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A novel co-processed directly compressible release-retarding polymer: In vitro, solid state and in vivo evaluation

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ABSTRACT

Directly compressible (DC) co-processed excipient capable of providing nearly zero order release with improved functionality was developed without any chemical modification by employed various techniques such as physical mixing, high shear mixer granulation and spray drying. Co-processed excipient was developed by using release retarding polymer Eudragit RSPO, separately, in combination with different concentration of hydroxyl propyl methyl cellulose 100 cps (Methocel K100 LV, HPMC), ethyl cellulose (Ethocel N50, EC) and hydroxyl propyl cellulose (Klucel EF, HPC). All co-processed excipients were evaluated for their flow properties in terms of angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. Out of eighteen combinations, the nine co-processed excipients exhibited promising flow properties were found suitable for direct compression and formulated as tablets. Metoprolol succinate, a BCS Class I drug, was selected as a model drug and the formulation was developed employing direct compression approach. The developed tablets were evaluated for physical parameters like uniformity of weight, thickness, hardness, friability and assay. *In vitro* dissolution study confirms that formulation prepared using co-processed excipient showed sustained drug release. The optimized tablet formulation was characterized by DSC, FTIR and PXRD which confirms the absence of any chemical change during co-processing. The optimized formulation was kept for stability study for six months as per ICH guidelines and found to be stable. *In vivo* pharmacokinetic study of optimized formulation in rats showed similar pharmacokinetic behaviour as was observed with the marketed brand. Study revealed that co-processed excipient has advantage over polymers with single property and can be utilised for sustained release formulation.

1. Introduction

Owing to busy and sedentary lifestyle these days, people are affected by a number of lifestyle diseases [1]. Majority of these require prolonged treatments leading multiple drug dosing within a day. Thus, numerous research has been done on controlled release products and technologies for a wide variety of drugs [2–4]. Still, achieving a perfect zero-order release has always remained a goal-post. Today, such a release profile is achievable only with advanced technologies like osmotically controlled drug delivery systems sometimes using laser drilling technology [5–7]. The other options of polymers do not offer such advantages because majority of the cellulose-based polymers are swellable in nature [8,9]. The initial swelling results in loss of geometry of dosage form, thus resulting in release profiles following Higuchi or Korsemeyer-Peppas models. Hydrophobic polymers like ethyl cellulose [10] and non-polar grades of Eudragits [11] are also employed for control of release of drugs. However, these polymers are mostly employed as additional coating materials owing to their inability to form matrices. Moreover, majority of these coatings employ non-aqueous solvents which is an environmental hazard too.

Waxy matrices such as carnauba wax [12], bees wax [13], glyceryl behenate [14] are non-swellable in nature and provide good release retardation but these polymers are also not able to provide a zero-order release. This is because the most common mechanism of drug release from waxy matrices is diffusion. Another problem associated with waxy matrices is the change in dissolution performance upon long term storage. Also, there are processability

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issues like sticking associated with these polymers particularly while using high speed machines.

Several co-processed excipients for immediate release formulation are available on the market e.g. Ludipress, Cellactose etc. The improved manufacturing efficiency and reduced cost of the final drug product can be obtained by using the co-processed excipient. But there is no commercially available co-processed excipient for sustained release matrix formulation.

Novel co-processed excipients can also be employed in oral sustained release dosage forms which deliver the drug for longer period and helps in producing the therapeutic effect for 24 h for those drugs which are having low plasma half-life.

Metoprolol Succinate, *((±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1)*, having molecular formula $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ is a white crystalline powder and freely soluble in water. The oral bioavailability of metoprolol is 50–70% and it has very low plasma half-life 2–5 h. Metoprolol succinate, β1-selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4–6 h and in normal course of therapy, frequent drug administration is required every 4–6 h, thus need the use of sustained release formulation for prolong action and to improve patient compliance by utilizing co-processed excipients.

In our study, we have developed a co-processed sustained release excipient utilizing a synthetic polymer and other filler via various preparation methods. This co-processed excipient is designed to be used for directly compressed sustained release matrix formulation, which can give near zero order release.

Hence, the objective of the current research was to develop a co-processed excipient which can be employed as directly compressible excipient, with minimum adjuncts, to provide a nearly zero-order release of highly soluble BCS Class I model drug (metoprolol succinate). For the purpose it was envisaged to co-process a non-polar, non-swellable methacrylic acid based excipient, Eudragit RSPO (containing about 5% hydrophilic amine group) with other swellable and non-swellable excipients in order to obtain a novel co-processed excipient.

2. Materials

Eudragit RSPO was purchased from M/s Evonik Industries, Mumbai, India. Metoprolol succinate was received as a gift sample from M/s Lupin Ltd., Pune, India. Hydroxypropyl methyl cellulose 100 cps (Methocel K100 LV, HPMC) and Ethyl cellulose (Ethocel N50, EC) were obtained from M/s Colorcon India, Goa. Hydroxypropyl cellulose (Klucel EF, HPC) was procured form M/s Ashland, Mumbai, India. All other reagents, chemicals and solutions used were of analytical grade.

3. Methods

3.1. Preparation of co-processed polymers

For co-processing, a non-swellable polymer, Eudragit RSPO (Eudragit) was co-processed with three different polymers, viz. hydroxypropyl methyl cellulose 100 cps (Methocel K100 LV, HPMC), ethyl cellulose (Ethocel N50, EC) and hydroxypropyl cellulose (Klucel EF, HPC). Colloidal silicon dioxide (Aerosil 200 Pharm) was added to enhance the flow the polymer blend. The various methods utilised for co-processed polymers are as follows:

3.1.1. Physical mixing

Eudragit was physically mixed with the three polymers as per Table 1. Colloidal silicon dioxide was added in a concentration of 0.5% in the polymer mixtures to obtain co-processed polymers, PM-1 to PM-6.

3.1.2. High shear mixer granulation

The excipients combinations as depicted in Table 2 were subjected to high shear granulation. Briefly, each individual polymer mixture along with 0.5% colloidal silicon dioxide was transferred to the bowl of high shear mixer and granulator (M/s Kevin, Ahmedabad, HSMG) and was thoroughly mixed for 10 min at an impeller speed of 150 rpm. The mixed polymers were granulated with a 1:1 mixture of isopropyl alcohol (IPA) and dichloromethane (DCM) employing impeller at a speed of 150 rpm for first 2 min followed addition of chopper mixing at 1500 rpm for additional 1 min. The kneading was repeated till the granulation end-point (2.3 AMP) was achieved. The wet mass was passed through 2 mm screen fitted at the outlet of HSMG. The wet granules were dried in a fluidized bed drier at temperature of 60 °C till an LOD of less than 2% w/w was achieved. The dried granules were milled through 40 G screen fitted in a co-mill at a speed of 4000 rpm to obtain co-processed polymers HG-1 to HG-6.

