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Research Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF METOPROLOL TARTRATE WITH NATURAL AND SYNTHETIC SUPERDISINTEGRANTS

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ABSTRACT

The main objective of the study is to formulate and evaluate orodispersible tablets of metoprolol tartrate with natural and synthetic superdisintegrants. Various formulations of metoprolol tartrate were prepared by direct compression method using different ratios of natural superdisintegrant (agar, treated agar) and synthetic superdisintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone) at the concentrations ranging from 3%-12%. The drug and excipients compatibility study was performed by FTIR to study the interaction between drug and excipients. The blend of all formulations were evaluated for various precompressional parameters such as angle of repose, bulk, tapped densities, compressibility index, Hausner's ratio and the prepared tablets were evaluated for various parameters like weight variation, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time, content uniformity and in vitro drug release. Formulations with treated agar have shown promising results compared to other formulations with semisynthetic superdisintegrants. The optimized formulation was subjected to stability studies for three months as per ICH guidelines. Disintegration times of formulations containing treated agar were found to be in the range 30-19sec and 95-100% drug release was observed in 5 min. The optimized formulation was found to be stable with insignificant change in the hardness, disintegration time, drug content and *in vitro* drug release.

Keywords: Orodispersible tablets, Superdisintegrants, Treated agar.

INTRODUCTION

Solid oral dosage forms like tablets and capsules are having wide acceptance about 50-60% of dosage forms and popularity because of ease of administration, accuracy in dosage, self medication and patient compliance. Drawback of these dosage forms is difficulty in swallowing with water. Often times patients experience inconvenience due to motion sickness (kinetosis), sudden episodes of coughing and unavailability of water allergic condition and bronchitis. Hence, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great attention[1]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as orally disintegrating tablets (ODTs) which disintegrate very rapidly (sec) in saliva without the need of water. Drug dissolution, absorption, drug bioavailability and clinical effect were observed to be significantly greater than conventional dosage form[2]. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia[3,4] and Centre for Drug Evaluation and Research (CDER).

Metoprolol tartrate is a beta blocker used in treatment of angina pectoris, management of hyper tension, congestive heart failure.ODTs with good taste and flavor increase the acceptability of bitter drugs like metoprolol tartrate by various groups of population. EP also specifies that orodispersible tablets should disintegrate within 3 min when subjected to conventional disintegration test used for tablets and capsules[5]. Various techniques are available for formulating ODTs include freeze drying, sublimation, spray drying, tablet molding and melt granulation[6] etc.

MATERIALS AND METHODS

Metoprolol tartrate was received as a gift sample from Natco Pharma, Pvt. Ltd, Hyderabad, India. Crospovidone, croscarmellose sodium, mannitol, aspartame, sodium starchglycolate were received as gift sample from Natco Pharma pvt Ltd, magnesium stearate, talc, microcrystalline cellulose, agar were purchased from S.D. Fine Chemicals Ltd., Mumbai, India.

Preparation of treated agar (TAG) [7,8]

Suitable quantity of agar powder (5-10 gm) weighed and added in distilled water (100ml). Agitation was done continuously for one day by stirrer to swell the contents. The swollen contents were dried for three days at room temperature. The dried powder was ground and passed through sieve number 100. **(See Fig 1)**

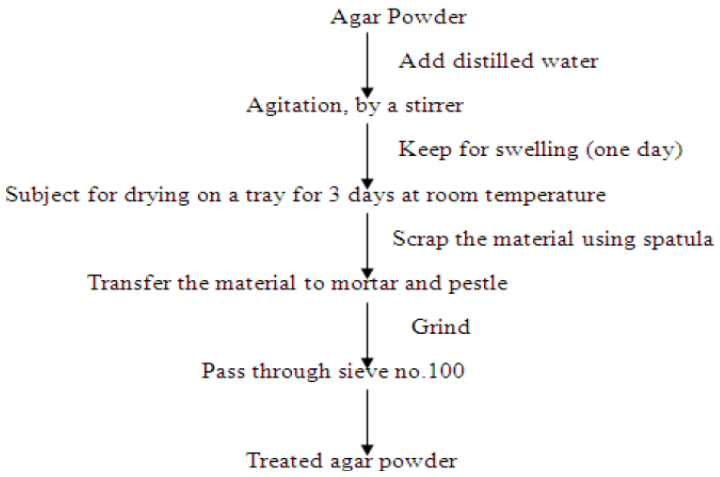


Fig. 1: Preparation of treated agar

Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Drug-excipient compatability study

