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DEVELOPMENT AND CHARACTERIZATION OF FAST DISSOLVING TABLETS OF ANTI-HYPERTENSIVE AGENT BY USING DIFFERENT SUPERDISINTEGRANTS

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ABSTRACT

Timolol maleate is a nonselective β- adrenergic blocker and it blocks both β-1 and β-2 adrenergic receptors to reduces blood pressure decreasing sympathetic outflow. The main object of this research work was to formulate the fast dissolving tablets of Timolol Maleate by direct compression technique using croscarmellose sodium as superdisintegrant. The FTIR compatibility studies for drug and excipient were subjected. The result indicated no interaction between drug and carriers. Fast dissolving tablets should give fast disintegration, dissolution, ease to swallowing, and gives quick onset of action. The prepared blends were evaluated and analyzed by using various parameters such as bulk density, tapped density, and angle of repose. The prepared tablets were evaluated for tablet thickness, tablet hardness, wetting time, disintegration time, and friability.

KEYWORDS: Timolol Maleate, Direct Compression Technique, Croscarmellose Sodium, Fast dissolving tablets.

INTRODUCTION

In oral dosage forms, tablets are the most widely used and accepted because out of 50-60% of total dosage forms the oral drug administration have widely accepted. Solid dosage forms have a number of advantages like easily administration, accurate dosage and most importantly the patient compliance (Bhowmik *et al.*, 2009). Fast dissolving Fast dissolving tablets (FDTs) are solid single-unit dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provide a quick onset of action. Comparison with other conventional tablets dosage forms the bioavailability of fast dissolving tablets drug is significantly greater (Jain *et al.*, 2011), Timolol maleate is a member of a family of drugs called nonselective beta adrenergic blocker. It is used alone or in combination with other antihypertensive agents, especially thiazide type diuretics. Timolol maleate was available for oral dosing and tablets and for injection and ophthalmic dosing as distinct sterile aqueous solutions. Timolol Maleate chemically described as (S)-1-tert-butylamino-3-(4-morpholino-1,2,5-thiadiazol -3-yloxy)propan-2-ol-hydrogen maleate and 50-60% bioavailability. It blocks both β-1 and β-2 adrenergic receptors to reduce blood pressure decreasing sympathetic outflow (Rathore *et al.*, 2010). The present investigation deals with the development of an effective and stable fast dissolving tablets of Timolol Maleate having enough hardness, low disintegration time. Fast dissolving tablets can be prepared by various conventional techniques (Anupama *et al.*, 2009).

MATERIALS AND METHODS

Materials

Timolol Maleate was gifted from Jackson Lab.Pvt.Ltd. Amritsar. Microcrystalline cellulose and Magnesium stearate were purchased from S D Fine-Chem Ltd. Mumbai. Sodium starch glycolate was purchased from Central drug house (P) Ltd. New Delhi. Starch was purchased from Thermo Fisher Scientific India Pvt. Ltd. Mumbai. Talc was purchased from Hi Media Laboratories Pvt. Ltd. Mumbai. Mannitol was purchased from Merck Specialities Pvt. Ltd. Mumbai.

Methods

The FDTs of Timolol Maleate were prepared by direct compression method using croscarmellose sodium, and sodium starch glycolate as a superdisintegrants. All the ingredients were passed through mesh screen no. 60 and weighed in geometrical order. All the materials were directly compressible so this uniformly mixed blend was compressed into tablets using single tablet punching machine. A flat punch 6 mm in diameter was used for tableting. Seventh formulations were prepared. The seventh formulation is control without any superdisintegrants. The composition of formulations is shown in Table 1.

Table 1: Formulation of Design Timolol Maleate FDTs.

S. No.	Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1.	Timolol Maleate	20	20	20	20	20	20	20
2.	Croscarmellose Sodium	5	10	15	-	-	-	-
3.	Sodium Starch Glycolate	-	-	-	5	10	15	-
5.	Mannitol	60	55	50	60	55	50	65
6.	Menthol	10	10	10	10	10	10	10
7.	Talc	10	10	10	10	10	10	10
8.	Magnesium Stearate	5	5	5	5	5	5	5
9.	Starch	10	10	10	10	10	10	10
10.	Microcrystalline Cellulose	30	30	30	30	30	30	30
11.	Flavor (Dry Orange)	5	5	5	5	5	5	5
12.	Aspartame	5	5	5	5	5	5	5
	Total Weight	160	160	160	160	160	160	160

- Formulation F_1, F_2 and F_3 contains croscarmellose sodium as superdisintegrant in 3.3%, 6.6% and 10% concentration.
- Formulation F_4, F_5 and F_6 contains sodium starch glycolate as superdisintegrant in 3.3%, 6.6% and 10% concentration.
- Formulation F_7 as a control formulation without any superdisintegrants.