3.1.3. Spray drying

Polymer combinations as depicted in Table 3 were employed for the purpose of spray drying. Eudragit was dissolved in a 1:1 mixture of acetone and IPA. The other polymer was dissolved in a 1:1 mixture of IPA and DCM. Both the solutions were mixed and colloidal silicon dioxide was added in a concentration of 0.5% w/w. The resultant mixture was kept under stirring and spray dried at an inlet temperature of 35 ± 3 °C with an atomization pressure of 0.9 ± 0.1 bar and an air flow of 40–60 cfm to obtain co-processed polymers SD-1 to SD-6.

3.2. Evaluation of co-processed polymers

3.2.1. Angle of repose

The angle of repose was determined by the funnel method. The determination of angle of repose by this method is referred to as static angle of repose. Powder is poured onto the centre of the dish from the funnel that can be raised vertically until the maximum cone height (h) is obtained. The angle of repose can be calculated by the given formula,

$$\alpha = \tan^{-1}(h/r)$$

where 'h' is height of pile and 'r' is radius of pile (As per USP method). The flow properties and corresponding angle of repose are given in Table 4.

3.2.2. Bulk density (BD)

Bulk density of various co-processed excipients was determined by USP bulk density apparatus (Electrolab). It was measured by

Table 1
Physical mixtures of excipients.

Excipients mixture	Ingredients	Ratio
PM-1	Eudragit: HPMC	1: 0.5
PM-2	Eudragit: HPMC	1: 0.75
PM-3	Eudragit: EC	1: 0.25
PM-4	Eudragit: EC	1: 0.5
PM-5	Eudragit: HPC	1: 0.5
PM-6	Eudragit: HPC	1: 0.75

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Table 2
Excipients combinations for high shear mixer granulation process.

Polymer mixture	Ingredients	Ratio
HG-1	Eudragit: HPMC	1: 0.5
HG-2	Eudragit: HPMC	1: 0.75
HG-3	Eudragit: EC	1: 0.25
HG-4	Eudragit: EC	1: 0.5
HG-5	Eudragit: HPC	1: 0.5
HG-6	Eudragit: HPC	1: 0.75

Table 3
Excipients combinations for spray drying process.

Excipients mixture	Ingredients	Ratio
SD-1	Eudragit: HPMC	1: 0.5
SD-2	Eudragit: HPMC	1: 0.75
SD-3	Eudragit: EC	1: 0.25
SD-4	Eudragit: EC	1: 0.5
SD-5	Eudragit: HPC	1: 0.5
SD-6	Eudragit: HPC	1: 0.75

Table 4
Flow property and their angle of repose values of pharmaceutical powders (as per USP).

S.No.	Flow property	Angle of repose (degrees)
1.	Excellent	25–30
2.	Good	31–35
3.	Fair (aid not needed)	36–40
4.	Passable (may hang up)	41–45
5.	Poor (must agitate, vibrate)	46–55
6.	Very poor	56–65
7.	Very, very poor	>66

pouring the weighed quantity of polymers into a 250 mL measuring cylinder, and the volume was noted [18]. It is expressed in gm/mL and is given by

$$D_b = M/V$$

where, M is the mass of polymer and V is the bulk volume of the polymer.

3.2.3. Tapped density (TD)

The tapped density was measured USP bulk density apparatus (Electrolab) by tapping the polymers of fixed mass for 100 and then 500 tapped until it reached a constant volume [18]. It is expressed in gm/mL and is given by

$$D_T = M/V_T$$

where, M is the mass of powder, V_T is the tapped volume of the powder.

3.2.4. Compressibility index (CI)

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula [18].

$$Compressibility\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

3.2.5. Hausner's ratio (HR)

It was calculated on the basis of bulk and tapped density data and given by

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

For the compressibility index and the Hausner ratio, the generally accepted scale of flowability is given in Table 5.

3.3. Formulation development of co-processed excipients

The nine co-processed excipient blends exhibiting promising flow properties and suitability for direct compression (compressibility) were formulated as tablets. Metoprolol succinate, a BCS Class I drug, was selected as a model drug for the purpose. The formulation was developed employing direct compression approach. The detailed composition of the tablets is depicted in Table 7. Briefly, required quantity of the drug substance (metoprolol succinate) and the co-processed excipients were sifted through # 30 ASTM sieve and blended for 20 min in a V-blender at a speed of 20 rpm. Magnesium stearate was sifted through # 60 ASTM sieve and added to the V-blender and blended for 5 min at a speed of 20 rpm. The lubricated blend was compressed into capsule-shaped tablets employing 15. 5 × 9.5 mm standard concave punches.

3.4. Evaluation of tablets

The prepared tablets are evaluated for hardness, friability, weight variation, thickness, length, assay, in vitro drug release, swelling index and fluid uptake studies.

3.4.1. Thickness and dimension

The thickness and dimension of the tablet in mm was measured using vernier calipers.

3.4.2. Hardness

The tablet crushing strength was tested by commonly used Monsanto type tablet hardness tester. A tablet was placed between the anvils and the crushing strength, which caused the tablet to break, was recorded [18].

3.4.3. Friability

The friability of the tablets was measured in a Erweka friabilator. Randomly 20 tablets were selected and weighed (Wo). After 100 revolutions (speed-25 RPM), the sample of 20 tablets was dedusted and weighed (W) again. Percentage friability was calculated from the loss in weight. Determinations were made in triplicate [18].

Table 5
Compressibility index, Hausner's ratio and their accepted scale of flowability (as per USP).

Compressibility index (%)	Flow character	Hausner's ratio
<10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

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$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

$$Swelling\ index = \frac{Volume\ after\ 24\ hrs - Initial\ volume}{Initial\ volume} \times 100$$

3.4.4. Weight variation test

It was performed as per the method given in the US pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated [18].

3.4.5. High-performance liquid chromatography (HPLC)

All the samples from assay, dissolution, stability and oral bioavailability experiments were analyzed for drug content using a validated HPLC method with minor modifications [14]. The HPLC system (Shimadzu Corporation, Kyoto, Japan) included a system 210 controller (SCL-10A), a pump (LC-10AT), a degasser (DGU-14A), an autosampler (SIL-10AD), a column oven (CTO-10AS and a UV detector (SPD-10AP) with Class-VP (Release 6.10) software. The analytical column used was LiChrospher® 100 RP-18e (250 mm × 4.6 mm, 5 μm), attached with a LiChroCART® 100 RP-18e guard column (4 mm × 4 mm, 5 μm) (Merck, Darmstadt, Germany). The mobile phase, Methanol: Water (80:20 v/v), (pH adjusted to 3.5 with ortho-phosphoric acid) was pumped in isocratic mode at a flow rate of 1.0 mL/min at ambient temperature. Tramadol hydrochloride was used as internal standard for all plasma samples to nullify any processing errors during extraction. The injection volume was 40 μL. The PDA detector was set at a wavelength of 252 nm.