The spectrum analysis of pure drug, polymer and physical mixtures of drug and different excipients used for preparation of tablets was studied by FTIR. Spectra were recorded by preparing drug potassium bromide (KBr) discs using a Shimadzu Corporation (Koyto, Japan) facilty (model - 8400S). The resultant disc was mounted in IR spectrophotometer and the spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} for 12 minutes.

Precompression parameters of the blend

All the ingredients were passed through mesh no 60. Required quantity of each ingredient was taken for each specified formulation. The powder blend was evaluated for precompression parameters and shown in **Table 1**

Angle of repose: This is the maximum angle possible between the surface pile of powder and horizontal plane. 100 gm of the blend was accurately weighed and carefully poured through the funnel whose tip was secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured until the apex of the conical pile just touches the tip of the funnel. Angle of repose is calculated by the following formula.

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

Where, θ = angle of repose, r=radius of the pile, h=height of the pile,

Bulk density: Bulk density is defined as a mass of a powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$*b = M/V*$$

Tapped density: The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 5 min). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula

$$*t = M/V_t$$

Hausner's ratio: Hausner ratio is an indirect index of ease of powder flow. It was calculated by the using the formula,

$$\text{Hausner's ratio} = *t/*d$$

Where *t=tapped density.*d=bulk density

Preparation of metoprolol tartrate orodispersible tablets

All ingredients were passed through #60 sieves. Then required quantities as given the **Table 1** were weighed for a batch size of 100 tablets and mixed uniformly except talc and magnesium stearate. Finally magnesium stearate and talc were added and mixed for 5 min in a polythene bag. Then mixed blend was compressed in to tablets using 9mm flat punches on a Rimek-1 station rotary tablet machine by direct compression method. Total weight of tablet was 200mg.

Table 1: Formulation of orodispersible tablets

Formulation Code	Drug (mg)	A (mg)	TA (mg)	SSG (mg)	CC (mg)	CP (mg)	Mannitol (mg)	MCC (mg)	Aspartame (mg)	Mg Stearate (mg)	Talc (mg)	Total wt (mg)
FA_1	25	6	--	--	--	--	80	70	15	2	2	200
FA_2	25	12	--	--	--	--	80	64	15	2	2	200
FA_3	25	18	--	--	--	--	80	58	15	2	2	200
FA_4	25	24	--	--	--	--	80	52	15	2	2	200
FT_1	25	--	6	--	--	--	80	70	15	2	2	200
FT_2	25	--	12	--	--	--	80	64	15	2	2	200
FT_3	25	--	18	--	--	--	80	58	15	2	2	200
FT_4	25	--	24	--	--	--	80	52	15	2	2	200
FS_1	25	--	--	6	--	--	80	70	15	2	2	200
FS_2	25	--	--	12	--	--	80	64	15	2	2	200
FS_3	25	--	--	18	--	--	80	58	15	2	2	200
FS_4	25	--	--	24	--	--	80	52	15	2	2	200
FC_1	25	--	--	--	6	--	80	70	15	2	2	200
FC_2	25	--	--	--	12	--	80	64	15	2	2	200
FC_3	25	--	--	--	18	--	80	58	15	2	2	200
FC_4	25	--	--	--	24	--	80	52	15	2	2	200
FP_1	25	--	--	--	--	6	80	70	15	2	2	200
FP_2	25	--	--	--	--	12	80	64	15	2	2	200
FP_3	25	--	--	--	--	18	80	58	15	2	2	200
FP_4	25	--	--	--	--	24	80	52	15	2	2	200

Evaluation of orodispersible tablets

The prepared tablets can be evaluated for various parameters like weight variation, thickness, hardness, friability, wetting time, water absorption ratio, content uniformity, disintegration time, *in vitro* dissolution studies.

