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Design, Evaluation and Characterization of Rapidly Dissolving Oral Strips of Metoprolol Succinate

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Abstract

The present investigation is an attempt to design and evaluate rapidly dissolving oral strips of metoprolol succinate, an anti-hypertensive agent. Rapidly dissolving oral strips were prepared by solvent casting technique using hydroxyl propylmethylcellulose-5 cps and polyvinyl alcohol as the film forming polymers. The prepared strips were evaluated for the characteristics such as thickness, folding endurance, percent elongation, tensile strength, surface pH, percent drug content, *in-vitro* disintegration time and *in-vitro* dissolution profiles. All the formulations fulfilled official criteria for evaluated parameters. The drug content of formulations was found to be in the range of 89 to 98%, disintegration time of all the formulations was found to be in the range of 17-29 sec, and *in-vitro* dissolution results showed 86.33 to 98.53%. The formulation F3 containing 1:3 drug-polymer ratio showed optimum performance when compared to other formulations. Hence, it was concluded from the results that, the rapidly dissolving oral strips of metoprolol succinate can be successfully developed in order to enhance the dissolution rate, there by better patient compliance and effective therapy.

Keywords: Rapidly dissolving; Oral strips; Metoprolol succinate; Folding endurance; Patient compliance

Introduction

Hypertension is the most common cardiovascular disease. In 80-95% of hypertension patients, the cause of increase in blood pressure is unknown such condition is considered as primary or essential hypertension. The remaining 5-20% cases of hypertension are secondary hypertension, in which the increase in blood pressure is caused by diseases of the kidneys, endocrines or some other organs [1]. The arterial pressure is the product of cardiac output and peripheral vascular resistance. Numerous pharmacological agents are used as antihypertensive agents, which lower the blood pressure by actions on peripheral resistance, cardiac output, or both [2-4].

Metoprolol, a β1-selective receptor antagonist widely used in the treatment of hypertension. Metoprolol also has been proven to be effective in chronic heart failure. Metoprolol is almost completely absorbed after oral administration, but bioavailability is relatively low (about 40%) because of first-pass metabolism. The half-life of metoprolol is 3 to 4 hours. Hence, to improve the pharmacokinetic property of metoprolol it need to formulate suitable dosage form which can protect the drug from first pass metabolism and helps to increase availability in blood circulation for longer time [2-5].

The research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules to the recent development of oral strip. Basically the oral strip can be considered as an ultra-thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. The advantages of convenience of dosing and portability of oral strip have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally. Oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane [3-6]. The epithelia of oral cavity are composed of an intercellular ground substance called as mucus which basically consists of proteins and carbohydrates. It maintains hydrated condition of the oral cavity, provides adequate lubrication, concentrates protective molecules such as secretory immunoglobulin's, and reduces the attachment of microorganisms. The negatively charged mucin contains sulfhydryl groups and sialic acid residues that are responsible for muco adhesion phenomena [7]. The saliva and salivary mucin contribute to the barrier properties of oral mucosa [8]. The drug absorption through the buccal cavity can take place either by transcellular or paracellular pathway. The mucosa in sublingual region is relatively more permeable leading to rapid absorption with improved bioavailability [9-11]. Based on the above facts in present study the effort was made to prepare and evaluated rapidly dissolving oral strips of metoprolol succinate.

Materials and Methods

Materials

Metoprolol succinate was obtained as a gift sample from Wockhardt Pharmaceuticals, Aurangabad, India. Hydroxy propyle methyl cellulose (HPMC 5 cps) was obtained from Signet, Mumbai, India. Poly ethylene glycol -300 (PEG-300) and polyvinyl alcohol (PVA) were obtained from SD Fine chemical, Mumbai, India. All other chemicals and reagents were obtained from Loba Chemicals, Mumbai, India and were of analytical grade.

Experimental methods

Preparation of rapidly dissolving oral strips of Metoprolol succinate: The solvent casting method was adopted to prepare rapidly dissolving trips by using hydrophilic polymers such as HPMC 5 cps, PVA, PEG and glycerin as a plasticizer and formulated according to the published

protocol [12]. As per the formulation composition mentioned in table 1, the calculated amount of polymer (200 mg) was dispersed in 3/4 volume of water with continuous stirring on a magnetic stirrer and the final volume was adjusted with distilled water. The weighed amount of drug (100 mg) was incorporated in the polymeric solution after levigation with required volume of PEG. The solution was casted and kept in hot air oven at 37°C. After sufficient period, the strips were taken out and stored in a decicator by keeping in an aluminum foil until further use.