3.4.6. Assay

Twenty tablets were individually weighed and finely powdered. An accurately weighed average quantity of the powder equivalent to 10 mg Metoprolol was taken in 100 ml volumetric flask and dissolved in 25 ml of methanol and shake for 15 min; it was further diluted up to the mark with 6.8 PO_4 buffer. The solution was mixed and filtered and5ml of the filtrate was further diluted to 50 ml with pH 6.8 PO_4 buffer to obtain sample solutions of desired concentrations. The HPLC chromatogram of resulting solution was measured at 252 nm wavelengths for the estimation of metoprolol (As per USP method).

3.4.7. Fluid uptake of tablets

The fluid uptake measures the volume occupied by a substance after swelling in excess of water. Fluid uptake of all formulations was determined by dipping the tablets in phosphate buffer for a period of 24 h. Initial and final weights of the tablets were recorded and percentage fluid uptake was determined employing the following equation [16,17]:

$$\%\ Fluid\ uptake = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

3.4.8. Swelling index of tablets

Swelling index is how much water (by volume, mass, weight) a substance can hold. For determination of swelling index, the tablets were immersed in phosphate buffer collected in a 25 mL graduated glass cylinder. The volume of the fluid in the cylinder was recorded initially and after 24 h [16,17]. Swelling index was determined employing the following equation:

3.4.9. In vitro dissolution studies

In vitro dissolution of all formulations was carried out using USP dissolution testing apparatus II (paddle type, Electrolab, Mumbai, India) at 50 rpm. The dissolution test was performed using 500 mL of phosphate buffer (pH 6.8) as described in the USP monograph. Dissolution test was carried out for a period of 24 h. The temperature of the dissolution medium is maintained at 37 ± 0.5 °C. A aliquot (5 mL) of the solution was withdrawn from the dissolution apparatus at regular intervals and replaced with the same volume of pre-warmed fresh dissolution medium. The samples were filtered through a 0.45 μm membrane filter and diluted to 10 mL to get a suitable concentration with respective media. The amount of drug release was determined from the comparison with standard response of pure drug (As per USP monograph). The drug release profiles of the nine formulations were compared with the release profile of the marketed sustained release formulation of Metoprolol succinate (Selekon® 200 mg) and pure drug substance (metoprolol succinate 200 mg).

The rate and mechanism of release of metoprolol succinate from the prepared tablets were analyzed by fitting the dissolution data into different rate equations such as,

Zero-order equation,

$$C = C_0\text{-}K_0\ t$$

where,

C = Amount of drug release or dissolved (assuming that release occur rapidly after the drug dissolved.)
C_0 = Initial amount of drug in solution (it is usually zero)
K_0 = Zero order rate constant
t = Time

For study of release kinetics, the graph plotted between cumulative amount of drug released vs time.

First order equation,

$$\log C = \log C_0\text{-}Kt/2.303$$

C_0 = Initial concentration of drug
K = First order constant
t = time

The data obtained are plotted as log cumulative percentage drug remaining vs time, which yield a straight line with slop = K/2.303.

Higuchi's equation,

$$Q = K_H\ t^{1/2}$$

where, Q is the percentage of drug released at time t, K_H is the Higuchi release rate constant.

Peppas equation,

$$M_t/M_\infty = k^*t_n$$

where, n is the release exponent; indicative of the mechanism of

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release, M_t/M_∞ is the fraction of the drug at time t, k is the release rate constant.

Coefficient of determination (r^2) of all the models and release exponent (n) values (Table 4) were calculated to determine the most appropriate kinetics model and mechanism of drug release. If the exponent $n = 0.45$, then the drug release follows the Fickian diffusion, and if $0.45 < n < 0.89$, then it is said to be non-Fickian or anomalous release [16].

3.5. Characterization of optimized tablet formulation

3.5.1. Differential scanning calorimetry (DSC)

DSC analysis was carried out in DSC (TA Q2000, New Castle, Delaware USA), equipped with a refrigerated cooling system and operating with TA Universal Analysis software. The instrument was calibrated for temperature and heat flow using high purity indium standard. Accurately weighed samples (3–5 mg) were scanned at heating rate of 10 °C/min in aluminum pans from 25 to 200 °C, under dry nitrogen purge of 50 mL/min.

3.5.2. Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of optimized tablet formulation were obtained on FTIR spectrometer (Nicolet Impact 410, Perkin Elmer Instrument, MA, USA) over the range 4000–500 cm^{-1}. Dry KBr (About 50 mg) was finely ground using mortar-pestle and samples (1–2 mg) of the polymorphs were subsequently added and gently mixed. A hydraulic press (Hydraulic Unit model 3912, Carver Inc., WI) was used to form the pellets at a pressure of 6.9 MPa.

3.5.3. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) patterns of samples were recorded at room temperature on Bruker's D8 Advance diffractometer (Karlsruhe, West Germany), Cu Kα radiation (1.54 A), at 40 kV, 40 mA passing through nickel filter with divergence slit (0.5°), anti-scattering slit (0.5°) and receiving slit (1 mm). The diffractometer was equipped with a 2θ compensating slit, and was calibrated for accuracy of peak positions with corundum. Samples were subjected to PXRD analysis in continuous mode with a step size and step time of 0.01° and 1 s respectively, over an angular range (2θ) of 3–40°. An accurately weighed amount of powder mixture (about 250 mg) was loaded in a 25 mm holder made of poly methyl methacrylate (PMMA) and pressed by a clean glass slide to ensure co-planarity of the powder surface with the surface of the holder. The sample holder was rotated in a plane parallel to its surface at 30 rpm during the measurements. Obtained diffractograms were analyzed with $DIFFRAC_{Plus}$ EVA (ver. 9.0) diffraction software.

3.5.4. Stability studies

The optimized tablet formulation was subjected to stability studies at accelerated condition of 40 ± 2 °C/75 ± 5% RH for a period of 6 months. At the end of 6 months, the tablets were analyzed for assay and dissolution and the results were compared with their corresponding initial values. The similarity factor, f_2, was calculated to ensure the similarity of release profile.

3.5.5. In vivo studies in animal model

All animal experiments were performed in accordance with the Committee for Purpose of Control and Supervision on Experiments on Animals (CPCSEA) guidelines and the experimental protocols were approved by the Institutional Animals Ethics Committee (IAEC/14/07). The wistar rats ranging from 250 ± 10 g were kept on fasting for 12 h before the start and were allowed free access to water before and during the experiment. Pure drug substance, optimized formulation T8 and the marketed formulation were evaluated for their *in vivo* performance. Pure drug substance (metoprolol succinate 25 mg), Selekon 25 mg (marketed formulation) and the optimized formulation T8 (compressed at a weight of 125 mg in order to contain 25 mg of drug substance) were employed for this purpose. A total of 12 rats were employed with 6 rats in each group. Blood samples were collected from retro-orbital plexus after 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h in heparinised microcentrifuge tubes. Plasma was separated immediately by centrifugation at 6500 rpm for 10 min at 10 °C and stored at −80 °C until processed. The samples were analyzed as per the procedure mentioned above, to obtain the plasma drug concentrations at different times.