Weight variation: Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness: The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by screw gauge. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging. The thickness in millimeters (mm) was measured individually for ten preweighed tablets using screw gauge. The average thickness and standard deviation were reported.

Hardness: The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester) and expressed in Kg/cm^2. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability: Friability of the tablets was determined using Roche Friabilator (Electrolab, India) that is set at 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with preweighed sample of 20 tablets. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

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

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

Wetting time: Five circular tissue papers of 10 cm diameter were placed in a petri dish with a 10 cm diameter. 10 ml of water at $37^0C+0.5^0C$ containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation

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

Where W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Content uniformity: 20 tablets were randomly selected and average weight was calculated and powdered in a glass mortar. Powder equivalent to 25mg of drug was weighed and dissolved in 100 ml of 6.8 pH phosphate buffer, filtered and drug content analyzed spectrophotometrically at 223 nm.

Disintegration time: Disintegration time was measured using a modified disintegration method. For this purpose, a petri dish was filled with 10 ml of water at $37^0C\pm0.5^0C$. The tablet was carefully put in the centre of the petridish and the time for the tablet to completely disintegrate into fine particles was noted.

***In vitro* release**

In vitro drug release of metoprolol tartrate orodispersible tablets was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 500 ml 6.8 pH phosphate buffer at $37^0C \pm 0.5^0C$. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 5, 10, 15, 20, 25, and 30min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO- 164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 223 nm and drug release was determined from standard curve.

Stability studies

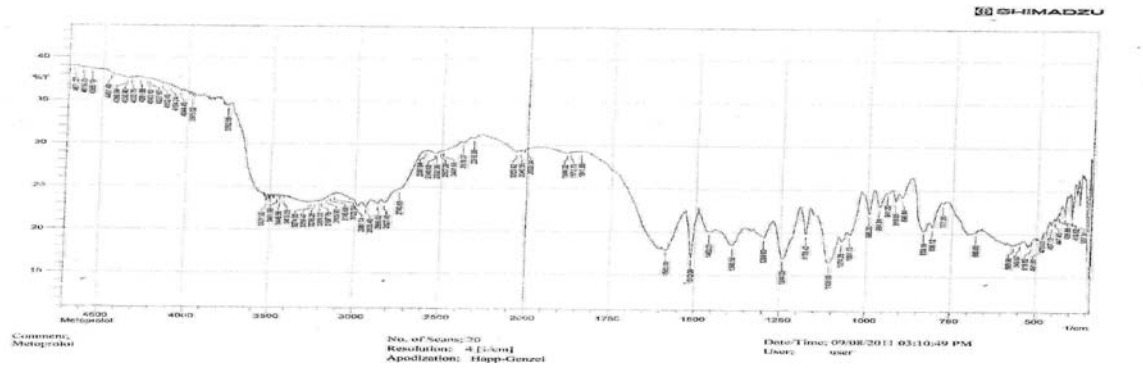
The optimized formulation was subjected to stability studies at $40^0C\pm2^0C/75\%\pm2\%RH$ for period of three months. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for three months. For every one month tablets were analyzed for the hardness, disintegration time, drug content and in-vitro drug release[9].

