ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

Formulation and evaluation of fast Dissolving tablets of Antihypertensive Drug

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ABSTRACT:
Over a decade, the demand for development of fast dissolving tablets (FDT) enormously increased as it has significant impact on the patient compliance. Fast dissolving tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. Hypertension is a medical condition in which blood pressure is chronically elevated, If not, effectively treated it may lead to stroke, myocardial infarction, heart failure and is a leading cause of chronic kidney failure. Antihypertensive are the class of drugs that are used to treat hypertension. Metoprolol tartarate is a β1-selective adrenergic blocking agent and is prescribed widely in cardiovascular diseases like hypertension. Administration of conventional tablets of Metoprolol tartarate has been reported to exhibit fluctuations in the plasma drug levels resulting in either manifestation of side effects or reduction in drug concentration at the receptor site. Administration to patients who cannot swallow, such as elderly, stroke victims, healthcare facility & bedridden patients such as those affected by renal failure; and the patient who refuse to swallow such as pediatric, geriatric and psychiatric patients which results in high evidence of inefficient therapy. The present study nine batches of fast dissolving tablets of Metoprolol tartarate were successfully prepared using Crospovidone, Sodium starch glycolate, Fenugreek and Isapghula husk by direct compression method. Based on results formulation containing Crospovidone (8%) and Sodium starch glycolate (8%) F(2), was identified as ideal and better formulation among all formulations developed for Metoprolol tartarate tablets. From study it is concluded that the formulated fast dissolving tablets of Metoprolol tartarate of batch F2, were superior and effective in achieving better patient compliance.

KEYWORDS: Metoprolol, Hypertension, Crospovidone, Fast dissolving tablets, Direct compression method.

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.[1.]

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance.[2.] Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications.[3.] ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active

Received on 21.08.2016 Modified on 22.09.2016
Accepted on 23.10.2016
Research J. Pharm. and Tech. 2017; 10(1): 155-160.
DOI: 10.5958/0974-360X.2017.00034.8

ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute.[4] Hypertension is a medical condition in which blood pressure is chronically elevated, If not, effectively treated it may lead to stroke, myocardial infarction, heart failure and is a leading cause of chronic kidney failure. Antihypertensive are the class of drugs that are used to treat hypertension.[5.] The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. FDT is one such dosage form which is useful for geriatric patients mainly suffering from conditions like hand tremors and dysphasia, pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.[6.] Metoprolol tartarate is a β1-selective adrenergic blocking agent and is prescribed widely in cardiovascular diseases like hypertension. Administration of conventional tablets of Metoprolol tartarate has been reported to exhibit fluctuations in the plasma drug levels resulting in either manifestation of side effects or reduction in drug concentration at the receptor site.[7.] With the view to all the above information, an attempt was made to develop rapidly disintegrating "Metoprolol tartarate fast dissolving tablets" which disintegrates in the oral cavity without the need of water within a matter of seconds, thereby improving dissolution rate and bioavailability of drug and onset of pharmacological actions.[8.]

Extensive literature survey showed Metoprolol tartarate has not yet been formulated as fast dissolving tablets. That's why the present paper has been undertaken to formulate "Metoprolol tartarate fast dissolving tablets".

MATERIALS AND METHODS:

Drug and Excipients

Table 1: Various drugs were used during study which were shown as follows,

Sr. no.	Drug	Manufacturer/supplier
1	Metoprolol tartarate	Emcure pharmaceuticals Pvt. Ltd, Pune
2	Crospovidone	Emcure pharmaceuticals Pvt. Ltd, Pune
3	Sodium starch glycolate	Emcure pharmaceuticals Pvt. Ltd, Pune
4	Fenugreek seeds powder	Arkashala, pvt.ltd, Satara
5	Isapghula husk seed powder	Arkashala, pvt.ltd, Satara
6	Mannitol	Loba Chemie, Mumbai
7	Micro crystalline cellulose	Loba chemie, Mumbai
8	Sodium lauryl sulphate	Loba chemie, Mumbai
9	Magnesium stearate	Loba chemie, Mumbai
10	Menthol	Loba chemie, Mumbai
11	Talc	Loba chemie, Mumbai

Metoprolol Tartarate USP:

Metoprolol tartarate is a selective β1-adrenergic receptor blocking agent and commonly used for the treatment of mild to moderate hypertension, stable angina and myocardial infarction.[9.]

