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Research Article

Design and characterization of mouth dissolving tablets of Metoprolol Tartrate

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ABSTRACT

The demand for mouth dissolving tablet (MDT) has been growing during the last decade especially for elderly and children who have swallowing difficulties. Metoprolol tartrate is a selective beta1-adrenoreceptor blocking agent used in Essential hypertension, prevention after a myocardial infarction, tachycardia, coronary heart disease, treatment of heart failure. Oral bioavailability of metoprolol tartrate is around 40% and having half life 3 to 5 hrs. In present work an attempt has been made to prepare mouth dissolving tablets of metoprolol tartrate with increased rate of dissolution may leads to increase bioavailability. Mouth dissolving tablet of metoprolol tartrate prepared using Indion 414, croscarmellose sodium and crospovidone as superdisintegrants by direct compression and sublimation methods. The tablets prepared were evaluated for various parameters like weight variation, hardness, friability, *in vitro* dispersion time, drug-polymer interaction, drug content water absorption ratio, wetting time, *in vitro* drug release, FTIR and DSC studies and short term stability studies. The tablets prepared by direct compression method possess a weight variation in the range 196 to 205 mg which is below ± 7.5%, hardness of 2.0 to 3.0Kg/cm², percentage friability of 0.54 to 0.81 %, *in vitro* dispersion time of 21 to 59 sec, drug content uniformity was in between 99.08 to 100.76%, water absorption ratio of 46.77 to 85.64%, wetting time of 37 to 50 sec, and *in vitro* drug release showed 69.12% --- 99.83% within 9 min. IR spectral analysis and DSC study showed that there was no drug interaction with formulation additives of the tablet, short term stability studies on the formulations indicated that there are no significant change in hardness, friability, drug content and *in vitro* drug release. ($p<0.05$). Similarly the tablets prepared by sublimation method possess a weight variation in the range 197 to 204 mg which is below ± 7.5%, hardness of 2.1 to 2.9 kg/cm², *in vitro* dispersion time of 18 to 48 sec. IR spectral analysis the pure drug characteristic absorption bands and formulations absorption bands have shown all most same range. As there is no variation and shift in the position of characteristic absorption bands it can be justified there is no interaction between drug and polymer. The DSC study during the formulation chemical reaction has not taken place to result into a single product. The DSC results shows that there was no drug interaction with the formulation additives of the tablet, drug content uniformity was in between 98.56 to 100.65%, water absorption ratio showed 51.15 to 85.15%, wetting time between 37 to 50 sec and *in vitro* drug release of 72.88 to 99.75% within 9 min respectively. Short term stability studies on the formulations indicated that there are no significant changes in drug content and in *in vitro* drug release ($p<0.05$). 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.

Keywords: Fast dispersible tablet; Metoprolol tartrate; croscarmellose sodium; sodium starch glycolate; crospovidone; indion 414; *in vitro* dispersion

INTRODUCTION

Solid dosage forms like tablet and capsule are most popular and preferred drug delivery system because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing and good physical and chemical stability (Sameer et al., 2008). Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. The scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects: 1. Physicochemical, pharmacokinetic and pharmacody---

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namic characteristics of the drug, 2. The anatomic and physiologic characteristics of the GIT, and 3. Physico-chemical characteristics and the drug delivery mode of the dosage form to be designed (Chien YW, 1992). Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional tablets and capsules. In case of motion sickness (kinetosis) water is not available and sudden episodes of coughing during the common cold, allergic conditions and bronchitis (Watanabe et al., 1995). For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people (Yonezawa et al., 1999). Many patient find difficulty to swallow tablet and hard gelatin capsule, consequently they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which result high incident of incompliance and ineffective therapy (Abdelbary et al., 2004). In the recent past, several new advanced technologies have been introduced for the formulation of mouth dissolving tablets (MDTs) with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients. The technologies utilized for fabrication of Mouth dissolving drug delivery systems includes lyophilization (Virely et al., 1990), moulding (Pebley et al., 1994), direct compression (Watanabe, 1995), cotton candy process (Myers GL et al., 1995), spray drying (Allen LV, Wang B, 1996), sublimation (Koizumi KI et al., 1997), mass extrusion (Bhaskaran S, Narmada GV, 2002), nanonization and quick dissolve film formation (Bess WS et al., 2006). These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability.

Metoprolol tartrate is a β1 selective antagonist. It suppresses the activation of the heart by blocking β1 adrenoreceptors and they reduce the work of the heart by decreasing cardiac output and blood pressure. Metoprolol is readily and completely absorbed from the gastrointestinal tract, but is subjected to very considerable first-pass metabolism in the liver and the bioavailability is only about 38 %. Peak plasma concentrations vary widely and occur about 1.5 to 2 h after a single oral dose. Various techniques can be used to formulate orodispersible tablets or fast dissolving tablets. Direct compression and sublimation are the techniques require incorporation of a superdisintegrants into the formulation to achieve fast tablet disintegration. The aim of purpose work was to formulate and characterization mouth dissolving tablets of Metoprolol tartrate for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of hypertension.

MATERIALS AND METHODS

Metoprolol tartrate was obtained as gift from Emcure pharma (Pune, India), Croscarmellose sodium and Sodium starch glycolate as gift from Signet (Mumbai, India), Crospovidone and aspartame from Cipla (Kurkhumb), Microcrystalline cellulose, Mannitol, Camphor, Magnesium stearate and all other chemicals were used are procured from SD fine Chem Ltd. (Mumbai, India). The mouth dissolving tablets of Metoprolol tartrate were prepared by direct compression and sublimation method.

