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FORMULATION AND EVALUATION THE FAST DISSOLVING TABLETS OF METOPROLOL TARTRATE

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The research was to formulate and evaluate the fast dissolving tablets of antianginal Drug. Metoprolol tartrate is a selective beta1-adrenoreceptor blocking agent. Chemically metoprolol tartrate is (±)-1-(isopropyl amino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (2:1) dextro-tartrate salt used in anginal pectoris essential hypertension, prevention after a myocardial infarction, tachycardia, coronary heart disease, treatment of heart failure. Oral bioavailability of Metoprolol tartrate is around 40% and having half-life 3 to 5 hrs. The Fast dissolving tablets were prepared by wet granulation method by using super disintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate and excipients like mannitol, talc, magnesium stearate. The physicochemical parameters like pre compression and post compression evaluation were performed by as per Pharmacopoeial standard. The compatibility study of the prepared tablets Metoprolol tartrate implies the information about no interaction between drug and polymer. Formulation containing 6% w/w of sodium starch glycolate is best having least disintegration time and release 91.2% of drug in 20 minutes. Stability study confirms that the drug is stable even after 3 months. The developed fast dissolving tablets of Metoprolol tartrate may be used in clinic as fast dissolving drug delivery system thereby it disintegrates within seconds improving the patient compliance.

KEY WORDS: Metoprolol Tartrate, Wet granulation, Fast dissolving Tablets, Super disintigrants, Stability Study, Release kinetics.

INTRODUCTION

The oral route of drug administration is the most important method of administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of paediatric and geriatric, bedridden, nauseous patients. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose. Fast dissolving tablets (FDT's) may show greater patient acceptability and convenience.[1-2.]

FDT"s help overcome some of these problems the rapid disintegration of the tablet into a solution (containing the drug) enables those who find difficulty in or experience discomfort when swallowing (dysphasia) and to have a more patient friendly experience[3]. There are several synonyms in use of FDT"s like oro-dispersible, orally disintegrating tablets, quick dissolving tablet, fast melt tablets, rapid disintegrating tablets and freeze dried wafers. These tablets release the medicament in the mouth for absorption through local oro-mucosal tissue and through pre-gastric (Oral cavity, Pharynx, and oesophagus), gastric (stomach) and post-gastric (small and large intestine) segments of Gastro Intestinal Tract (GIT)[4].

Metoprolol succinate is a cardio selective beta-1 adrenoreceptor blocker mostly used in the treatment of acute disorders such as angina pectoris and hypertension. It is a BCS (Biopharmaceutical Classification System) class-1 drug. It has high solubility and high permeability. Metoprolol succinate is freely soluble in water and methanol. The half life of Metoprolol succinate is approximately 3 to 4 hours. It undergoes extensive first pass hepatic metabolism resulting in 40% oral bioavailability. Hence the prepared sublingual tablet of Metoprolol succinate lead to enhance the bioavailability and avoidance of first pass hepatic metabolism.[5]

The purpose of this research was to formulate and evaluate the fast dissolving tablets of antianginal Drug. Metoprolol tartrate is a selective beta1-adrenoreceptor blocking agent. Chemically metoprolol tartrate is (±)-1-(isopropyl amino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (2:1) dextro-tartrate salt used in anginal pectoris essential hypertension, prevention after a myocardial infarction, tachycardia, coronary heart disease (prevention of angina attacks), treatment of heart failure. Oral bioavailability of Metoprolol tartrate is around 40% and having half-life 3 to 5 hrs.

MATERIALS AND METHODS

MATERIALS

Metoprolol tartarate is obtained gift sample from EmcurePharma, Pune. Croscarmellose Sodium,Crospovidone and Sodium starch glycolate were obtined gift sample from AurobindhoPharma Ltd.,Hyderabad,india. Other Polymers and

Excipients were used were in Pharma grade materials. Allother chemicals were used is in analytical grade.

METHODS

PREFORMULATION STUDIES

IR Incompatability Study

Drug polymer interaction study was performed by following incompatibility study of FTIR. IR spectra for pure drug and the best formulations F9 recorded in a Fourier transform infrared (FTIR) spectrophotometer (Shimadzu corporation Japan) with KBr pellets.

Pre-compression parameters

Angle of repose (θ)[6]

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

Bulk density[6]

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Tapped density[7]

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated.

Hausner ratio[6]

Hausner ratio is an indirect index of ease of power flow.