RESULTS AND DISCUSSION

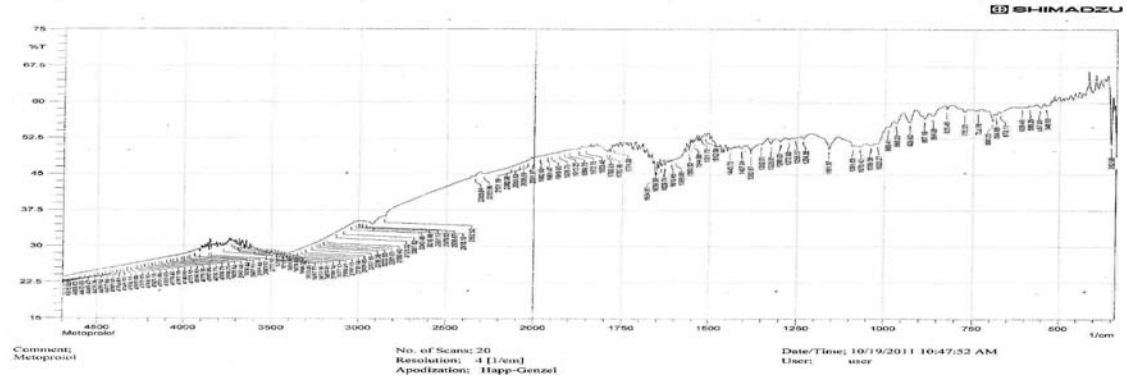
Preformulation studies

IR graphs the peaks representing the pure drug were similar in all the graphs suggesting that there is as such no interaction and the pure drug is not altered functionally as shown in the **Fig 2**

All formulation blends were evaluated for precompression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The angle of repose between 31-35 indicates good free flowing material and >40° with poor flow properties. Values for angle of repose were found in the range of 30.04±0.60° to34.87±1.32° showing that the blend of powder has good free flowing and can be used for direct compression. The value for carr's index was in between 14±1.32 to 20.±1.158 indicating that most batches of powder blends were having good or fair compressibility. Hausner's ratio was found to be within limits (<1.25). All formulation blends showed good flow properties and hence tablets were prepared by direct compression method. The two most important attributes for the direct compression method are good flow and good compressibility. Interparticulate interactions influence the flow properties of powder.



(a)



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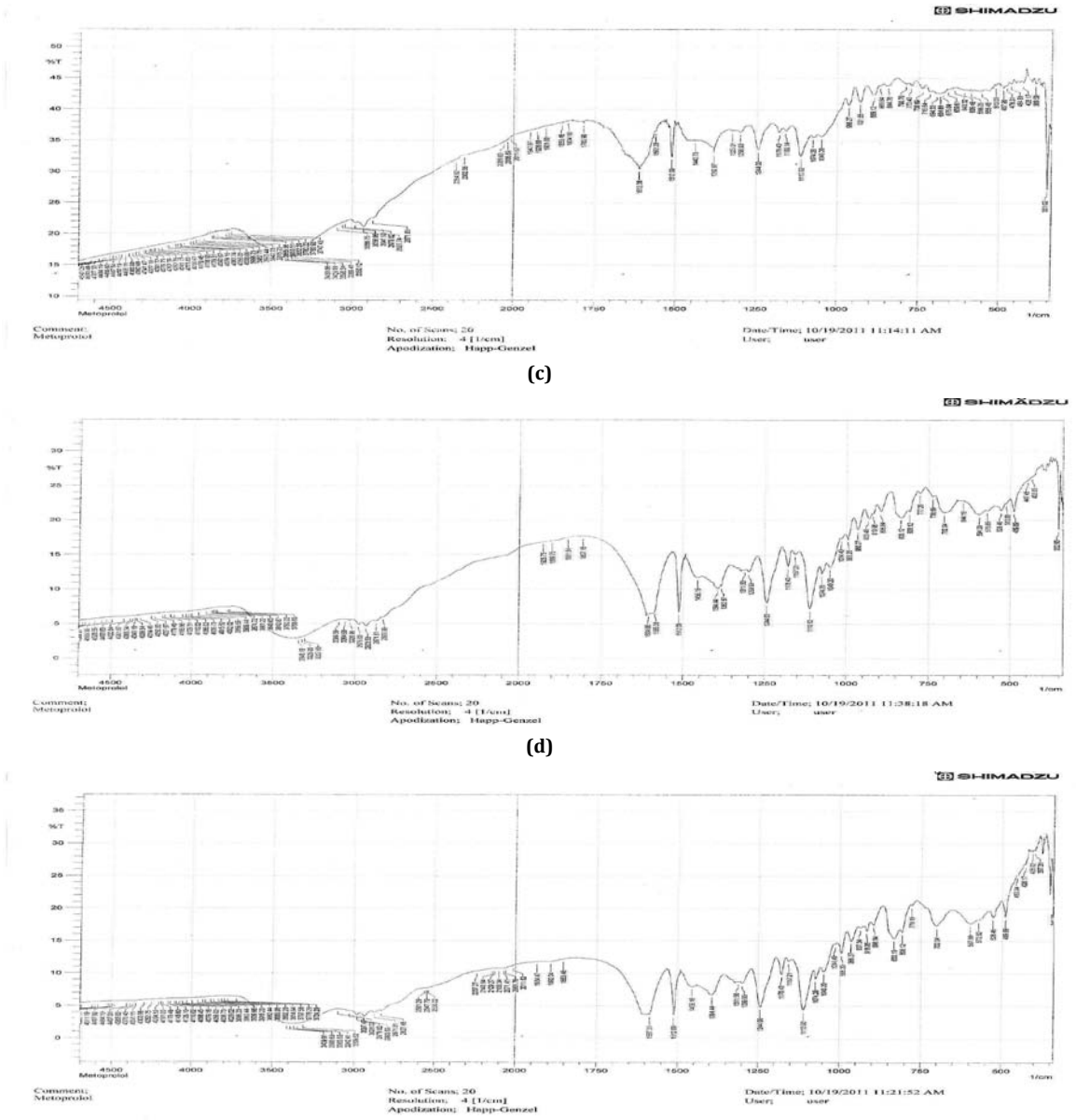

