Research Article

Design and Optimization of Fast Dissolving Tablet of Terbutaline Sulphate

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ABSTRACT
Terbutaline sulphate is chemically 2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol sulphate. It is used as anti-asthmatic drug which is highly water soluble. The bioavailability of Terbutaline sulphate is very less due to extensive pre-systemic metabolism.
The aim of the present study was to optimize the best fast dissolving tablet of terbutaline sulphate prepared by direct compression method using 3^2 full factorial design by comparing natural superdisintegrant, plantago ovate husk powder with synthetic disintegrant, crospovidone with pearlitol SD 200 and microcrystalline cellulose pH 102 as diluents.
Drug-excipient compatibility study was carried out by fourier transform infrared (FT-IR) spectroscopy. Fast dissolving tablet was formulated and evaluated for various pre-compression and post-compression parameters and concluded that natural superdisintegrant, plantago ovate husk powder is suitable for formulating fast dissolving tablet with quick onset of action due to faster disintegration and dissolution, non-toxic, biocompatible, cheap in cost and easy availability. The optimized formulation was compared with marketed formulation and proceeded for accelerated stability studies at 45°C ± 2°C and 75%RH ± 5% RH for one month.

Keywords: Terbutaline sulphate, plantago ovate husk powder.

INTRODUCTION

High incidence of non-compliance and ineffective therapy[1] in conventional oral drug delivery is primarily due to dysphagia (approximately one-third of the population, especially geriatric and pediatric patients[2]). Sudden episodes of allergic attacks or coughing, unavailability of water, hand tremors, increased intake of water for swallowing conventional dosage form results in frequent urination, nocturia and motion sickness are other problems in conventional oral drug delivery. The above said problems were overcome by formulating fast dissolving tablets which disintegrates instantaneously.
'Fast Dissolving Tablet (FDT) is one of the patient acceptable novel drug delivery system (NDDS) suitable for pediatrics and geriatics with easy administration of drug molecule. A fast dissolving tablet is the one which disintegrates or dissolve rapidly in saliva without the need of water or chocking. FDT usually dissolve in the oral cavity within 15 seconds to 3 minutes. In other words, fast dissolving tablet is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing[2].
Fast dissolving tablet is also called as orodispersible tablet, melt-in-mouth, rapid disintegrating tablet, repimelts, porous tablets and quick dissolving tablet[3]. Their growing importance was underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablets" as a tablet that to be placed in the mouth where it disperse or disintegrate in less than three minutes[3].
Chemically Terbutaline sulphate[4] is 2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol sulphate. It is used as anti-asthmatic drug. It is freely soluble in water. The bioavailability of Terbutaline sulphate is very less due to extensive pre-systemic metabolism.
The present study was carried out to optimize fast dissolving tablet of Terbutaline sulphate using 3^2 full factorial design by comparing natural superdisintegrant, plantago ovate husk powder with synthetic disintegrant, crospovidone.

MATERIALS AND METHODS

Terbutaline sulphate was purchased from Jayco chemical industries, Maharastra. Microcrystalline cellulose pH 102, crospovidone, pearlitol SD 200, talc and magnesium stearate were gift samples from Dr. Reddy's Laboratories, Hyderabad. Plantago ovate husk powder was purchased from local medical shop, Chennai. All other chemicals were of analytical grade.

Preformulation study

Determination of λ max for Terbutaline sulphate in distilled water

About 100 mg of Terbutaline sulphate was accurately weighed into 100 ml volumetric flask and dissolved in small amount of distilled water which was then made upto 100 ml using distilled water. From this solution 20 ml was pipetted out and diluted to 100 ml in 100 ml volumetric flask using distilled water. The above solution was scanned in the range of 200-400nm using Shimadzu ultra violet (UV) spectrophotometer with distilled water as blank solution. From the spectrum obtained, the λmax for Terbutaline sulphate in distilled water was confirmed to be 276.4nm using Shimadzu UV probe ver.2.35.

Determination of λ max for Terbutaline sulphate in pH 6.8 phosphate buffer

About 100 mg of Terbutaline sulphate was accurately weighed into 100 ml volumetric flask and dissolved in small amount of in pH 6.8 phosphate buffer which was then made upto 100 ml using in pH 6.8 phosphate buffer. From this solution 20 ml was pipetted out and diluted to 100 ml in 100 ml volumetric flask using in pH 6.8 phosphate buffer. The above solution was scanned in the range of 200-400nm using Shimadzu ultra violet (UV) spectrophotometer with pH 6.8 phosphate buffer as blank solution. From the spectrum obtained, the λmax for Terbutaline sulphate in pH 6.8 phosphate buffer was confirmed to be 277 nm using Shimadzu UV probe ver.2.35.

Calibration curve for Terbutaline sulphate in distilled water

About 100 mg of Terbutaline sulphate was weighed accurately and taken in a 100 ml volumetric flask. Then it was dissolved in small amount of distilled water and the volume was made upto 100 ml with distilled water. Solutions ranging from 10 to 100 µg/ml were prepared using distilled water separately and their absorbances were measured at λmax of 276.4 nm using UV spectrophotometer with distilled water as blank solution. The concentrations and its absorbances were subjected to linear regression analysis by Shimadzu UV probe Ver. 2.35 software and the regression equation was found to be $y = 0.00665x + 0.00349$ and correlation coefficient (r^2) was found to be 0.99711.