Compatibility Studies (Fourier Transform Infrared Spectroscopic studies)

Drug-excipients compatibility studies are carried out by mixing definite properties of drug and excipients are kept in glass vials, which are stored at 40^0C + 75% RH in stability chamber for one month. By using KBr pellet method to carry out the drug excipients interaction study. To study the compatibility of various formulation excipients with Timolol Maleate, drug–excipient mixtures were prepared in the form of KBr pellets and it was filled and characterized by using Fourier transform infrared spectroscopy (FTIR).

U.V. SPECTROSCOPY ANALYSIS OF DRUG

Determination of λ_{max} of Timolol Maleate in water

Stock solution of Timolol Maleate was prepared by dissolving 10 mg of accurately weighed amount of Timolol Maleate in 50 ml of distilled water and then the volume was adjusted to 100 ml (100µg/ml), then pipette out 10 ml these prepared solution add into 100ml volume metric flask (10µg/ml). This solution was scanned at range of 200-400 nm wavelengths light corresponding scan spectrum curve was noted the corresponding wavelength having highest absorbance is noted as λmax. The λmax of the drug was found to be 295nm.

Construction of calibration curve of Timolol Maleate in water

Procedure: Stock solution of Timolol Maleate was prepared by dissolving 100 mg of accurately weighed amount of Timolol Maleate in 50 ml of distilled water and then the volume was adjusted to 100 ml (1000µg/ml), then pipette out 10 ml these prepared solution add into 100ml volume metric flask (100µg/ml).

The above stock solution of drug was subsequently diluted with distilled water to get 2µg to 20µg, of drug per ml. Then calibration curve of Timolol Maleate was plotted by measuring absorbances of 2µg /ml to 20µg/ml of solution at a λmax of 295 nm (Putta *et al.,* 2015).

EVALUATION PARAMETERS

PRE-COMPRESSION PARAMETERS

Bulk Density and Tapped Density

The bulk density determined by pouring the mixture into graduated cylinder, and the initial volume was observed. The measuring cylinder containing a known volume mixture was tapped 100 times using density apparatus. The minimum volume occupied in the cylinder was measured. The bulk density, and tapped density were calculated using the following formulae.

$$\text{Bulk Density} = W/V_O$$

$$\text{Tapped Density} = W/V_F$$

Where, W = weight of the granules, V_O = initial volume of the granules, V_F = final volume of the granules.

Angle of Repose

It is the indication of the frictional forces existing between the mixture particles. It is the maximum angle possible between the surface of the pile of blend and the horizontal plane:

$$\tan \theta = h / r$$

Where, θ is the angle of repose; 'h' is the height of the heap of powder and 'r' is the radius of the heap of the powder. Therefore $\theta = \tan^{-1} (h/r)$.

Table 2: Grading of powders according to angle of repose.

S. No.	Angle of repose (θ)	Type of Flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Fixed funnel method was employed. Weighed quantities of the mixture were poured through the funnel from the fixed height onto the graph paper. Then the height of heap was measured. The circumference of the heap was marked by pencil. On the basis of large squares and

small squares present inside the circle the area of the circle was calculated and angle of repose was then calculated on the parameter 'r' which was found out from the area of circle.

POST COMPRESSION PARAMETERS

Tablets Thickness

To measured the thickness of the tablets by using Vernier Calipers. The thickness was determined by checking the thickness of the three tablets of each formulation.

Tablets Hardness

The hardness of each batch of tablet was checked by using hardness tester. It is measured in term kg/cm^2. The three tablets were chosen randomly and tested for hardness.

Friability

10 tablets were weighed and the initial weight of these tablets was recorded and placed in friabilator and rotate at the speed of 25 rpm for 100 revolutions. Afterward the tablets were removed from friabilator and again weighed and the weight was recorded. By using the following formula the percentage friability was calculated:

$$\%\text{Frability} = \frac{\text{initial weight of tablets} - \text{Final weight of tablets}}{\text{Intial weight of tablets}} \times 100$$

In-vitro Dispersion Time

In-vitro Dispersion time is the time required to tablet for its complete dispersion. The tablet was dropping a beaker containing 50 ml solution. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed (Pratibha *et al.*, 2014).