Drug-Polymer compatibility studies by FTIR and DSC

Drug- Polymer compatibility studies were performed by Fourier transform infrared spectroscopy (FTIR) (Alagusundaram M et al., 2011)and Differential scanning colorimetry (DSC) (Sachan NK et al., 2012). In order to confirm that the entrapment of drug within the polymeric systems involves only the physical process and no interaction between the drug and polymer, FTIR absorption spectra and DSC curve of pure drug and all the polymers used for the formulation and the combination of drug and polymer were analyzed shown no significant interaction between the drug and polymers. The FTIR spectra and DSC curve are shown in figures 1-3, 4 and 5 respectively.

Preparation of mouth dissolving tablets by direct compression technique

Mouth dissolving tablets of Metoprolol tartrate were prepared by direct compression method according to the formula given in table. All the ingredients were passed through 60 mesh sieve separately. The drug and microcrystalline cellulose was mixed by small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed of 8 mm sizes flat round punch to get tablet using Rimek Compression machine. The composition of Metoprolol tartrate mouth dissolving tablets prepared by direct compression technique was presented in the table 1.

Preparation of mouth dissolving tablets by sublimation method

Metoprolol tartrate tablets were prepared by sublimation technique. The basic principle involved in preparing mouth dissolving tablets by sublimation technique is inert solid ingredients (E.g. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. The tablets dissolve

within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Sixteen formulations were developed by varying concentration of subliming agent i.e. camphor. Accurately weighed ingredients were sifted through sieve no. 44 and thoroughly mixed for 10 min. The magnesium stearate and other ingredients were added to the blend and thoroughly mixed. The tablets were compressed using Rimek tablet punching machine. The compressed tablets were then subjected to sublimation at 80°C for 30 min. The schematic pro---cess was shown in the figure 6 and the composition of Metoprolol tartrate mouth dissolving tablets prepared by sublimation method were presented in the table 2.

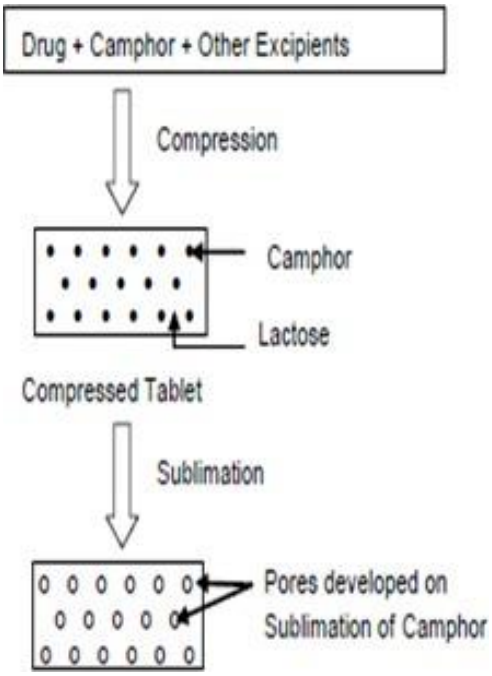

Figure 1: Schematics process of sublimation method for design of mouth dissolving tablets

Physiochemical evaluation of buccoadhesive bilayerd tablets

The powder materials used for the various formula---tions were evaluated for its micoromeritic properties (Bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio) and the prepared tablets were evaluated for physicochemical parameters of hardness, friability, thickness, weight variation and content uniformity as per the procedure stated in ac---credited pharmacopoeia (Alagusundaram M et al., 2011, The united states pharmacopoeia, 2005). The results were presented in the table 3, 4 and 5, 6 re---spectively.

Wetting time

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petridish (i.d. = 6.5 cm) containing 10 ml of wa---ter, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined (Yunxia B et al., 1996).

***In vitro* dispersion time**

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.

Water absorption ratio (R)

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. Wa---ter 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**

Dissolution rate was studied by using USP type-II appa---ratus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C; aliquot of dissolution medium was withdrawn at every 1 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 223 nm and concentra---tion of the drug was determined from standard calibra---tion curve.

Stability studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to re---main within its physical, chemical, therapeutic and tox---icological specifications. 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 an light and enables recom-mended storage conditions, re-test periods and shelf lives to be established. ICH specifies the length of study and storage conditions: Long term testing 25°C ± 2° C / 60 % RH ± 5 % for 12 months, Accelerated testing 40°C ±2 °C / 75 % RH ± 5 % for 6 months and In the present study, stability studies were carried out at25°C/ 60% and 40° C / 75 % RH for a specific time period up to 6 months for the selected formulations (Dandagi PM et al., 2005).

