ECO SCIENCE JOURNALS

DESIGN AND CHARACTERIZATION OF METOPROLOL SUCCINATE RAPIMELTS USING CO-PROCESSED SUPERDISINTEGRANTS

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Article Info: Received: 08 May 2026, Accepted: 02 Jun 2026, Published: 07 Jun 2026

ABSTRACT:

Metoprolol succinate belongs to the class of selective β-1-adrenoreceptor blocking agent and is widely used for the treatment of hypertension, angina pectoris and heart failure. The purpose of the present work was designed to enhance the oral bioavilability of the drug metoprolol succinate by formulating it into rapimelts by using super disintegrants of both natural super disintegrants such as FGP (Fenugreek seed powder) & IHP (Ispaghul husk powder) and synthetic super disintegrants such as SSG (Sodium starch glycolate) & CCS (Croscarmellose sodium). by its combination.

Keywords: Metoprolol succinate, β-1-adrenoreceptor, oral bioavailability, Fenugreek, super disintegrants, hypertension.

INTRODUCTION:

It has been known for centuries that buccal and sublingual oral administered drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, and braciocephalic vein and are then drained into the systemic circulation. Therefore, it can be easily by pass the hepatic first-pass elimination of drugs. The mucosa has a rich blood supply and it is relatively permeable. The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply.[1]

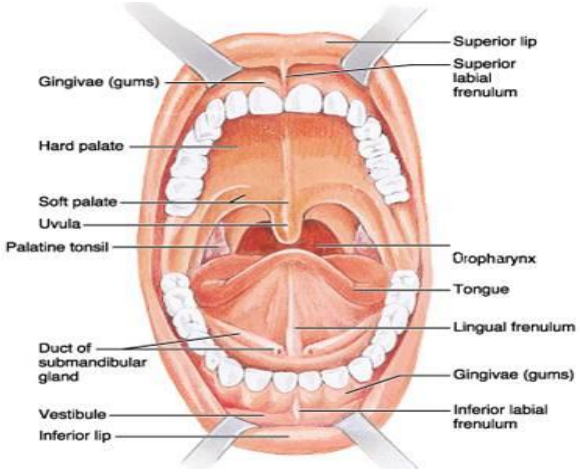

FIG-1. Structural features of oral cavity.

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Citation: Jeevan reddy (2026). Design and characterization of metoprolol succinate rapimelts using co-processed superdisintegrants Eco Science Journal.2026 3(3).

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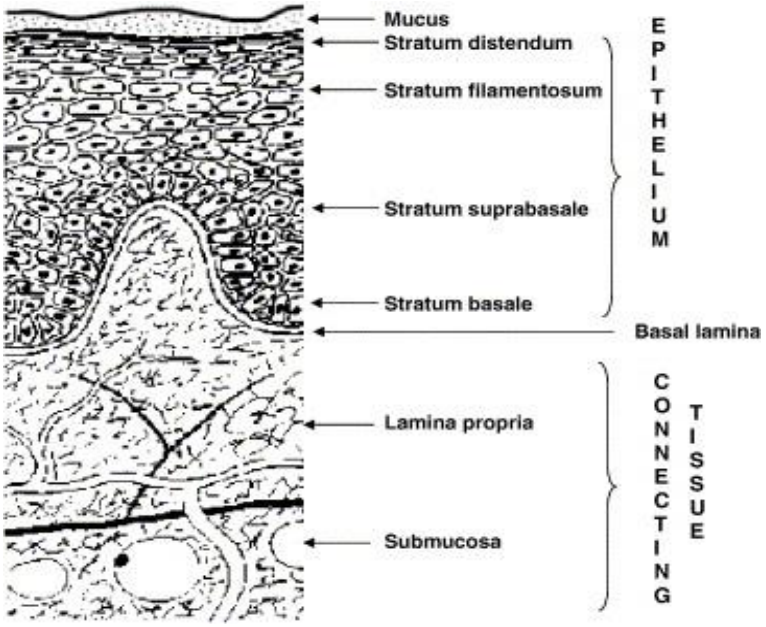

FIG-2. Layers of oral mucosa.