Wetting Time

A circular tissue paper was placed in a Petri dish of 10cm diameter. 10ml of water containing a water soluble dye was added to the Petri dish. Dye also used to identify complete wetting of tablet surface. Tablet was carefully placed on the surface of the tissue paper in the Petri dish at 25°C. When to reach the upper surface of the tablets and to completely wet them was noted as the wetting time (Chowdary *et al.*, 2013).

RESULTS

Analytical studies

The absorbance of the solution was measured at 295nm, using UV spectrometer with water as blank. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 20µg/ml. The results are shown in figure 1. Regression equation was derived from the slope of the curve (y = 0.0209x + 0.00076; R^2 =0.999). Also the analytical method so developed was validated for linearity.

Table 3: Standard calibration curve for Timolol Maleate in water.

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.053
2	4	0.094
3	6	0.132
4	8	0.172
5	10	0.212
6	12	0.260
7	14	0.301
8	16	0.342
9	18	0.385
10	20	0.429

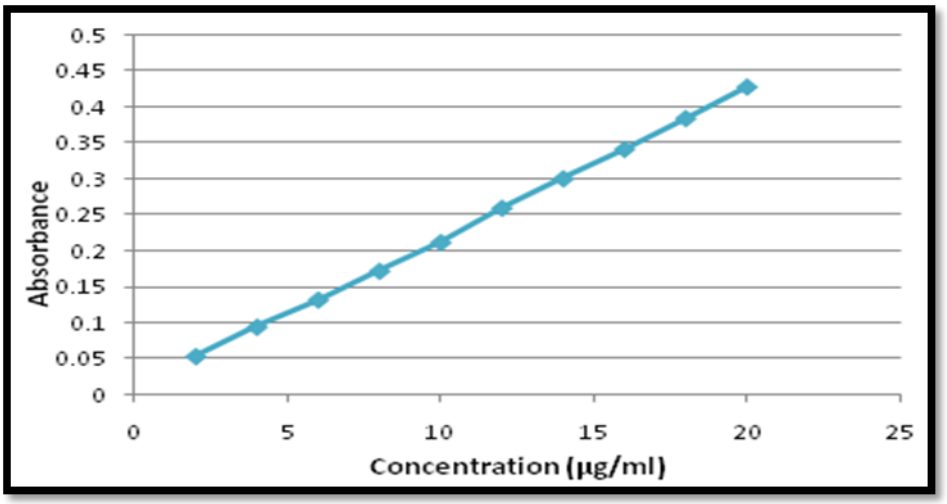

Figure 1: Standard Calibration Curve for Timolol Maleate.

FTIR

The FTIR spectra of Timolol Maleate were recorded using Infra-Red spectrophotometer. The spectrum was scanned over a frequency range 200-4000cm^{-1}.

The characteristic peaks for Timolol Maleate can be observed at following wave numbers:

Table 4: FTIR characteristic peak of Timolol Maleate and Polymer.

S.No.	Functional Groups	Frequency Ranges	Observed Peak	
			Timolol Maleate	Timolol Maleate with Croscarmellose Sodium
1	N-H	3400-3250 cm^{-1}	3311	3291
2	C=O	1820-1650 cm^{-1}	1705	1704
3	C=C	1400-1600 cm^{-1}	1497	1495
4	C-O-C	1300-1000 cm^{-1}	1120	1120

The above characteristic peaks were observed in IR spectra figure 2. There is no change in the FTIR spectra of Timolol Maleate with the polymer showing in figure 3.

