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Research article

Formulation and evaluation of controlled release metoprolol succinate matrix tablet using natural waxes for the management of hypertension

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ABSTRACT

Metoprolol succinate is a cardio selective β-blocker used in the management of secondary hypertension complications. Metoprolol succinate is prescribed to suppress the hypertension condition and to minimize the cardiac related disorder. In the present study, metoprolol succinate sustained-release tablets were successfully prepared by the wet granulation method. Carnauba and beeswax as natural resources were used as drug release modifying polymers in varying ratios of 1:0, 0:1, and 1:1 respectively. All developed tablets were passed the uniformity of weight, friability, uniformity of thickness, and uniformity of diameter test respectively. The crushing strength of formulated tablet was in ranges of 1.4 to 2.4megapascal (MPa) and showed the optimum tensile strength. The formulated tablet's percentage of drug content and content of uniformity had97.50 and 99.24.The formulated batch F3 (ratio of 1:0) which are capable for provide the desirable drug release over a twelve hours period. The stability study shows the formulation batch F3 was stable. Therefore, this formulation method is economically it may be suitable for the pharmaceutical industries to use this type of simple technology for the development of advanced formulations.

Keywords: Metoprolol succinate, Carnauba wax, Beeswax, Sustained release tablet, Matrix tablet, Polymer ratio.

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INTRODUCTION

Sustained drug delivery system that achieves slow release of drug over an extended period of time with emergence to effectively cured disorder condition and ensure that comply patient compliances with their medication [1]. The system is capable to deliver a steady plasma concentration and avoid differential fluxes in plasma concentration of conventional dosage form. These systems are fruitful to patients for increasing their compliances to medication. Daily once dose of sustained drug delivery system makes sure that patients do not avoid their medication. Additionally, formulate matrix tablet of sustained release dosage forms has unique innovation for novel drug delivery systems [2]. Matrix formulation is composition of one or more drugs with using gelling agent such as hydrophilic polymers [3]. In matrix tablet, excluding multifaceted production procedures such as coating and palletization throughout manufacturing. In the formulation used different type and ratio of polymer which is controlled the drug release rate from the dosage form [4]. The role of hydrophilic polymers in sustained release matrix tablet was to discharge the drugs in a steady and consistent way for to achieve constant peak plasma level. The release of drug from such type of sustained release matrix mainly arises by degradation or diffusion [5]. Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Increase blood pressure was affect to all organ of the body such as heart, kidney, and arteries respectively. Therefore, need was increase to developed of suitable drug to manage the hypertension condition. Metoprolol succinate is salt of succinate which used to management of secondary hypertension by blocking cardio selective β-receptor [6]. Metoprolol succinate has no intrinsic sympathomimetic activity and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Because of these desired pharmacodynamics properties, Metoprolol succinate is used popularly for management of hypertension. Metoprolol succinate was classified in biopharmaceutics classification system (BCS) category of class I, i.e. freely soluble & highly permeable so its bioavailability is more and half life is less [7]. Its long-lasting use in the management of hypertension makes it a good candidate for formulation into a sustained release matrix tablet, which may enhance patient compliance due to reduced rate of administration.

MATERIALS AND METHODS

Metoprolol succinate was obtained from Zim Laboratories, Nagpur. Carnauba wax, Bees wax, microcrystalline cellulose, Talc powder and Magnesium stearatewere obtained from LobaChem, Mumbai. All other reagents and chemicals were of analytical grade. Double distilled water was used throughout the study.

Formulation of tablets

Metoprolol sustained release matrix tablets were prepared using 50 mg of metoprolol succinate and concentration of polymer and excipients as shown in Table 1.Drug release modifying polymers in varying ratio of 1:1 was used for three different formulation (F7, F8, F9). Microcrystalline cellulose was used as diluent whiles magnesium stearate and talc were used a lubricant and glidant respectively.

Table 1: Composition of sustained release matrix metoprolol succinate Tablets.