Oral mucosa Structure: The total area of the oral cavity is about 100 cm^2 [2]. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The keratinized and non-keratinized regions of the oral epithelium differ from each other in terms of lipid composition of the cells. The keratinized epithelium has predominantly neutral lipids (e.g: ceramides) while the non-keratinized epithelium has few but polar lipids, particularly cholesterol sulphate and glucosyl ceramides[3]. Buccal membrane has numerous elastic fibers in the dermis, which is another barrier for diffusion of drug across the buccal membrane. Drug that penetrates this membrane enters the systemic circulation via network of capillaries and arteries. The lymphatic drainage almost runs parallel to the venous vascularization and ends up in the jugular ducts. The oral mucosal surface is constantly washed by the saliva (daily turn out is about 0.5 to 2 liters). The drug absorption across the oral mucosa occurs in the non-keratinized sections for protein/peptide delivery buccal route offers distinct benefits over other mucosal routes like nasal, vaginal, rectal, etc.

Metoprolol Succinate (butanedioic acid; {2-hydroxy-3-[4-(2methoxyethyl)phenoxy]propyl}(propan-2-yl)amine) blocks β1 adrenergic receptors in heart muscle cells, thereby decreasing the slope of phase 4 in the nodal action potential (reducing Na^+ uptake) and prolonging repolarization of phase 3 (slowing down K^+ release). It also suppresses the norepinephrine-induced increase in the sarcoplasmic reticulum (SR) Ca 2^+ leak and the spontaneous SR Ca 2^+ release, which are the major triggers for atrial fibrillation[4].

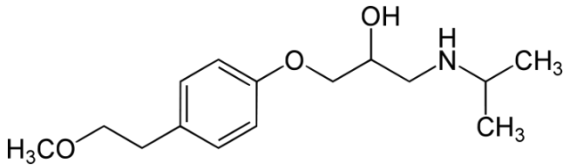

FIG-3. Chemical structure of Metoprolol Succinate.

MATERIALS AND METHODS:

Metoprolol succinate, Camphor, Lactose, Sodium starch glycolate, Croscarmellose sodium, Fenugreek seed powder, Ispaghul husk powder, Magnesium stearate, Sodium saccharine, Talc were obtained and used as API, Subliming agent, Diluent, Superdisintrgrant, Lubricant, Sweetening agent, Anti – adherent.

Preparation of calibration curve of Metoprolol: 5 mg of Metoprolol succinate was accurately weighed and transferred into a 50 ml standard flask and then volume was made up to 50 ml with methanol. Pipette out 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml from above solution and transferred into a 10 ml standard flask and then diluted to 10 ml with salivary simulated fluid of pH 6.8.

Absorbance of the prepared solutions was determined spectrophotometrically at 222 nm. The experiment was repeated for three times. Salivary simulated fluid of pH 6.8 was used as blank solution. A graph was plotted with concentration of metoprolol succinate (µg/ml) on X- axis against absorbance on Y-axis[5].

Preparation of Co-processed Super Disintegrants:- The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of natural superdisinegrants (FGP & IHP) and synthetic superdisintegrants (CCS & SSG) in the weight ratios of 1:1 were added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was passed through # 44-mesh sieve. The powder was dried in a hot air oven at 60°C for 20 minutes. The dried powder was sifted through # 44-mesh sieve and stored in airtight

Ingredients	F1	F2	F3	F4	F5	F6
Metoprolol succinate	50	50	50	50	50	50
Camphor	20	20	20	20	20	20
CCS & FGP	6	----	-----	-----	-----	-----
CCS & IHP	----	6	-----	-----	-----	-----
SSG & FGP	----	-----	6	-----	-----	-----
SSG & IHP	-----	-----	-----	6	-----	-----
CCS & SSG	-----	-----	-----	-----	6	-----
FGP & IHP	-----	-----	-----	-----	-----	6
Sodium saccharine	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1 .5	1 .5	1 .5	1.5	1.5	1.5
Talc	1	1	1	1	1	1
Lactose	73	73	73	73	73	73
Total weight (mg)	150	150	150	150	150	150

All ingredients are taken in mgs

Table 1. Composition of Metoprolol succinate rapimelts (F1 To F6).

Preparation of Rapimelts:- Metoprolol succinate and lactose were mixed with super disintegrants for 15 minutes in mortar, passed through sieve no 60.this blend was mixed with talc ,and magnesium state for 5 min and processed for direct compression by using 7mm round flat faced of rotary tablet machine.

The fast disintegrating rapimelts were prepared by different combinations of super disintegranting agents such as sodium starch glycolate and cross carmellose sodium, FGP, IHP by Direct compression technique[7].

