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 this study was to formulate and evaluate the oro dispersible tablets of metoprolol tartrate with natural and synthetic superdisintegrants. Various formulations were prepared by direct compression using different percentages of natural superdisintegrant i.e. locust bean gum and synthetic superdisintegrants namely sodium starch glycolate, crospovidone, and croscarmellose sodium ranging from 3%-12%. The drug and excipients compatibility study was performed by FTIR and the study revealed no interaction between drug and excipients. The blend of all formulations were evaluated for various precompression parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and were found to be satisfactory. The tablets were evaluated for various parameters like weight variation, thickness, and hardness, friability, wetting time, water absorption ratio, disintegration time, content uniformity and in vitro drug release. The disintegration time was found to be 17 seconds for the optimized formulation of Locust Bean Gum 3. The optimized formulation was subjected to stability studies for three months as per ICH guidelines. The formulation was found to be stable with insignificant change in the physical appearance, hardness, disintegration time, drug content and in vitro drug release.

INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most important patient compliance. The different dosage forms include tablets and capsules. The important drawback of these dosage forms for pediatric and geriatric patients is being difficulty in swallowing. Nearly 35% of the general population, especially the elderly patients and children suffer from dysphasia or difficulty in

swallowing, which results in high incidence of noncompliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non co-operative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water. To overcome these problems, formulators have

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considerably dedicated their effort to develop a novel type of tablet dosage form for oral administration, i.e. one, which disintegrates and dissolves rapidly in saliva without the need for drinking water. The tablet is placed in the mouth, allowed to disperse or dissolve in the saliva. These tablets usually dissolve within 15 seconds to 1minute. The faster the drug goes into solution, the quicker the absorption and onset of clinical effect[1].

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 disintegrate within 3 min when subjected to conventional disintegration test used for tablets and capsules[2]. Various techniques are available for formulating ODTs include freeze drying, sublimation, spray drying, tablet molding and melt granulation etc.

MATERIALS AND METHOD

Metoprolol tartrate, Crospovidone, croscarmellose sodium, mannitol, aspartame, sodium starchglycolate was received as gift sample from Natco Pharma Pvt Ltd. Magnesium stearate, talc, microcrystalline cellulose was purchased from S.D Fine Chemicals, Mumbai, India. Locust bean gum was purchased from Hi Media lab.pvt.ltd.Mumbai, India.

Locust Bean Gum[3,4,8]

Locust bean gum (LBG, also known as carob gum, carob bean gum, carobin, E410) is a galactomannan vegetable gum extracted from the seeds of the carob tree, mostly found in the Mediterranean region. The long pods that grow on the tree are used to make this gum. Locust bean gum occurs as a white to yellow-white powder. It consists chiefly of high-molecular-weight hydro-colloidal poly-saccharides, composed of glactose and mannose units combined through glycosidic linkages, which may be described chemically as galactomannan. It is dispersible in either hot or cold water, forming a sol having a pH between 5.4 and 7.0, which may be converted to a gel by the addition of small amounts of sodium borate. LBG is used as a thickening agent and gelling agent in food technology.

Preformulation Studies[5,6,7]

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 - Excipients Compatibility Study by FT-IR

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for the preparation of tablets was studied by FT-IR. FT-IR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes.

Pre-compression Parameters of the Powder Blend

Angle of Repose

This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co-efficient friction (μ) between the particles. Hence the rougher & more irregular the surface of particles the greater will be angle of repose.

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

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 250). 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

$$*t=M/V_t$$

Compressibility Index

The simplest way for measurement of free flow of powder is compressibility an indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which is calculated using the formula,

$$\text{C.I (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

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

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

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

Preparation of Metoprolol Tartrate Oral Dispersible Tablets[5,6,7]

All ingredients were passed through #60 sieve. Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant and mixed for 5min. This uniformly mixed blend was compressed in to tablets containing 25mg drug using 9mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method. Total weight of tablet was kept 200mg.

Evaluation of Orodispersible Tablets [5,6,7]

Weight Variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percentage deviation from the average was calculated.

Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter 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. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. 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 10 pre weighed tablets by using screw gauge. The average thickness and standard deviation were reported.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces. It was measured using a tablet hardness tester (Monsanto hardness tester). 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). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula.

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

Table 1: Formulations of metoprolol tartrate containing different superdisintegrants

Formuln code	Drug (mg)	SSG (mg)	CC (mg)	CP (mg)	LBG (mg)	Aspartame (mg)	Magnesium stearate (mg)	Talc (mg)	MCC (mg)	Mannitol (mg)	Total wt (mg)
FS$_1$	25	6	--	--	--	15	2	2	70	80	200
FS$_2$	25	12	--	--	--	15	2	2	64	80	200
FS$_3$	25	18	--	--	--	15	2	2	58	80	200
FS$_4$	25	24	--	--	--	15	2	2	52	80	200
FC$_1$	25	--	6	--	--	15	2	2	70	80	200
FC$_2$	25	--	12	--	--	15	2	2	64	80	200
FC$_3$	25	--	18	--	--	15	2	2	58	80	200
FC$_4$	25	--	24	--	--	15	2	2	52	80	200
FP1	25	--	--	6	--	15	2	2	70	80	200
FP2	25	--	--	12	--	15	2	2	64	80	200
FP3	25	--	--	18	--	15	2	5	58	80	200
FP4	25	--	--	24	--	15	2	2	52	80	200
FLBG1	25	--	--	--	6	15	2	2	70	80	200
FLBG2	25	--	--	--	12	15	2	2	64	80	200
FLBG3	25	--	--	--	18	15	2	2	58	80	200
FLBG4	25	--	--	--	24	15	2	2	52	80	200

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 $37^0C \pm 0.5^0C$ containing eosin, a water-soluble dye was added to the petridish. 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. Tablets were powdered in a glass mortar. Powder equivalent to 25mg was weighed and dissolved in 100 ml of 6.8pH phosphate buffer, filtered and drug content analyzed spectrophotometrically at 223 nm.

In-vitro 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 $37^0 C \pm 0.5^0C$. 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 900 ml 6.8pH phosphate buffer at $37^0C \pm 0.5^0C$. The speed of rotation of paddle was set at 100 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.

Accelerated Stability Studies

The optimized formulation was subjected to stability studies at $40^0C \pm 2^0C/75\% \pm 5\%RH$ 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 physical appearance, hardness, disintegration time, and drug content and *in-vitro* drug release.

RESULTS AND DISCUSSION

Preformulation Studies

FTIR study was done to verify if there was any interaction between the pure drug and various excipients were employed. The various FTIR graphs both of pure drug and various excipients were mixed and the blend was formulated into IR pellet and scanned. The different plots are given below.

Precompression parameters of all formulations blend were evaluated for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The two most important attributes for the direct compression formula are good flow and good compressibility. The angle of repose gives important information about the flow characteristics of the powder mixture. The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, and compressibility), the bulk powder properties (e.g., size distribution, compaction) and the processing environment (e.g., storage, humidity). The angle of repose <30° indicates free flowing material and >40° with poor flow properties. Values for angle of repose were found in the range of 30.42 ± 0.78^0 to 34.87 ± 1.32^0 showing that the blend of powder was free flowing and can be used for direct compression. The value for Carr's index was in

between 13 ± 2.14 to 20 ± 1.15 indicating that all batches of powder blends were having good compressibility. Hausner's ratio was to be within the limits 1.16(<1.25). All the formulations showed good blend properties and hence tablets were prepared by direct compression method.