Calibration curve for Terbutaline sulphate in pH 6.8 phosphate buffer

About 100 mg of Terbutaline sulphate was weighed accurately and taken in a 100 ml volumetric flask. Then it was dissolved in small amount of pH 6.8 phosphate buffer and the volume was made upto 100 ml with pH 6.8 phosphate buffer. Solutions ranging from 10 to 100 µg/ml were prepared using pH 6.8 phosphate buffer separately and their absorbance were measured at λmax of 277 nm using UV spectrophotometer with pH 6.8 phosphate buffer as blank solution. The concentrations and its absorbances were subjected to linear regression analysis by Shimadzu UV Probe Ver.2.35 software and the regression equation was found to be $y = 0.00506x + 0.02873$ and correlation coefficient (r^2) was found to be 0.99870.

Drug excipient compatibility studies by fourier transform infra red (FTIR) spectroscopy

The spectrums for Terbutaline sulphate alone and with 1:1 combination of Terbutaline sulphate with excipients like crospovidone, plantago ovate husk powder, microcrystalline cellulose pH 102, pearlitol SD 200, talc and magnesium stearate were recorded by FTIR spectroscopy (Perkin elmer) using potassium bromide disk method in the scanning range of 450 to 4000 cm^{-1}. The spectrum for Terbutaline sulphate obtained was compared with the reference spectrum in fingerprint region of Indian pharmacopoeia[5] to identify the active pharmaceutical ingredient.

Swelling index[6]

Swelling index of the superdisintegrants was studied in pH 6.8 phosphate buffer. One gram of each sample was transferred to a 100 ml measuring cylinder. To this pH 6.8 phosphate buffer was added up to 25 ml. The measuring cylinder was shaken intermittently for the first 1 hour and then kept aside for next 3 hours. Volume occupied by the material at the end of 4 hours was measured. Swelling index was calculated by the formula, swelling index = (Final volume-initial volume/initial volume) X 100 and the result is shown in Table 3.

Optimization of fast dissolving tablet of Terbutaline sulphate

The optimization of fast dissolving tablets of Terbutaline sulphate was done by using 3^2 full factorial design which is shown in Table 1. In this design, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. The amount of plantago ovate husk powder (X_1) and crospovidone (X_2) were selected as independent variables and *in vitro* disintegration time and wetting time were selected as dependent variables[7].

Fast dissolving tablets of Terbutaline sulphate were prepared by direct compression method according to the formula is shown in Table 2. Accurately weighed amount of Terbutaline sulphate was mixed with remaining excipients which were already passed through sieve no.60 seperately in a geometrical order except talc and magnesium stearate. Finally, talc and magnesium stearate were added and mixed well which was compressed into tablets using 7 mm flat round punch in a 8-station kambert tablet compression machine.

Table 1: 3^2 Full Factorial Design Layout*

Formulation Code		Variable levels	
		X_1	X_2
F1		-1	-1
F2		-1	0
F3		-1	+1
F4		0	-1
F5		0	0
F6		0	+1
F7		+1	-1
F8		+1	0
F9		+1	+1
Checkpoint	C1	- 0.5	- 0.5
	C2	+ 0.5	+ 0.5
Coded Values		Actual Values	
		X_1	X_2
-1		0	0
0		2.5	2.5
+1		5	5

* X_1 indicates the amount of plantago ovate husk powder (% w/w) and X_2 indicates the amount of crospovidone (% w/w)

Table 2: Formula for preparation of Terbutaline sulphate fast dissolving tablet

Ingredients (mg)	Formulation code									Check points	
	F1	F2	F3	F4	F5	F6	F7	F8	F9	C1	C2
Terbutaline sulphate*	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05	3.05
Plantago ovate husk powder	0	0	0	2.5	2.5	2.5	5	5	5	1.25	3.75
Crospovidone	0	2.5	5	0	2.5	5	0	2.5	5	1.25	3.75
Microcrystalline cellulose pH 102	20	20	20	20	20	20	20	20	20	20	20
Pearlitol SD 200	73.95	71.45	68.95	71.45	68.95	66.45	68.95	66.45	63.95	71.45	66.45
Talc	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	100	100	100	100	100	100	100	100	100	100	100

* Terbutaline sulphate contains 2.05 mg Terbutaline. Then, 3.05 mg Terbutaline sulphate contains 2.5 mg of Terbutaline.

Evaluation of pre-compression parameters[8]

The powder blend of each formulation was subjected to evaluation of pre-compression parameters like bulk density, tapped density, carr's index and hausner's ratio. Bulk density of the powder blend was determined by introducing weighed amount of blend into 100 ml measuring cylinder without compacting which was carefully leveled and unsettled bulk volume, Vo was recorded. The bulk density was calculated using the formula, $\boldsymbol{\rho_b = M / Vo}$ where ρ_b , M and Vo were bulk density, weight of sample and bulk volume of powder, respectively. The above blend was tapped for 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2 % and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm/ml, using the formula $\boldsymbol{\rho_{tap} = M / V_f}$ where ρ_{tap}, M and V_f were tapped density, weight of sample and tapped volume of powder respectively. Carr's index and hausner's ratio were calculated from the formulas, **Carr's Index** $= \boldsymbol{100(\rho_{tap} - \rho_b) / \rho_{tap}}$, and **Hausner's Ratio** $= \boldsymbol{\rho_{tap} / \rho_b}$, where $\boldsymbol{\rho_b}$ and $\boldsymbol{\rho_{tap}}$ are bulk density and tapped density, respectively. Various pre-compression parameters of powder blend are tabulated in Table 4.

