1.39	1.21 ± 0.04
F8	0.51 ± 0.007	0.62 ± 0.02	33.04 ± 1.34	17 ± 2.20	1.21 ± 0.03
F9	0.53 ± 0.007	0.63 ± 0.01	32.28 ± 1.26	15 ± 2.01	1.18 ± 0.03
F10	0.52 ± 0.007	0.65 ± 0.01	33.52 ± 1.20	18 ± 2.12	1.25 ± 0.04
F11	0.51 ± 0.007	0.62 ± 0.02	34.19 ± 1.26	17 ± 1.51	1.21 ± 0.03
F12	0.55 ± 0.007	0.65 ± 0.01	32.26 ± 1.20	15 ± 1.39	1.14 ± 0.03
F13	0.52 ± 0.007	0.62 ± 0.02	33.03 ± 1.56	16 ± 1.20	1.19 ± 0.04
F14	0.53 ± 0.007	0.63 ± 0.01	33.72 ± 1.41	15 ± 1.67	1.18 ± 0.02
F15	0.51 ± 0.007	0.62 ± 0.02	32.85 ± 1.33	17 ± 1.41	1.21 ± 0.03
F16	0.53 ± 0.007	0.64 ± 0.02	34.14 ± 1.67	17 ± 2.51	1.20 ± 0.03

Note: Values in parenthesis are standard deviation (±SD)

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Table 3.
Post-compression parameters of fast dissolving tablets.

Formulation code	Hardness ± SD, n=3	Friability ± SD, n=3	Water absorption ratio ± SD, n=3	Drug content* ± SD, n=3	Wetting time ± SD, n=3	*In vitro* dispersion time (sec) ± SD, n=3	Thickness ± SD, n=3
F1	2 ± 0.11	0.58 ±0.12	85 ± 1	99.18 ± 0.72	37 ± 2.51	18 ± 2.78	4.69 ±0.12
F2	2.1 ± 0.11	0.54 ± 0.11	82 ± 1.52	99.81 ± 1.07	39 ± 2.0	21 ± 1.0	4.82 ±0.15
F3	2.3 ± 0.10	0.75 ± 0.13	81 ± 1.35	99.54 ± 0.50	48 ± 2.40	22 ± 1.0	4.74 ±0.10
F4	2.2 ± 0.12	0.57 ±0.11	78 ± 1.58	98.12 ± 0.73	40 ± 1.89	26 ± 2.0	4.85 ± 0.10
F5	2.8 ± 0.18	0.51 ± 0.12	67 ± 1.21	99.30 ± 0.87	50 ± 2.20	33 ± 1.5	4.59 ± 0.17
F6	2.1 ± 0.10	0.68 ±0.09	70 ± 1.57	99.23 ± 0.90	48 ± 1.0	30 ± 1.7	4.69 ± 0.15
F7	2.1 ± 0.15	0.65 ± 0.07	72 ± 1.20	100.03 ± 1.07	43 ± 2.25	27 ± 2.8	4.72 ± 0.12
F8	2.1 ± 0.21	0.58 ± 0.06	80 ± 1.05	99.63 ± 0.39	41 ± 2.15	25 ± 1.45	4.58 ± 0.09
F9	2.1 ± 0.10	0.59 ± 0.07	81 ± 1.73	99.50 ± 0.77	40 ± 1.0	19 ± 1.28	4.67 ± 0.19
F10	2.4 ± 0.21	0.75 ± 0.11	58 ± 1.85	99.96 ± 0.27	42 ± 2.25	22 ± 1.11	4.72 ± 0.21
F11	2.5 ± 0.15	0.69 ± 0.13	63 ± 1.88	99.56±0.76	40 ± 1.75	30 ± 2.15	4.78 ± 0.15
F12	2 ± 0.10	0.58 ± 0.14	57 ± 1.15	100.09±0.76	41 ± 1.35	38 ± 1.55	4.71 ± 0.25
F13	2.3 ± 0.05	0.60 ± 0.13	60 ± 1.18	100.65±1.23	42 ± 1.21	43 ± 2.10	4.60 ± 0.14
F14	2.2 ± 0.20	0.77 ± 0.08	55 ± 1.08	99.08±2.65	47 ± 1.79	37 ± 1.21	4.73 ± 0.28
F15	2.4 ± 0.15	0.73 ± 0.07	52 ± 1.05	100.76±0.33	49 ± 1.71	48 ± 1.08	4.79 ± 0.20
F16	2.6 ± 0.42	0.81 ± 0.07	48 ± 1.81	99.99±1.79	42 ± 2.41	44 ± 2.0	4.63 ± 0.08

Note: Values in parenthesis are standard deviation (±SD)

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Table 4.
Results of stability studies of fast dissolving tablets of metoprolol tartrate.

