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FORMULATION AND EVALUATION OF ORO DISPERSIBLE TABLETS OF METOPROLOL TARTRATE BY DIRECT COMPRESSION USING SUPER DISINTEGRANTS

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ABSTRACT
The objective of the present investigation was to prepare orodispersible tablets of metoprolol tartrate by direct compression method using three super disintegrants, cross carmellose sodium, cross povidone and sodium starch glycolate at different concentrations. Oro dispersible tablet is the fast growing and highly accepted drug delivery system, convenience of self administration, compactness and easy manufacturing. Metoprolol tartrate is a antihypertensive agent, half life is 3 hrs and bioavailability is 40%. It is completely absorb after oral administration. Microcrystalline cellulose is used as diluent. The bland was examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The tablets were evaluated for thickness, hardness, friability, and weight variation, content uniformity, wetting time, Water absorption ratio, *In-vitro* dispersion time, dissolution studies and FTIR studies. Twelve formulations F1 to F12 were prepared with three super disintegrants with different concentration. The optimum formulation was chosen and their optimum results were found to be in close agreement with experimental finding.
KEYWORDS: Oro dispersible tablets, Super disintegrants, Metoprolol tartrate, direct compression.

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INTRODUCTION

Most of the oral pharmaceutical dosage form like conventional tablets and capsules are formulated but it was difficult to swallow for elderly and children. This problem is also applicable to active working or travelling people who do not have ready access to water[1]. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating convenient dosage form to administration[2]. One such approach is oro dispersible tablets (ODTs). An oro dispersible tablet is a solid dosage form that disintegrates and dissolves in mouth without water within 60 seconds or less[3]. The various technologies used to prepare ODTs includes freeze drying and sublimation[4]. The commonly used super disintegrants are cross carmellose sodium, cross povidone and sodium starch glycolate[5]. In many orally disintegrating tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence dissolution and also effervescent agent also further hastens the process of disintegration.

Metoprolol tartrate is an antihypertensive agent, bioavailability is approximately 40% half life is 3 to 7 hrs and it is completely absorbed after oral administration. Metoprolol tartrate ODTs was prepared by direct compression method using three super disintegrants, cross carmellose sodium, cross povidone and sodium starch glycolate at different concentrations. The blend and prepared tablets were evaluated and compared with three super disintegrants, effect on the *in vitro* dispersion time, *In Vitro* drug release and FTIR studies were observed. From the twelve formulations, the optimum formulations were selected.

MATERIALS AND METHOD

Metoprolol tartrate was obtained from as a gift sample from Dr. Reddys, Hyderabad, sodium starch glycolate, cross carmellose sodium was obtained as gift sample from AET LABORATORIES Hyderabad .cross povidone were gift sample from LOBA chemie pvt. Ltd,

Mumbai. All other chemicals and reagents were of pharmacopoeial grade.

Preparation Of Metoprolol Tartrate Tablets

Tablets are prepared by direct compression method. Accurately weigh amount of drug to this super disintegrants (sodium starch glycolates, cross carmellose sodium and cross povidone at different concentrations 3% ,6%,9%&12%),micro crystalline cellulose, mannitol, aspartame ,aerosol, magnesium stearate were added and mixed properly passed through sieve no.#20. Tablets were punched by using 8mm flat punch by rotary tablet compression machine. Twelve batches F1 to F12 were prepared with various proportion of super disintegrants and excipients as shown in **table 1**.

Characterization of Oro dispersible tablets

Evaluation of blends

Angle of repose

Angle of repose was determined using funnel method[6]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap(r) was measured and the angle of repose (ϴ) was calculated using the formula.

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

Bulk Density

Apparent bulk density (p_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula[6].

$$p_b = M/ V_b$$

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time.The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (p_t)[6] was calculated by using formula.

$$p_t = M/ V_t$$

Compressibility Index

The simplest way for measuring of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I)[6] which is calculated as follows.

$$I = (V_0 - V_t/ V_0)\ 100$$

Where, vo is the bulk volume and vt is tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics, where as above 25% indicates poor flowability.

Hausner's Ratio

Hausner's ratio[7] is an indirect index of ease of powder flow. It is calculated by the following method

$$\text{Hausner ratio} = p_t / p_d$$

Where p_t is tapped density and p_d is bulk density lower Hausner's ratio (<1.25) indicates better flow properties than higher ones[8](>1.25).

Evaluation of Tablets

Weight Variation

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and were compared with average weight[6].

Friability

Friability of the tablets was determined using roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$F = (1-W_0/W)\ 100$$

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

Hardness

Hardness was measured using Monsanto tablet hardness tester[6].