Evaluation of post-compression parameters

The prepared tablets from each formulation were evaluated for various post-compression parameters like general appearance, thickness, weight variation, hardness, friability, *in vitro* disintegration time, *in vitro* dispersion time, wetting time, water absorption ratio, fineness of dispersion, uniformity of drug content and *in vitro* release study. All the tablets were evaluated for its elegance[9]. Thickness of randomly selected tablets from each formulation was measured with vernier caliper[9]. Hardness of six tablets was measured using the Monsanto hardness tester[9]. The friability of a sample weight equal to 6.5 grams was dusted and placed in a Roche friabilator and operated for 100 revolutions which was then re-dusted and weighed[10]. Percentage loss was calculated using the formula, (initial weight-final weight/initial weight) x 100. Weight variation test was conducted with randomly selected twenty tablets from each formulation using Shimadzu electronic balance. The individual weight of each tablet was compared with the average weight and percentage deviation was calculated[11]. *In vitro* disintegration time for 6 tablets from each formulation was measured using USP disintegration tester (Lab India DT 1000) in pH 6.8 phosphate buffer at 37°C ± 0.5°C[12]. *In vitro* dispersion time was measured for three tablets from each formulation by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37°C ± 0.5°C and the time required for complete dispersion was determined[13]. The results for thickness, hardness, friability, weight variation, *in vitro* disintegration time and *in vitro* dispersion time are shown in Table 5.

Wetting time for three tablets was determined by placing a tablet on the surface of tissue paper folded twice in a petri dish with internal diameter of 5 cm containing 6 ml of purified water. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time[14]. Water absorption ratio, R was calculated from the formula, (Wa-Wb/Wb) x 100 where Wa and Wb were the weight of a tablet after wetting and before wetting[14]. Fineness of dispersion was determined by placing two tablets in a beaker containing 100 ml of purified water, mixed well and passed through a sieve no. 22 (nominal mesh aperature of 710 µm). There should not be any solid mass present over the sieve was observed as uniform dispersion[15]. Uniformity of drug content was performed for each formulation. Twenty tablets from each formulation were individually weighed and pulverized to a fine powder and amount of powder equivalent to 2.5 mg of Terbutaline sulphate was extracted into pH 6.8 phosphate buffer. About 1 ml of solution was withdrawn and its volume was made upto 10 ml using pH 6.8 phosphate buffer and absorbance was measured at 277 nm for Terbutaline sulphate using pH 6.8 phosphate buffer as blank in UV spectrophotometer[16]. The drug content was determined from standard calibration curve. The results for wetting time, water absorption ratio, fineness of dispersion and drug content are shown in Table 6. The graphical representation for *in vitro* disintegration time, *in vitro* dispersion time and wetting time are shown in Figure 8 to10.

Invitro dissolution studies of the fast dissolving tablets of Terbutaline sulphate were performed in USP Type-II dissolution apparatus (Lab India Disso 2000) employing a paddle stirrer revolved at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37°C ± 0.5°C as dissolution medium for 6 tablets from each formulation. About 10 ml of sample was withdrawn for 60 minutes at the interval of one minute and replaced immediately with equal volume of fresh medium in apparatus. The samples collected were filtered and their absorbances were measured at 277 nm for Terbutaline sulphate using pH 6.8 phosphate buffer as blank in UV spectrophotometer[17]. The results of $T_{50\%}$ and $T_{90\%}$ for Terbutaline sulphate are shown in Table 6 with graphical representation for $T_{50\%}$ shown in Figure 11 and $T_{90\%}$ shown in Figure 12. $T_{50\%}$ is the time at which 50% of the drug was released and $T_{90\%}$ was the time at which 90% of the drug was released.

Optimization of formulation

Optimization of formulation was done by using 3^2 full factorial design. In this design, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. Nine batches of formulations (F1 to F9) and check-point formulations (C1 and C2) were prepared. The amount of plantago ovate husk powder (X_1) and crospovidone (X_2) were selected as independent variables and *in vitro* disintegration time and wetting time were selected as dependent variables. Polynomial equation for 3^2 full factorial design is

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where Y is dependent variable, b_0 is arithmetic mean response of nine batches and b_1 is the estimated coefficient for factor X_1. The main effects (X_1 and X_2) represent the average results of changing one factor at a time from its low to high value. The interaction tem (X_1X_2) shows the response changes when two factors are simultaneously changed. The polynomial terms X_1^2 and X_2^2 are included to investigate non-linearity. Polynomial equation for full model was derived for *in vitro* disintegration time and wetting time by linear regression analysis using SPSS software. The fitted equations relating to *in vitro* disintegration and wetting time responses to the transformed factor for

Terbutaline sulphate fast dissolving tablets is shown in Table 7. The magnitude of coefficient and the mathematical sign it carries like positive or negative were concluded from polynomial equations. Analysis of variance (ANOVA) was performed to identify insignificant factors is shown in Table 8 for Terbutaline sulphate.

Accelerated stability studies[18]

Optimized batch tablets were packed in HDPE bottles contain 2 numbers of silica gel canisters each of 1 gram. The bottles were loaded at accelerated conditions like 40^{O}C/75%RH for 1 month. Post-compression parameters like hardness, friability, *in vitro* disintegration time and drug content at initial stage and at the end of one month were determined as per international conference on harmonization guidelines. The result of this study for Terbutaline sulphate is shown in Table 9.

RESULTS AND DISCUSSION

Preformulation study

Drug excipient compatibility studies by fourier transform infra red (FTIR) spectroscopy

Fourier transform infra red spectrums for Terbutaline sulphate alone and 1:1 combination of drug with various excipients like crospovidone, plantago ovate husk powder, microcrystalline cellulose pH 102, pearlitol SD 200, talc and magnesium stearate were recorded and analyzed for chemical interaction.