Ingredients (mg/tablet)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol succinate	50	50	50	50	50	50	50	50	50
Carnauba wax	49	43	37	--	--	--	24.5	21.5	18.5
Bees wax	--	--	--	49	43	37	24.5	21.5	18.5
Microcrystalline Cellulose	24.5	30.5	36.5	24.5	30.5	36.5	24.5	30.5	36.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1	1	1	1	1	1	1	1	1
Total weight of tablet	125	125	125	125	125	125	125	125	125

Formulation and evaluation of tablet granules

The formulation of metoprolol succinate sustained release matrix tablets were successfully done by wet granulation method [8]. All of the above ingredients (Table 1) were weighed and mixed in dilution according to the method. Using granulating fluid (water) mixed thoroughly to prepare a wet mass. This wet mass was separate over a 2360 (micrometre) µm mesh to prepare the granules. Afterwards, the wetted granules were dried up for 1 h at 60 °C and passed over 1180 µm mesh and packed in air-tight containers. Metoprolol succinate prepared granules for tablets were evaluated using numerous methods. Further, evaluation of prepared granules carried out by determination of angle of repose according to fixed height method. The bulk and tapped densities were used for the determination of percentage of compressibility [9]. Single punch tableting machine was used to compress the granules into tablets. Lubricants and glidants were added before to compression process.

Drug and excipients compatibility study

Compatibility study of drug and excipients were done to use of Fourier Transform Infrared Spectroscopy. FTIR was recorded the spectra for metoprolol succinate tablets and prepared granules using scanning range of 4000-400 cm^{-1}. The IR spectra of metoprolol succinate overlaid to IR spectra of prepared granules [10].

Evaluation of tablets

The evaluation of tablets was carried out as the methods described in British Pharmacopoeia [11]. Physical parameters including diameter, hardness, thickness, weight variation and friability also selected randomly for determination of thickness and diameter using digital Vernier caliper and the results of thickness and diameter of each tablet are reported in millimeters [12]. The obtained results of friability were recorded in percentage and hardness results in kilograms.

Drug content analysis

Nine tablets were arbitrarily selected for drug content analysis test. Each tablet was crushed and active ingredients of metoprolol succinate transferred to 100 mL volumetric flask and add 20 mL of methanol, sonicated to dissolve. Make volume to 100 mL with acid buffer PH 6.8 shake for 15 to 20 min and filtered. The amount of drug in each tablet was determined using a UV spectrophotometer at a wavelength of 273 nm. The quantity was calculated in mg [13].

In vitro dissolution study

In vitro dissolution study of metoprolol succinate sustained release matrix tablets were performed by using USP apparatus (paddle method) [14]. The dissolution conditioned of the standard drug and prepared granules were tested for all formulation. Phosphate buffer (pH 6.8) was used as dissolution medium. At pre-set time period 10 mL samples were withdrawn and the sample volume was swapped with fresh dissolution medium to keep sink conditions. All vessels were kept enclosed for the period of the test and maintain the temperature at 37 °C of the medium for all times. The concentration of metoprolol succinate in each sample was analysed using a UV spectrophotometer (Shimadzu 1800) at a wavelength of 273 nm. The cumulative percentage drug released was calculated with the equation obtained from a calibration curve [15]. Further, formulation had applied for kinetic model fitting depicted in Table 6.

X-ray diffraction (XRD) analysis

XRD analysis was used to identify drug polymorphic form. Analytical Expert PRO MPD diffractometer equipped with Xceletor and monochromator beam along with applying voltage of 45KV, 0.050 step size,2θ/min scanning speed and wavelength of 1.54 Å was used for XRD analysis of polymorphic form of metoprolol succinate sustained release matrix tablets [16].

Differential scanning calorimetry (DSC) analysis

Perkin Elmer, Pyris 6 DSC was used for DSC analysis of metoprolol succinate sustained release matrix tablets. This technique was performed to analyse the difference in energy inputs into a substance and reference material is measured as a function of

temperature as the specimens are subjected to controlled temperature program [17].

Accelerated stability study

Twenty tablets were wrapped in aluminium foil of thickness 0.04mm and stored at 30±2^{0}C temperature with relative humidity of 65±5%. The sampling was done after one month and evaluation done for appearance, thickness, hardness, friability, drug content and percent drug release [18].