Weight Ratios	Combinations of Superdisintegrants
1:1	CCS & FGP
1:1	CCS & IHP
1:1	SSG & FGP
1:1	SSG & IHP
1:1	CCS & SSG
1:1	FGP & IHP

Table 2. Ratios of co-processed superdinintegrants.

EVALUATION METHODS:

The prepared blend was evaluated for Pre-compression properties like Angle of repose, Bulk density, Tapped density, Carr's index, Hausner's ratio.

The prepared formulations were evaluated for post compression for Thickness, Hardness, Uniformity of weight, Disintegration time, *In-vitro* drug release, Friability test, *In-vitro* dispersion time test, Wetting time, Water absorption ratio, Accelerated Stability study[8].

RESULTS:

S.No	Formulation code	Bulk density	Tapped density	Carr,s index	Hausner,s ratio	Angle of repose (0)
1	F1	0.49	0.57	14.05	1.16	25.3
2	F2	0.41	0.46	11.5	1.15	25.1
3	F3	0.57	0.63	15.1	1.17	22.1
4	F4	0.54	0.61	13.5	1.17	21.4
5	F5	0.48	0.51	13.9	1.15	21.6
6	F6	0.42	0.49	12.2	1.12	20.2

Table 3. Precompression parameters of powder blend.

The bulk density of all formulations powder blend containing co-processed excipients was found to be in the range of 0.41 to 0.57 gm/ml, whereas the tapped density was observed between 0.46 to 0.63 gm/ml. From the values of bulk density and tapped density the values for Compressibility index and Hausner's ratio were calculated. The values for Compressibility index were found between 11.50 to 14.05 %. The values for Hausner's ratio were found to be less than 1.12 to 1.17. All these values are within the specified limits which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall, these values indicate good flow properties of powder blend, uniform die fill and better compression ability. Therefore, from this data so obtained, it was decided to go for direct compression of tablets from the powder blends.

S.No	Formulation code	Hardness (kg/cm^2)	Thickness (mm)	% Friability	% Weight variation
1	F1	3.9	2.66	0.9	1.61
2	F2	3.7	2.73	0.12	0.94
3	F3	3.7	2.74	0.7	1.26
4	F4	3.5	2.56	0.6	1.85
5	F5	3.9	2.45	0.8	1.21
6	F6	3.6	2.59	0.96	1.32

Table 4. Post compression parameters of Metoprolol succinate rapimelts.

The weight variation of all formulations was found to be in the range of less than 2%. None of the tablet was found to deviate from the average weight of tablets (variation with deviation less than ± 7.5, which complies with I.P specification) signifies that there is uniformity in flow of powder blend which leads to uniform die fill. Hardness test for all formulations was carried out and observations obtained were in the range of 3.0 to 4.0 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that tensile strength of all formulations was maintained after direct compression. Test for friability was conducted for all formulations, % friability was found to be in the range of 0.6 to 1.3. Friability test for all formulations indicated that % friability was less than 1%, which complies the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The thickness of all formulations was found to be uniform as it was obtained in the range of 2.45 to 2.74 mm. The values for thickness and diameter signify uniformity and it was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement.

S.No	Formulation code	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio	% Drug content	Mouth feel
1	F1	35	30	29	84.26	94.34	Good
2	F2	34	28	27	86.35	94.27	Good
3	F3	35	25	28	87.53	96.85	Good
4	F4	31	22	26	87.98	94.39	Good
5	F5	29	20	20	91.23	97.75	Good
6	F6	25	18	19	96.44	96.64	Good

Table 5. Evaluation tests for Metoprolol succinate rapimelts.

From the above results it is observed that F6 formulation shows decrease in wetting time, disintegration time, in vitro dispersion time and more water absorption ratio. It indicates that high capillary action of both natural superdisintegrants (FGP & IHP) In the weight ratio of (1:1).It indicates that high capillary action of the co-processed superdisintegrants(IHP & FGP) in the weight ratio of (1:1) shown the better fundamental properties of the dosage forms mentioned in the table 5.

Co-processing by solvent evaporation gives more synergy between the superdisintegrants than physical mixing. F6 formulation shows better results due to solvent evaporation of superdisintegrants. The mouth feel of the tablets also good due to mannitol and sweetening agent masks the bitter taste of metoprolol. Wetting time of tablets are found in the range of 28 to 35 sec. and the water absorption ratio was found in the range of 84.26 to 96.44 %. As the porosity of formulation is increased by the superdisintegrating agents and water uptake is increased due to increased capillary action, the formulation is showing less wetting time. The less wetting time helps in the quick dispersion of the formulation when come in contact with the saliva and having linear relationship with disintegration time.

