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FORMULATIONS AND EVALUATION OF METOPROLOL TARTRATE ORODISPERSIBLE TABLET BY DIRECT COMPRESSION CO-PROCESSED BY USING EXCIPIENT ISABGOL

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Abstract
This study investigates the formulation and evaluation of orodispersible tablets (ODTs) of Metoprolol tartrate using Isabgol as a co-processed excipient. The primary goal was to enhance patient compliance, particularly for individuals with swallowing difficulties. A series of formulations were developed, incorporating various superdisintegrants, and subjected to thorough characterization. Evaluation of the powder blends demonstrated good flow properties, compressibility, and uniformity. Post-compression studies indicated satisfactory hardness, low friability, and acceptable disintegration times, with the optimized formulation exhibiting a disintegration time of 32 seconds. In vitro drug release studies showed that the optimized formulation released 99.02% of Metoprolol tartrate within 300 seconds. Stability studies confirmed the robustness of the formulation, maintaining its performance under different temperature conditions over four weeks. Overall, the results suggest that the developed ODTs can provide an effective and patient-friendly alternative to conventional tablet formulations.

Keywords: Metoprolol tartrate, orodispersible tablets, Isabgol, formulation development, patient compliance, superdisintegrants, drug release, stability studies.

Introduction

Metoprolol tartrate is a selective beta-1 adrenergic antagonist extensively used in the management of cardiovascular conditions, including hypertension, angina pectoris, and certain arrhythmias. This medication works by selectively blocking beta-1 receptors in the heart, leading to reduced heart rate and myocardial contractility, ultimately lowering blood pressure and alleviating cardiac workload. Despite its therapeutic benefits, adherence to Metoprolol therapy can be compromised, particularly among populations with swallowing difficulties, such as the elderly or pediatric patients (Khan et al., 2020).

Orodispersible tablets (ODTs) represent a promising alternative to conventional dosage forms, designed to disintegrate rapidly in the oral cavity without the need for water. This feature enhances patient compliance and allows for improved bioavailability of the drug due to quicker absorption in the oral mucosa. ODTs are especially beneficial for individuals with dysphagia, as they provide a convenient and palatable means of administration (Prajapati et al., 2011). The formulation of

effective ODTs relies heavily on the selection of appropriate excipients that promote rapid disintegration, improve mouthfeel, and mask unpleasant tastes.

The incorporation of natural excipients in pharmaceutical formulations has garnered attention due to their safety and functional advantages. Isabgol, derived from the seeds of *Plantago ovata*, is a natural polymer recognized for its gel-forming and mucilage properties. When mixed with water, Isabgol can form a gel-like matrix that aids in moisture absorption and enhances the texture of solid dosage forms. Its unique properties make it a potential candidate for use in ODT formulations, where it can improve disintegration and dissolution rates of the active pharmaceutical ingredient (Sikdar et al., 2021; Tiwari et al., 2017).

This study aims to formulate and evaluate Metoprolol tartrate orodispersible tablets using Isabgol as a co-processed excipient. The primary objectives include developing ODTs with varying concentrations of Isabgol and assessing their characteristics, including disintegration time, dissolution profile, hardness, friability, and taste masking. The investigation of the in vitro drug release profile of Metoprolol tartrate from these ODTs, in comparison to conventional tablets, will provide insight into the potential benefits of this formulation approach.

The significance of this research lies in its potential to enhance patient compliance and therapeutic outcomes through the development of Metoprolol tartrate orodispersible tablets co-processed with Isabgol. By utilizing the natural properties of Isabgol, this formulation may offer a more acceptable and effective alternative to traditional dosage forms, particularly for patients facing challenges with swallowing.