Fig. 2: FTIR spectrum of Metoprolol tartrate (a) pure drug, (b)agar, (c)treated agar, (d)physical mixture of drug+ agar and (e)drug +treated agar.

Table 2: Precompression parameters of the powder blend of all formulations.

Formulation	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Hausner's ratio	Compressibility Index (%)
FA_1	31.19±1.42	0.55±0.005	0.64±0.02	1.16±0.03	14±2.41
FA_2	31.27±1.5	0.55±0.004	0.64±0.05	1.16±0.09	14±1.95
FA_3	32.16±1.03	0.55±0.005	0.65±0.01	1.18±.0.02	15±1.47
FA_4	30.12±1.12	0.55±0.005	0.64±0.02	1.16±0.05	14±1.68
FT1	31.26±0.69	0.55±0.007	0.64±0.006	1.16±0.002	14±1.32
FT2	30.76±0.76	0.55±0.013	0.64±0.005	1.105±0.009	14±1.14
FT3	30.15±0.90	0.54±0.020	0.63±0.009	1.10±0.009	14±2.39
FT4	30.04±0.60	0.55±0.017	0.64±0.06	1.09±0.004	14±1.19
FS1	33.03±1.56	0.520±0.007	0.62±0.002	1.190±0.04	16±1.20
FS2	33.72±1.41	0.53±0.007	0.63±0.01	1.18±0.02	15±1.67
FS3	32.85±1.33	0.51±0.007	0.62±0.02	1.21±0.03	17±1.41
FS4	34.14±1.67	0.52±0.003	0.63±0.002	1.21±0.03	17±2.51
FC1	32.43±1.48	0.50±0.007	0.63±0.01	1.26±0.03	20±1.158
FC2	32.72±1.22	0.52±0.007	0.63±0.02	1.21±0.04	17±1.55
FC3	34.87±1.32	0.51±0.007	0.62±0.38	1.21±0.04	17±1.39
FC4	30.47±1.34	0.54±0.007	0.65±0.02	1.20±0.03	16±2.20
FP1	32.26±1.26	0.52±0.007	0.62±0.01	1.19±0.03	16±2.01
FP2	33.52±1.20	0.52±0.007	0.63±0.01	1.21±0.04	17±2.12
FP3	34.19±1.26	0.54±0.007	0.64±0.02	1.18±0.03	15±1.51
FP4	32.26±1.20	0.55±0.007	0.65±0.01	1.14±0.03	15±1.39

All values are of mean±SD, n=3

Evaluation of orodispersibile tablets

In the present work metoprolol tartrate orodispersible tablets were prepared by using synthetic super disintegrants namely(sodium starch glygcolate, croscarmellose sodium and crospovidone) and natural super disintegrants (agar and treated agar). All the formulations were evaluated for various parameters like hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and *in vitro* drug release studies. The hardness of the tablets was found to be in between 3.5 ± 0.1 to 4.0 ± 0.05 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 4.58± 0.21mm to 4.87± 0.15 mm . All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%. The drug content was found to be 99.08 to 100.84 %, indicating uniform distribution of drug in the tablets. Disintegration times and wetting times of the tablets are given in **Table 3** and shown in the **Fig 3-5.**