Carr's compressibility index[6]

The compressibility index of the granules was determined by Carr's compressibility index.(%).

FORMULATION STUDIES

Formulation of Fast Disintegrating Tablets

Granules of Metoprolol tartrate were prepared by wet granulation technology. All the ingredients as per the formula e mentioned in table no. 4.4 were weighed and grinded to fineness in a mortar and pestle. The powder blend was then passed through sieve # 120. The powder was then kneaded with a clean and dry pestle using starch paste. The wet mass so obtained was passed through mesh # 16. The particles were then subjected to drying for 2-3 h in an oven at 40 °C. The dried granules were then passed through mesh # 20. Fine particles to an extent of 20 % were blended thoroughly with the particles of #16/20 and this powder blend was used for further processing.

Post-Compression parameters:

Hardness test[8]

Tablets require a certain amount of strength, or hardness and resistance tofriability, to withstand mechanical shocks of handling in manufacture, packaging and the hardness of the tablets were determined using Monsanto Hardness tester. Itis expressed in Kg/cm2. Three tablets were randomly picked from each formulation andthe mean and standard deviation values were calculated.

Friability test[8]

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using VeegoFriabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal).

Weight variation test[8]

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

In all the formulations the tablet weight was more than130mg and less than 324mg, hence 7.5% maximum difference allowed.

Uniformity of thickness[8]

The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a slidingcaliper scale. The tablet thickness was measured using screw gauge.

Drug content uniformity[8]

Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml distill water. Its concentration 1000mcg/ml. 10ml from this stock

Table 1: Formula of fast dissolving tablets of metoprolol tartrate

S.No	Ingredients (mg/tab)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	Metoprolol tartrate	100	100	100	100	100	100	100	100	100
2.	Cross carmelose sodium	20	40	60	-	-	-	-	-	-
3.	Crospovidone	-	-	-	20	40	60	-	-	-
4.	Sodium starch glyconate							20	40	60
5.	Starch paste	75	75	75	75	75	75	75	75	75
6.	Talc and magnesium	10	10	10	10	10	10	10	10	10
7.	Aspartame	3	3	3	3	3	3	3	3	3
8.	Mannitol	42	22	2	42	22	2	42	22	2
Total tablet weight(mg)		250	250	250	250	250	250	250	250	250

Table: 2 Interpretation of IR Spectrums of Metoprolol tartrate

IR Spectrum	Peaks (cm^{-1})	Groups	Stretching / Deformation
Metoprolol tartrate	138.08	CH_3	Deformation
	1616 .40	COOH	Stretching
	2833 .52	C-H	C-H Stretching OF CH_2
	3053 .42	O-H	Stretching
Physical mixture of Metoprolol tartrate and croscarmilose sodium, crospovidone	1383 .01	CH_3	Deformation
	1624 .12	COOH	Stretching
	2877 .84	C-H	C-H Stretching of
			CH_2
	3163 .36	O-H	Stretching

Table: 3 RESULT OF PRE-COMPRESSION PARAMETER

Formulation	Bulk density	Tapped density	Hauser's Ratio	Compressibility Index	Angle of repose
F1	0.62 ±0.002	0.71 ± 0.04	1.12 ±0.02	10.05±0.08	20.44±0.54
F2	0.68±0.0 02	0.74±0.043	1.13±0.097	13.07±0.08	21.84±0.38
F3	0.58±0.0 01	0.69±0.002	1.21±0.001	12.04±0.08	22.41±0.78
F4	0.67±0.0 45	0.73±0.0	1.13±0.09	13.06±0.05	22.28±0.78
F5	0.51±0.05	0.69±0.0	1.13±0.08	14.19±0.07	22.05±0.89
F6	0.67±0.02	0.68±0.0	1.14±0.05	13.89±0.05	22.24±0.03
F7	0.58±0.03	0.64± 0.02	1.12±0.09	12.09±0.09	24.05±0.98
F8	0.61±0.09	0.68±0.03	1.15±0.08	13.08±0.09	21.42±0.47
F9	0.68±0.0 27	0.67±0.0	1.18±0.035	12.26±0.04	23.68±0.89