Evaluation of Orodispersible Tablets

In the present study metoprolol tartrate orodispersible tablets were prepared by using synthetic super disintegrants namely cross povidone, cross carmellose sodium, sodium starch glycolate and natural super disintegrant locust bean gum. 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 3.4 ± 0.42 to 4.0 ± 0.21 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 4.13 ± 0.26 to 4.28 ± 0.14. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. $\pm7.5\%$. The drug content was found to be 99.08 ± 2.65 to$100.7\pm0.33\%$, indicating uniform distribution of drug in the tablets. Disintegration times and wetting time were given below.
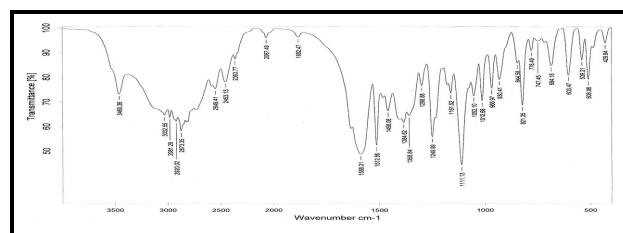

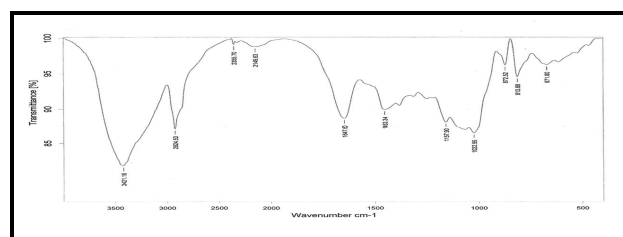Figure 1: IR Spectra of Metoprolol Tartrate Pure Drug

Figure 2: IR Spectra of Locust bean gum

Table 2: Precompression parameters of the powder blend of all formulations of locust bean gum, cross povidone, cross carmellose sodium and sodium starch glycolate

Formulation Code	Angle of Repose(θ) [*]	Bulk density (gm/cm³) [*]	Tapped density (gm/cm³) [*]	Hausner's Ratio [*]	CI (%) [*]
FLBG1	31.24±1.64	0.55±0.002	0.65±0.04	1.16±0.045	15±1.27
FLBG2	31.42±0.82	0.55±0.004	0.64±0.02	1.16±0.08	14±2.48
FLBG3	31.54±0.66	0.55±0.005	0.63±0.01	1.14±0.28	13±2.14
FLBG4	30.42±0.78	0.55±0.004	0.64±0.04	1.16±0.16	14±1.24
FS1	33.03±1.56	0.520±0.007	0.62±0.02	1.19±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±1.15
FC2	32.72±1.22	0.52±0.007	0.63±0.02	1.21±0.04	17±1.15
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

FLBG = Locust bean gum; FS = Sodium starch glycolate; FC = Cross carmellose sodium; FP = Cross povidone. Values are expressed as Mean ±SD, *n=3
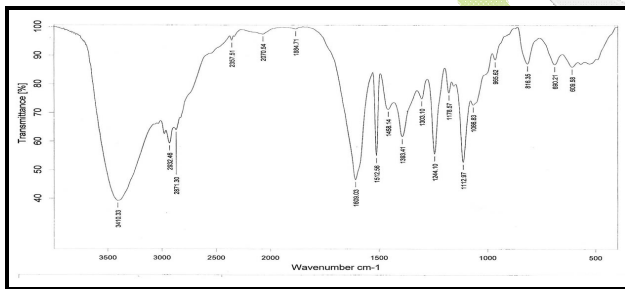

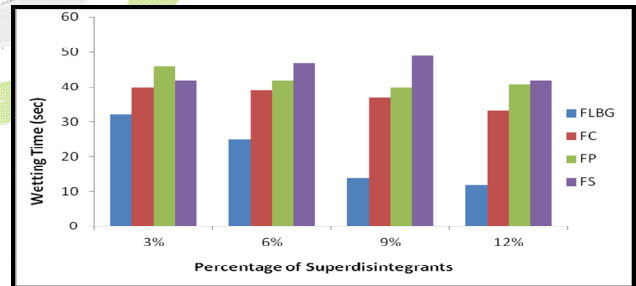Figure 3: IR Graph of Physical Mixture of Metoprolol Tartrate and Locust bean gum