RESULTS AND DISCUSSION

Properties of formulated metoprolol succinateSR matrix granules

The formulated granules were evaluated physically to their flow properties which suitable for the tablets for compression [19].The compressibility index, angle of repose and the Hausner's ratio indicated that F1, F2, F3 and F7 granules had a good flow, F4, F5 and F6 granules had a fair flow whiles F8 and F9 had excellent flow properties show in Table 2.

Table 2: Properties of formulated metoprolol succinate SR matrix granules

Formulations codes	Bulk density (g/ml)	Tapped Density (g/mL)	Compressibility Index	Hausners ratio	Angle of repose (°)	Flow
F1	0.4021± 0.02	0.4596±0.03	12.51±0.03	1.14±0.05	28.78±0.03	Good
F2	0.4226±0.03	0.4736±0.04	10.77±0.03	1.12±0.02	32.08±0.02	Good
F3	0.4439±0.04	0.5056±0.01	12.20±0.02	1.13±0.03	31.06±0.04	Good
F4	0.4074±0.02	0.4521±0.02	9.89±0.02	1.10±0.03	29.67±0.01	Fair
F5	0.4242±0.02	0.4786±0.04	11.37±0.03	1.12±0.01	28.55±0.02	Fair
F6	0.4505±0.02	0.4995±0.02	9.81±0.02	1.10±0.03	32.08±0.01	Fair
F7	0.4054±0.02	0.4558±0.01	11.06±0.01	1.12±0.03	31.06±0.01	Good
F8	0.4264±0.02	0.4734±0.04	9.93±0.03	1.11±0.02	19.67±0.02	Excellent
F9	0.4495±0.03	0.5007±0.02	10.22±0.03	1.11±0.03	18.13±0.02	Excellent