RESULTS AND DISCUSSION

The main objective of this research was to design and characterize mouth dissolving tablets of Metoprolol tartrate prepared by direct compression and sublima---tion method using different superdisintegrants such as Indion 414, crospovidone, Sodium Starch Glycolate and

Table 1: Composition of Metoprolol tartrate mouth dissolving tablets prepared by direct compression method

Ingredients	DCI_1 (mg)	DCI_2 (mg)	DCI_3 (mg)	DCI_4 (mg)	DCC_1 (mg)	DCC_2 (mg)	DCC_3 (mg)	DCC_4 (mg)	DCP_1 (mg)	DCP_2 (mg)	DCP_3 (mg)	DCP_4 (mg)	DCS_1 (mg)	DCS_2 (mg)	DCS_3 (mg)	DCS_4 (mg)
Metoprolol tartrate	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Indion	6	12	18	24	--	--	--	--	--	--	--	--	--	--	--	--
CCS	--	--	--	--	6	12	18	24	--	--	--	--	--	--	--	--
CP	--	--	--	--	--	--	--	--	6	12	18	24	--	--	--	--
SSG	--	--	--	--	--	--	--	--	--	--	--	--	6	12	18	24
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Methyl cellulose	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
D-Mannitol	94	88	82	76	94	88	82	76	94	88	82	76	94	88	82	76
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Composition of Metoprolol tartrate mouth dissolving tablets prepared by sublimation method

Ingredients	SBI_1 (mg)	SBI_2 (mg)	SBI_3 (mg)	SBI_4 (mg)	SBC_1 (mg)	SBC_2 (mg)	SBC_3 (mg)	SBC_4 (mg)	SBP_1 (mg)	SBP_2 (mg)	SBP_3 (mg)	SBP_4 (mg)	SBS_1 (mg)	SBS_2 (mg)	SBS_3 (mg)	SBS_4 (mg)
Metoprolol tartrate	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Indion	6	12	18	24	--	--	--	--	--	--	--	--	--	--	--	--
CCS	--	--	--	--	6	12	18	24	--	--	--	--	--	--	--	--
CP	--	--	--	--	--	--	--	--	6	12	18	24	--	--	--	--
SSG	--	--	--	--	--	--	--	--	--	--	--	--	6	12	18	24
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Camphor	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Methyl cellulose	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
D-Mannitol	74	68	62	56	74	68	62	56	74	68	62	56	74	68	62	56
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Croscarmellose sodium in varying proportions. The powder blend is evaluated for its micromeritic properties and the prepared tablets were evaluated for physicochemical parameters of hardness, friability, thickness, weight variation and content uniformity. The obtained results were complying with the standards specified in accredited pharmacopoeia. The results were presented in the table 3, 4 and 5, 6 respectively.

Drug- Polymer compatibility studies were performed by Fourier transform infrared spectroscopy (FTIR) and Differential scanning colorimetry (DSC). FTIR absorption spectra and DSC curve of pure drug and all the polymers used for the formulation and the combination of drug and polymer were analyzed shown no significant interaction between the drug and polymers. The FTIR spectra and DSC curve are shown in figures 1-3, 4 and 5 respectively.

The *in vitro* dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion within several minutes was observed in all the formulations. The *in vitro* dispersion time of metoprolol tartrate prepared by direct compression and sublimation method were found to be in the range of 18 to 59 sec fulfilling the official requirements. Based on the *in vitro* disintegration time, formulation DCI_1 (9% Indion 414) and SBI_3 (3% Indion 414) were found to be promising and showed a dispersion time of 21 and 18 sec respectively (Amin P et al., 2006). Disintegrating study showed that the disintegrating times of the tablets decreased with increase in the concentration of croscarmellose sodium, crospovidone and indion-414. However, disintegration times increased with increase in the concentration sodium starch glycolate in the tablets. It indicates that increase in the concentration sodium starch glycolate had a negative effect on the disintegration of the tablets. The results are in consistent with other results (Martino PD et al., 2005, Bhagawati ST et al., 2005). The results of comparison of Indion 414, CCS, SSG, CP superdisintegrants in the mouth dissolving tablets showed that the Indion 414 shows least disintegration time for the Roxithromycin, Dicyclomine and Montelukast sodium. In case of Aceclofenac mouth 26 dissolving tablets *in vitro* dispersion time of tablet deceased from (41-34 sec) with increase in concentration of CCS. *In vitro* dispersion time increased with increase in concentration of sodium starch glycolate 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. In case of mouth