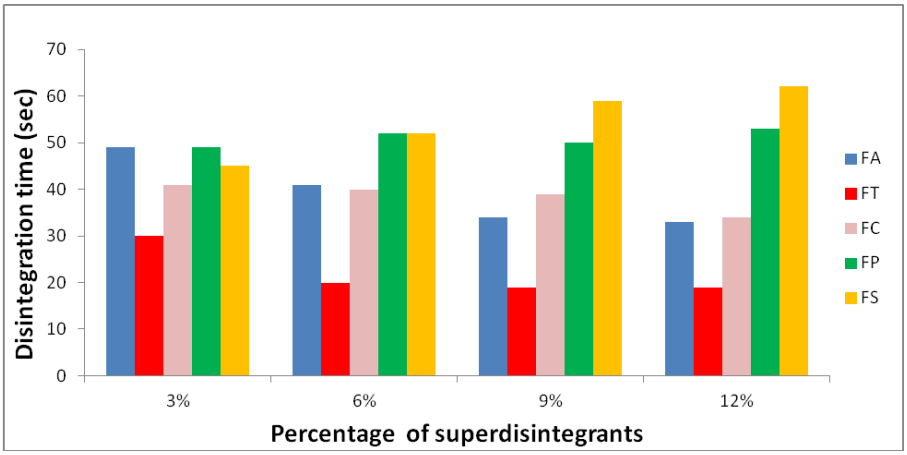

Fig. 3: Disintegration time of tablets containing different superdisintegrants with different percentages

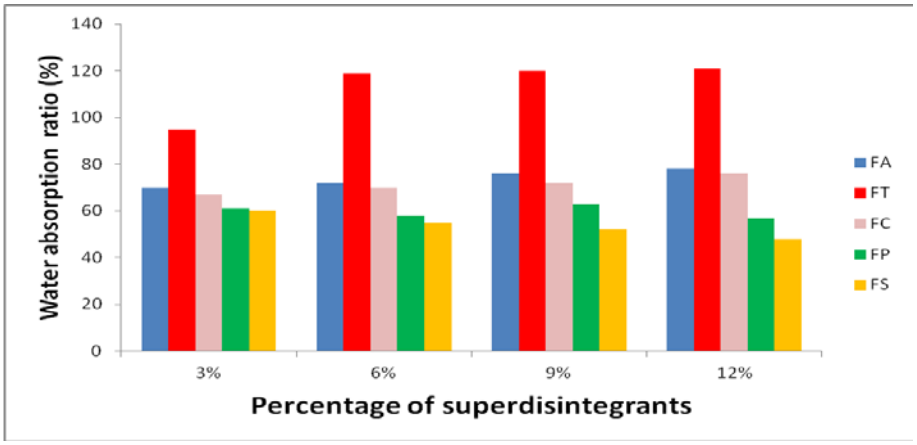

Fig. 4: water absorption ratio of different superdisintegrants with different percentages