The various pharmacokinetic parameters were calculated from mean plasma concentration-time profiles using the Thermo Kinetica software, (V5.0, Thermo Fischer Scientific, USA). Statistical significance for pharmacokinetic parameters was compared using the paired *t*-test assuming equal variances.

4. Results

4.1. Evaluation of co-processed excipients

The values of angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and particle size distribution were calculated and presented in table. Out of the eighteen co-processed excipients, only nine combinations of co-processed excipients exhibited good/excellent flow properties based on flow criteria mentioned in Table 6.

The batches PM-1, PM-3, PM-5, HG-1, HG-3, HG-5, SD-1, SD-3 and SD-6 showed angle of repose between 20 and 30° and compressibility index and Hausner's ratio between 1.08 ± 0.03 to 1.17 ± 0.08, which indicates good flow property and compressibility (as per USP) of all the nine batches. Hence, these batches were considered further for formulation development with metoprolol succinate as tablet dosage forms.

4.2. Evaluation of tablets

4.2.1. Physical evaluation

The values of average weights of tablets of all nine formulations ranged between 493 and 510 mg, hardness ranged between 120 and 160 N and thickness values ranged between 5.01 and 5.15 mm. The friability values of all formulations were observed to be less than 0.50%. The assay values of all the formulations were well within the limits of 95.0%–105.0%. The data of physical evaluation of tablets are presented in Table 8.

4.2.2. Fluid uptake and swelling index studies

It has been observed that, formulation T8 showed the lowest swelling index and fluid uptake throughout the study period. This may be related to the low affinity of matrix (Eudragit RSPO + EC N50) to the test medium because of their non-swelling nature. The maximum swelling index of this formulation was 2.6 ± 1.6 achieved after 24 h. On the other hand, significant increase ($p < 0.05$) in the swelling indices and fluid uptake were observed with the other formulations batches [15–17]. Fig. 1 depicts the results of fluid uptake and swelling index studies of the nine formulations.

4.2.3. In vitro dissolution studies

Fig. 2 depicts the in vitro drug release profiles of the nine formulation batches in comparison with the marketed formulation and pure drug substance.

High solubility nature of Metoprolol succinate caused its rapid dissolution when came in contact with dissolution medium and more than 90% of drug gets dissolved in 1 h.

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Table 6
Flow evaluation of co-processed excipients.

Co-processed excipient	Excipient employed with Eudragit	Ratio	Angle of repose (degrees)	BD (g/mL)	TD (g/mL)	CI	HR	Flow behavior
PM-1	HPMC	1: 0.5	26.6	0.52	0.61	14.75	1.17	Good/Excellent
PM-2	HPMC	1: 0.75	38.3	0.49	0.63	22.22	1.29	Fair/Passable/Poor
PM-3	EC	1: 0.25	28.2	0.43	0.47	8.51	1.09	Good/Excellent
PM-4	EC	1: 0.5	40.6	0.39	0.50	22.00	1.28	Fair/Passable/Poor
PM-5	HPC	1: 0.5	24.8	0.40	0.45	11.11	1.13	Good/Excellent
PM-6	HPC	1: 0.75	38.9	0.37	0.48	22.92	1.30	Fair/Passable/Poor
HG-1	HPMC	1: 0.5	26.7	0.58	0.65	10.77	1.12	Good/Excellent
HG-2	HPMC	1: 0.75	38.2	0.55	0.67	17.91	1.22	Fair/Passable/Poor
HG-3	EC	1: 0.25	23.1	0.50	0.55	9.09	1.10	Good/Excellent
HG-4	EC	1: 0.5	40.3	0.53	0.63	15.87	1.19	Fair/Passable/Poor
HG-5	HPC	1: 0.5	27.1	0.52	0.57	8.77	1.10	Good/Excellent
HG-6	HPC	1: 0.75	42.6	0.47	0.59	20.34	1.26	Fair/Passable/Poor
SD-1	HPMC	1: 0.5	21.9	0.40	0.43	6.98	1.08	Good/Excellent
SD-2	HPMC	1: 0.75	37.4	0.41	0.49	16.33	1.20	Fair/Passable/Poor
SD-3	EC	1: 0.25	25.2	0.38	0.42	9.52	1.11	Good/Excellent
SD-4	EC	1: 0.5	35.8	0.35	0.43	18.60	1.23	Fair/Passable/Poor
SD-5	HPC	1: 0.5	28.5	0.37	0.40	7.50	1.08	Good/Excellent
SD-6	HPC	1: 0.75	40.3	0.33	0.40	17.50	1.21	Fair/Passable/Poor

Table 7
Composition of directly compressed tablets.

Ingredients	Quantity (mg/tablet)								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
Metoprolol succinate	200	200	200	200	200	200	200	200	200
PM-1	295								
PM-3		295							
PM-5			295						
HG-1				295					
HG-3					295				
HG-5						295			
SD-1							295		
SD-3								295	
SD-5									295
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total tablet weight (mg)	500	500	500	500	500	500	500	500	500

In case of marketed formulation, more than 80% of drug released from tablet dosage form and get dissolved in dissolution medium within 20 h.

The various formulation batches T1, T2, T3, T4, T5, T6 and T9 shows sustained drug release from dosage forms but they released more than 80% of drug within 5–10 h. The batch T7 also shows sustained release and more than 80% of drug released within 18 h. Hence, these batches were not considered for further studies.

In case of batch T8, 80.5% of drug was released in more than 20 h which was good for prolongation of drug release means tablet released the drug in a controlled manner due to non-swellable nature of co-processed excipient which sustained the drug release for more than 20 h.

In-vitro dissolution data were analyzed by different kinetic models in order to evaluate the coefficient of determination values and release exponent (n) values of all formulations, which describe the kinetics and mechanism of drug release. The kinetic data of all the formulations shows best fit in zero-order and Peppas model followed by non-Fickian or anomalous diffusion mechanism ($n = 0.61$ to 0.79). All the kinetics data are summarized in Table 9. Formulation T8 and marketed formulation shows highest coefficient of correlation (r^2) for zero order model [15–17].

The similarity factor f_2 value of optimized formulation T8 was found to be 66.71, which indicates similarity with the marketed formulation.

So, batch T8 was selected as an optimum batch for the solid state characterization, pharmacokinetic studies and stability study.