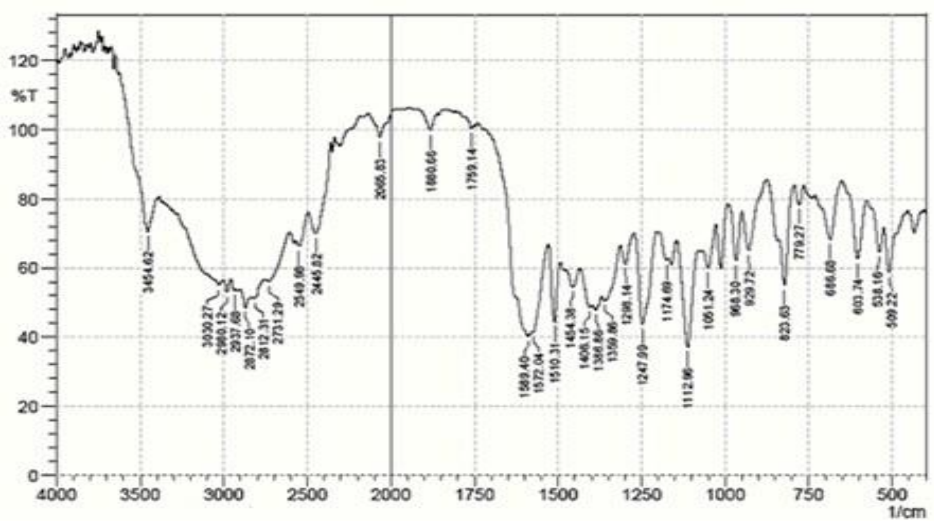

Figure 2: FTIR spectra of Metoprolol tartrate

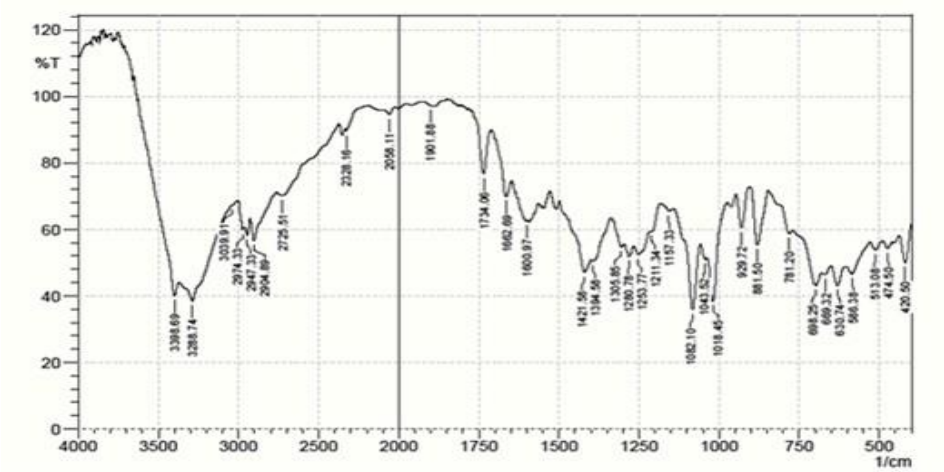

Figure 3: FTIR spectra of formulation (DCl_3)

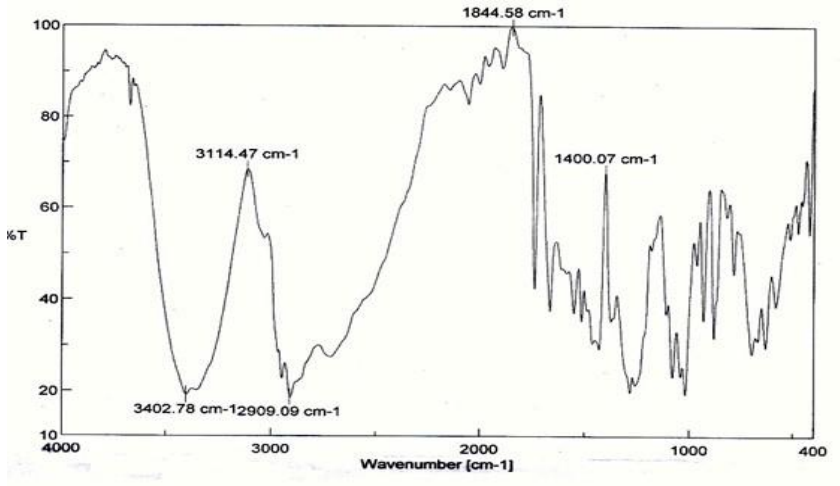

Figure 4: FTIR spectra of formulation (SBI1)

dissolving tablets of carbamazepine the CCS shows least *in vitro* dispersion time with increasing the con---centration of CCS in comparison with Indion 414, CP, SSG (Zhao NA et al., 2005). The disintegration times of crospovidone and indion-414 containing tablets are comparatively lower than tablets containing croscar---mellose sodium and sodium starch glycolate due to its rapid capillary activity and pronounced hydration with little tendency to gel formation with crospovidone. Thus, these results suggest that the disintegration times can be decreased by using wicking type disinte---grants (crospovidone). As the method of preparation of tablets changed to sublimation, the disintegration time decreased significantly regardless of the diluent used.