Table : 4 RESULTS OF POST-COMPRESSIONAL TABLETS

Formulation code	Thickness (mm)	Weight (mg)	Friability (%)	Hardness (kg/cm2)	% Drug content
F1	6.30±0.01	249.65	0.48±0.00	3.17±0 .057	99.07±0.24
F2	6.35±0.02	249.66	0.77±0.0002	2.84±0 .045	99.15±0.35
F3	6.34±0.03	250.33	0.39±0.0003	2.94±0 .098	98.10±0.66
F4	6.34±0.00	251.54	0.68±0.0004	3.34±0.09	99.9±0.27
F5	6.34±0.03	258.54	0.43±0.0003	2.45±0.07	98.22±0.94
F6	6.32±0.02	251.66	0.67±0.0005	3.36±0.03	98.48±0.45
F7	6.34±0.04	249.33	0.66±0.0002	3.27±0.08	98.35±0.71
F8	6.35±0.02	250.33	0.49±0.0002	2.67±0.04	98.47±0.75
F9	6.34±0.03	249.66	0.44±0.001	2.94±0.02	98.86±0.77

Solution taken and diluted to 100ml distilled water, it makes 100µg/ml. Then 20µg/ml solution prepared by taking 2ml from stock solution and diluted to 10ml. Absorbance measure at 223nm.

Wetting time[9]

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petridish (i.d.= 6.5 cm) containing 10 ml of water, tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

Water absorption ratio[9]

A piece of tissue paper folded twice was placed in a small petridish containing6ml of water. A tablet was put on the paper and time required for complete wetting was measured.

***In vitro* disintegration time**[9]

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined usingdisintegration test apparatus as per I.P. specifications.I.P. Specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (stimulated saliva fluid)

Maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between30 cycles per minute in the pH 6.8 maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In vitro* dissolution studies**[9]

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rmp) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at37±0.5°C, aliquot of dissolution medium was withdrawn at every 1 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 223 nm and concentration of the drug was determined from standard calibration curve.

***In vitro* drug release studies**

Apparatus used in USP XXIII dissolution test apparatus. Dissolution medium 6.8 pH phosphate buffer solution. Dissolution medium volume of 900 ml. Temperature 37±0.5°C. Speed of basket paddle in 50 rpm. Sampling intervals was 1 min. Sample withdraw in 5 ml. Absorbance measured in 223nm.

RESULTS AND DISCUSSION

In the present study FDT's of Metoprolol tartrate were prepared and evaluated for achievement of fast action of active moiety. The tablets were prepared by wet compression method by using the super disintegrants like cross-carmillose, crosspovidone, sodium starch glycolate. Fast disintegration of tablets was achieved by using superdisintegrants. In the absence of water or fluid intake such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds.

The melting point of Metoprolol tartrate was found to be 120°C, which complied with IP standards thus indicating purity of obtained drug sample.

IR Incompatability Study

FTIR Spectra of pure drug, polymer and their physical mixture were recorded. The drug, polymer and physical mixtures of drug and polymers were scanned for absorbance. The IR spectral graphs of Metoprolol tartrate alone and with excipient combination graphs were shown in Table no: 2. The spectra obtained from the physical mixtures showed all the principal peaks at or around the requisite wave numbers of pure drugs with minor shift of the peaks. Thus it may be inferred that there was no interaction between Metoprolol tartrate and polymers, the excipients. It can be taken consideration to continue the formulation of Fast disintegrating tablet by using these excipients was confirmed by this incompatibility study.

Pre-Compression Parameter for Tablet Prepared By Wet Compression

The data obtained from results were tabulated in table no 3. Angle of repose for all the formulations were found to be in the range of 20.4` and 24.0`. All the formulations prepared by both the methods showed the angle of repose less than 24, which reveals good flow property. The bulk density for the blend was performed. The bulk density for the entire formulation blend varied from 0.59 gm/cm 3 to 0.68 gm/cm3 respectively. The tapped density

for the blend was performed. The tapped density for the entire formulation blend varied from 0.63 gm/cm 3 to 0.75 gm/cm3 respectively. The compressibility index of the blend was in the range between 10. 0 to 14.1. Hausner ratio of entire formulation showed between 1.1 to 1.2 indicates better flow properties.