4.3. Characterization of optimized tablet formulation

4.3.1. DSC

During DSC analysis, the optimized formulation T8 exhibited melting endothermic event at 135.89 °C corresponding to the melting endotherm of metoprolol succinate at 137.85 °C. The DSC thermogram of the optimized formulation depicted the similar melting point as observed with the pure drug substance. DSC thermogram of optimized formulation also shows some step changes in heat curve. These step changes are glass transition temperature which indicates amorphous nature of other components of formulation like eudragit, ethylcellulose etc. Fig. 3(a) and (b) depict the DSC thermograms of pure drug substance (metoprolol succinate) and optimized formulation T8 respectively.

4.3.2. FTIR

The FTIR scans of the tablets of Formulation T8 did not show any

Table 8
Physical evaluation of directly compressible tablets.

Formulation batches	Average weight (mg)	Hardness (N)	Friability (%)	Assay (%)
T1	498.21 ± 2.33	120.2 ± 2.18	0.386 ± 0.012	98.3 ± 3.9
T2	499.32 ± 3.67	143.7 ± 0.11	0.464 ± 0.018	98.9 ± 3.6
T3	493.84 ± 4.77	138.9 ± 0.21	0.473 ± 0.023	98.4 ± 3.2
T4	496.71 ± 4.74	156.9 ± 0.11	0.547 ± 0.016	101.2 ± 3.5
T5	499.57 ± 2.89	160.6 ± 0.49	0.231 ± 0.004	101.6 ± 2.7
T6	507.75 ± 5.89	141.7 ± 0.19	0.398 ± 0.004	98.6 ± 3.2
T7	510.31 ± 2.32	156.8 ± 0.56	0.321 ± 0.011	100.4 ± 2.1
T8	506.27 ± 3.62	159.7 ± 0.82	0.435 ± 0.001	99.8 ± 1.67
T9	509.46 ± 2.85	160.6 ± 0.73	0.356 ± 0.045	101.4 ± 2.57

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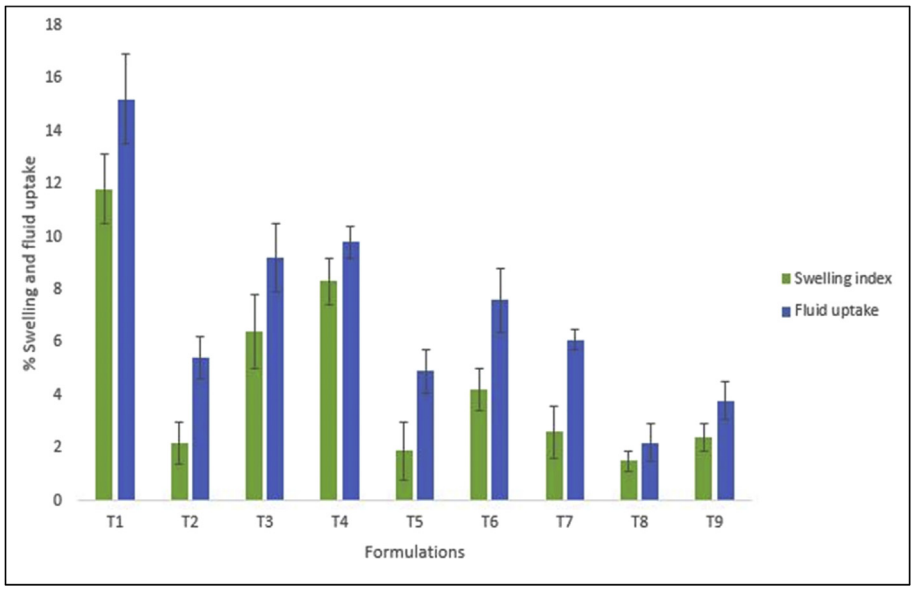

Fig. 1. Fluid uptake and swelling index studies of the nine formulations.

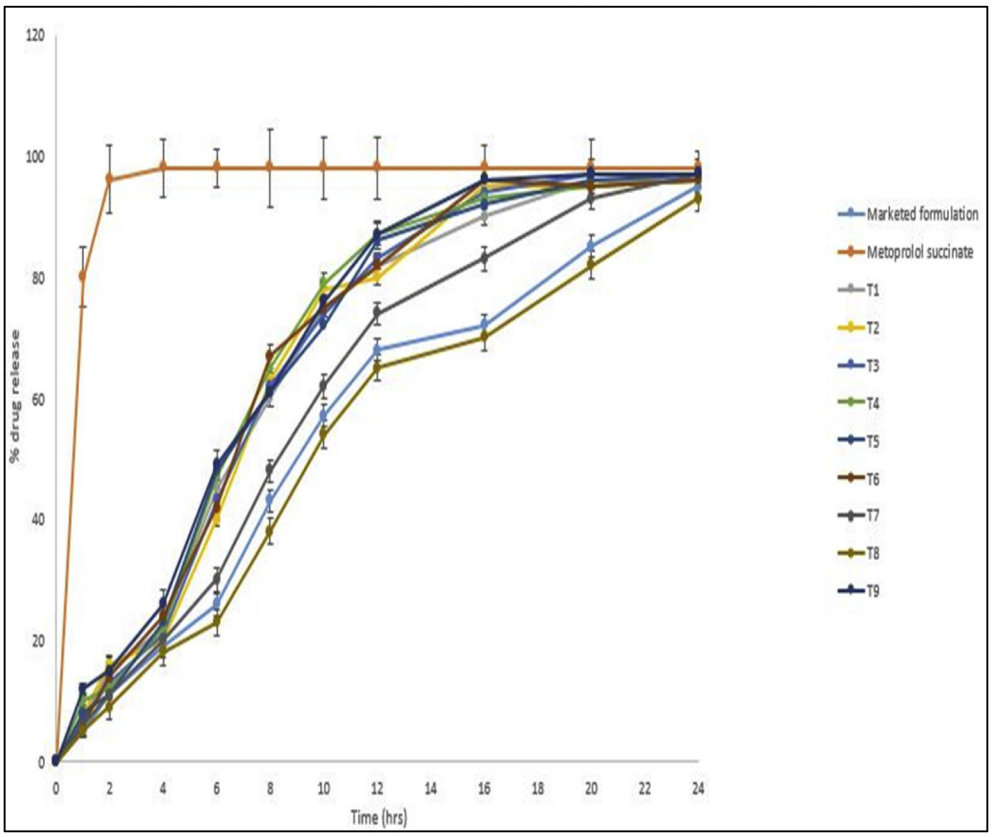

Fig. 2. In vitro drug release profiles of the nine formulation batches in comparison with the marketed formulation and pure drug substance (metoprolol succinate).

significant difference in absorption spectra at particular wave numbers vis-à-vis the pure drug. Fig. 4 (a) and 4 (b) depict the FTIR spectra of pure drug substance (metoprolol succinate) and optimized formulation T8 respectively.