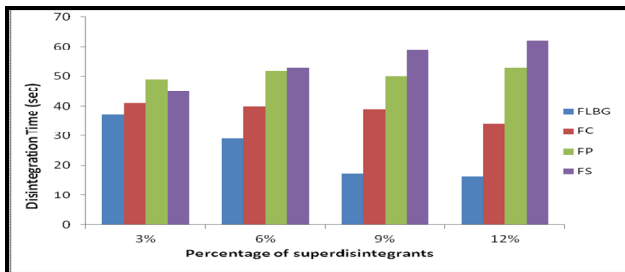Figure 5: Wetting time of different superdisintegrants with different Percentages

Figure 4: Disintegration time of tablets containing different superdisintegrants with different percentages
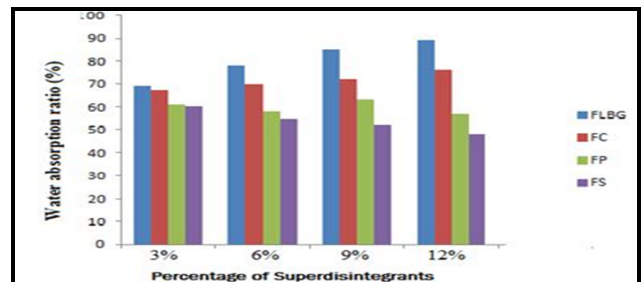

Figure 6: Water absorption ratio (%) of different superdisintegrants with different percentages

Table 3: Comparison of disintegration time, wetting time, water absorption ratio of FLBG, FC, FP and FS using one way ANOVA (tukey's multiple comparison test)

Sr.No	Parameters of ODT	FLBG vs. FC	FLBG vs. FP	FLBG vs. FS	F value	P value
1.	Disintegration Time	NS	**	***	14.33	0.0003
2.	Wetting Time	***	**	***	15.98	0.0002
3.	Water absorption Ratio	NS	**	***	17.99	0.0001

Note: N=3; one way ANOVA (tukey's multiple comparison test); NS = non-significant, *** (p<0.0001); ** (p<0.001); * (p<0.01). One way ANOVA of FLBG, FC, FP and FS formulations suggested that there was significant difference in disintegration time (P < 0.0003), wetting time (P<0.0002) and water absorption ratio (P<0.0001) with LBG in comparision to FC, FP and FS.
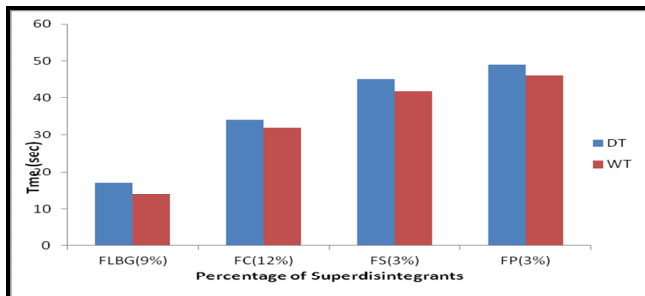

Figure 6: Comparison of Disintegration time and Wetting time of FLBG3, FC4, FP1 and FS1.

Dissolution Studies

In vitro drug release of all formulations was shown 90-95% in 10-30min, but formulations with 9% locust bean gum have shown 95-100 % in 10-30 min as shown in Fig 9. So, it is considered as a material with good tabletting properties, lower disintegration time.
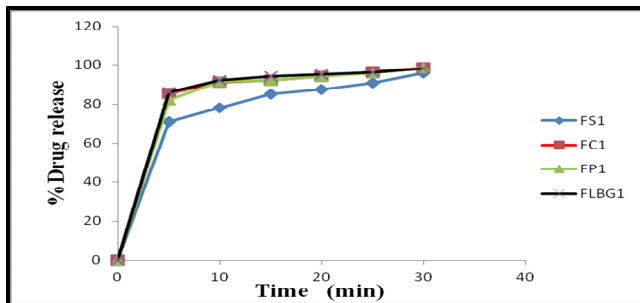