Preparation of fast dissolving tablets:

Nine batches (F1 to F9) of fast dissolving tablets of Metoprolol tartarate were prepared by using direct compression technique. In this present work, fast dissolving tablets were prepared by using four superdisintegrants in which crospovidone and sodium starch glycolate are synthetic and fenugreek and Isapghula husk are natural one. Each superdisintegrants was used in 6%, 12%, and 18% respectively.[10,11]

Formulation development:

Metoprolol tartarate fast dissolving tablets were manufactured in 9 formulations F1 to F9 using the ingredients mentioned in table No.5 by keeping the various formulation batches were prepared according to formula shown in table No. 5 .

Table No. 2: Formulation Composition of fast dissolving tablets of Metoprolol tartarate (Batch F1 to F9) (All weights are in mg.)

Formulation variables	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol tartarate (mg)	50	50	50	50	50	50	50	50	50
Crospovidone	15	20	25	-	-	-	7.5	10	12.5
Sodium Starch Glycolate	15	20	25	-	-	-	7.5	10	12.5
Fenugreek	-	-	-	15	20	25	7.5	10	12.5
Isapghula husk	-	-	-	15	20	25	7.5	10	12.5
Mannitol	70	70	60	70	70	60	70	70	60
Microcrystalline Cellulose	70	60	60	70	60	60	70	60	60
Sodium lauryl sulphate	3	3	3	3	3	3	3	3	3
Magnesium stearate	10	10	10	10	10	10	10	10	10
Menthol	7	7	7	7	7	7	7	7	7
Talc	10	10	10	10	10	10	10	10	10
Total weight	250	250	250	250	250	250	250	250	250

Metoprolol tartarate was used with the crospovidone, sodium starch glycolate, fenugreek and Isapghula husk to formulate fast dissolving tablets.[12,13] All the ingredients with drug except Magnesium stearate and Talc were taken in mortor.The powder blend was then mixed well by using mortor and pestle for 15 to 30 minutes and then each mixture was passed through #80 sieves.[14,15] Finally magnesium stearate and talc were added as lubricants and mixed thoroughly. The powder blend was compressed using hand operated tablet punching machine to produce flat faced tablets of Metoprolol tartarate weighing 250 mg having diameter 13mm.[16-19.]

EVALUATION OF FAST DISSOLVING TABLETS:

Precompression parameters

Evaluation of blend for the following parameters to be carried out before compression of FDT's[20]

Untapped Bulk Density:

Powder weighing 10 g is placed into 100 ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and bulk density is calculated.[21-23]

Tapped Bulk Density:

Powder weighing 10 g is placed into 100 ml measuring cylinder. The cylinder is then subjected to a fixed number of taps (~100 times) until the powder bed volume had reached the minimum level. The final volume is recorded and the tap density is calculated.[24]

Compressibility, Hausner Ratio was also calculated.

Angle of repose:

The angle of repose gives an indication of the flow ability of the substance. Funnel is adjusted such that the stem of the funnel lies 2 cm above the horizontal surface.[25] The drug powder is allowed to flow from the funnel under the gravitational force till the apex of the pile just touched the stem of the funnel, so the height of the pile is taken as 2 cm. drawing a boundary along the circumference of the pile and taking the average of six diameters determined the diameter of the pile.[26-28]

In vitro Drug Release Studies:

The in vitro drug release is studied using USP dissolution apparatus II (paddle type) at 50 rpm in 900 ml of phosphate buffer (pH 6.8) at37±0.5ºC.[29,30] At different time intervals, 2 ml of sample is withdrawn and filtered. An equal volume of the medium is introduced into the container after each withdrawal to maintain a constant volume. The absorbance of the samples is determined by UV Spectrophotometer at given max. The mean values of drug released are plotted as cumulative % drug release vs. time.[31]

IR Spectrum of Metoprolol Tartrate:

The IR spectrum of Metoprolol tartrate microspheres was recorded using Fourier transform infrared spectroscopy (FTIR). (Shimadzu, Japan).[32]

a] FTIR spectroscopy:

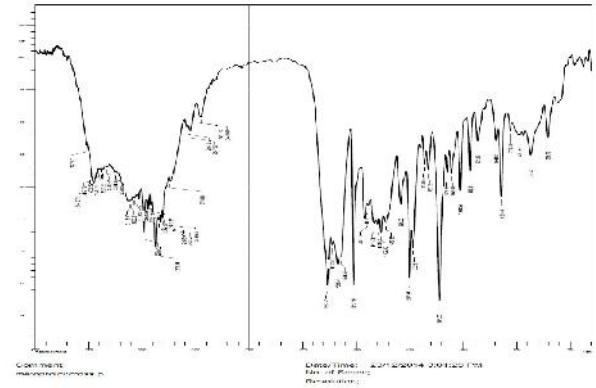

Fig. No. 1:- IR spectrum of physical mixture of Metoprolol tartarate and crosspovidone