Evaluation of strips: The prepared strips were evaluated for the following parameters:

Physical appearance and surface texture: Physical appearance and surface texture of the prepared strips were checked simply with visual inspection of films and evaluation of texture by feel or touch.

Weight uniformity of strips [13]: Three strips in a formulation batch were weighed individually using digital balance and average weights were calculated.

Thickness of strips [14]: Thickness of the films was measured using screw gauge with a least count of 0.01 mm at different spots of the strips and average was taken.

Folding endurance of strips [15,16]: The folding endurance was determined by repeatedly folding a film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Surface pH [17]: The film to be tested was placed in a petri dish, moistened with 0.5 ml of distilled water and kept for 1 hour. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the film and kept for 1 min to allow equilibrium condition.

Tensile strength and percent elongation [18]: The tensile strength indicates the ability of strips to withstand mechanical stress. Using micrometer or equivalent width measurement device with capacity of 0.25 mm, weight required to break the small strip of film was measured, simultaneously, the length of film before and after maximum elongation was also measured in triplicate. The tensile strength and % elongation were calculated using equations:

Tensile strength=force required to break the strip/initial cross sectional area of the film (mm) and

Percent elongation=(increase in length of strip elongation /original length of strip)/100

In-vitro disintegration time [19]: Disintegration time study was slightly modified in the laboratory to mimic the biological conditions. For this study, films required for a single dose delivery were placed on a stainless steel wire mesh containing 10 ml distilled water. Time required for the film to break and disintegrate was noted as the *in-vitro*

disintegration time. Ten milliliter medium was used because the film is expected to disintegrate in the mouth in presence of saliva.

Drug content uniformity [20]: A film was put in 30 ml volumetric flask containing solvent methanol: water (80:20 % v/v). This was then shaken on a mechanical shaker for 1 hour to get a homogeneous solution and was filtered through nylon disc filter. The drug content was determined using UV Spectrophotometer with the help of standard calibration curve.

***In-vitro* drug release study [21]:** *In-vitro* dissolution of the films were studied in USP XXIV dissolution apparatus II (Electrolab, (USP) TDT-08L)employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5°C as a dissolution medium. The film of 5 mg equivalent of drug was used in the test. The aliquots (5 ml each) were withdrawn at specified time intervals and replaced with equal volume of fresh medium. The sample was filtered and absorbance was measured at 275 nm using double beam UV spectrophotometer (Lab-India 3200). The samples were analyzed for drug content with the help of standard calibration curve.

FTIR spectroscopy [22]: IR study was carried out to check compatibility between drug and excipients. IR spectra of drug, mixture of drug and excipients and a drug loaded strip were determined by Infrared spectrophotometer (Bruker Alpha T) using KBr pellet method. In this method sample and KBr (1:100) were mixed, then compressed into transparent pellet under hydraulic press. The IR spectrums were scanned in range of 600-4000 cm^{-1}.

Differential scanning calorimetry [23]: DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug and the prepared strips (DSC-60, Shimadzu, Japan). The sample were sealed in the aluminum pans and heated at the rate of 10°C /min, covering a temperature range of 100 to 300°C under nitrogen atmosphere of flow rate 100 ml/min. It was performed by using Shimadzu DSC 60.

Scanning electron microscopy: The surface morphology of the drug and optimized strips was evaluated by scanning electron microscopy (Joel 840 A, Japan). The samples were scattered individually onto a thin film of epoxy resin and coated with a platinum layer and mounted onto the hub of the instrument and the objects were focused at different magnifications at room temperature and photographed with direct data capture of the images on to a personal computer.

Results and Discussion

Physical appearance and surface texture of strips

These parameters were checked simply with visual inspection of strip and by feel or touch. The observation suggests that the strips are having smooth surface and they are elegant enough to see.

Weight uniformity of strips: The weight of drug loaded rapidly dissolving strips was determined using digital balance and the average weight of all films was given in table 2. The weight of strip for all the batches (F1-F7) was found in the range of 48.59 ± 0.55 and 53.21 ± 0.33 mg. The formulation F6 showed minimum weight due to concentration of both the polymers. In all the cases calculated standard deviation values are very low which suggest that the prepared strips were uniform in weight.