4.3.3. PXRD

X-ray diffraction studies were carried out to disclose the crystalline modifications of drug during the preparation. The X-ray diffractograms of metoprolol succinate and optimized formulation T8 are shown in Fig. 5. The diffractograms of the metoprolol succinate showed sharp peaks at an angle of 7.05, 14.10, 14.38, 20.04, 21.26 23.16, 24.23, and 26.20 (°2θ).

The diffractograms of optimized formulation T8 showed diffraction peaks corresponding to the peaks of metoprolol

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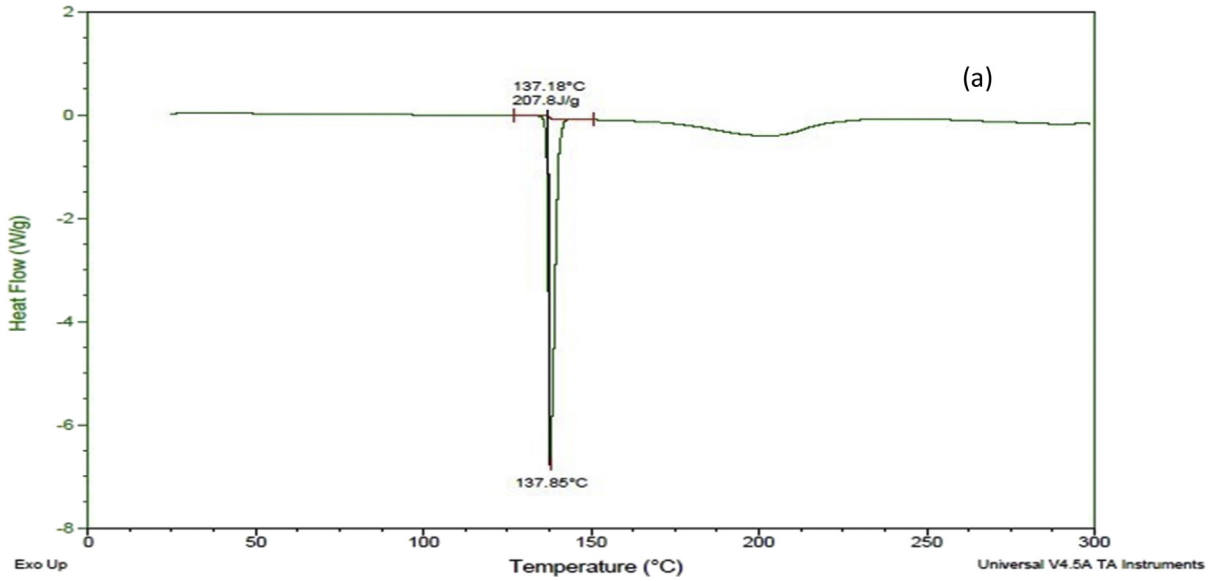
Table 9
In-vitro Drug Release Kinetics Model Fitting (Analyzed by the regression coefficient method).

Formulation batches	Zero order, r^2	First order, r^2	Higuchi model, r^2	Peppas model	
				r^2	n
Marketed formulation	0.998	0.892	0.971	0.991	0.71
T1	0.985	0.891	0.932	0.992	0.67
T2	0.983	0.876	0.945	0.983	0.63
T3	0.991	0.878	0.967	0.964	0.61
T4	0.984	0.883	0.964	0.978	0.67
T5	0.991	0.889	0.932	0.988	0.68
T6	0.993	0.884	0.961	0.984	0.68
T7	0.991	0.874	0.982	0.967	0.64
T8	0.998	0.897	0.991	0.993	0.70
T9	0.991	0.891	0.965	0.991	0.64



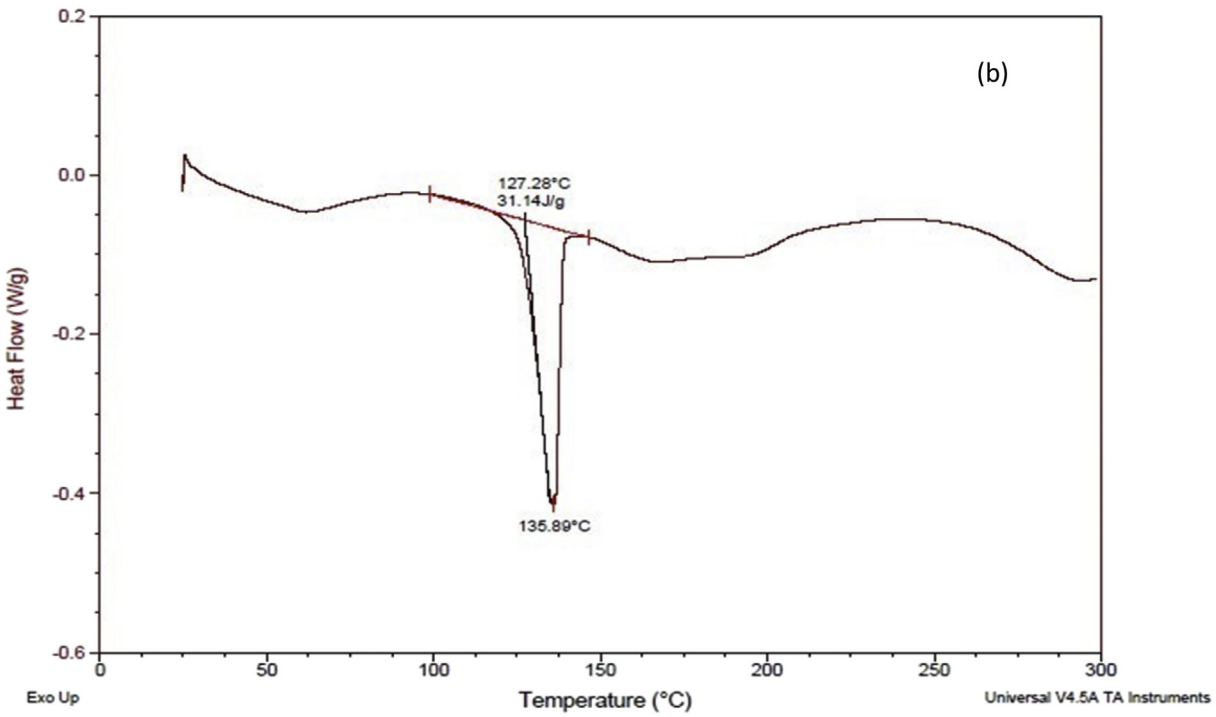


Fig. 3. DSC thermograms of the (a) pure drug substance (metoprolol succinate) and (b) optimized formulation T8.