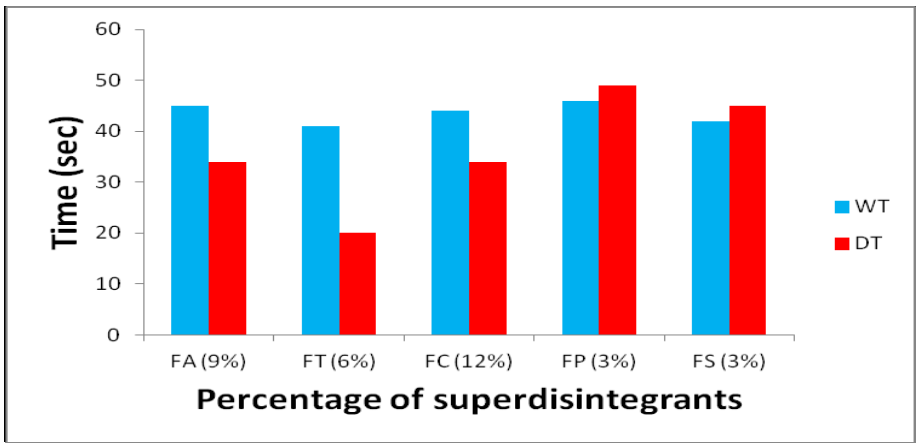

Fig. 5: Wetting time of different superdisintegrants with different percentages

Dissolution studies

In vitro drug release of all formulations was above 90% within 10-15min, but formulations with 6% treated agar have shown above 95-100 % within 5 min as shown in **Fig 6-9.** So, it is considered as a material with good tabletting properties, lower disintegration times and also improved the dissolution of the drug. The formulations containing treated agar showed lower disintegration times compared to other formulations containing higher percentages of superdisintegrants because agar swells when hydrated (treated agar) and becomes porous. After drying these pores will be retained and helps in faster uptake of media which results in lower disintegration times (increased wicking and swelling properties).

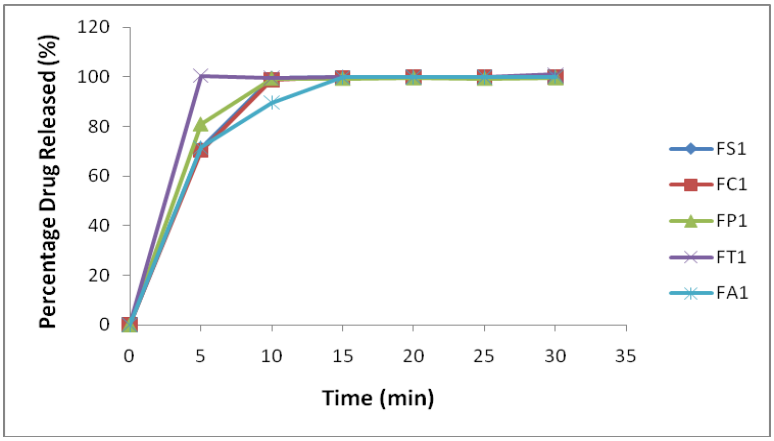

Fig. 6: Dissolution profile of metoprolol tartrate orodispersible tablets of FS1, FC1, FP1, FT1 and FA1

Note: FA = Agar , FT = Treated agar , FS = Sodium starch glycolate , FC = Croscarmellose sodium , FP = Crospovidone

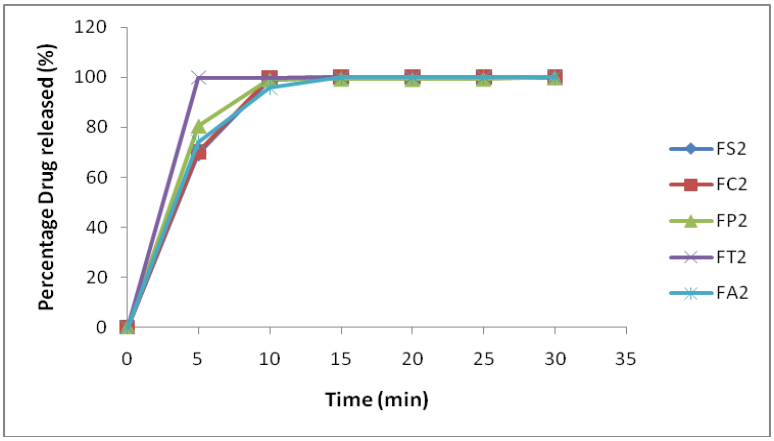

Fig. 7: Dissolution profile of metoprolol tartrate orodispersible tablets of FS2, FC2, FP2, FT2 and FA2.