Thickness of strip: The thickness of drug loaded rapidly dissolving strips was measured using screw gauge micrometer and the average thickness of all strips was given in table 2. The thickness was found in the range of 0.111 ± 0.001 and 0.128 ± 0.005.The thickness increased as the concentration of polymers increased. In all the cases the calculated standard deviation values are very low which suggest that prepared films were uniform in thickness. The results are presented in table 2.

Folding endurance: The folding endurance of drug loaded rapidly dissolving strips of was determined by repeatedly folding a small strip

Ingredients	F1	F2	F3	F4	F5	F6	F7
Metoprolol Succinate (mg)	100	100	100	100	100	100	100
HPMC 5 cps (mg)	200	250	300	-	-	-	150
PVA (mg)	-	-	-	200	250	300	150
PEG-300 (ml)	0.035	0.046	0.053	0.035	0.046	0.053	0.035
Tween-80	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid (mg)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Distilled Water (ml)	10	10	10	10	10	10	10

Table 1: Formulation details of rapidly dissolving oral strips

of formulation at the same place till it broke and the average folding endurance of all strips were given in table 2. It was found in the range of 223.00 ± 12.50 and 278.00 ± 12.50. Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer increases, folding endurance also increases. The results are presented in table 2.

Surface pH of the strips: Considering the fact that acidic or alkaline pH may cause irritation to the oral mucosa and influence the degree of hydration of polymer, the surface pH of the strip was determined to optimize drug penetration and given in table 2. The surface pH of drug loaded rapidly dissolving strip was determined by pH meter. It was found in the range of 6.87 and 7.10. The attempts were made to keep the surface pH as close to salivary pH as possible.

Tensile strength and percent elongation: The results of tensile strength and percent elongation are given in the table 2. Tensile strength was found in the range of *2.17 ± 0.02* and *3.54 ± 0.01* N/mm² whereas; percent elongation was in the range of 24 ± 2.0 and 35 ± 3.0. Tensile strength and percent elongation results revealed that, optimized formulation (F3) showed acceptable tensile strength and moderate percent elongation. The results are presented in table 2.

***In-vitro* disintegration time:** *In-vitro* disintegration time of drug loaded rapidly dissolving strip was found to be in the range of 17.66 to 28.64 seconds. Formulation F3 showed fastest disintegration time. The results are presented in table 2.

Drug content uniformity: The drug content uniformity of drug loaded rapidly dissolving oral strip formulations was found in the range of 89.12 ± 0.43 and 98.45 ± 0.20% as shown in table 2. The formulation F2 showed less amounts of drug content and F3 showed highest drug content. This may be due to high concentration of drug dispersed within the formulations and vice versa. The results are presented in table 2.

***In-vitro* drug dissolution studies:** The *in-vitro* drug release study of all the drug loaded rapidly dissolving oral strips was carried out by using USP Type II (basket) dissolution test apparatus using phosphate buffer pH 6.8 as a medium. The plot of % drug release V/s time (sec) were plotted and depicted as shown in figures 1 and 2. The drug release study of rapidly dissolving oral strips formulations was found in the range of 86.33% and 98.53%. From the *in-vitro* dissolution data, it was found that the drug release was more from the batches prepared with HPMC than with PVA. As the concentration of HPMC increased the dissolution rate was also proportionally increased, this may be due to hydrophilicity and pores formed in the matrix. Whereas, in case of PVA as the concentration increased, drug release was found to be decreased. Formulation with PVA as a polymer showed slightly decreased in dissolution rate due to less pores formed in the matrix. Formulation F3 showed highest drug release among all other batches. The dissolution profiles are shown in figure 1 and photographs in figure 2.

Compatibility studies between drug and polymers by FTIR: FTIR spectroscopy is a qualitative analytical technique offers the possibilities of detecting chemical interaction between drug and polymers used in the formulation. The compatibility study between drug and polymers used in the rapidly dissolving strip formulations was done. The characteristics peaks of drug were found to retain in the formulations prepared with both the polymers. The peaks remaining intact and unaffected in the final strip formulations, hence it can be concluded that drug is compatible with polymers used indicating absence of chemical interaction. The IR spectra are shown in figure 3.