n=3

Drug and excipients compatibility study

Figure 1: FTIR spectra of metoprolol succinate active pharmaceutical ingredient

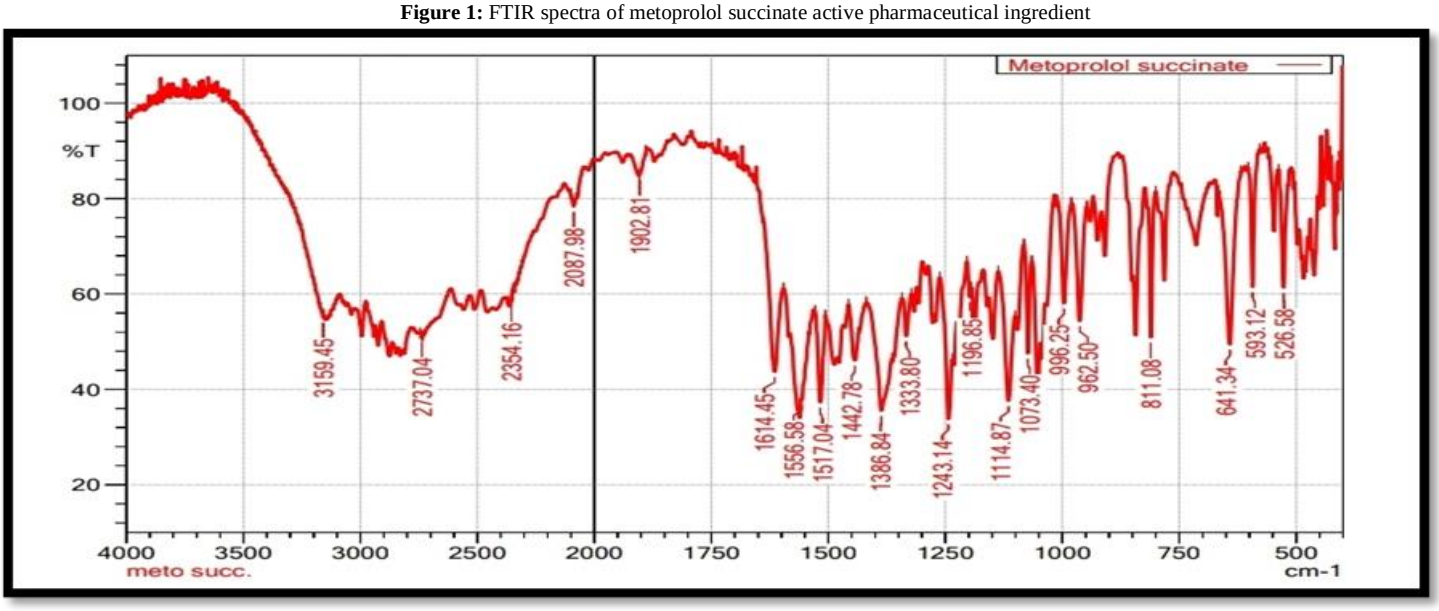
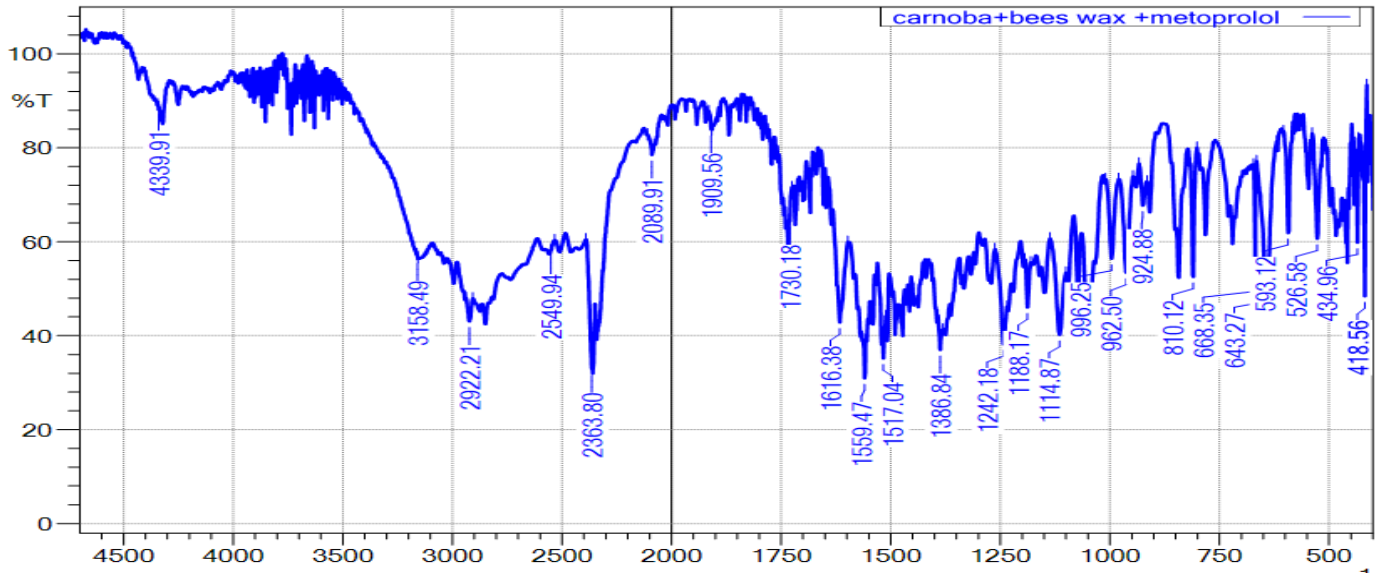


Figure 2: FTIR spectra of metoprolol succinate and tablet excipients showing no interaction between metoprolol succinate and tablet excipients



The IR spectra of metoprolol succinate and physical mixture of metoprolol succinate, carnauba and beeswax (1:1) were taken in the range of 400-4000cm^{-1}.showed the following characteristic features; broad band O-H stretching at 3127.63, 2736.07 cm $^{-1}$, C−O stretching at 1242.18 cm $^{-1}$, N−H deformation at 1614.45 cm $^{-1}$, C=O stretching at 1796.72 cm $^{-1}$, CH3−O stretching at 2829.62 cm $^{-1}$. Powder mixture of metoprolol succinate and excipients (Figure 1) showed that there was no loss of the distinctive functional peaks of metoprolol succinate. Thus, there was not any interaction between the metoprolol succinate and excipients.

Evaluation of formulated tablets

Uniformity of weight

Formulated batches of metoprolol succinate sustained release matrix tablets had passes through uniform weight (Table 3). Based on the result of weight uniformity, the flow properties of the granules filled into die cavity during the tableting process depicted in Table 2.