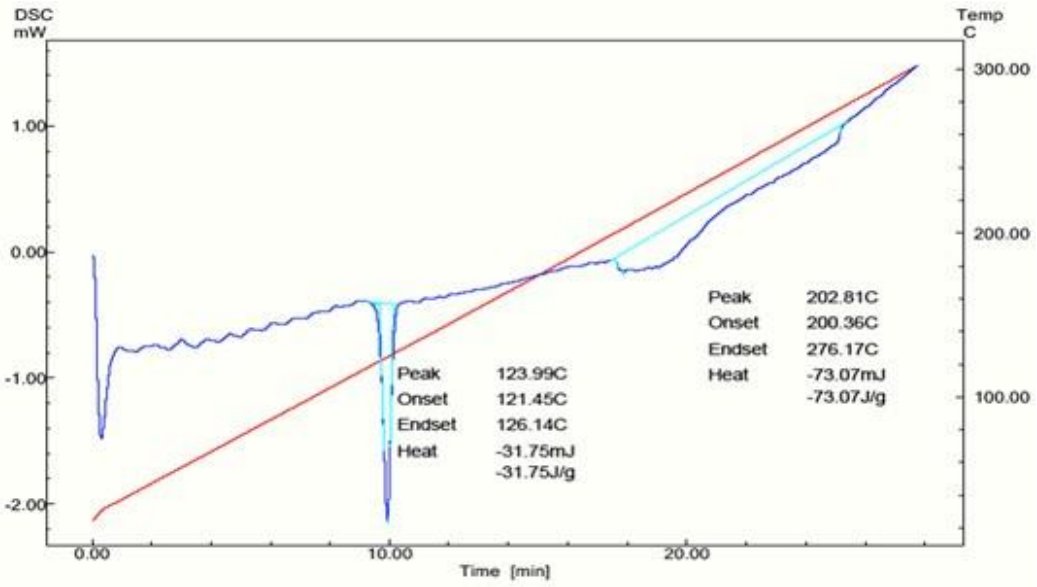

Figure 5: DSC curve of Metoprolol tartrate

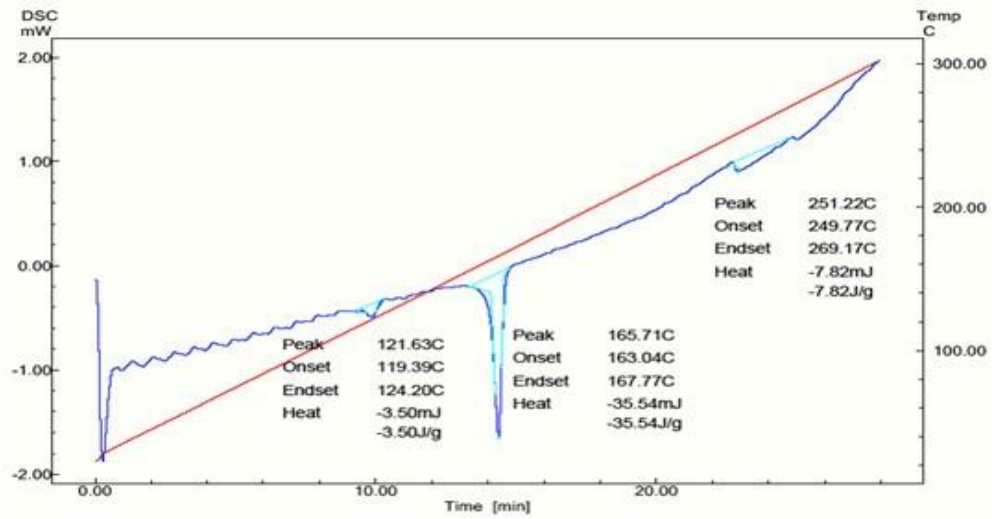

Figure 6: DSC curve of formulation (DCI_3)

It is because tablets prepared by sublimation method rapidly exhibits high pores and disintegrate the tablet rapidly. Above results shows that tablets prepared with 5 % superdisintegrant and 20 % camphor (sublimation method) showed least disintegration time in comparison with the all other formulations because of their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates wicking action of croscarmellose sodium in bringing about faster disintegration (Kaushik D et al., 2004).

The wetting time of metoprolol tartrate prepared by direct compression and sublimation method were found to be in the range of 37 to 50 sec. Promising formulations DCI_3 (9% Indion 414) and SBI_1 (3% Indion 414) showed a wetting time of 48 and 37 sec respectively, which facilitate the faster dispersion in the mouth. The formulations prepared by both the technique shows wetting time in the range 48 to 85 % formulations containing only 3% of superdisintegrant shows lower water absorption ratio when compared to formulations 12% of superdisintegrant, the water absorption ratio also decreases due to less swelling property. It was observed that as concentrations of CCS increases water absorption ratio increases due to CCS is made by cross- linking reaction of sodium CMC (Chaudhari PD et al., 2007). The post compressional parameters of *in vitro* dispersion time, wetting time and water absorption ratio results of the tablets prepared by direct compression and sublimation were presented in the table 7 and respectively.

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50rpm) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C; aliquot of dissolution medium was withdrawn at every 1 minute interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 223nm and concentration of the drug was determined from standard calibration curve. These values changed with change of method of preparation of tablets (Wade A and Weller PJ, 1994).

Table 3: Micromeritic properties of powder blend for direct compression

Formulation code	Bulk density (gm/cc) ±SD, n=3	Tapped density (gm/cc) ±SD, n=3	Angle of repose(θ) ±SD, n=3	Carr's index (%) ±SD,n=3	Hausner's ratio ±SD, n=3
DCI_1	0.52±0.007	0.63±0.01	29.25±1.56	17±1	1.21±0.03
DCI_2	0.53±0.007	0.63±0.01	30.02±1.56	15±1.51	1.18±0.04
DCI_3	0.53±0.007	0.64±0.01	30.1±1.56	17±1.20	1.20±0.03
DCI_4	0.55±0.007	0.65±0.01	30.20±1.56	15±2.51	1.18±0.03
DCC_1	0.50±0.007	0.63±0.01	28.43±1.56	20±1.58	1.26±0.03
DCC_2	0.52±0.007	0.62±0.01	30.72±1.56	17±1.55	1.21±0.04
DCC_3	0.51±0.007	0.65±0.01	29.87±1.56	17±1.39	1.20±0.03
DCC_4	0.54±0.007	0.62±0.01	28.04±1.56	16±2.20	1.19±0.03
DCP_1	0.52±0.007	0.63±0.01	26.08±1.56	16±2.01	1.21±0.04
DCP_2	0.52±0.007	0.64±0.01	27.52±1.56	17±2.12	1.18±0.03
DCP_3	0.54±0.007	0.65±0.01	29.16±1.56	15±1.51	1.04±0.03
DCP_4	0.55±0.007	0.62±0.01	28.26±1.56	15±1.39	1.19±0.04
DCS_1	0.52±0.007	0.62±0.01	29.03±1.56	16±1.20	1.18±0.02
DCS_2	0.53±0.007	0.63±0.01	28.72±1.56	15±1.67	1.21±0.03
DCS_3	0.51±0.007	0.62±0.01	28.58±1.56	17±2.51	1.18±0.02
DCS_4	0.52±0.007	0.63±0.01	30.14±1.56	17±2.54	1.21±0.03