Batch Code	Weight Uniformity (mg)	Average thickness (mm)	Folding endurance (Sec)	Surface pH	Tensile Strength (N/mm²)	Percent Elongation	Distn. Time (Sec)	% Drug content
F1	49.33 ± 0.78	0.121 ± 0.003	224.66 ± 30.53	7.03	2.92 ± 0.02	25 ± 2.0	28.64	95.73 ± 0.74
F2	51.33 ± 0.61	0.124 ± 0.001	236.33 ± 0 9.01	7.10	3.14± 0.03	35 ± 1.0	25.33	89.12 ± 0.43
F3	52.24 ± 0.73	0.128 ± 0.005	246.66 ± 27.53	7.06	3.54± 0.01	26 ± 2.0	17.66	98.45 ± 0.20
F4	50.29 ± 0.83	0.120 ± 0.001	231.00 ± 17.77	7.01	2.98± 0.02	36 ± 4.0	22.64	96.83 ± 0.25
F5	50.78 ± 0.37	0.122 ± 0.001	245.33 ± 09.45	6.87	2.23± 0.02	24 ± 2.0	19.00	96.00 ± 0.29
F6	53.21 ± 0.33	0.126 ± 0.001	278.66 ± 12.50	6.98	2.17± 0.02	35 ± 3.0	18.62	98.03 ± 0.60
F7	48.59 ± 0.55	0.111 ± 0.001	223.00 ± 14.50	7.08	2.51± 0.02	28 ± 1.0	18.27	94.56 ± 0.29

Table 2: Evaluation data of rapidly dissolving oral strips
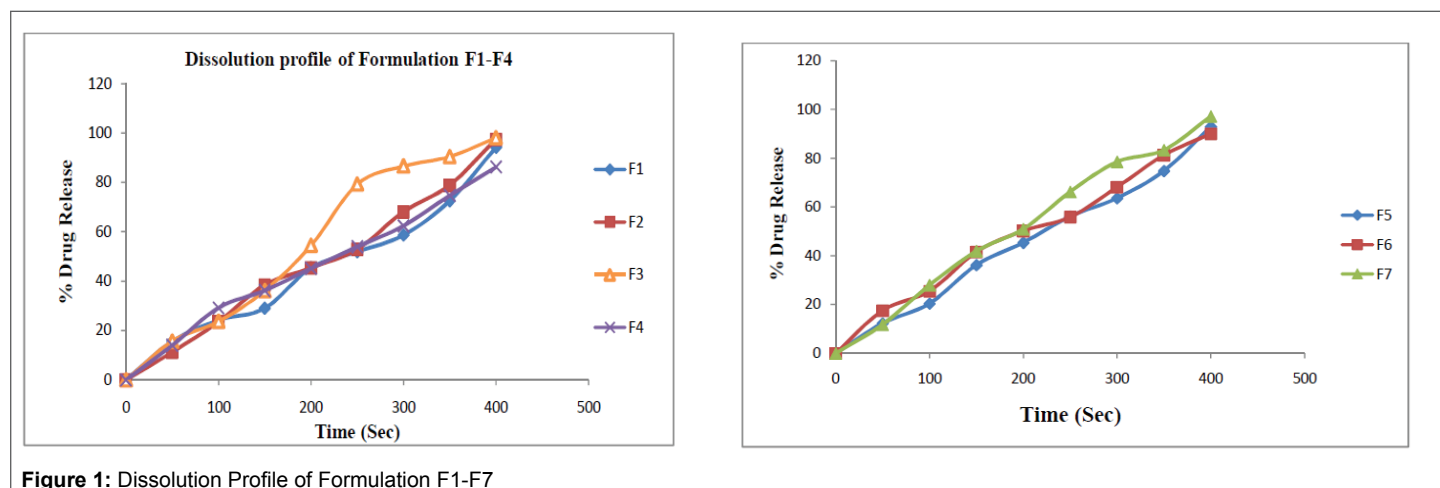Distn. Time=Disintegration Time, N=3 determination, ± SD