Formulation code	Hardness ± SD, n=3	Friability ± SD, n=3	Drug content* ± SD, n=3	*In vitro* dispersion time (sec) ± SD, n=3
F1	2.0 ± 0.16	0.56 ± 0.14	99.16 ± 0.74	19 ± 2.66
F2	2.1 ± 0.14	0.52 ± 0.12	99.84 ± 1.072	22 ± 1.1
F3	2.3 ± 0.18	0.73 ± 0.11	99.56 ± 0.54	23 ± 1.4
F4	2.2 ± 0.14	0.56 ± 0.14	98.14 ± 0.71	27 ± 2.1
F5	2.8 ± 0.14	0.52 ± 0.10	99.32 ± 0.84	35 ± 1.4
F6	2.1 ± 0.16	0.66 ± 0.098	99.25 ± 0.88	32 ± 1.6
F7	2.1 ± 0.14	0.63 ± 0.09	100.01 ± 1.02	29 ± 2.4
F8	2.1 ± 0.20	0.56 ± 0.04	99.68 ± 0.34	28 ± 1.6
F9	2.1 ± 0.12	0.57 ± 0.04	99.54 ± 0.84	21 ± 1.12
F10	2.4 ± 0.18	0.73 ± 0.10	99.94 ± 0.24	24 ± 1.22
F11	2.5 ± 0.14	0.67 ± 0.13	99.58 ± 0.74	34 ± 2.11
F12	2.0 ± 0.12	0.57 ± 0.12	100.04 ± 0.73	40 ± 1.22
F13	2.3 ± 0.05	0.62 ± 0.11	100.04 ±1.12	45 ± 2.00
F14	2.2 ± 0.22	0.78 ± 0.07	99.01 ± 2.13	39 ± 1.18
F15	2.4 ± 0.16	0.74 ± 0.47	100.22 ± 0.34	49 ± 1.12
F16	2.6 ± 0.32	0.80 ± 0.09	99.94 ± 1.44	46 ± 2.2

Note: Values in parenthesis are standard deviation (±SD)

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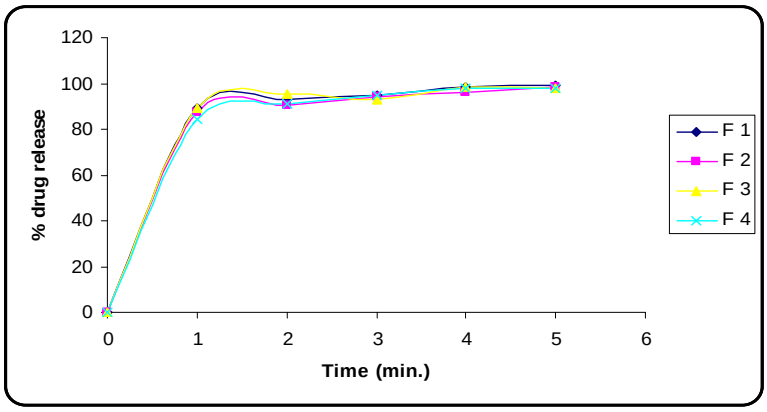