Table 3: Summary of uniformity of weight on the different formulations of metoprolol succinate SR matrix Tablets (n= 20).

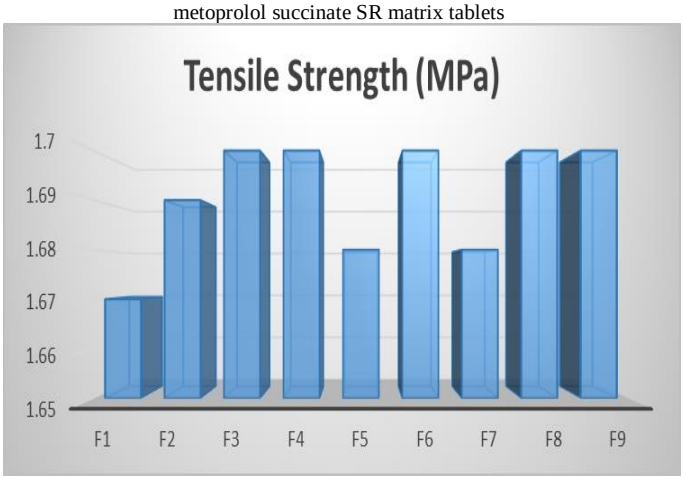
Formulation Codes	Uniformity of weight				
	Total weight in mg set	Mean weight	No. of Tablets deviating by ±5%	No. of Tablets deviating by ±10%	Inference
F1	125	126.2±1.12	Nil	Nil	Passed
F2	125	127.4±2.04	Nil	Nil	Passed
F3	125	125.2±1.21	Nil	Nil	Passed
F4	125	126.6±1.81	Nil	Nil	Passed
F5	125	123.5±2.12	Nil	Nil	Passed
F6	125	129.5±1.75	Nil	Nil	Passed
F7	125	126.8±2.41	Nil	Nil	Passed
F8	125	128.4±1.39	Nil	Nil	Passed
F9	125	126.2±2.04	Nil	Nil	Passed

n=3

Strength of formulated tablets

All formulated batches had sufficient hardness (Table4) and found, all formulated tablets had a percentage friability not more than 1% (Table4) and therefore, friability test passed by all formulated batches. The tensile strength was calculated of the formulated tablets (Figure 3) shows that no noteworthy variance for all tablets containing polymers [20].

Figure 3: Effect of ratio of natural waxes on Tensile strength of formulated metoprolol succinate SR matrix tablets



Dimensional tests

Necessity of the formulated tablets had consistence weight for to a key parameter is to check the uniformity in the thickness and diameter [21]. This is processes which done to check quality control test for that whether tablets failing or passing. The formulated batches of tablets had some limitation that is their diameter average below ±3% and thickness average below ±5 % (Table 4) which conformed that applied compression strength and die volume used in the formulation of the tablets were steady and uniform during the tableting formulation.

Table 4: Physical properties of formulated metoprolol succinate SR matrix tablets (F1-F9).

Formulation Codes	Thickness (mm) *n* = 10	Friability (%) *n* = 11	Diameter (mm) *n* = 10	Hardness (N) n= 20
F1	3.9±0.02	0.595±0.044	8.01±0.2	4.23±0.14
F2	3.6±0.01	0.630±0.046	8.02±0.23	4.47±0.09
F3	3.8±0.03	0.583±0.058	8.01±0.2	4.36±0.10
F4	3.3±0.02	0.622±0.029	8.04±0.34	4.54±0.13
F5	3.5±0.01	0.782±0.031	8.01±0.2	4.57±0.11
F6	3.2±0.02	0.813±0.023	8.03±0.13	4.67±0.08
F7	3.4±0.02	0.782±0.031	8.01±0.2	4.75±0.08
F8	3.5±0.03	0.757±0.047	8.02±0.23	4.23±0.14
F9	3.5±0.02	0.697±0.027	8.04±0.34	4.36±0.10

n=3

Drug content

Drug content of all formulated batches of metoprolol succinate SR matrix tablet were exists in the specified range (Table 5). This is significantly showing that the all-formulated batches had contained the requisite amount of active ingredients which required to elicit the desirable therapeutic effects and would not produce any unwanted side effects.