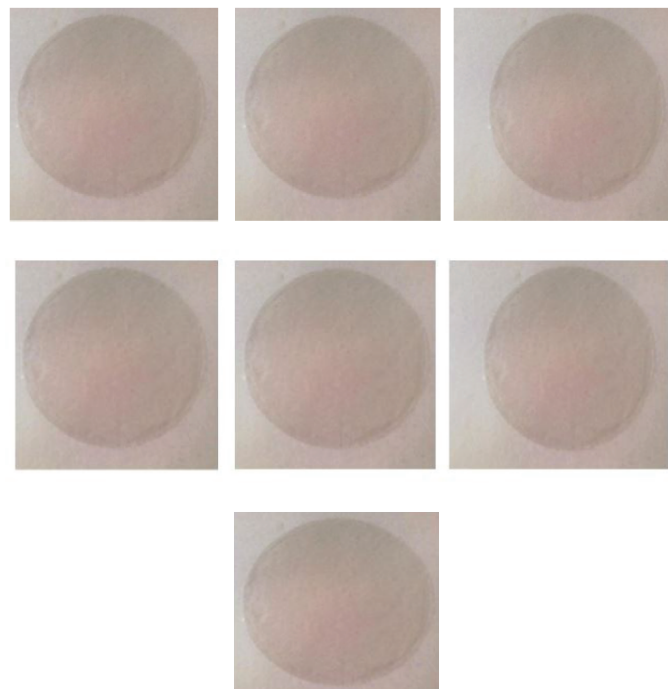**Figure 1:** Dissolution Profile of Formulation F1-F7

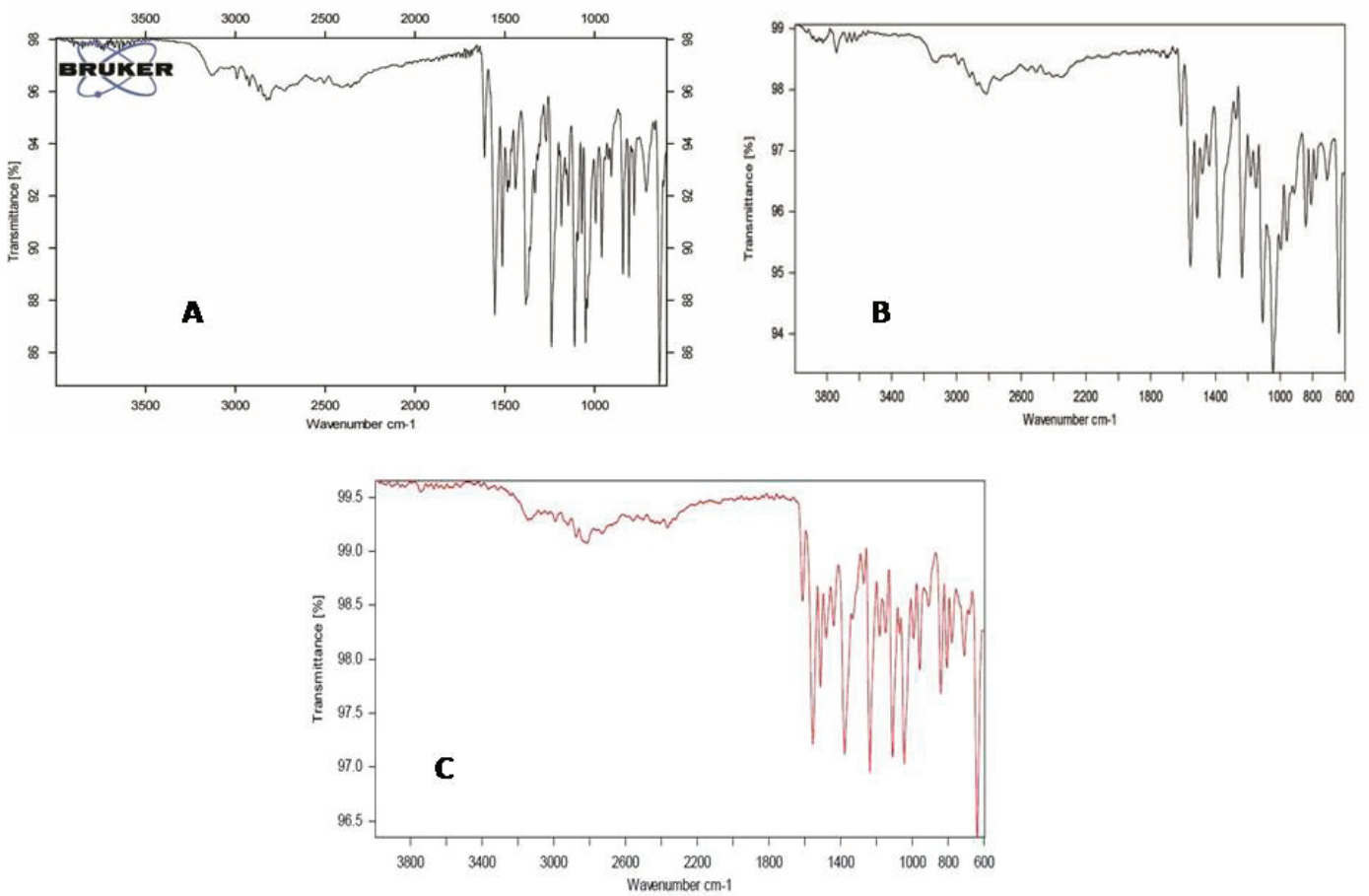**Figure 2:** Photographs of rapidly dissolving Oral Strips of Metoprolol Succinate (F1–F7)