Figure 2. Dissolution profiles of formulations F1 – F4

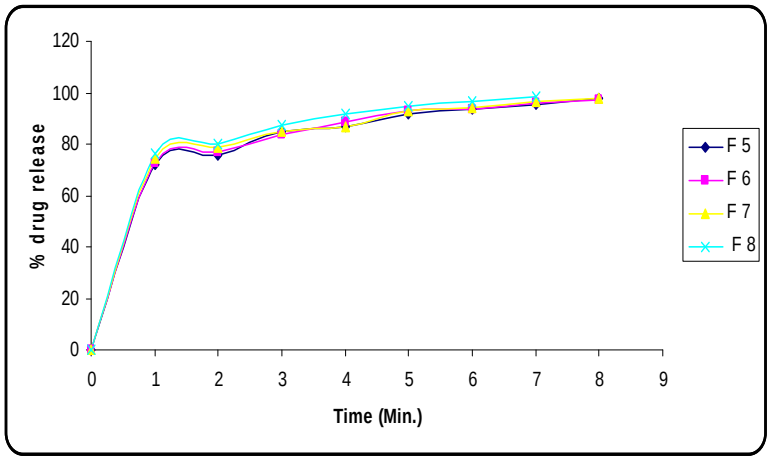

Figure 3. Dissolution profiles of formulations F5 - F8

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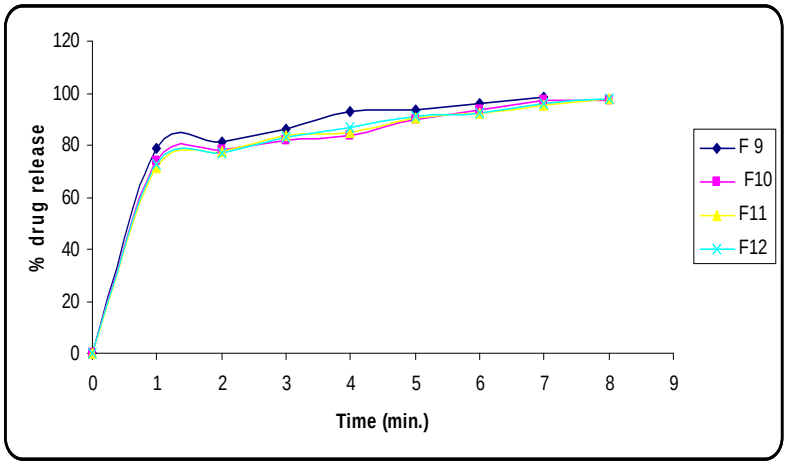

Figure 4. Dissolution profiles of formulations F9 – F12

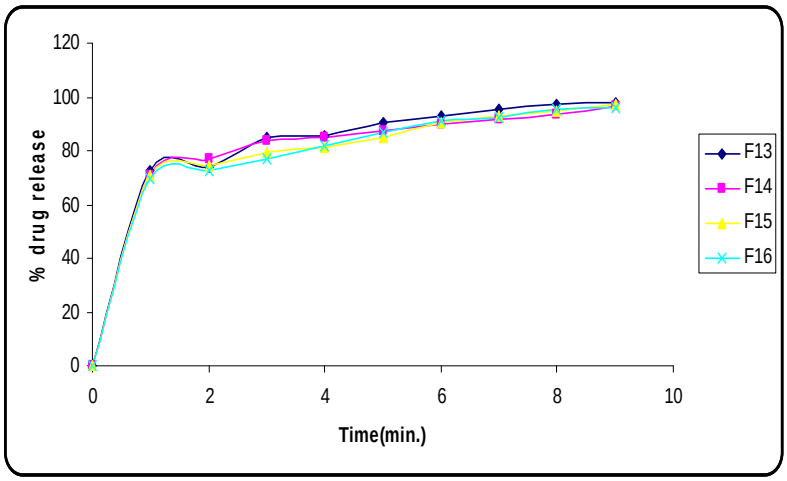

Figure 5. Dissolution profiles of formulations F13 – F16

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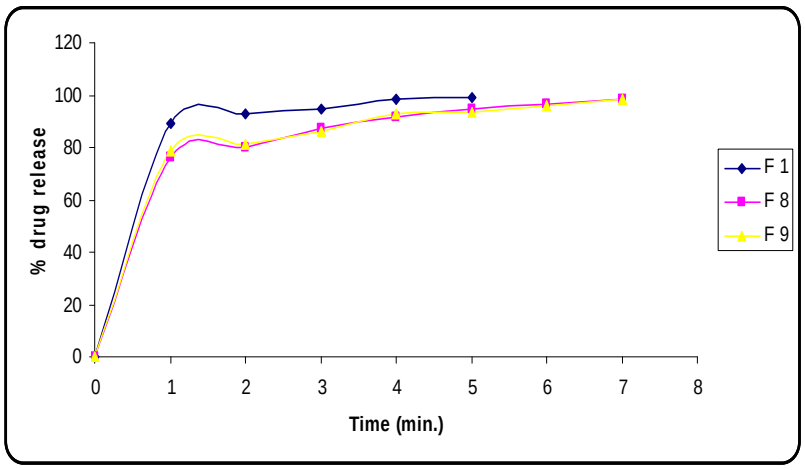

Figure 6. Dissolution profiles of best formulations F1, F8, and F9.