Table 5: Drug content of metoprolol succinate SR matrix tablets.

Formulation Codes	Average Absorbance	Drug Content (%)
F1	0.430±0.1651	97.50±0.28
F2	0.421±0.3430	95.39±0.21
F3	0.491±0.5221	99.71±0.17
F4	0.413±0.7036	96.44±0.08
F5	0.493±0.8808	99.63±0.16
F6	0.438 ±0.0015	95.80±0.11
F7	0.497±0.3340	99.88±0.06
F8	0.484±0.5441	98.45±0.08
F9	0.490±0.6136	99.35±0.06

n=3

*In vitro*dissolution studies

Natural waxes, carnauba and beeswax in the different ratio was taken to formulate the metoprolol succinate sustained release matrix tablets (F1-F9). In dissolution study, multiple parameters were used to measure the dissolution specification for controlled release drug. Entire formulated batches were capable to deliver a sustained release over twelve-hour period (Figure 2, 3 and 4). Although, batches F1 to F3 were qualify to particular time point's measures of putative pharmacopoeia limits also the result was compared with the standard drug (Antiblok). These measuresindicated that their drug release should be in between 10-30 % within primitive two hours, at eight hours should be 50% drug release and near to 80% after twelve hours. Formulated batches F4 to F9, drug release was unable to reach

dissolution time points measure which may happen due to high amount concentration of waxes that limited release of the active ingredients.

Figure 4: *In-vitro* drug release profiles of formulations F1, F2, F3 for 12hrs

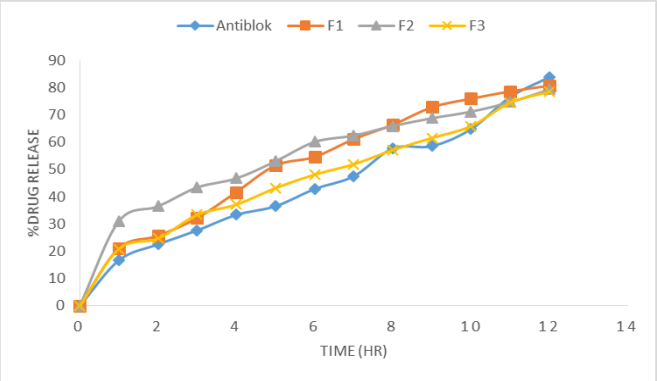


Figure 5: *In-vitro* drug release profiles of formulations F4, F5, F6 for 12hrs

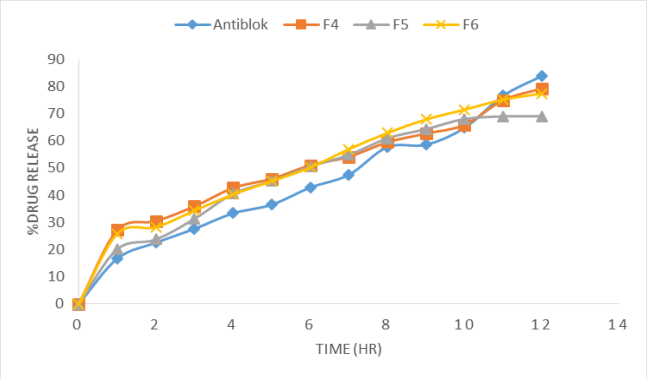
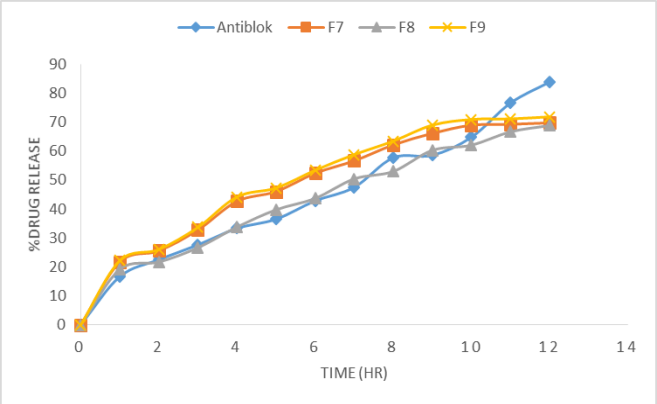


Figure 6: *In-vitro* drug release profiles of formulations F7, F8, F9 for 12hrs.