Figure 3: FTIR spectra of Pure drug (A); Formulation F3 (B); Formulation F6 (C)
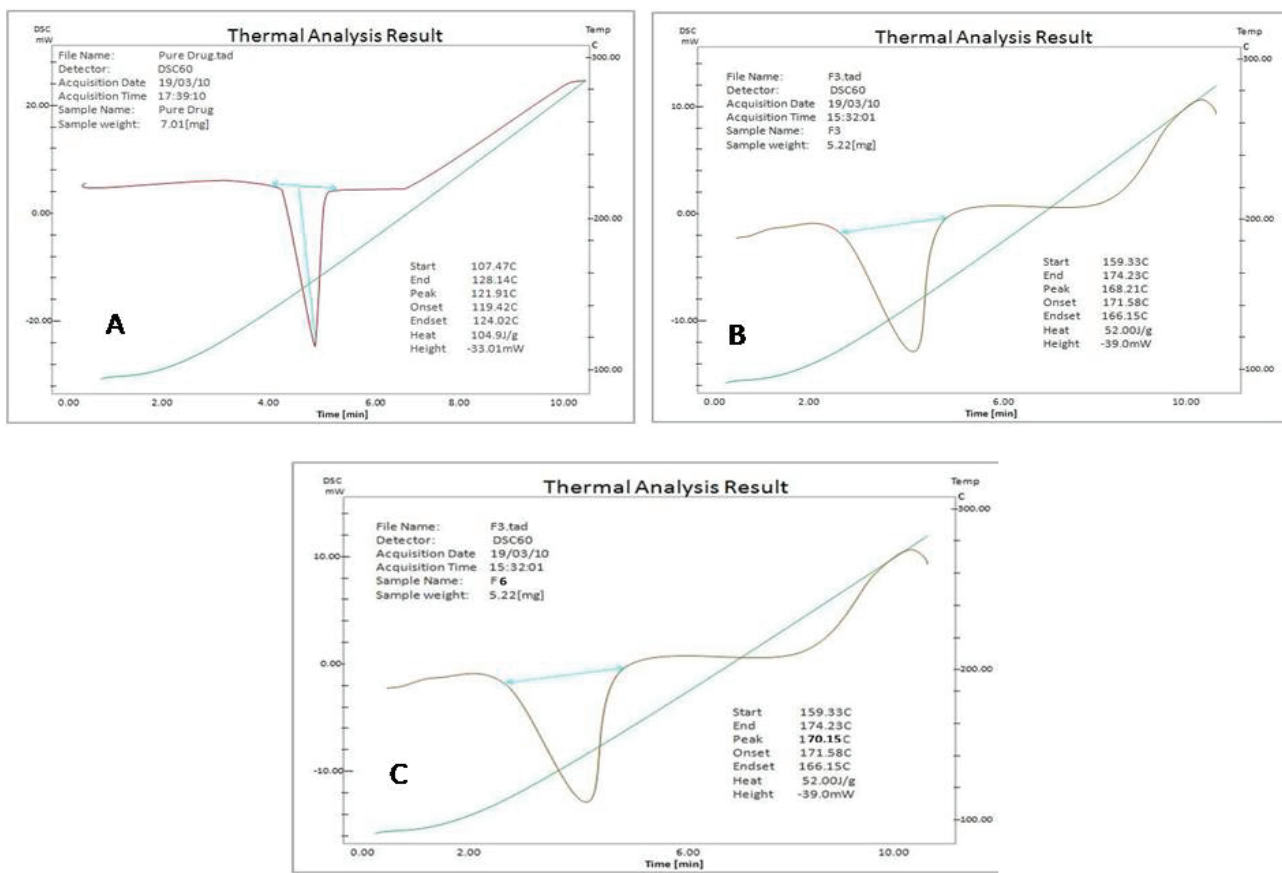
Figure 4: DSC thermograms of Pure drug (A); Formulation F3 (B); Formulation F6 (C)
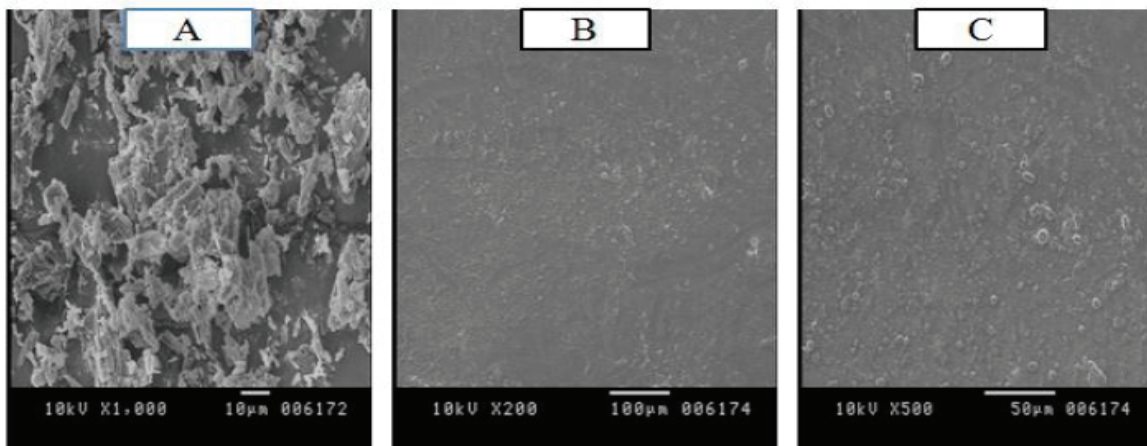