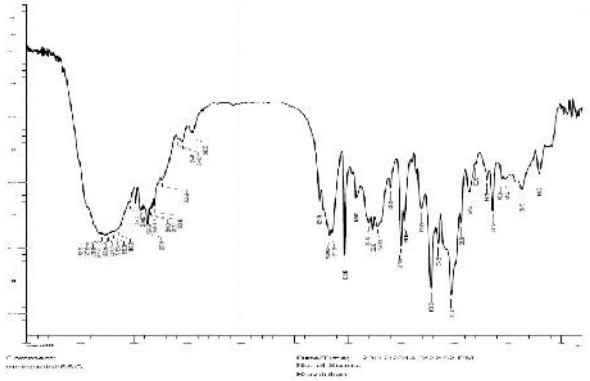

Fig. No. 2:- IR spectrum of physical mixture of Metoprolol tartarate and Sodium starch glycolate.

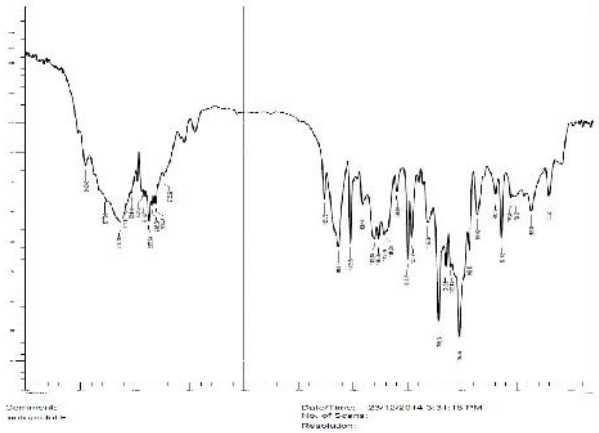

Fig. No. 3:- IR spectrum of physical mixture of Metoprolol tartarate and fenugreek.

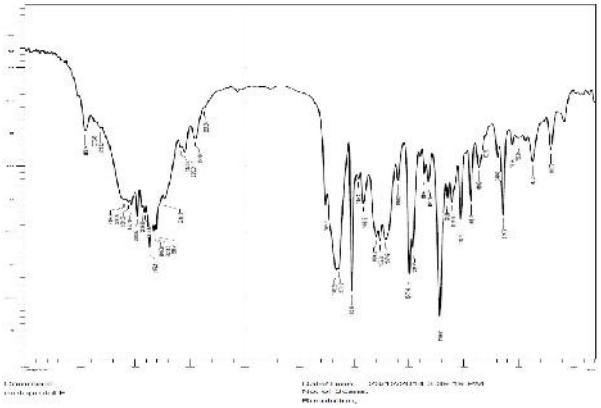

Fig. No. 4:- IR spectrum of physical mixture of Metoprolol tartarate and Isapghula husk

Differential Scanning Calorimetery (DSC):
The thermograms of Metoprolol tartrate microspheres, at a scanning rate of 10°C/min conducted over a temperature range of 25–350ºC respectively. (DSC Q20 V24.11 Build 124, Instruments).

RESULT AND DISCUSSION:

Compatibility Study:
The drug and excipients polymers must be compatible with one another to produce a product that is stable, effective, attractive, easy to administer and safe.

From the FTIR spectra of pure drug and the representative polymer, it was observed that all the important peaks that were found to be present in FTIR spectrum of drug were found to be present in FTIR spectrum of polymer. Neither any additional peak was observed in the IR spectrum of representative formulation nor was any important peak of the drug found to be missing. Thus from the FTIR spectra of both drug and the representative polymer, it could be concluded that both the drug and the excipients were compatible with each other.

EVALUATION OF METOPROLOL TARTARATE FAST DISSOLVING TABLETS:

Preformulation studies for Fast dissolving tablet:
Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors list is long and includes physical, mechanical as well as environmental factors. Therefore; determination of bulk density, tapped density angle of repose, Carr's index, and Hausner's ratio is important before formulation because it influence compressibility, tablet porosity and dissolution. All the Formulations were found to be acceptably flowing according to angle of repose, Carr's index and Hausner's ratio. Precompression parameters like angle of repose, compressibility index and Hausner's ratio of all batches of Metoprolol tartarate fast dissolving tablets are shown in Table No.3.