Table 4: Micromeritic properties of powder blend for sublimation

Formulation code	Bulk density (gm/cc) ±SD, n=3	tapped density (gm/cc) ±SD, n=3	Angle of repose (θ) ±SD, n=3	Carr's index(%) ±SD, n=3	Hausner's ratio ±SD, n=3
SBI_1	0.52 ± 0.007	0.65 ± 0.01	29.25±1.56	20±1	1.31±0.03
SBI_2	0.55±0.007	0.63±0.01	30.02±1.56	12±1.51	1.18±0.04
SBI_3	0.43±0.007	0.64±0.01	30.1±1.56	17±1.20	1.20±0.03
SBI_4	0.45±0.007	0.65±0.01	30.20±1.56	15±2.51	1.18±0.03
SBC_1	0.50±0.007	0.63±0.01	28.43±1.56	20±1.58	1.26±0.03
SBC_2	0.52±0.007	0.62±0.01	30.72±1.56	17±1.55	1.21±0.04
SBC_3	0.51±0.007	0.65±0.01	29.87±1.56	17±1.39	1.20±0.03
SBC_4	0.54±0.007	0.62±0.01	28.04±1.56	16±2.20	1.19±0.03
SBP_1	0.52±0.007	0.63±0.01	26.08±1.56	16±2.01	1.21±0.04
SBP_2	0.52±0.007	0.64±0.01	27.52±1.56	17±2.12	1.18±0.03
SBP_3	0.54±0.007	0.65±0.01	29.16±1.56	15±1.51	1.04±0.03
SBP_4	0.55±0.007	0.62±0.01	28.26±1.56	15±1.39	1.19±0.04
SBS_1	0.52±0.007	0.62±0.01	29.03±1.56	16±1.20	1.18±0.02
SBS_2	0.53±0.007	0.63±0.01	28.72±1.56	15±1.67	1.21±0.03
SBS_3	0.51±0.007	0.62±0.01	28.58±1.56	17±2.51	1.18±0.02
SBS_4	0.52±0.007	0.63±0.01	30.14±1.56	17±2.54	1.21±0.03

In case of tablets prepared by direct compression technique the $t_{50\%}$ and $t_{90\%}$ values decreased with in---crease in the concentration of croscarmellose sodium, Crospovidone and Indion-414. However, t_{50}% and t_{90}% values increased with increase in concentration of so---dium starch glycolate. The rapid increase in dissolution of metoprolol tartrate with the increase in croscarmel---lose sodium may be due to rapid swelling and disinte---grating tablets rapidly into apparently primary particles (Zhao N and Augsburger LL, 2005). While tablets for---mulated with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling into primary particle but more slowly due to the formation of a viscous gel layer by sodium starch glycolate, Crospovidone and Indion-414 containing tablets rapidly exhibits high capillary activity and pro---nounced hydration with a little tendency to gel for---mation and disintegrates the tablets rapidly but into larger masses of aggregated particles (Shimizu T et al., 2003, Bolhuis GK et al., 1997).Thus difference in the size distribution generated with different superdisinte---grants might have contributed to difference in the $t_{50\%}$ and $t_{90\%}$ values with the same amount of superdisinte---grants in the tablets. Although, disintegration times are lesser in Crospovidone and Indion-414 containing tab---lets, comparatively higher $t_{50\%}$ and $t_{90\%}$ values are ob---

Table 5: Physicochemical evaluation of tablets prepared by direct compression method

Formulation code	Hardness (kg/cm^2)± SD	Friability (%)	Thickness (mm)±SD	Weight variation (mg) ±SD	Drug content (%) ±SD
DCI_1	2.5±0.11	0.56	4.60±0.12	202±1.78	99.48±0.72
DCI_2	2.3±0.18	0.66	4.75±0.15	203±1.32	99.81±1.07
DCI_3	2.2±0.15	0.62	4.71±0.10	198±0.56	99.54±0.54
DCI_4	2.1±0.12	0.58	4.80±0.10	204±1.97	98.12±0.73
DCC_1	2.8±0.13	0.57	4.85±0.17	201±0.65	99.30±0.87
DCC_2	2.1±0.10	0.57	4.87±0.15	200±1.93	99.23±0.90
DCC_3	2.8±0.11	0.67	4.72±0.12	196±1.21	99.95±1.07
DCC_4	2.1±0.15	0.75	4.65±0.09	199±1.50	99.63±0.39
DCP_1	2.3±0.18	0.59	4.61±0.19	200±0.18	99.50±0.77
DCP_2	2.2±0.14	0.65	4.58±0.21	203±0.62	99.96±0.27
DCP_3	2.3±0.19	0.60	4.64±0.15	200±1.85	99.56±0.24
DCP_4	2.0±0.13	0.52	4.73±0.25	197±0.96	99.69±0.76
DCS_1	2.1±0.14	0.63	4.69±0.17	196±1.69	99.65±0.76
DCS_2	2.2±0.16	0.73	4.73±0.28	200±1.73	99.08±2.65
DCS_3	2.4±0.18	0.82	4.59±0.20	205±1.62	99.84±0.33
DCS_4	2.5±0.15	0.77	4.65±0.08	198±1.45	99.99±1.79