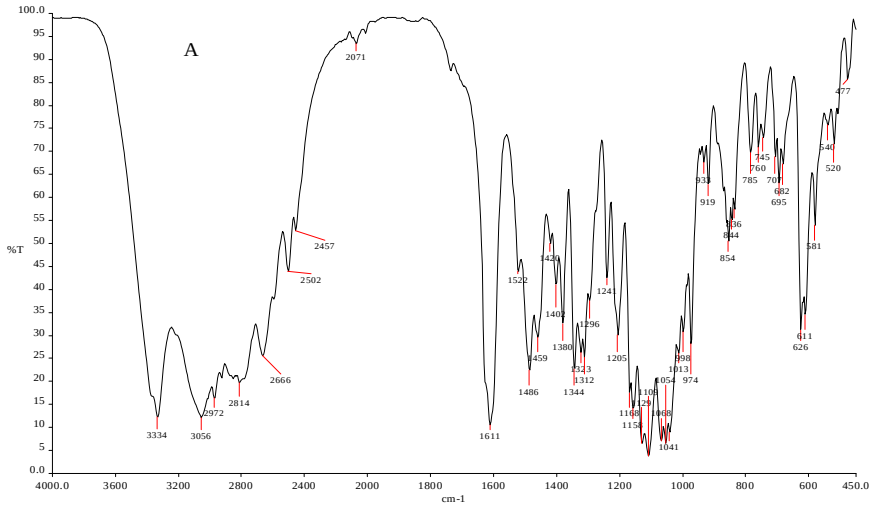

Fig. 1: FT-IR spectrum of Terbutaline sulphate

In the Figure 1 shown above, NH-stretching and OH-streching was merged and appeared between 3334 cm^{-1} and 3384 cm^{-1}, CH sp^{2} aromatic stretching was appeared at 3056 cm^{-1}and CH sp^{3} stretching was appeared at 2972 cm^{-1}. Spectrum of the sample was compared with reference spectrum in fingerprint region of Indian Pharmacopoeia[5]. All the peaks produced by the sample are coinciding with the reference spectrum. Therefore it is confirmed that the given sample is Terbutaline sulphate. The spectrums of Terbutaline sulphate with various excipients in 1:1 ratio are shown in figure 2 to 7 were compared with spectrum of Terbutaline sulphate and found that there was no chemical interaction with drug and excipients.

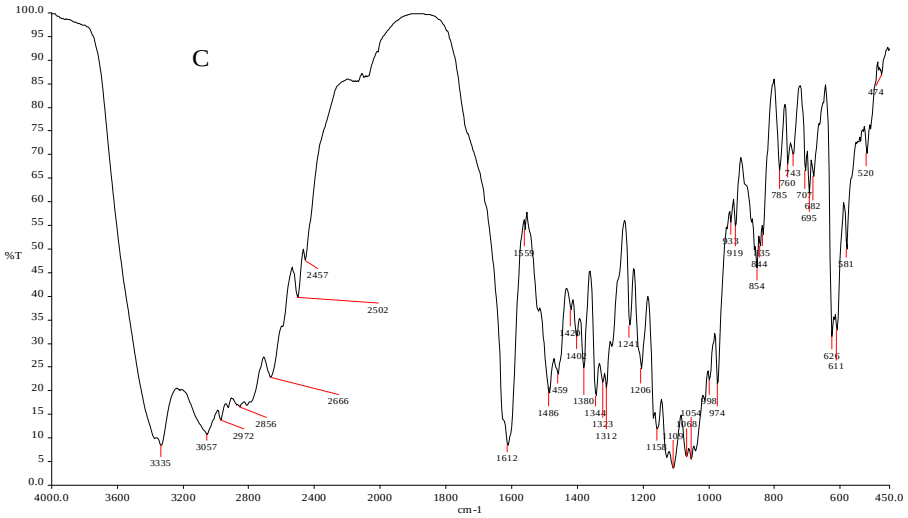

Fig. 2: FT-IR spectrum of Terbutaline sulphate and Plantago ovate husk powder in 1:1 ratio