Material and Methods

Material

The formulation of orodispersible tablets for Metoprolol tartrate involved a range of chemicals sourced from various suppliers. The active pharmaceutical ingredient, Metoprolol tartrate, was obtained as a gift sample from Pharmaceutical Company. Key excipients included sodium starch glycolate, croscarmellose sodium, and crospovidone, sourced from S. D. Fine Chem. Ltd. and Qualigens Fine Chemicals, Mumbai, which serve as superdisintegrants to enhance tablet disintegration. Magnesium stearate and talc, supplied by Jiangsu Huaxi International and Loba Chemie Pvt. Ltd., respectively, were used as lubricants to improve tablet manufacturing. Lactose, another excipient from Loba Chemie, acted as a filler, while KH_2PO_4, ethanol, methanol, hydrochloric acid (HCl), and sodium hydroxide (NaOH), all from S. D. Fine Chem. Ltd., were employed in various preparative and analytical processes. Isabgol, sourced from Adonis Laboratories Pvt. Ltd., Mumbai, was utilized as a natural co-processed excipient to further enhance the properties of the orodispersible tablets.

Methods

Formulation of orodispersible tablets of Metoprolol tartrate

The orodispersible tablets of metoprolol tartrate were prepared using the subliming agents i.e camphor, menthol Croscarmellolose sodium as synthetic superdisintegrant and Plantago husk powder (Isabgol) as natural superdisintegrant, Lactose as a diluent, aspartame as sweetening agent (Tahir *et al.,* 2010).

All the ingredients except magnesium stearate and starch were shifted through sieve #100 separately and add mixed together by means of geometrical mixing for about 15min to make a uniform blend. Magnesium Stearate and Talc both have passed through sieve #100separately and mixed with the above blend for sufficient time usually 5-7 min. were directly compressed using a 10mm,round, flat faced tooling to make the tablet of said compression specifications as mentioned in Table 1, using 10 station punching machine. The tablet press setting was kept constant across all formulations.

Table 1: Formulation of Metoprolol Tartate Orodispersible Tablet

Ingradients	Formulation Code					
	F1	F2	F3	F4	F5	F6
Metoprolol tartrate	25	25	25	25	25	25
Camphor	15	15	15	15	15	15
Microcrystalline Cellulose	30	30	30	30	30	30
Aspartame	10	10	10	10	10	10
Lactose	150	145	140	150	145	140
Cross Carmellose Sodium	10	15	20	--	--	--
Isabgol	--	--	--	10	15	20
Magnesium Stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total	250	250	250	250	250	250

Evaluation of Blend

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, "h" was obtained (Schiermeier and Schmidt, 2002). Diameter of heap "D" was measured. The repose of angle θ, was calculated by formula:

$\tan \theta = 2h/D$

Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined (Late *et al.,* 2008). The bulk density was calculated using the formula: $\rho_b = M/V_b$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum (V_1) occupied in the cylinder and the weight (M) of the bland was measured. The tapped density (ρ_t) was calculated using the formula: $\rho_t = M / V_1$

Carr's index

It is expressed in percentage and is expressed by: I = Dt – Db / Dt

Where, Dt is the tapped density of the powder, Db is the bulk density of the powder.

Evaluation of orodispersible tablets

Weight variation test

10 tablets were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight (Mizumoto *et al.,* 2005).

Test for uniformity

Two tablets were placed in a 100 ml of water and stirred until completely dispersed. A smooth dispersion produced through passed through a sieve screen with a nominal mesh aperture of 710 mm (20 meshes). The formulation posses the values with in the official limit (Shenoy *et al.,* 2003).

Drug estimation

10 tablets were taken their weight accurately. Average weight is calculated and equivalent to 25 mg of drug was taken for estimating the drug content in the total tablet. It was within official limit (Mahajan *et al.,* 2004). Percentage of drug content is calculated by Y/X ×100

Where Y = Actual drug content (mg)

X = Labeled amount of drug (mg)

Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in plastic chamber revolving at 25 rpm and dropping the tablets at height of 6 inches in each revolution (Kaushik *et al.,* 2004). Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

The friability (f) is given by the formula:

$F = (1\text{-}W_0/W) \times 100$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablet after the test.

Hardness

Hardness or tablet crushing strength (Fc) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester (Amin *et al.,* 2005).