Table 6: Physicochemical evaluation of tablets prepared by sublimation method

Formulation code	Hardness (Kg/cm^2) ±SD	Friability (%)	Thickness (mm) ±SD	Weight variation mg) ±SD	Drug content (%) ±SD
SBI_1	2±0.11	0.58	4.69±0.12	200±0.78	98.48±0.72
SBI_2	2.1±0.11	0.54	4.82±0.15	201±1.02	98.81±1.07
SBI_3	2.3±0.10	0.75	4.74±0.10	199±1.56	99.14±0.54
SBI_4	2.2±0.12	0.57	4.85±0.17	203±0.97	98.12±0.73
SBC_1	2.8±0.18	0.51	4.69±0.15	205±1.75	99.30±0.87
SBC_2	2.1±0.10	0.68	4.72±0.12	200±0.63	99.23±0.90
SBC_3	2.1±0.15	0.65	4.58±0.09	196±1.42	99.95±1.07
SBC_4	2.1±0.21	0.58	4.67±0.19	198±0.50	99.63±0.39
SBP_1	2.1±0.10	0.59	4.72±0.15	204±1.38	99.50±0.77
SBP_2	2.4±0.21	0.75	4.78±0.21	205±0.82	99.96±0.27
SBP_3	2.5±0.15	0.69	4.71±0.25	201±0.25	99.56±0.24
SBP_4	2.0±0.10	0.58	4.60±0.14	199±0.92	99.69±0.76
SBS_1	2.3±0.05	0.60	4.73±0.28	204±1.43	99.65±0.76
SBS_2	2.2±0.20	0.77	4.79±0.20	197±0.69	99.08±2.65
SBS_3	2.4±0.15	0.73	4.63±0.08	201±0.59	99.84±0.33
SBS_4	2.6±0.42	0.81	4.72±0.20	198±0.65	99.99±1.79

served in Crospovidone containing tablets. As the method of preparation of tablets changed to sublima---tion, the dissolution of the drug from the tablets pre---pared by camphor sublimation method was quicker than those prepared by other method. This may be due to their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates wicking action of croscarmellose sodium in bringing about faster disintegration. All the formulations showed rapid % drug release (69.12% --- 99.83%) due to fast disintegration of tablets and the results were graphically represented in the figures 7 and 8.

The promising formulations were subjected to short term stability study by storing the formulations at 25°C/65% and 40°C/75% RH up to six month. The for---mulations DCI_1, DCI_3, DCC_4 and SBI_1, SBC_4, SBP_1 were selected. After six months the tablets were again ana---lyzed for the hardness, friability, drug content uni--formity and dispersion time. The increase in the disin---tegration time was observed in case of tablets pre---pared with direct compression method. This may be due to increase in the hardness of the tablets during storage. Decrease in the disintegration time was ob---served in tablets prepared by camphor sublimation method. Since during the preparation of tablets by camphor sublimation method, only 6 hrs at 50^OC was used, where as 90 days and 45^oC were used during stability studies. No change was observed in the disin---tegration time and hardness of tablets prepared by other technique. No significant change was observed in

Table 7: Post compression parameters of tablets prepared by direct compression method

Formulation code	*In vitro* dispersion time (sec)±SD	Wetting time (sec) ±SD	Water absorption ratio ±SD
DCI_1	27±2.78	47±2.51	80±1.54
$DC1_2$	25±1.0	49±2.0	83±1.86
DCI_3	21±1.0	48±2.40	85±1.35
DCI_4	30±2.0	50±2.20	78±1.58
DCC_1	41±1.5	48±1.0	67±1.21
DCC_2	39±2.8	43±2.25	70±1.57
DCC_3	34±1.45	44±2.15	72±1.20
DCC_4	49±1.28	46±1.0	76±1.05
DCP_1	52±1.11	42±1.35	61±1.73
DCP_2	50±2.15	40±1.75	58±1.58
DCP_3	53±1.55	41±1.35	63±1.88
DCP_4	45±2.10	42±1.15	57±1.15
DCS_1	52±1.21	47±1.21	60±1.18
DCS_2	59±1.08	491.79	55±1.08
DCS_3	56±1.3	42±1.71	52±1.05
DCS_4	52±2.0	44±2.41	48±1.81

Table 8: Post compression parameters of tablets prepared by sublimation method

Formulation code	*In vitro* dispersion time (sec) ±SD	Wetting time (sec) ±SD	Water absorption ratio ±SD
SBI_1	20±2.78	43±2.51	84±1.54
SBI_2	27±1.0	49±2.0	83±1.86
SBI_3	22±1.0	48±2.4	85±1.35
SBI_4	30±2.0	50±2.2	78±1.58
SBC_1	41±1.5	48±1.0	67±1.21
SBC_2	39±2.8	43±2.25	70±1.57
SBC_3	34±1.45	44±2.15	72±1.20
SBC_4	49±1.28	46±1.0	76±1.05
SBP_1	52±1.11	42±1.35	61±1.73
SBP_2	50±2.15	40±1.75	58 ±1.58
SBP_3	53±1.55	41±1.35	63±1.88
SBP_4	45±2.1	42±1.15	57±1.15
SBS_1	52±1.21	47±1.21	60±1.18
SBS_2	59±1.08	491.79	55±1.08
SBS_3	56±1.3	42±1.71	52±1.05
SBS_4	52±2.0	44±2.41	48±1.81