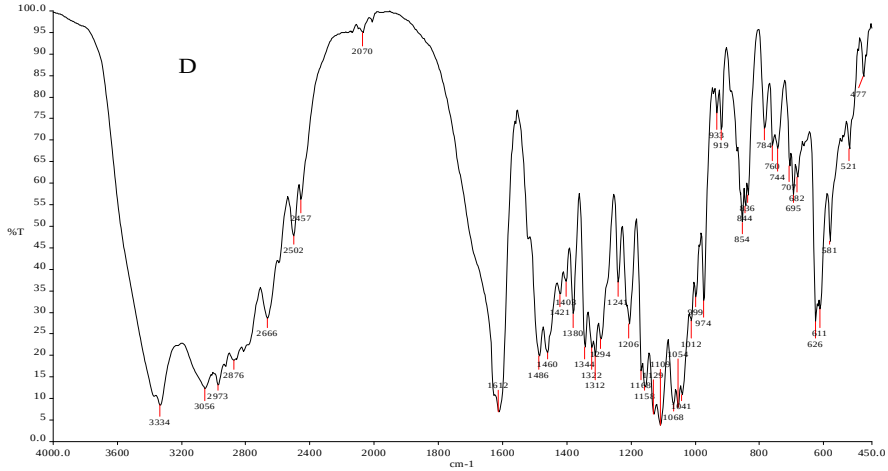

Fig. 3: FT-IR spectrum of Terbutaline sulphate and Crospovidone in 1:1 ratio

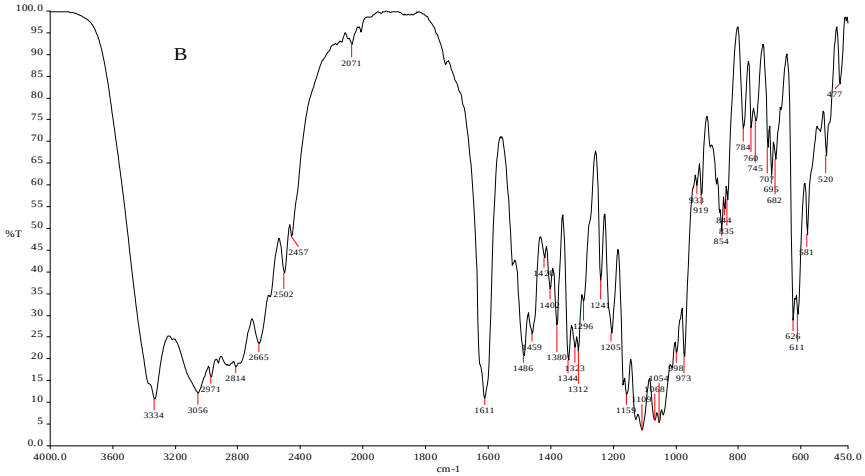

Fig. 4: FT-IR spectrum of Terbutaline sulphate and Microcrystalline cellulose pH 102 in 1:1 ratio