Kinetic Model Fitting

The various models ware used to evaluate the discharge of drug from the formulations out of these Korsmeyer Peppas model fitted for batch F3. Korsmeyer-Peppas was a simple model known as "Power law" describing drug release from a polymeric system. Korsmeyer-Peppas model describe some release mechanisms simultaneously such as the diffusion of water into the matrix, swelling of the matrix and dissolution of the matrix as shown in Table 6.

Table 6: Kinetic model fitting for all formulations

Kinetic Model	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	0.9558	0.8696	0.9409	0.8741	0.9029	0.9089	0.8811	0.9447	0.8831
T-test	10.785	5.841	9.213	5.969	6.967	7.230	6.179	9.558	6.241
1st order	0.9882	0.9693	0.9836	0.9738	0.9839	0.9913	0.9776	0.9939	0.9798
T-test	21.370	13.074	18.109	14.191	18.248	25.000	15.419	29.914	16.267
Matrix	0.9829	0.9899	0.9874	0.9917	0.9932	0.9924	0.9942	0.9869	0.9936
T-test	17.719	23.192	20.666	25.545	28.227	26.779	30.664	20.300	29.259
Peppas	0.9892	0.9793	0.9969	0.9805	0.9900	0.9793	0.9895	0.9841	0.9892
T-test	22.384	16.058	33.056	16.554	23.305	16.041	22.757	18.347	22.398
Hix.Crow.	0.9950	0.9699	0.9847	0.9620	0.9670	0.9800	0.9569	0.9862	0.9599
T-test	33.050	13.213	18.718	11.690	12.593	16.339	10.926	19.772	11.364

X-ray diffraction (XRD) study

XRD study is important method to analyses polymorphic form of drugs in which ability of solid material exist in two forms with different arrangement and conformation in the crystal lattice [22].XRD pattern of metoprolol succinate sustained release matrix tablets were shown in Forms I and II (Figure 5) and the characteristic diffraction peaks at 3.834, 7.668, 10.666, 14.253, 19.450, 23.348, 23.406 and so forth, which means that Form II is a new polymorphic form of Metoprolol succinate.

Differential scanning calorimetry (DSC) study

DSC study is a thermal analysis to measure the changes in physical properties of compounds by applying temperature against time [23]. The endothermic peaks of two crystal form were observed. Form II has melting point at 126^{0}C which significantly lower than Form I at 138^{0}C. In this study, indicated that Form II is a new polymorphic form and at the same time, only a single endothermic peak was observed that means it was a pure crystalline powder and not any phase transformation during heating [23].

Figure 7: XRD diffractograms of Form I and Form II

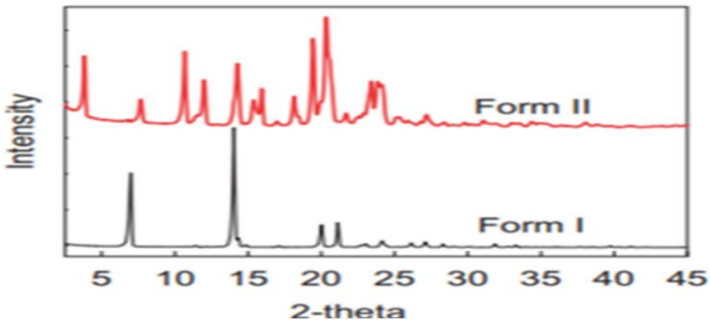
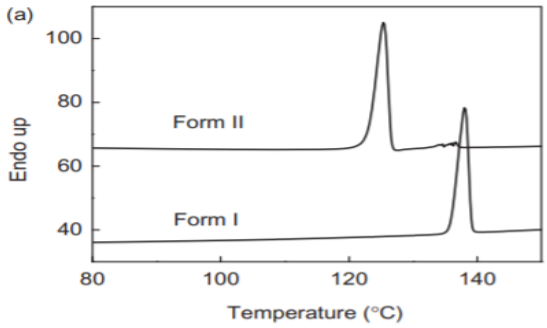