Disintegration time for all formulations was found to be in the range of 19 to 29 sec. Disintegration study explained that there was decrease in disintegration time with successive increase in concentration of sodium starch glycolate but comparatively solvent evaporation co-processed formulations take least time for disintegration with respect to their physical mixture formulations. Such a difference in disintegration time between both of these formulations indicates that in solvent evaporation co-processed formulation there might be increase in capillary action of Superdisintegrants which might have led to improved water uptake. *In vitro* dispersion time indicates complete dispersion of formulation in the saliva and it was found to be in the range of 21sec to 32sec and it is due to more porosity of superdisintegrant. Quick dispersion of formulation favours fast disintegration of formulation. Drug content of all formulations was observed between 94.39 to 97.74. Drug content for all formulations showed uniformity which indicated that there was a uniform flow and uniform distribution of drug.

S. No	Time (min)	Formulation code		
		F1	F2	F3
1	2	49.4±0.34	50.2±1.34	50.8±0.53
2	4	56.7±0.65	59.3±0.65	61.3±0.42
3	6	69.5±0.32	71.3±0.98	74.8±0.89
4	8	75.4±0.68	76.7±1.22	79.3±1.02
5	10	79.6±0.87	82.8±0.82	84.3±0.63
6	12	82.2±0.45	84.3±0.52	**87.5±0.49**

Table 6. Dissolution data of formulation containing physical mixing co-processed superdisintegrants.

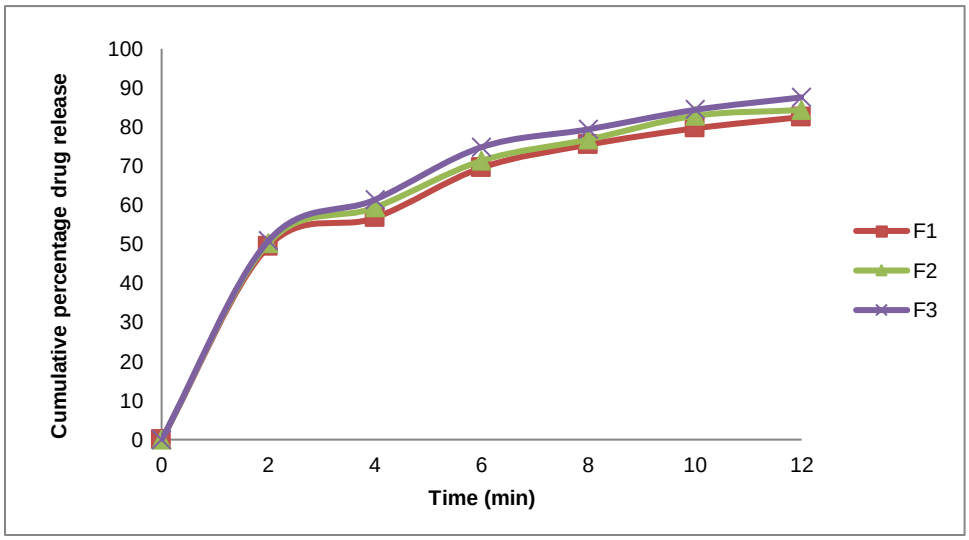

FIG-4. Dissolution profile of formulation containing physical mixing co-processed superdisintegrants

S. No	Time (min)	Formulation code		
		F4	F5	F6
1	2	52.31±0.93	54.25±0.37	54.98±0.59
2	4	58.74±0.29	61.34±0.97	63.43±0.47
3	6	71.51±0.76	73.38±0.56	76.85±0.49
4	8	79.43±1.02	80.27±0.38	82.53±0.79
5	10	81.34±0.87	85.83±0.65	89.33±0.83
6	12	86.54±0.27	91.23±0.86	**97.00±0.48**

Table 7. Dissolution studies of formulation containing solvent evaporation co-processed superdisintegrants