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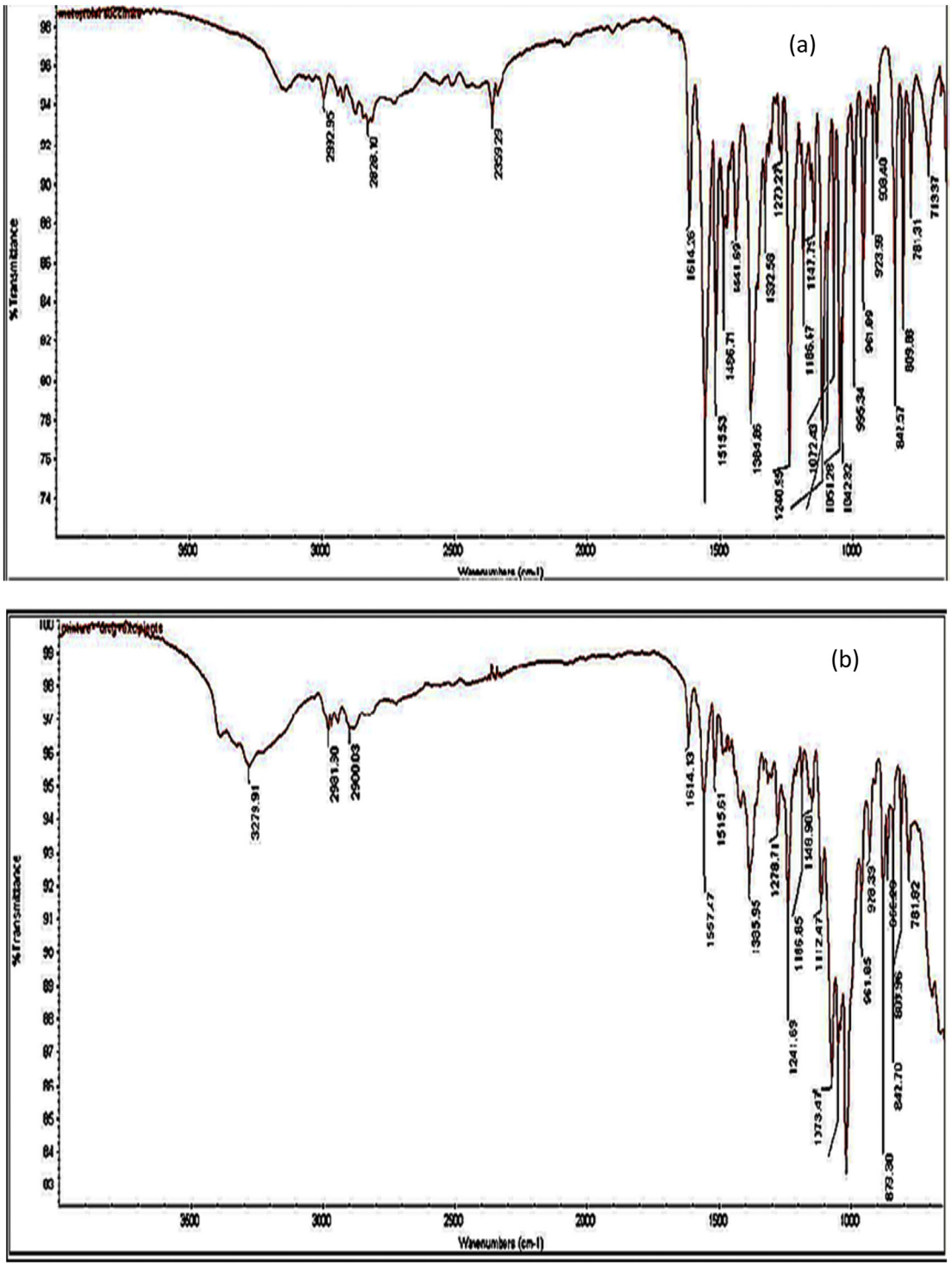

Fig. 4. FTIR spectra of (a) pure drug substance (metoprolol succinate) and (b) optimized formulation T8.

succinate but decreased intensity of the drug peaks indicating a decrease in the crystallinity of the drug due to the compression force applied during the preparation of tablets.

4.3.4. In vivo pharmacokinetic studies

Plasma metoprolol concentration versus time profiles of the pure drug substance (metoprolol succinate), marketed formulation and optimized T8 formulation are presented in Fig. 6. As metoprolol succinate is highly soluble drug, it shows T_{max} around 1–1.5 h and C_{max} corresponding to test T8 and marketed formulation.

T_{max} (5–6 h) and C_{max} (170 mcg/mL) of test T8 and marketed formulation were not significantly ($p > 0.05$) different from each other as both formulation shows sustained plasma level of metoprolol succinate. The graph depicted that the plasma drug levels of the optimized formulation were nearly superimposing with the plasma levels obtained after administration of the marketed formulation.

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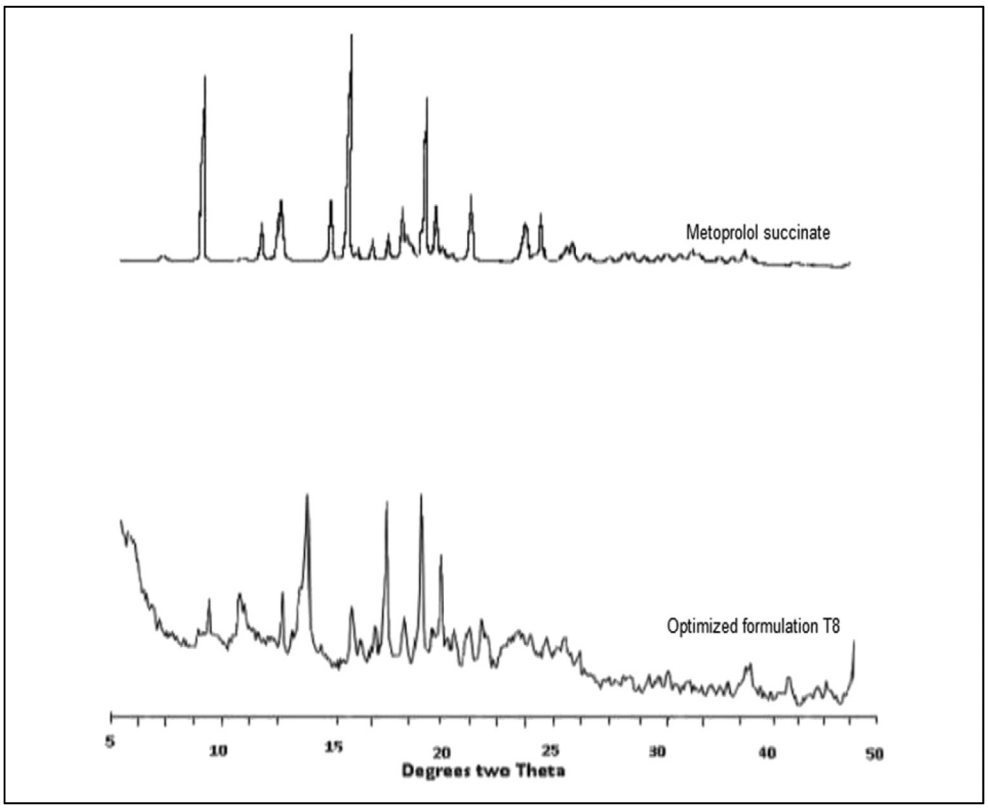

Fig. 5. Overlay of PXRD diffractogram of pure drug substance (metoprolol succinate) and optimized formulation T8.