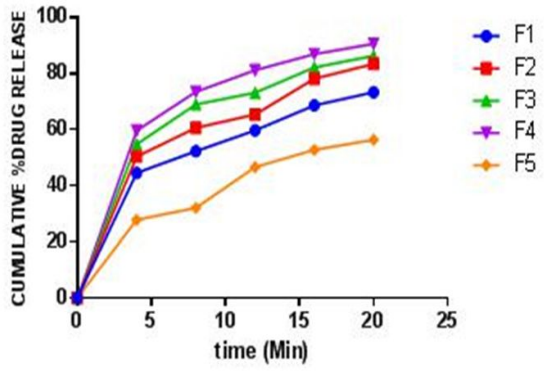

Fig 1 Percentage Drug Release of Formulations

Post-Compressional Tablets Prepared By Wet Granulation

The data obtained from results were tabulated in table no 4. The hardness of all the tablets prepared by both methods was maintained with in the 2.6 kg/cm2 to 3.6 kg/cm2. The mean hardness test results are tabulated. The friability was found in all designed formulations in the range 0.37 to 0.75% to be well within the approved range (<1%).

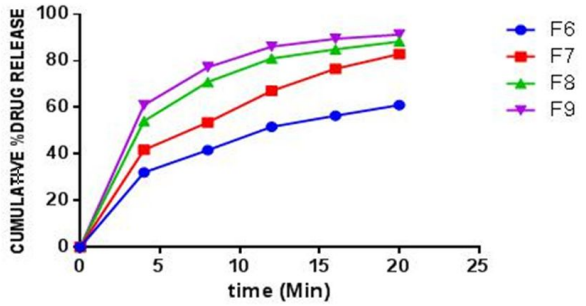

Fig 2 Percentage Drug Release of Formulations

The weight variation was found in all designed formulations in the range 248 to 251 mg. The mean weight variation test results are tabulated. All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e. in the pharmacopoeial limits. The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 6.32-6.34 mm. The standard deviation values indicated that all the formulations were within the range.

Wetting time is closely related to the inner structure of the tablet. The results of wetting time are shown in table no. 10 and 11. The wetting time of metoprolol tartrate prepared by wet compression method was found to be of 29 to 125 sec. Promising formulations F8 (9% sodiumstarch glycolate) and F9 (sodium starch glycolate) showed a wetting time of 31 and 29 sec respectively, which facilitate the faster dispersion in the mouth. The disintegration time for the tablets of F1 and F2 was found to be > 60 mins while for tablets of F8 and F9 containing starch as disintegrant was found to be >30 mins, indicating that the addition of superdisintegrants is necessary for the rapid disintegration of the tablets, hence for the formulation of fast dissolving tablets. The rapid disintegration of the FDTs of the formulations was due to the penetration of saliva into the pores of the tablet, which lead to the swelling of superdisintegrant s to create enough hydrodynamic pressure for faster disintegration of the tablet.

The drug release profile was shown in figure number 1 and 2. Dissolution efficiency of pure Metoprolol tartrate and all the physical mixtures and solid dispersion formulations at 4 minutes and 20 minutes were calculated which is shown in Tables 5.6 and 5.7. As the dissolution time was increased from 4 to 20 minutes, the dissolution efficiency was increased in all the formulations. Among the formulations F9 has shown maximum dissolution efficiencies of 91.2% and 89.4% at sixteen minutes and twenty minutes. However, F1, F2, F3, F7, F8 also produce comparable results on terms of dissolution efficiency.

CONCLUSION

The present work fast dissolving tablets of metoprolol tartrate were prepared by wet compression method using super disintegrants such as sodium starch glycolate, croscarmellose sodium and crospovidone. All the tablets of Metoprolol tartrate were subjected to weight variation, hardness, friability, in vitro dispersion, drug polymer interaction, drug content uniformity, water absorption ratio, wetting time, and in vitro drug release. Based on the above studies following conclusions as follows.

Tablet prepared by wet compression and were found to be good. The low values of the standard deviation of average weight of the prepared tablets

indicate weight uniformity within the batches prepared. The hardness of the prepared tablets was found to be in the range of 2.5 to 3.5 Kg/cm². The friability values of the prepared tablet were found to be less than 1%. IR spectroscopic and DSC studies indicated that the drug is compatible with all the excipients. The in vitro dispersion time of Metoprolol tartrate prepared by wet compression were found to be in the range of 27 to 125 secs. Fulfilling the official requirements. Based on the in vitro disintegration time, promising formulations F8 (9% sodium starch glycolate) and F9 (sodium starch glycolate) shows 29sec and 27sec respectively and a wetting time of 31 and 29 sec respectively, which facilitate the faster dispersion in the mouth.

The drug content of tablets was uniform in all the batches and was between 98.1to 99.1%. 99.01% drug release within 5 minute.

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