Figure 5: SEM photographs of Pure drug (A); Formulation F3 (B); Formulation F6 (C)

Differential scanning calorimetry: One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and excipient in the formulation. The supporting evidence for compatibility between drug and excipients was obtained from DSC studies. The DSC thermogram of drug alone showed endothermic peak at 124°C which is close to the melting point of drug. There was no significant shift in the endothermic peaks of drug was found in the thermograms of strip formulations.

The absence of detectable peak of drug in the formulations F3 clearly indicates that drug is dispersed completely in the formulation, thus converting it to amorphous form. The reduction in the intensity of peak in the thermogram of formulation F3 may be due to change in thermal property of drug without any interaction with excipients. Hence, from the DSC thermograms, it could be concluded that there is compatibility between drug and excipients. The DSC thermograms are shown in figure 4.

Scanning electron microscopy: The surface morphology (Figure 5) of prepared drug loaded rapidly dissolving strips was found to be clear. The scanning electron photomicrographs of the formulation F3 and F6 showed that the drug is uniformly distributed throughout polymeric matrix in the strips. The surface of strips found to smooth with few pores without any scratches or transverse striations.

Summary and Conclusion

The main objective of the study was to develop the rapidly dissolving oral strips of metaprolol succinate by solvent casting method with the hydrophilic polymers which can swell easily. In this present study, we have made systematic efforts to prepare rapidly dissolving oral strips of metaprolol succinate by using two hydrophilic polymers. Formulations with both the polymers could significantly reduce the disintegration time and increase the dissolution time. Thus, based on these preliminary studies, these oral strip formulations appear better than conventional tablets. However, thorough clinical investigation is necessary before extrapolating the results to humans.

Acknowledgments

Declaration of Interest

The authors report no conflicts of financial interest. Authors alone are responsible for the content and writing of the paper.

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