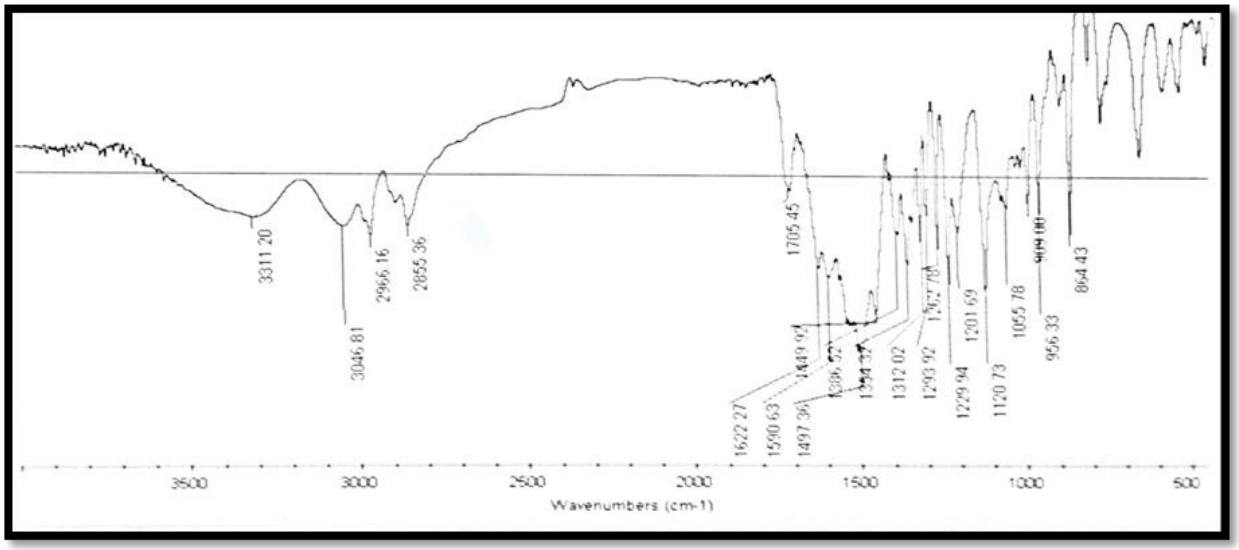

Figure 2: FTIR of Timolol Maleate.

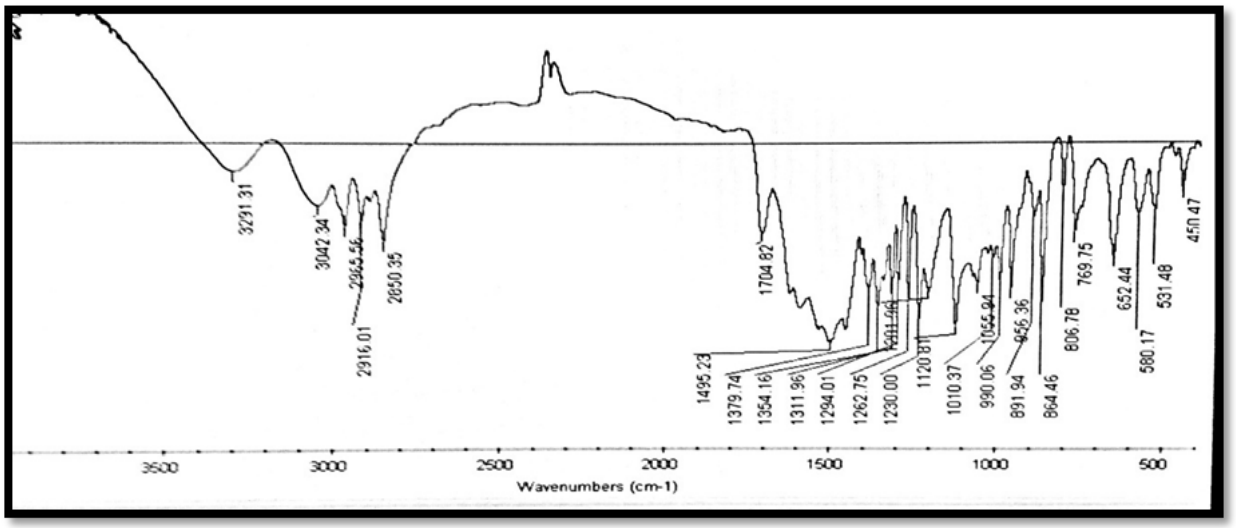

Figure 3: FTIR of Timolol Maleate with Croscarmellose Sodium.

Pre-compression Parameters

FDTs of Timolol Maleate were formulated by using direct compression method using sodium starch glycolate and croscarmellose sodium as a superdisintegrants. The prepared blends were evaluated and analyzed by using various parameters such as bulk density, tapped density, and angle of repose and the results were obtained. The results obtained were given in Table 5.

Table 5: Pre-compression parameters of Timolol Maleate F_1-F_7 powder blends.