Bulk density of all the formulations was found to be in the range of **0.42-0.49 g/cc,** where as tapped density of all the formulations was found to be in the range of **0.49-0.54 g/cc.** Angle of repose was observed to be less than **30o**. Carr's index was found between **4.66-16.3** which was well within the range of **8-16**. All the formulations exhibited Hausner's ratio less than **1.25**. All these values indicates good flow properties of the tablet blend, uniform die fill and direct compressibility of the powder blend. Therefore direct compression method was employed for compressing the powder blend.

In vitro drug release:
In- vitro dissolution studies for all the fabricated tablets of Metoprolol tartarate were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was 6.8 phosphate buffer (900 ml) maintained at 37 ± 0.5 0C. Aliquots of dissolution media were withdrawn (5ml) at different intervals and content of Metoprolol tartarate was measured by determining absorbance at 276nm. 5ml aliquot was withdrawn at the 2 min, 4 min to be continued at the 10 min. intervals and filtered by whatman filter paper, suitably diluted and analyzed at 276nm using UV- Visible spectrophotometer. An equal volume of fresh medium which was pre-warmed at 37 0C was replaced in to the dissolution medium after each sampling to maintain the constant volume throughout the test. Absorbance was taken at 276nm and percentage release was calculated. The results are listed in Table No. 4. The *In vitro* release profiles of Metoprolol tartrate fast dissolving tablets in phosphate buffer of pH 6.8 are shown in Table No. 1, 2. It was observed that Formulation F2 shows fast drug release upto **92.43 %** after 10min.

Table 3: Preformulation studies for Fast dissolving Tablets

Formulation Code	Angle of repose(ø)	Bulk density (g/cc)	Tapped density(g/cc)	Carr's index	Hausner's ratio
F1	20.55±0.47	0.44±0.01	0.53±0.01	16.3±4.1	1.2±0.06
F2	**21.30±0.56**	**0.42±0.05**	**0.49±0.02**	**14±2.6**	**1.17±0.04**
F3	22.29±0.20	0.49±0.01	0.51±0.01	4.66±0.5	1.04±0.01
F4	21.43±0.10	0.44±0.03	0.54±0.01	17.33±8	1.22±0.12
F5	20.82±0.11	0.43±0.01	0.48±0.01	8.33±0.5	1.09±0.01
F6	20.45±0.22	0.43±0.02	0.50±0.01	13.4±2.5	1.16±0.04
F7	20.84±0.78	0.47±0.02	0.54±0.01	12.33±6.6	1.14±0.09
F8	21.25±0.54	0.45±0.01	0.50±0.01	7±5.1	1.09±0.05
F9	21.27±0.47	0.42±0.02	0.49±0.02	13±1	1.16±0.02

*****mean ±S.D. n=3.

Table No. 4: *In Vitro* drug release data of F1- F9 Batches

Time	% Cumulative Drug Release								
(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	42.02	**32.14**	35.18	38.91	37.06	35.46	44.06	32.08	40.29
4	54.32	**50.26**	53.42	51.35	51.54	52.63	59.58	47.18	54.4
6	68.12	**66.05**	63.53	68.56	62.86	64.82	72.36	65.36	68.87
8	79.53	**76.62**	81.48	78.67	72.73	76.04	83.27	78.73	80.61
10	88.37	**92.43**	89.62	82.09	80.24	84.41	91.04	85.58	89.05

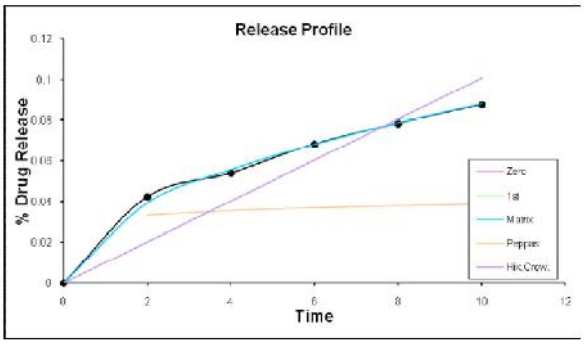

Fig. 5: Kinetic release profile of F2 batch of Metoprolol tartarate tablets with model fitting

Table No. 5: Results of Model fitting for batch F2 of Metoprolol tartarate tablets.

MODEL	R	K
Zero order	0.9468	0.0079
First order	0.9469	0.0001
Higuchi matrix	0.9987	0.0271
Korsmeyer peppas	0.9950	0.0303
Hixon-Crowel	0.9469	0.0000

By comparing the R values of different models, **Matrix model** was found to be best fit, which has higher values of correlation coefficient. The n value of the Matrix model for optimized formulation F2 was found to be **0.4490**.