Thickness

Ten tablets were taken from each formulation and their thickness was measured using digital Vernier calipers (Mitutoyo corp, Kawasaki,Japan).

Wetting Time and Water Absorption Ratio

The method reported by Yunixia *et al*[9] was following to measure the tablet wetting time. A piece of tissue paper (12cm×10.75cm) folded twice was placed in a petridish containing 6ml of simulated saliva pH 10, a tablet was put on the paper ,the time required for complete wetting was measured. The wetted tablet was taken and weighed. Water absorption ratio (R) was determined using following equation

$$R = 100 \times (W_a - W_b)/ W_b$$

Where W_b is weight of tablet before water absorption and W_a is weight of tablet after water after water absorption.

***In-Vitro* Dispersion Time**

Tablets were placed in 10 ml beaker containing 6ml of 6.8 pH phosphate buffer and time taken for complete dispersion was observed[11].

Dissolution Study

Dissolution rate was studied by using USP type 2 apparatus at 50 rpm. 6.8 pH phosphate buffer 900ml was used as dissolution medium. Temperature $37^0 \pm 0.5^0$c.Absorption of filtered solution was checked by UV Spectroscopy at 275 nm and drug content was determined from standard calibration curve.

Fourier Transform Infra Red Spectroscopy (FTIR)

FTIR studies were performed on drug, excipient and the optimized formulation using (SHIMADZU) FTIR. The sample were analysed between wave numbers 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

Twelve formulations of Metoprolol tartrate were prepared by direct compression method with varying concentration of three super disintegrants sodium starch glycolate, cross povidone, cross carmellose sodium. Taste masking was done by flavours and sweeteners and microcrystalline cellulose was used as diluents. Metoprolol tartrate tablets and blend evaluated for various parameters as explained earlier. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio for the prepared tablet blend **Table 2**. The angle of repose between 30 and 33, this indicates passable flowability the percentage compressibility index and Hausner's ratio are within the limits of all the formulation were shown in the table 2.

The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in **table 3**. For all the batches were found to be within the acceptable limits. All the formulations were found to pass the weight variation. The drug content was found in the range of 94% to 105% (acceptable limits) and the hardness of the tablets between 2-2.5kg/cm^2 (table 3). Friability for all formulations was shown less than 0.90% indicating a good mechanical strength of tablets (table 3). All the parameters were found well within the specified limits for uncoated tablets. The wetting time was determined for all the formulations prepared. The wetting time for the optimized formulation this indicates quicker disintegration of the tablets (table II) below one minute.

In-vitro dispersion test was done for all the formulation. Tablet disintegration was affected by the wicking and swelling of the disintegrants from the 12 formulations F5 shown less disintegration time, 24 seconds when compared with others super disintegrants. Cross povidone is used as a super disintegrants in F5 formulation. Water absorption ratio for F5 is 84.1%. So it shows good water absorption capacity (table 3).

In-vitro drug release studies of prepared tablets F1 to F12 using different super disintegrating agents by different concentrations. The maximum drug release for the formulation F1, F2, F3and F4 using different concentration of cross carmellose sodium, at the end of the 15 minutes are 95.9%, 96.1%, 97.2%, 96.3% **(table 4, Fig 1**) respectively for the formulations F5, F6, F7 and F8 using cross povidone at different concentrations. The drug release was found to be 96.8%, 96.1%, 95.3% and 95.6% at the end of 15 minutes, it shown in **(table 5, fig 2**). It concluded that F5 formulation gives maximum drug release within 10 minutes respectively for the formulation F9, F10, F11 and F12 using sodium starch glycolate at different concentrations. The drug release was found to 83.2%, 86.8%, 83.9% and 81.4% at end of 15minutes (**table 6, fig 3**) from these three different super disintegrating agent 3% cross povidone formulation F5 show good drug release.

The graph were plotted cubic root of 100-cubic root of drug remained vs time, the drug release for the optimized formulation F5 according to hixon and crowell equation. From the results drug release of F5 formulation shows Hixons Crowell mechanisms. It indicates a change in the surface area and diameter of the tablet with the progressive dissolution of tablet as the function time. FTIR spectra of the drug, excipients and optimized formulation were recorded in range of 4000-400cm^{-1}. In the optimized formulation F5 shows the presence of all the characteristics peaks of metoprolol tartrate indicates lack of any strong interaction between the drug and the excipients.