Figure 7: Dissolution profile of metoprolol tartarate oral dispersible tablet of FS1, FC1, FP1 and FLBG1 Note: FS = sodium starch glycolate, FC = cros carmellose sodium, FP = crospovidone, FLBG = locust bean gum
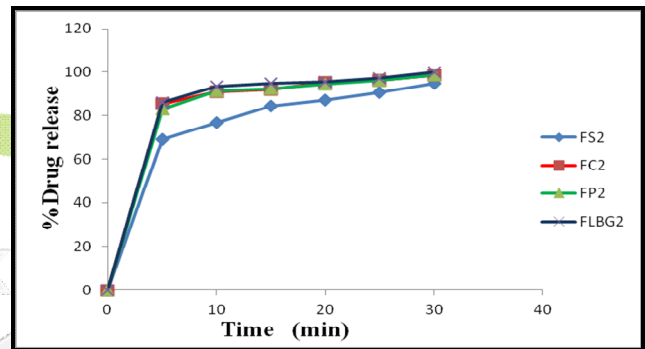

Figure 8: Dissolution profile of metoprolol tartrate oral dispersible tablet of FS2, FC2, FP2 and FLBG2

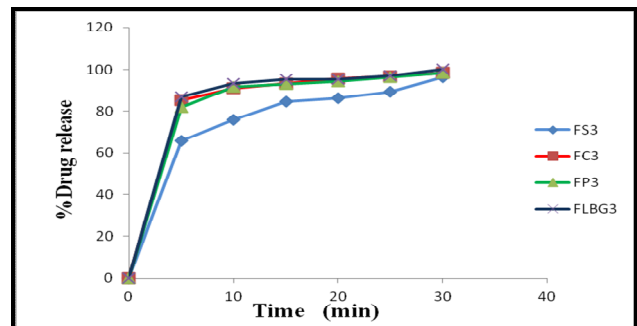Note: FS = sodium starch glycolate, FC = cros carmellose sodium, FP = crospovidone, FLBG = locust bean gum

Figure 9: Dissolution profile of metoprolol tartrate oral dispersible tablet of FS3, FC3, FP3 and FLBG3

Note: FS = sodium starch glycolate, FC = cros carmellose sodium, FP = crospovidone, FLBG = locust bean gum
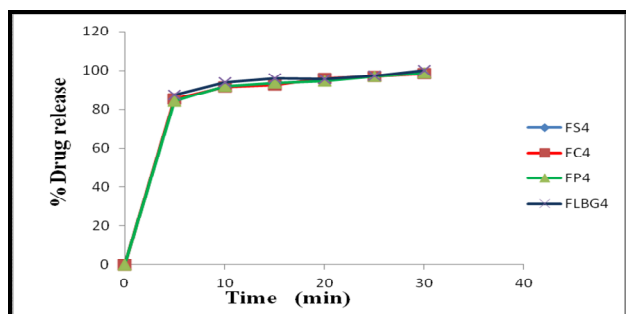
Figure 10: Dissolution profile of metoprolol tartrate orodispersible tablets of FS4, FC4, FP4 and FLBG4

other formulations containing higher percentages of superdisintegrants due to its swelling, porosity and wicking action.

From the above data, it can be concluded that superdisintegrant (Locust bean gum) 9% (FLBG3) is having better disintegrant property than other disintegrants namely sodium starch glycolate, crosscarmellose sodium and crospovidone. Results revealed that locust bean gum acts as super disintegrating agent and also enhances or promotes the dissolution of the drug.

Table 4: Accelerated stability studies

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Physical appearance	No change	No change	No change	No change
Hardness (kg/cm^2)	3.5±0.32	3.4±0.11	3.5±0.13	3.5±0.15
DT (sec)	17±0.72	17±0.69	16±0.682	16±0.562
Drug content (%)	100.24±0.13	100.14±0.83	99.97±0.19	100.20±1.20
In-vitro drug release (%)	101.70±0.17	100.82±0.32	100.63±0.28	100.98±0.13

Note: FS = sodium starch glycolate, FC = cros carmellose sodium, FP = crospovidone, FLBG = locust bean gum

Stability Studies

The stability of the optimized formulation was studied as shown in Table 4 for three months at accelerated conditions of 40 ± 2^0C/$75\pm5\%$ 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, FLBG3 formulation was concluded as an optimized formulation due to its less disintegration time. Formulations containing natural polymer (locust bean gum) showed lower disintegration times when compared to

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