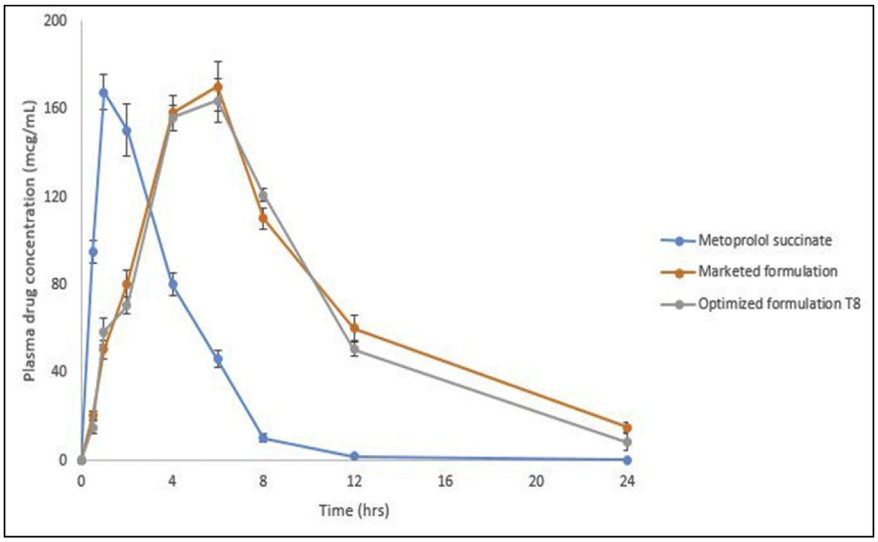

Fig. 6. Plasma levels of Metoprolol after oral administration of the metoprolol succinate, optimized formulation T8 and the marketed formulation.

4.3.5. Stability studies

Accelerated stability studies were conducted for the optimized formulation by packing tablets in a HDPE screwcapped containers and stored at 40 ± 2 °C/75 ± 5% RH for 6 months. Samples were removed at 3 and 6 months and analyzed for physical appearance, average weight, assay and in-vitro dissolution.

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. The average weight, hardness, and assay of all the formulations complied with the compendia standards for tablets. The drug-release profiles of optimized formulation T8 did not change significantly after storage at 40 ± 2 °C/75 ± 5 %RH for a period of 6 months.

5. Discussion

As depicted in Table 6, the flow properties of physical excipient

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mixtures deteriorated with an increase in the concentration of excipients like EC, HPMC and HPC. This can be attributed to the fact that Eudragit itself has excellent flow properties (measured individually angle of repose < 20°) whereas the constituent excipients do not (Angle of repose for HPMC ~ 40°, HPC ~ 43° and EC ~ 35°). Since physical mixing does not employ any specific flow-improvement process, the flow properties of the constituent excipients directly affect the flow of the blend. However, in case of high shear mixer granulation, the effect of processing is clearly visible on the flow properties of excipients blend. The results of spray dried co-processed excipients were also in consonance with the high shear mixer granulation (HSMG) results wherein the good flow properties were exhibited only excipient blends prepared with low polymer concentration [16].

The values of physical parameters of formulated tablets were found to be within the specified limits as per all major pharmacopeia's. This ratifies the judicious selection of the process as well as excipients. The assay values of all the formulated tablets were found to be between 95% and 105% again corroborating the judicious selection of product and process parameters.

As depicted in Fig. 2, more than 80% of drug was released in 10 h in case of formulation prepared employing physically mixed polymers. This can be attributed to the inability of these physically mixed polymers to form a dense polymer matrix. Out of the three physically mixed polymers, Formulation T1 exhibited most controlled release profiles due to inherent swelling tendency of HPMC. Eudragit, on the other hand, does not exhibit promising swelling characteristic due to lesser content of hydrophilic amine group (~5%). Formulation T2 showed nearly complete release in 8 h due to the fact that it contains two non-swelling polymers which were unable to interact during processing. Formulation T3 exhibited a relatively controlled behaviour than T2 due to the presence of moderately swelling HPC.

Similarly, formulations T4, T5 and T6 also behaved on the same heels of Formulations T1, T2 and T3. However, the release was a bit more controlled due to high shear granulation of constituent polymer prior to compression which led to surface interaction in presence of granulating fluid. In case of spray dried polymers, however, both the polymers were dissolved in a common solvent. This led to a synergistic molecular amalgamation among the polymers, thus forming a co-processed polymer with enhanced release controlling properties as compared to individual as well as granulated polymers. Out of the three spray dried polymer blends, Formulation T7 and T8 exhibited similar release profiles as compared to the marketed formulation.

Studies on swelling index and fluid uptake depicted that the physical mixture of polymer blends containing HPMC exhibited maximum swelling and fluid uptake. This was observed due to the presence of free HPMC in the tablet matrix. The least swelling was observed with Formulation T8 which was due to the presence of two amalgamated non-swelling polymers.

Also, Formulation T8 exhibited nearly similar drug release profile as compared to the marketed formulation and a perfect zero-order release which is not usually obtainable with other directly compressed matrices.

The DSC thermograms of the optimized formulation was exhibiting the melting endotherm at around 135 °C which was matching with the corresponding endotherm observed with the pure drug substance (around 137 °C). PXRD diffractograms confirms the crystallinity of metoprolol in optimized formulation T8. The presence of characteristic peaks of drug substance in the FTIR spectra (placebo nullified) of Formulation T8 indicated the absence of any interaction between the polymers and the drug substance.

Stability studies indicated that the optimized formulation T8 was stable up to 6 months at accelerated conditions. This further shows the robustness of the developed formulation commonly encountered external stimuli of heat and moisture.

In vivo pharmacokinetic studies depicted that the optimized formulation T8 behaved in a similar manner as was observed with the marketed brand. Thus, the studies successfully depict the development of a simple directly compressible formulation bio-equivalent with the marketed formulation developed employing multiparticulate system (MUPS) technology.

6. Conclusion

Directly compressible co-processed excipients with improved functional property was developed using eudragit RSPO and ethylcellulose NC50 without any chemical changes by spray drying method. Developed co-processed excipient showed good sustained drug release property and could be alternate way to overcome the problems associated with single polymer alone. The present studies successfully demonstrate the development of a novel co-processed free-flowing directly compressible polymer capable of providing a near zero-order release with minimum distortion of dosage form geometry.

Declaration of interest

The authors report no declarations of interest.

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