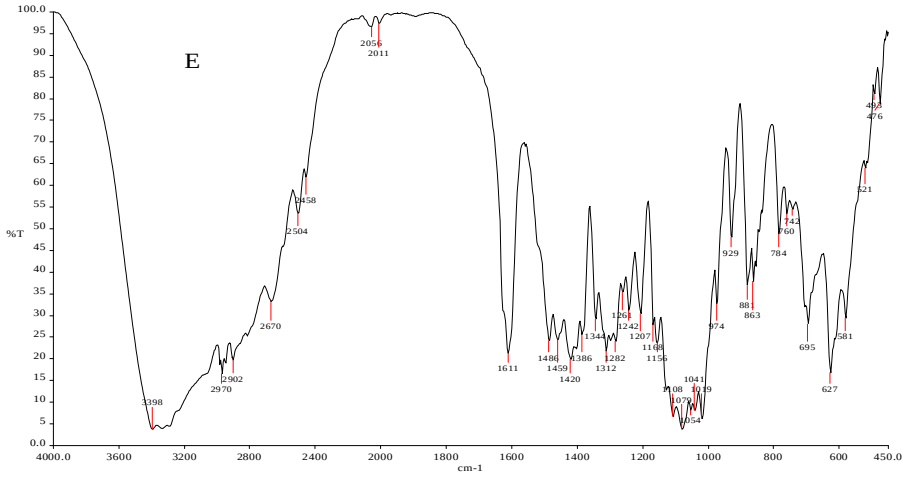

Fig. 5: FT-IR spectrum of Terbutaline sulphate and Pearlitol SD 200 in 1:1 ratio

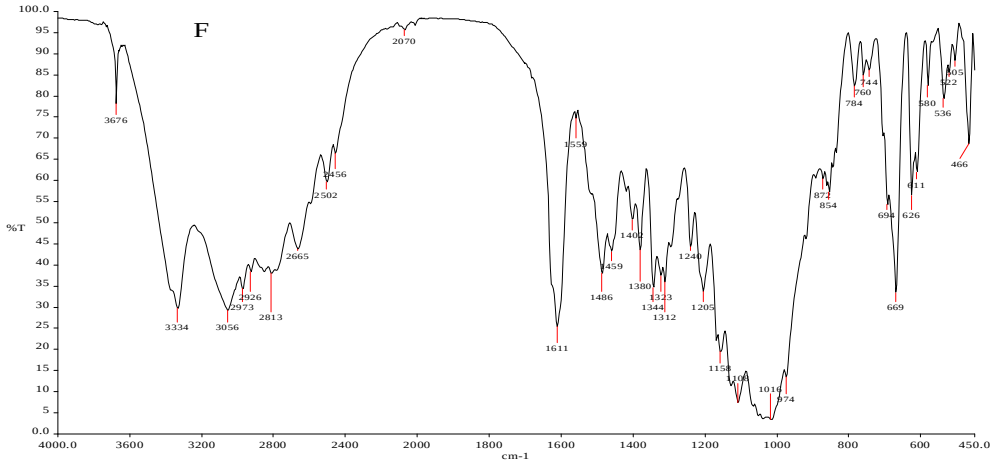

Fig. 6: FT-IR spectrum of Terbutaline sulphate and Talc in 1:1 ratio

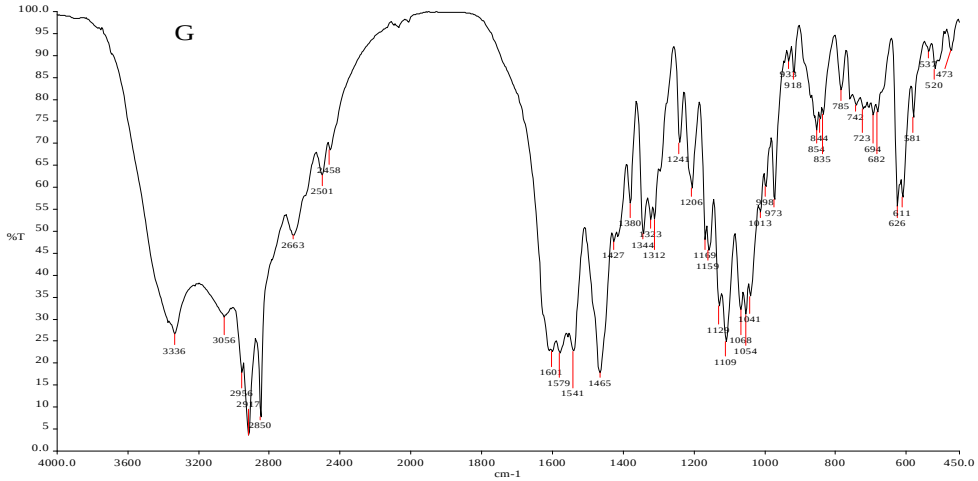

Fig. 7: FT-IR spectrum of Terbutaline sulphate and Magnesium stearate in 1:1 ratio

Swelling index

Table 3: Swelling index for Superdisintegrants

Name of superdisintegrants	Swelling index (%v/v)
Plantago ovate husk powder	91
Crospovidone	54

The swelling index for plantago ovate husk powder was found to be high than crospovidone.

Evaluation of pre-compression parameters of Terbutaline sulphate fast dissolving tabletS

Pre-compresssion evaluation of blend was done by determining bulk density, tapped density, compressibility index and Hausner ratio. From the results shown in table 4 below, the flow property of all formulations was found to be excellent.

Table 4: Pre-compression parameters of powder blend

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's Ratio
F1	0.4124	0.4431	6.93	1.07
F2	0.4189	0.4505	7.01	1.08
F3	0.4428	0.4795	7.65	1.08
F4	0.4702	0.5111	8	1.09
F5	0.4252	0.4724	9.99	1.11
F6	0.4436	0.4929	10	1.11
F7	0.4684	0.5091	7.99	1.09
F8	0.4634	0.5037	8	1.09
F9	0.4528	0.4922	8	1.09
C1	0.466	0.5065	7.99	1.09
C2	0.4414	0.4904	9..99	1.11

Evaluation of post-compression parameters

Table 5: Post-compression parameters of fast dissolving tablets of Terbutaline sulphate

Formulation Code	Weight variation (g) (n = 20) Avg.wt.± S.D	Thickness (mm) (n = 6) Avg ± S.D	Hardness (Kg/cm^2) (n = 6) Avg ± S.D	Friability (%)	*Invitro* Disintegration Time (Sec) (n= 6) Avg ± S.D	*Invitro* Dispersion Time (Sec) (n=3 Avg ± S.D
F 1	0.093 ± 0.005	0.3 ± 0	3.67 ± 0.41	0.87	81.17 ± 0.75	91.67 ± 0.58
F 2	0.096 ± 0.18	0.303 ± 0.008	3.83 ± 0.26	0.90	14.5 ± 0.55	18.33 ± 0.58
F 3	0.098 ± 0.005	0.3 ± 0	4.22 ± 0.52	0.31	10.17 ± 0.75	13 ± 0
F 4	0.0995 ± 0.006	0.278 ± 0.004	3.58 ± 0.20	0.85	20 ± 0.63	25 ± 1
F 5	0.0965 ± 0.006	0.272 ± 0.004	4.08 ± 0.49	0.32	7.67 ± 0.52	10.33 ± 0.58
F 6	0.0975 ± 0.007	0.3 ±0	2.42 ±0.20	0.88	5.83 ± 0.75	7.33 ± 0.58
F 7	0.0975 ± 0.004	0.297 ± 0.005	2.33 ± 0.26	0.92	12.5 ± 0.55	15 ± 1
F 8	0.095 ± 0.005	0.28 ± 0.004	3.67 ± 0.26	0.30	14.67 ± 0.52	16.67 ± 0.58
F 9	0.0985 ± 0.007	0.282 ± 0.004	2.67 ± 0.52	0.61	4.17 ± 0.75	5 ± 1
C1	0.0965 ± 0.006	0.28 ± 0.005	3.17 ± 0.41	0.46	9.33 ± 0.52	11.33 ± 0.58
C2	0.0955 ± 0.006	0.297 ± 0.005	2.58 ± 0.20	0.91	6.83 ± 0.75	8 ± 0

Table 6: Post-compression parameters of fast dissolving tablets of Terbutaline sulphate

Formulation Code	Fineness of Dispersion	Wetting time (Sec) (n= 3) Avg ± S.D	Water absorption ratio	Drug content (mg)	$T_{50\%}$ (min)	$T_{90\%}$ (min)
F 1	Pass	51.67 ± 0.58	92	99.28	12	23
F 2	Pass	6.67 ± 0.58	58	99.85	7	13
F 3	Pass	4.33 ± 0.58	50	99.31	3	7
F 4	Pass	8.67 ± 0.58	65	100.01	10	19
F 5	Pass	5.67 ± 0.58	48	100.56	5	10
F 6	Pass	3.33 ± 0.58	43	99.42	3	7
F7	Pass	5.33 ± 0.58	55	99.36	4	8
F 8	Pass	7.33 ± 0.58	59	101.02	7	13
F 9	Pass	1.33 ± 0.58	38	100.56	2	5
C1	Pass	7 ± 0	48	99.75	8	15
C2	Pass	4 ± 1	52	99.89	4	10
Marketed formulation	-	-	-	-	15	24