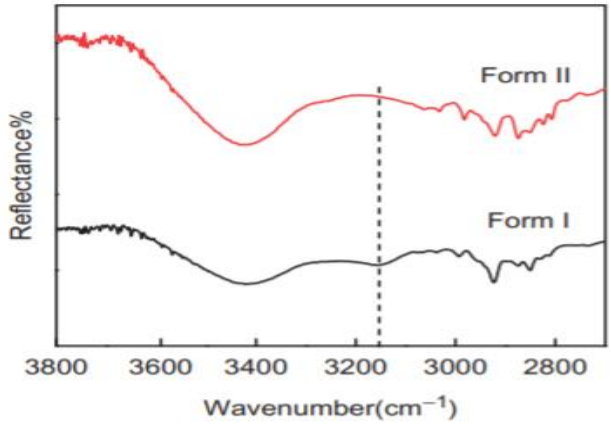
Figure 8: DSC of Form I and Form II



Fourier transform infrared (FTIR) study

FTIR study was perform to identify the functional groups of compounds. Peaks were exhibit in broader and towards blue shift which indicatedfree –OH or –NH groups for to observe hydrogen bond occurred in two polymorphic products. In this study, Form II has only one broad peak at 3420 cm^{-1} while in Form I has two peaks at 3410 cm^{-1} and 3150 cm^{-1}. From this result, observed that differences between the IR pattern of the two-crystal form. Therefore, we concluded that different hydrogen bond formation in Form I and Form II.

Figure 9: FTIR spectra of Form I and Form II wave number (2500-3800 cm^{-1})



Accelerated Stability Study

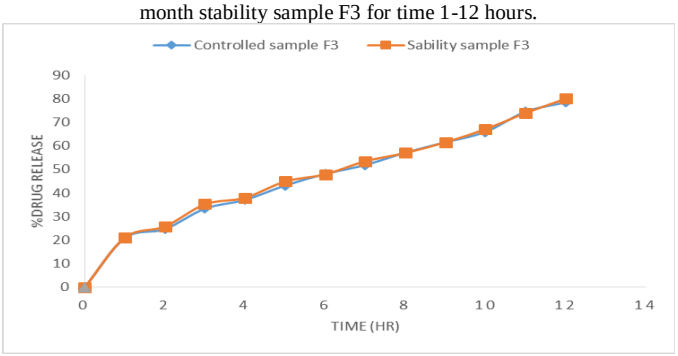
Based on drug release study, formulation F3 has selected for stability study. The formulated batch F3 has sampled labelled as controlled and stability sample which kept for one month and evaluated parameter such as appearance, thickness, hardness, friability; drug content [Table 7] and percent drug release [Figure 10].

Table 7: Evaluation of Stability sample with controlled sample

Parameter	Controlled sample	Stability sample
Appearance of SR	White colour, Circular, Biconvex, Uncoated tablet	White colour, Circular, Biconvex, Uncoated tablet
Thickness (mm)	3.9±0.02	3.9±0.02
Diameter (mm)	8.01±.02	8.01±.02
Hardness (kg/cm^3)	4.47±0.09	4.46±0.05
Friability (%)	0.70±0.04	0.583±0.058
Drug content (%)	99.61±0.8	99.71±0.17
% Drug release (up to 12 hrs.)	78.477±0.92	80.011±0.86

N=3

Figure 10: *In-vitro* release profile of formulation of controlled sample & one-month stability sample F3 for time 1-12 hours.



CONCLUSIONS

Metoprolol succinate sustained release matrix tablets have been successfully formulated using natural waxes such as carnauba and beeswax in the ratios of 1:0, 0:1 and 1:1 respectively. Although, the formulated batch F3 (ratio of 1:0) which are capable for provide the desirable drug release and stable over a twelve hours period. Another, formulated batches (ratio of 0:1 & 1:1) has retarded the drug release and did not provide the desirable drug release after twelve hours period.

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CONFLICT OF INTEREST

The authors stated no conflict of interest for the publication of this research article in the Journal.

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