IR Spectrum of Metoprolol Tartrate:

Infrared absorptions of F2 formulation were investigated. The functional group peaks of Metoprolol tartrate were found in the Spectrum.

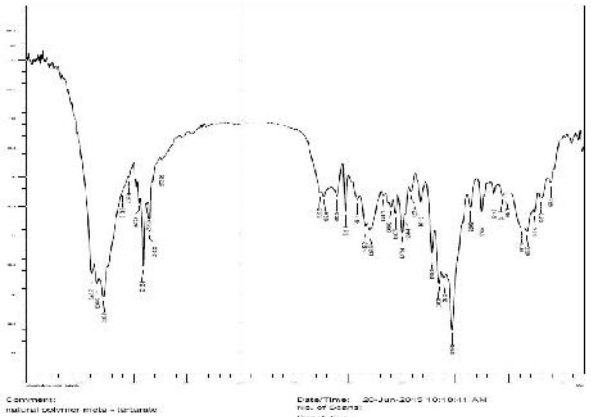

Fig. No. 6: Infrared spectrum of F2 formulation

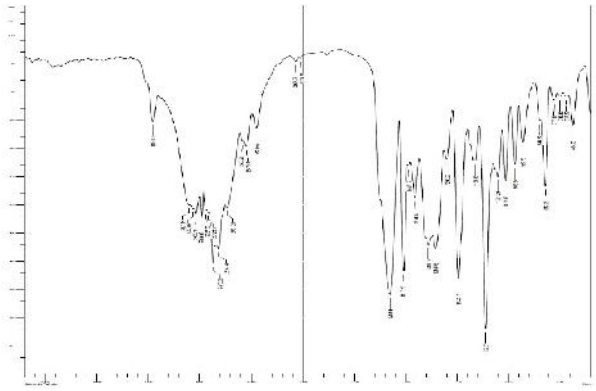

Fig. No. 7:- IR spectrum of Metoprolol tartrate.

FT-IR spectra of Metoprolol tartrate and Metoprolol tartrate fast dissolving tablets (F2) were compared fig. No.6. The FT-IR spectra of Metoprolol tartrate fast dissolving tablets showed the characteristic peaks of pure drug indicating that there was no interaction between drug and polymers.

DSC studies were performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with polymers in the formulation. Pure Metoprolol tartrate showed a single sharp endothermic melting peak at **127.95ºC** (fig. 7), in F2 batch which was slightly shifted from their original positions in the thermogram of powdered sample of fast dissolving tablets (fig.5) evidencing the absence of interactions. Melting peak at **124.95ºC** indicate that drug is dispersed in polymer in the form of metastable molecular dispersion.

Differential Scanning Calorimetery (DSC)

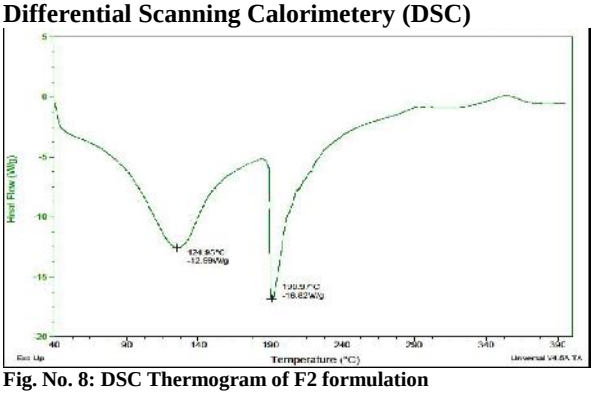

Fig. No. 8: DSC Thermogram of F2 formulation

CONCLUSION:

The data obtained from the study of "Formulation and Evaluation of Fast Dissolving Tablets of Anti-hypertensive drug reveals that Metoprolol tartarate did not interfere with the polymers used in study. Nine batches of fast dissolving tablets of Metoprolol tartarate were successfully prepared using Crospovidone, Sodium starch glycolate, Fenugreek and Isapghula husk by direct compression method. The tablets were evaluated for parameters like in vitro drug release studies. Based on results formulation containing Crospovidone (8%) and Sodium starch glycolate (8%) F(2), was identified as ideal and better formulation among all formulations developed for Metoprolol tartarate tablets. In vitro release of optimized formulation of Metoprolol tartarate fast dissolving tablets of batch F2 was found to be **92.43%** drug release within 10 min with in vitro dispersion time **10 sec**. From the present study it can be concluded that the formulated fast dissolving tablets of Metoprolol tartarate of batch F2, were superior and effective in achieving better patient compliance.

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