* Avg.wt =Average weight S.D=Standard deviation

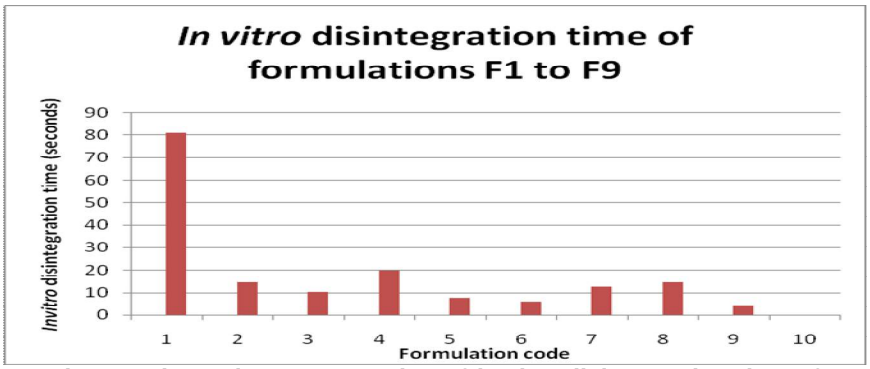

Fig. 8: Schematic representation of *in vitro* disintegration time of different formulations of Terbutaline sulphate fast dissolving tablet

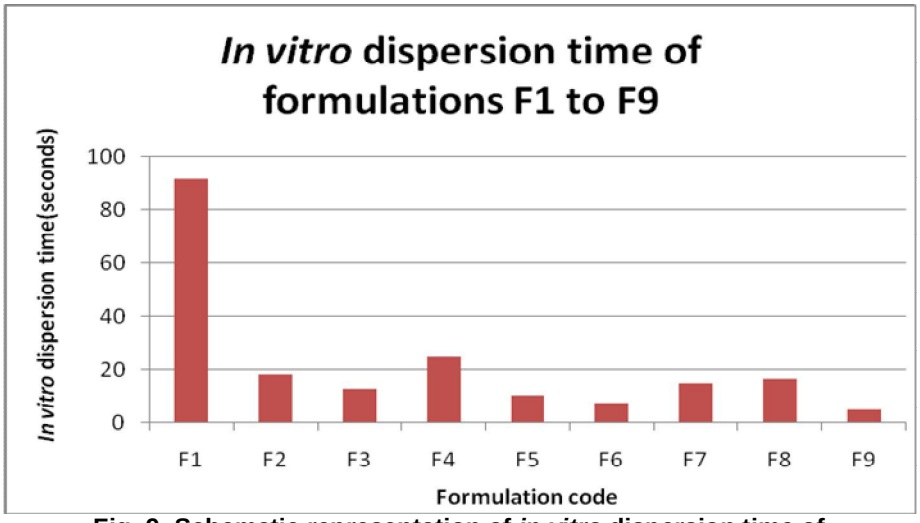

Fig. 9: Schematic representation of *in vitro* dispersion time of different formulations of Terbutaline sulphate fast dissolving tablet

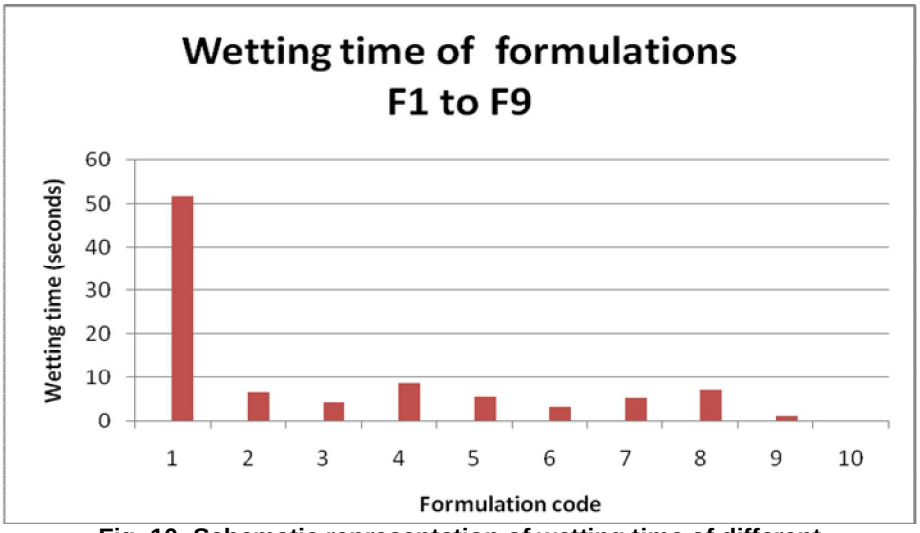

Fig. 10: Schematic representation of wetting time of different formulations of Terbutaline sulphate fast dissolving tablet