Thickness

The individual crown-to crown thickness of 10 tablets was determining using slide caliper for each batch. The simple mean and standard deviation of each batch tablets were calculated (Zhao and Augsburger, 2005).

***In vitro* Disintegration test**

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in water bath at 37 ± 20C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets (Bhagwati *et al.,* 2005).

***In vitro* dispersion test**

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and in vitro dispersion time was performed.

Drug content

Twenty tablets were taken randomly and individual tablet were crushed, an amount of the powder equivalent to 40mg of Metoprolol tartrate was dissolved in the 50 ml of 6.8 pH phosphate buffer. Shaken for 30 min and added sufficient to produce 100 ml and filtered, diluted suitably and analyzed for drug content at 224nm using UV-Visible spectrophotometer (Labindia 3000+).

Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 6 ml of simulated saliva pH 6.8. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time. Three tablets from each formulation were randomly selected and the average wetting time was noted. Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a petridish.

Dissolution Studies

The release rate of Metoprolol tartrate from orodispersible tablets was determined using USP Dissolution Testing Apparatus II (Paddle type) (Avinash *et al.,* 2003). The dissolution test was performed using 900 ml of 6.8 pH phosphate Buffer, at 37 ± 0.5^0C and 50 rpm. A sample (5 ml) of

the solution was withdrawn from the dissolution apparatus every interval up to 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatmann filter paper no. 41. Absorbance of these solutions was measured at 224 nm using UV spectrophotometer. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Stability studies

Stability studies were carried out on optimized formulation as per ICH specifications. The tablets were stored at 25 ± 2^0C / 60 ± 5% RH and 40 ± 2 ^{0} C / 75 ±5% RH for duration of three month. After an interval of one month samples were withdrawn and tested for various physical tests and *in vitro* drug release.

Results and Discussion

The formulation and evaluation of orodispersible tablets (ODTs) for Metoprolol tartrate demonstrated promising results across various parameters, indicating the suitability of the developed formulations for patient administration.

The evaluation of the powder blends (Table 2) showed that the formulations (F1-F6) exhibited acceptable flow properties, which is crucial for ensuring uniformity during tablet production. The angle of repose values ranged from 30° to 32°, indicating good flowability, while bulk densities varied between 0.51 and 0.58 gm/cm³. Tapped densities were slightly higher, demonstrating the ability of the powders to consolidate under pressure. The % compressibility index values ranged from 16.41% to 22.05%, suggesting that the blends had adequate compressibility, which is essential for effective tablet formation. Hausner's ratios, ranging from 1.19 to 1.28, also confirmed that the formulations were of good quality, with values below 1.25 indicating acceptable flow characteristics.

Post-compression evaluations (Table 3) indicated that all formulations had satisfactory hardness (ranging from 3.2 to 3.6 kg/cm²) and low friability (between 0.51% and 0.71%), which is indicative of their mechanical strength and stability during handling. The thickness of the tablets was consistent across formulations, suggesting uniformity in tablet dimensions. All formulations passed the weight variation test, ensuring that the tablets contained the appropriate amount of Metoprolol tartrate.

Disintegration and wetting times (Table 4) are critical parameters for ODTs, as rapid disintegration in the oral cavity is desired for patient convenience. The optimized formulation (F4) exhibited a disintegration time of 32 seconds and a wetting time of 11 seconds, both of which are favorable for ODTs. This performance could be attributed to the inclusion of Isabgol and superdisintegrants, which enhance moisture absorption and tablet disintegration.

The in-vitro drug release profiles (Table 5) showed that formulation F4 achieved the highest cumulative drug release at 300 seconds (99.02%), demonstrating its effectiveness in delivering Metoprolol tartrate quickly and efficiently. Other formulations also showed substantial release profiles, indicating that the use of Isabgol and selected excipients positively influenced the dissolution characteristics of the tablets.

Stability studies (Tables 6 and 7) revealed that the optimized formulation (F4) maintained its disintegration time and drug release profile under various temperature conditions over four weeks. Notably, the disintegration time remained stable, even at elevated temperatures (50°C), suggesting good thermal stability of the formulation. The in-vitro drug release percentage also demonstrated minimal variation over time, affirming the robustness of the formulation.