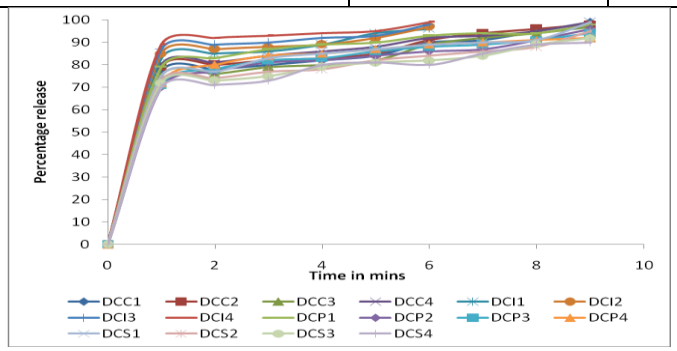

Figure 7: Comparative release profiles of formulations prepared by direct compression

the drug content of all formulation. The stability studies results were presented in the tables 9 and 10.

CONCLUSION

In the present work mouth dissolving tablets of metoprolol tartrate were prepared by direct compression and sublimation methods using superdisintegrants such as indion 414, sodium starch glycolate, croscarmellose sodium and crospovidone. In sublimation method, camphor is used as subliming agent. All the tablets of metoprolol tartrate were subjected to weight variation, hardness, friability, *in vitro* dispersion, drug

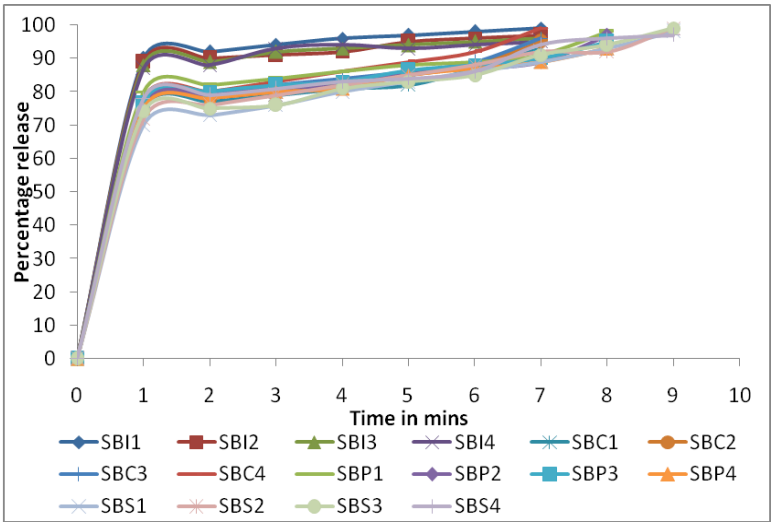

Figure 8: Comparative release profiles of formulations prepared by sublimation

Table 9: Result for 25°C/60% RH for 3 months

Sl. no	Formulation code	Hardness Kg/m³	Percentage friability	Dispersion time (second)	Percentage drug release
1	DCI_1	3.2	0.60	29	98.01
2	DCI_3	3.8	0.64	25	97.88
3	DCC_4	3.4	0.52	15	98.09
4	SBI_1	2.5	0.62	22	98.12
5	SBC_4	2.6	0.80	14	97.28
6	SBP_1	2.5	0.71	12	98.56

Table 10: Result for 40°C/75% RH for 3 months (Accelerated stability testing)

Sl. no	Formulation code	Hardness Kg/m³	Percentage friability	Dispersion time (second)	Percentage drug release
1	DCI_1	3.3	0.61	25	97.93
2	DCI_3	3.7	0.73	24	98.56
3	DCC_4	3.5	0.45	13	99.03
4	SBI_1	2.5	0.68	25	98.22
5	SBC_4	2.7	0.71	17	96.73
6	SBP_1	2.6	0.80	10	98.88

polymer interaction, drug content uniformity, water absorption ratio, wetting time, and *in vitro* drug release. Tablet prepared by direct compression and sublimation methods were found to be good and were free from chipping nd capping. The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared. The hardness of the prepared tablets was found to be in the range of 2 to 3 Kg/cm². IR spectroscopic and DSC studies indicated that the drug is compatible with all the excipients. The *in vitro* dispersion time of metoprolol tartrate prepared by direct compression and sublimation method were found to be in the range of 18 to 59 sec fulfilling the official requirements. Based on the *in vitro* disintegration time, formulation DCI_3 (9% Indion 414) and SBI_1 (3% Indion 414) were found to be promising and showed a dispersion time of 21 and 18 sec, wetting time of 48 and 37 sec respectively, which facilitate the faster dispersion in the mouth. The formulation DCI_3 and SBI_1 have displayed good water absorption ratio of 85.77 and 85.15%, which indicate better and faster swelling ability of the disintegrants in presence of little amount of water. The drug content of tablets was uniform in all the batches and was between 98.12 to 100.76%. The drug release from mouth dissolving tablets of Metoprolol tartrate prepared by direct compression and sublimation methods were found to be in the range of 96.05 to 99.56% and the result of DCI_3 and SBI_1 showed 97.83% and 99.01% drug release within 5 minute. The stability study shows that no significant changes in tablets after six month study. Among the two methods used namely direct compression and sublimation, the sublimation method was found to be superior to direct compression method. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. Removal of volatile material by sublimation generated a porous structure. The tablets dissolve within 10-20 seconds and exhibit

sufficient mechanical strength, which is effective than the direct compression method.

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