CONCLUSION

The formula was optimized for metoprolol tartrate oro dispersible tablets to give fast relief and to increase the patient compliance. The tablets containing 3% cross povidone F5 formulation is optimized due to its fast *In-vitro* dispersion when compare to other formulation. The wetting time is below one minute. The FTIR studies are done for optimized formulation there is no interaction between the drug and the excipients.

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Table 1: Formulation of Metoprolol Tartrate Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metoprolol tartrate	25	25	25	25	25	25	25	25	25	25	25	25
Cross camellose sodium	6	12	18	24	_	_	_	_	_	_	_	_
Cross povidone	_	_	_	_	6	12	18	24	_	_	_	_
Sodium stach glycolate	_	_	_	_	_	_	_	_	6	12	18	24
Microcrystalline cellulose 102	52	52	52	52	52	52	52	52	52	52	52	52
Mannitol	94	88	82	76	94	88	82	76	94	88	82	76
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Tablet Blend Evaluation Test

Formulations	Angle of repose	Bulk density	Tapped density	percent compressibility index	Hausner ratio
F1	31.6	0.49	0.65	17	1.22
F2	32.2	0.30	0.36	16.6	1.20
F3	32.6	0.25	0.31	19.3	1.24
F4	30.2	0.21	0.25	16.0	1.19
F5	31.7	0.22	0.25	12.0	1.13
F6	30.9	0.37	0.43	13.9	1.16
F7	33.1	0.37	0.42	11.9	1.13
F8	32.5	0.33	0.37	10.8	1.12
F9	31.6	0.25	0.30	16.6	1.20
F10	30.9	0.25	0.30	16.6	1.21
F11	31.2	0.37	0.45	17.7	1.21
F12	31.3	0.21	0.25	16.0	1.19

Table 3: Prepared Tablets Evaluation Test

Formulations	Weight in (mg)	Hardness Kg/cm2	Friability (%)	Thickness (mm)	Content uniformity (%)	Wetting Time (seconds)	In vitro Disintegration time	Water Absorption Ratio
F1	200.15±1.83	2.3+0.057	0.069	4.48±0.02	96	52±0.81	74±1.24	66.3± 0.54
F2	199.7±1.99	2.3±0.173	0.79	4.44±0.03	97	53±0.21	69 ±1.34	71.3± 0.56
F3	201.4±1.13	2.3±0.115	0.69	4.61±0.02	95	42±0.24	54 ±1.32	77.4± 0.45
F4	201.6±1.16	2.3±0.058	0.64	4.49±0.03	97	55±0.25	73 ±1.26	74.6± 0.64
F5	200.8±0.74	2.3±0.115	0.54	4.55±0.09	99	18±0.85	24 ±1.26	84.1 ±0.88
F6	194.6±0.33	2.3±0.17	0.64	4.38±0.06	98	24±0.92	46 ±1.34	78.3± 0.78
F7	201.7±0.14	2.3±0.152	0.73	4.49±0.03	95	33±0.95	53 ±1.45	77.3± 0.24
F8	205.9±0.28	2.3±0.05	0.59	4.58±0.03	94	35±0.13	63 ±1.24	72.0± 0.45
F9	198.2±0.23	2.3±0.058	0.59	4.65±0.08	98	68±1.24	128± 0.98	62.6± 0.65
F10	197.5±1.15	2.3±0.0	0.54	4.61±0.07	104	71±0.25	142 ±1.12	59.6± 0.48
F11	203.1±1.38	2.3±0.1	0.74	4.60±0.01	103	69±0.87	183 ±1.54	53.8± 0.95
F12	205.7±0.74	2.3±0.05	0.59	4.67±0.02	98	73±0.99	197 ±1.25	49.0± 0.35

Table 4: *In-vitro* Drug Release Studies Of Cross Carmellose Sodium

Time (min)	F1	F2	F3	F4
0	0	0	0	0
2	51.8± 0.23	52.3± 0.33	56.3± 0.46	52.7± 0.37
5	59.7± 0.28	75.5± 0.62	68.2 ±0.22	60.3± 0.34
7	76.8± 0.26	87.8± 0.53	79.3± 0.25	75.9± 0.36
10	87.8± 0.59	92.4± 0.43	85.9± 0.06	89.1± 0.19
15	95.9± 0.52	96.1 ±0.79	97.4± 0.04	96.3± 0.64
30	95.2 ±0.33	92.7± 0.40	96.3± 0.29	95.8± 0.38
45	93.8 ±0.43	91.1± 0.89	95.7± 0.30	95.1± 0.58