Table 2: Evaluation of Powder blend

Formulation Code	Evaluation Parameters				
	Angle of Repose	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	% Compressibility Index	Hausner's Ratio
F1	32±0.02	0.53±0.04	0.65±0.02	18.46±0.04	1.22±0.08
F2	31±0.01	0.51±0.05	0.63±0.05	19.04±0.03	1.23±0.09
F3	30±0.05	0.56±0.05	0.67±0.03	16.41±0.03	1.19±0.05
F4	31±0.03	0.53±0.04	0.68±0.02	22.05±0.05	1.28±0.05
F5	30±0.02	0.58±0.02	0.71±0.08	18.30±0.03	1.22±0.07
F6	32±0.05	0.54±0.03	0.69±0.05	21.73±0.02	1.27±0.07

Table 3: Evaluation of Post compression studies

Formulation Code	Evaluation Parameters			
	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight Variation (mg)
F1	3.2±0.02	0.68±0.01	4.32±0.03	Pass
F2	3.5±0.06	0.53±0.04	4.51±0.05	Pass
F3	3.2±0.05	0.71±0.02	4.62±0.07	Pass
F4	3.3±0.07	0.67±0.05	4.79±0.02	Pass
F5	3.6±0.05	0.62±0.04	4.73±0.01	Pass
F6	3.3±0.08	0.51±0.04	4.68±0.05	Pass

Table 4: Evaluation of Post compression studies

Formulation Code	Evaluation Parameters		
	Disintegration time (s)	Wetting time (s)	Drug content (%)
F1	50±8	17±3	96.50±0.25
F2	45±6	20±5	97.65±0.14
F3	40±3	15±2	98.85±0.34
F4	32±4	11±4	99.67±0.45
F5	40±7	14±3	96.45±0.32
F6	45±2	15±2	97.74±0.44

Table 5: In-vitro release study of Metoprolol tartate orodispersible tablet

Time (Sec)	Cumulative % of Drug release					
	F1	F2	F3	F4	F5	F6
0	0.000	0.000	0.000	0.000	0.000	0.000
30	32.25	36.28	40.23	42.25	32.23	30.22
90	39.95	41.19	43.32	55.65	40.56	39.98
120	48.85	53.46	56.58	63.32	48.89	47.45

150	53.32	56.09	63.32	71.12	56.65	55.63
180	57.74	62.62	69.23	79.98	67.77	64.45
210	68.87	71.87	77.94	86.65	72.25	70.65
240	78.85	81.54	84.45	90.23	81.12	76.65
270	81.12	85.12	89.98	96.65	86.65	83.32
300	89.98	92.23	93.32	99.02	90.23	91.12

Table 6: Stability study parameter for change in disintegration time

Product code	Temperature	**Change in disintegration time(sec) of the optimized formulation**			
		At 0 week	**At 2 weeks**	**At 3weeks**	**At 4 weeks**
F4	25^0C	38	42	35	30
	4^0C	38	40	39	30
	40^0C	38	38	30	26
	50^0C	38	30	28	26

Table 7: Stability Study Parameter for Change in Release Study

Product code	**Temperature**	**In-vitro % Drug release profile**			
		At 0 week	**At 2 weeks**	**At 3weeks**	**At 4 weeks**
F4	25^0C	99.46	98.7	98.14	97.83
	4^0C	99.46	98.95	98.99	98.14
	40^0C	99.46	98.85	98.86	98.23
	50^0C	99.46	98.94	98.94	98.54

Conclusion

The formulation of Metoprolol tartrate orodispersible tablets using Isabgol and various excipients proved successful in achieving desirable characteristics for rapid disintegration and drug release. The formulations exhibited excellent flow properties, mechanical strength, and stability, making them suitable for enhancing patient compliance. Further studies may focus on in vivo evaluations to confirm the therapeutic benefits of the developed ODTs.

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