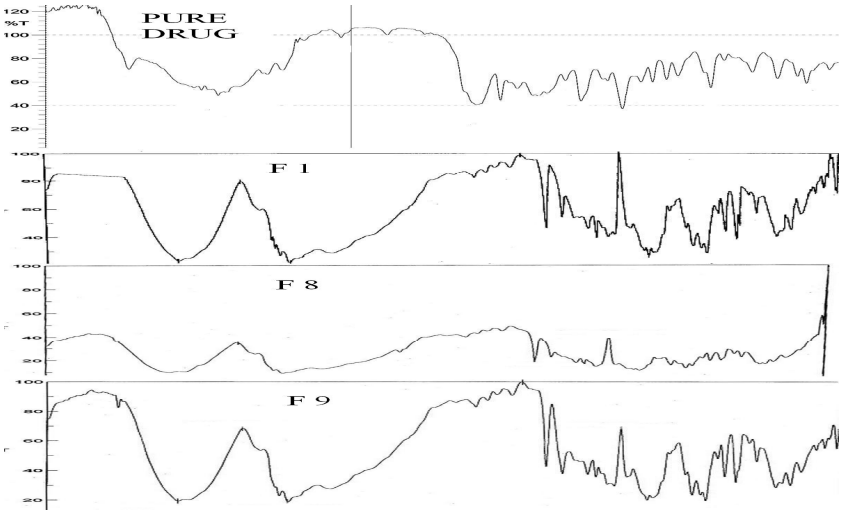

Figure 7. IR spectrum of Metoprolol tartrate, IR spectrum of formulations F1, F8, F9.

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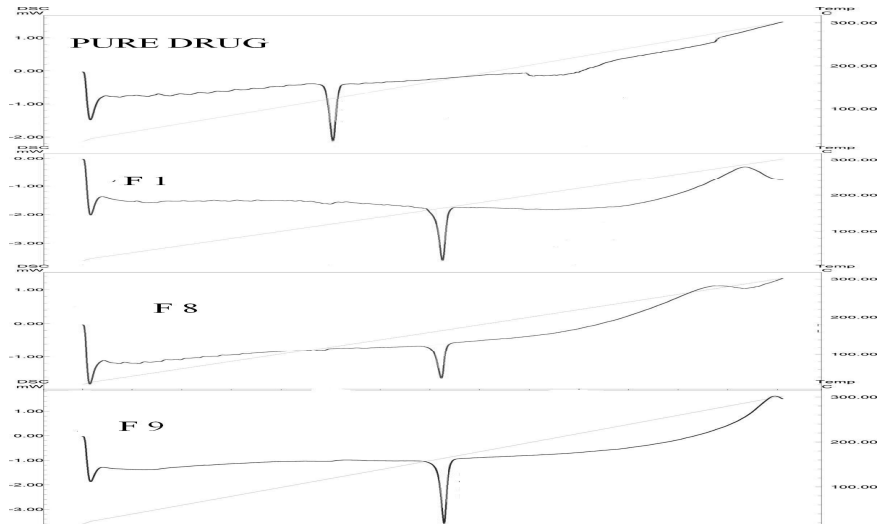

Figure 8. DSC thermograms of Metoprolol tartrate, formulations F1, F8, F9.

CONCLUSION

In present study, different concentrations of superdisintegrants with camphor differed in their ability to disintegrate the metoprolol tartrate tablets. Such difference can potentially affect drug dissolution and is proposed as model formulation for disintegrants performance testing and quality control purposes. The results concluded that fast dissolving tablets of metoprolol tartrate showing enhanced dissolution will lead to improved bioavailability and effective therapy by using sublimation method, and F1 best promising formulation.

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