Table 5: *In-vitro* Drug Release Studies Of Cross Povidone

Time (min)	F5	F6	F7	F8
0	0	0	0	0
2	63.4±0.01	60.5±0.19	60.2±0.22	58.4±0.65
5	77.6±0.91	72.3±0.22	73.1±0.54	72.5±0.39
7	89.8±0.69	87.6±0.46	84.8±0.68	85.2±0.59
10	97.3±0.26	96.9±0.33	94±0.34	93.3±0.15
15	96.8±0.21	96.1±0.62	95.3±0.68	95.6±0.22
30	95.4±0.84	94.2±0.79	95.1±0.23	94.8±0.59
45	93.8±0.67	93.8±0.48	93.6±0.65	92.3±0.84

Table 6: *In-vitro* Drug Release Studies Of Sodium Starch Glycolate

Time[min]	F9	F10	F11	F12
0	0	0	0	0
2	50.6±0.41	50.9±0.62	49.6±0.84	48.7±0.22
5	53.5±0.35	54.8±0.41	53±0.22	53.8±0.15
7	63.6±0.76	62.7±0.26	66.7±0.84	62.9±0.35
10	74.9±0.74	71.8±0.33	69.7±0.52	73.9±0.46
15	83.2±0.84	86.8±0.54	83.9±0.45	81.4±0.33
30	95.8±0.61	96.1±0.45	92.4±0.64	88.8±0.52
45	93.7±0.12	94.2±0.33	94.5±0.35	92.5±0.39

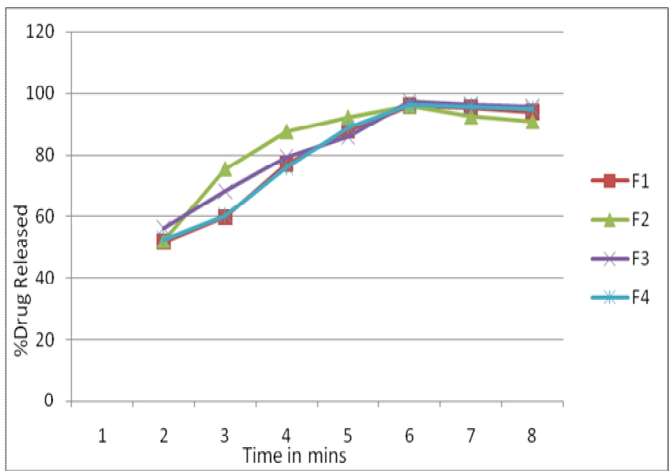

Fig 1: Plot Of *In Vitro* Drug Released Studies Of Cross Carmellose Sodium

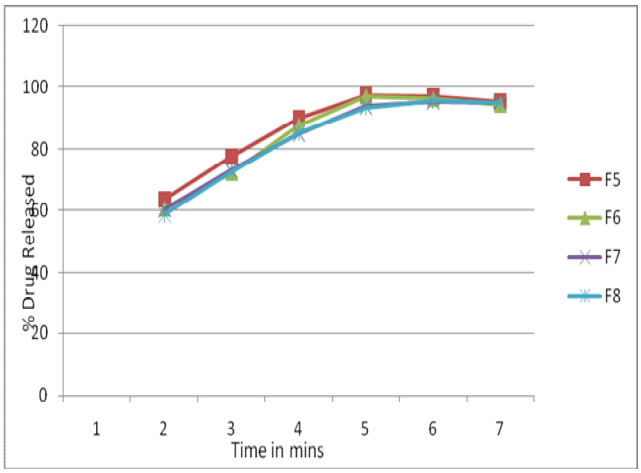

Fig 2: Plot Of *In Vitro* Drug Released Of Cross Povidone

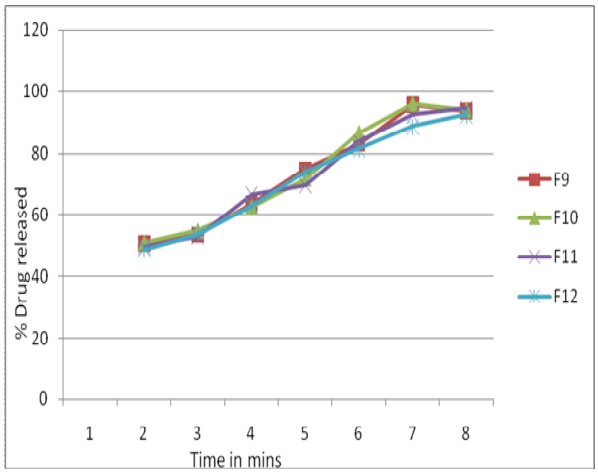

Fig 3: *In Vitro* Drug Release Studies Of Sodium Starch Glycolate

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