Formulation Code	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose ($^0\theta$)
F_1	0.55	0.66	30.18
F_2	0.51	0.63	28.46
F_3	0.52	0.65	27.53
F_4	0.54	0.69	30.04
F_5	0.53	0.64	28.81
F_6	0.49	0.59	30.65
F_7	0.50	0.62	29.34

Values expressed as Mean ± SD (n=3)

Post Compression Parameters

FDTs of Timolol Maleate were formulated by using direct compression method using sodium starch glycolate and croscarmellose sodium as a superdisintegrants. The prepared tablets were evaluated for tablet thickness, tablet hardness, wetting time, disintegration time, and friability. The results of post compressional studies have shown in the Table 6.

Table 6: Post compression parameters of F_1-F_7 Timolol Maleate FDTs.

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Wetting Time (sec)	Disintegration Time (sec)
F_1	5.3±0.05	5.4±0.05	0.61	30±1.24	21±1.36
F_2	5.1±0.21	3.9±0.18	0.43	27±1.28	17±1.34
F_3	5.5±0.10	5.7±0.13	0.57	32±1.35	23±1.35
F_4	5.6±0.18	5.2±0.08	0.52	46±1.64	32±1.24
F_5	5.9±0.11	5.1±0.12	0.73	40±1.36	40±1.30
F_6	5.8±0.07	5.5±0.64	0.69	52±1.48	52±1.28
F_7	5.2±0.24	5.08±0.34	0.49	31±1.37	40±1.67

Values expressed as Mean ± SD (n=3)

DISCUSSION

A total of seven formulations were prepared and evaluated. Croscarmellose sodium was selected as superdisintegrant and menthol was selected as sublimating agent. The promising result was shown by batch F_2 containing 10 mg of menthol (DT 17±1.34 seconds, Friability 0.43%). Hence, for further studies, 10 mg of menthol was optimized. In all the formulations, hardness was within 3.9 kg/cm^2 to 5.5 kg/cm^2. Uniformity of drug contents was more than 95% in all the formulations. DT is an important criterion for selecting an optimum orally fast dissolving tablets formulation. It was observed that when the superdisintegrants concentrations are increased, DT was also decreased. F_2 batch have the lower DT as compared with other formulation and this batch did not cross the friability limit.

CONCLUSION

Fast dissolving tablets of Timolol maleate were formulated and evaluated. Timolol maleate was found to be an effective fast dissolving tablet by taking the super disintegrant croscarmellose sodium. All the formulations have been shown good flow properties along with good drug release. It is conclude that the F_2 formulation showed all evaluation parameters within limit. The F_2 batch is showed better onset of action. So, it is concluded that all the croscarmellose sodium containing tablet showed good release of drug as compared to sodium starch glycolate containing tablet.

REFERENCES

A. Jain, A. Purohit, R. Jatav and R. V. Sheorey, A. Sharma, "Formulation and evaluation of Aceclofenac fast dissolving tablets" *Int. J. Pharm. Life Sci.*, 2011; 2(4): 681-686.

1. D. Bhowmik, B. Chiranjib, Krishnakanth, Pankaj, R.M. Chandira, "Fast dissolving tablet: An overview" *J. Chem. Pharm. Res.*, 2009; 1(1): 163177.
2. K.S. Rathore, Dr. R. K. Nema, Dr. S. S. Sisodia, "Timolol maleate a gold standard drug in glaucoma used as ocular films and inserts: An overview" *Int. J. Pharm. Sci. Rev. Res.*, 2010; 3(1): 23-29.
3. K. Anupama, B. Neena, K. Shelly, "formulation and evaluation of mouth dissolving tablets of oxcarbazepine" Int. J. Pharm. and Pharm. Sci., 2009; 1(1): 12-23.
4. Pratibha, N. D. Kumar, G.G. Keshavshetti, "Design and evaluation of fast dissolving tablets of Metoclopramide hydrochloride using synthetic and natural superdisintegrants" *Unique J. Pharm. Biol. Sci.*, 2014; 2(1): 16-24.
5. K. P. R. Chowdary & K. V. N. R. Aishwarya, "Preparation and evaluation of fast dissolving tablets of paracetamol employing superdisintegrants" *J. Global Trend Pharm. Sci.*, 2013; 4(4): 1329-1334.
6. R. K. Putta, R. K. Shankar, *et al.*, "Formulation and evaluation of benazepril hydrochloride immediate release tablets" European. J. Biomed. Pharm. Sci., 2015; 2(8): 452-472.