Note: FA = Agar , FT = Treated agar , FS = Sodium starch glycolate , FC = Croscarmellose sodium , FP = Crospovidone

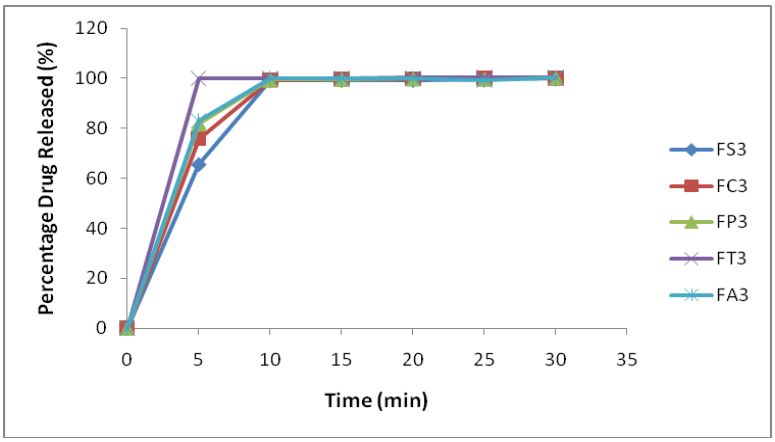

Fig. 8: Dissolution profile of metoprolol tartrate orodispersible tablets of FS3, FC3, FP3, FT3 and FA3.

Note: FA = Agar , FT = Treated agar , FS = Sodium starch glycolate , FC = Croscarmellose sodium , FP = Crospovidone

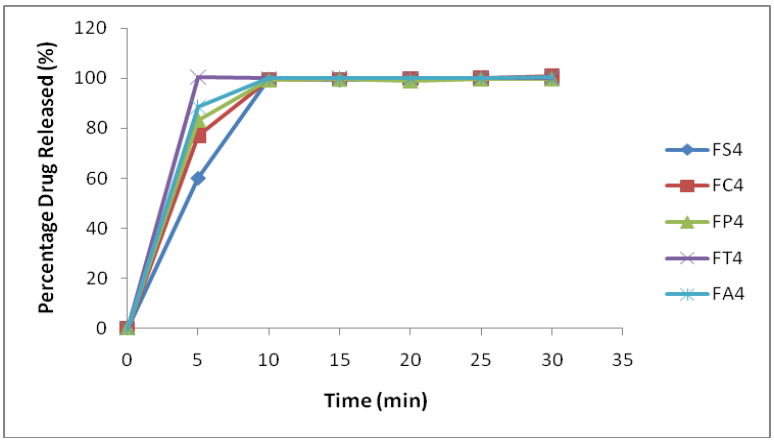

Fig. 9: Dissolution profile of metoprolol tartrate orodispersible tablets of FS4, FC4, FP4, FT4 and FA4.

Note: FA = Agar, FT = Treated agar , FS = Sodium starch glycolate , FC = Croscarmellose sodium , FP = Crospovidone

Table 4: Accelerated stability studies

Parameters	Time in months			
	Initial	1st month	2nd month	3rd month
Hardness[a] (kg/cm^2)	3.8±0.32	3.6±0.11	3.5±0.13	3.6±0.15
Disintegration time[b] (sec)	19±0.808	19±0.673	18±0.710	18±0.639
Drug content[c] (%)	100.21±0.69	100.14±0.83	99.97±0.19	100.20±1.20
In vitro drug release[d] (%)	99.79±0.17	99.82±0.32	99.63±0.28	99.98±0.13

a,c:mean±SD,n=5; b:mean±SD, n=6; d:mean± SD, n=3

Stability studies

The stability of the optimized formulation was studied as shown in **Table 4** for three months at accelerated conditions of 40±2^{0}C/75±2% RH. The formulations were found to be stable, with insignificant change in the hardness, disintegration time and drug content and *in vitro* drug release pattern.

CONCLUSIONS

In conclusion, it can be stated that the objective of the study has been achieved. From the above study, FT2 formulation was concluded as an optimized formulation due to its less disintegration time. From the above data, it can be concluded that superdisintegrant (treated agar) 6% (FT2) is having better disintegrant property than other disintegrants namely, sodiumstarch glycolate, crosscarmellose sodium and crospovidone. Formulations containing natural polymer (agar) also show good disintegration properties and both can be used as a substitutes in place of synthetic superdisintegrants. Results revealed that treated agar acts as super disintegrating agent and also enhances or promotes the dissolution of the drug.

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