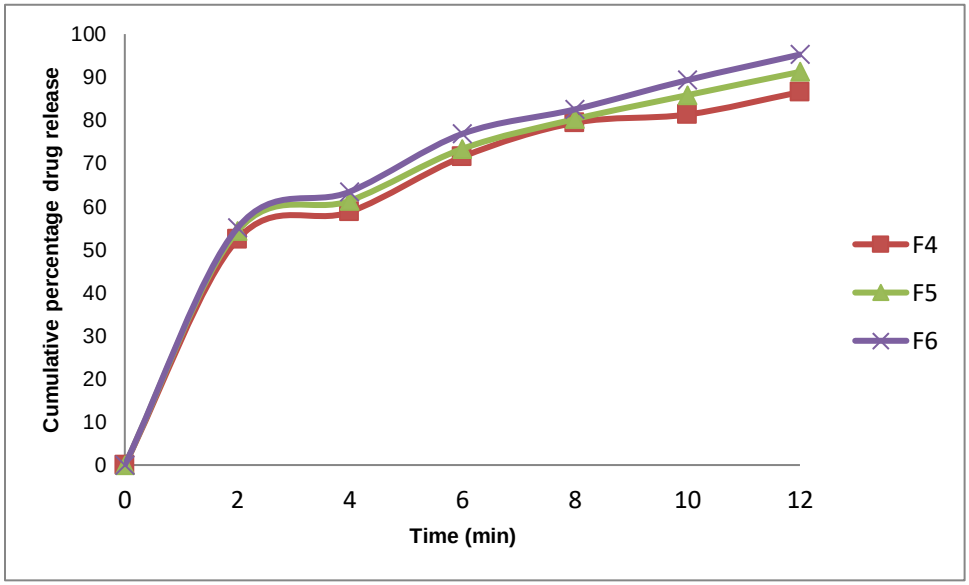

FIG-5. Dissolution profile of formulation containing solvent evaporation co-processed superdisintegrants.

S. No	Time (min)	Formulation code					
		F1	F2	F3	F4	F5	F6
1	2	49.4±0.34	50.2±1.34	50.8±0.53	52.31±0.93	54.25±0.37	54.98±0.59
2	4	56.7±0.65	59.3±0.65	61.3±0.42	58.74±0.29	61.34±0.97	63.43±0.47
3	6	69.5±0.32	71.3±0.98	74.8±0.89	71.51±0.76	73.38±0.56	76.85±0.49
4	8	75.4±0.68	76.7±1.22	79.3±1.02	79.43±1.02	80.27±0.38	82.53±0.79
5	10	79.6±0.87	82.8±0.82	84.3±0.63	81.34±0.87	85.83±0.65	89.33±0.83
6	12	82.2±0.45	84.3±0.52	87.5±0.49	86.54±0.27	91.23±0.86	**97.00±0.48**

Table 8. Comparative Dissolution studies of Metoprolol succinate rapimelts.

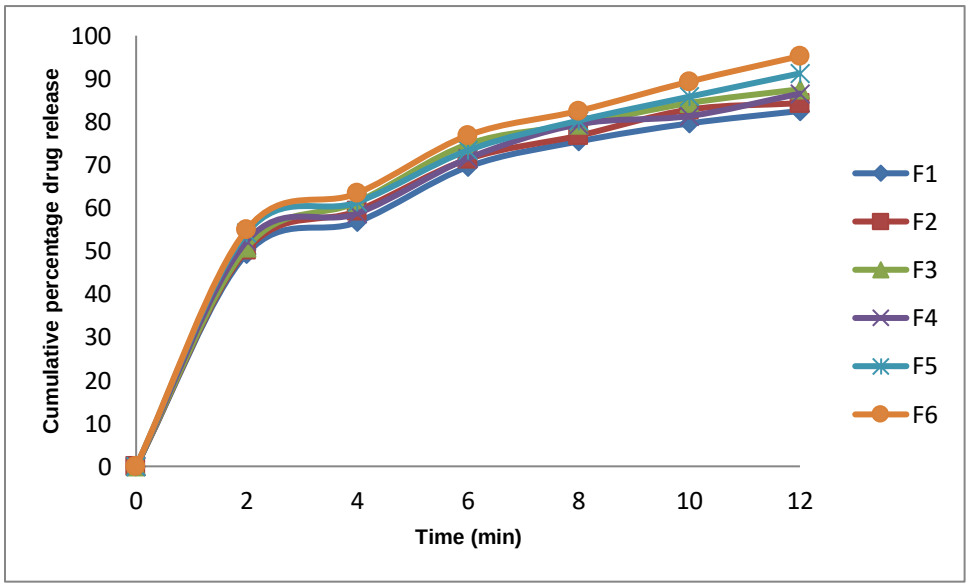

FIG-6. Dissolution profile of Metoprolol succinate rapimelts.

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