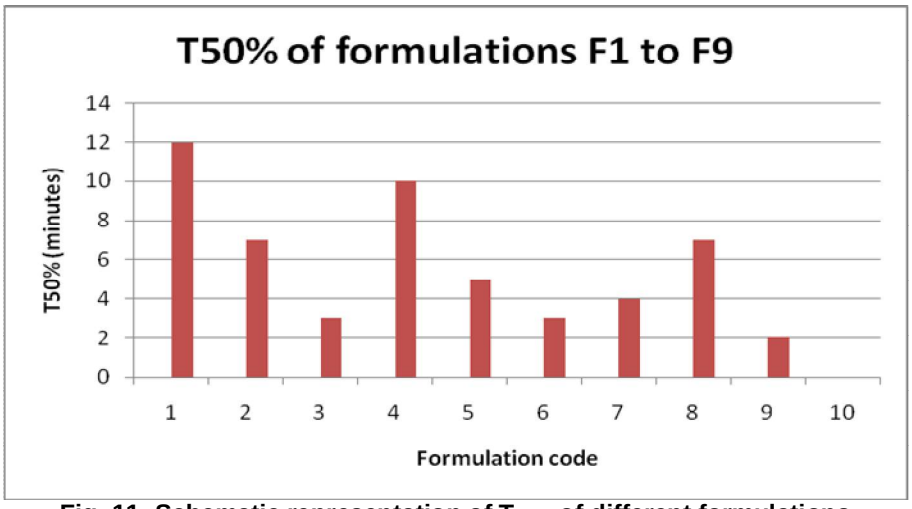

Fig. 11: Schematic representation of $T_{50\%}$ of different formulations of Terbutaline sulphate fast dissolving tablet

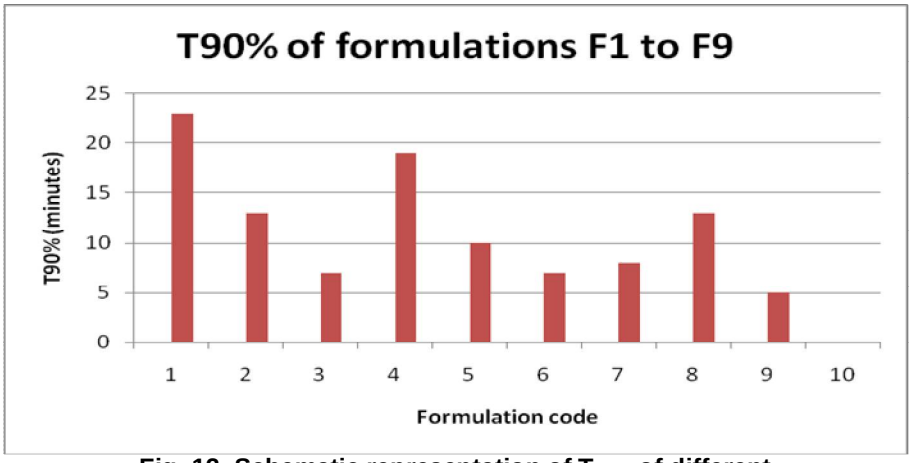

Fig. 12: Schematic representation of $T_{90\%}$ of different formulations of Terbutaline sulphate fast dissolving tablet

The tablets from all formulations were evaluated for physical appearance, weight variation, thickness, hardness, friability, *in vitro* disintegration time, *in vitro* dispersion time, wetting time, water absorption ratio, fineness of dispersion, uniformity of drug content and *in vitro* dissolution study.

From the results of terbutaline sulphate fast dissolving tablets, it was observed that all the formulations were good in appearance with no cracking. Average weight of tablets in all formulations was in the range of 0.093 to 0.0985 gram and it was in limit of ± 10% deviation. Thickness, hardness and friability of all the formulations were in the range of 0.28 to 0.303 mm, 2.42 to 4.22 kg/cm^2 and 0.31 to 0.92% respectively and all were within limits. *In vitro* disintegration time, *in vitro* dispersion time, wetting time and water absorption ratio of all formulations were in the range of 4 to 82 seconds, 5 to 92 seconds, 1 to 52 seconds and 38 to 92 respectively. All formulations passed fineness of dispersion. Drug content, $T_{50\%}$ and $T_{90\%}$ in all formulations were in the range of 99.28 to 101.02 mg, 2 to 12 minutes and 5 to 23 minutes. $T_{50\%}$ and $T_{90\%}$ of marketed formulation were found to be 15 and 24 minutes.

Optimization of formulation

Optimization of formulation was done by using 3^2 full factorial design. In this design, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. Nine batches of formulations (F1 to F9) and check-point formulations (C1 and C2) were prepared. The amount of plantago ovate husk powder (X_1) and crospovidone (X_2) were selected as

independent variables and *in vitro* disintegration time and wetting time were selected as dependent variables. Polynomial equation for 3^2 full factorial design is

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where Y is dependent variable, b_0 is arithmetic mean response of nine batches and b_1 is the estimated coefficient for factor X_1. The main effects (X_1 and X_2) represent the average results of changing one factor at a time from its low to high value. The interaction tem (X_1X_2) shows the response changes when two factors are simultaneously changed. The polynomial terms X_1^2 and X_2^2 are included to investigate non-linearity.

From the results, dependent variables, *in vitro* disintegration time and wetting time of all formulations are dependent on selected independent variables, amount of plantago ovate husk powder and crospovidone. Polynomial equation for full model was derived for *in vitro* disintegration time and wetting time by linear regression analysis using SPSS software. The fitted equations relating to *in vitro* disintegration and wetting time responses to the transformed factor for Terbutaline sulphate fast dissolving tablets is shown in Table 7.

Table 7: Summary of results of regression analysis for Terbutaline sulphate fast dissolving tablets*

For disintegration time						
Response	**bo**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	23.07	-3.16	-3.09	0.18	0.32	0.05
For wetting time						
Response	bo	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	7.77	0.08	0.35	-0.02	-0.07	-0.23

* FM indicates full model

The magnitude of coefficient and the mathematical sign it carries like positive or negative were concluded from polynomial equations. Analysis of variance (ANOVA) was performed to identify insignificant factors is shown in Table 8 for Terbutaline sulphate. The high values of correlation coefficient for disintegration time and wetting time (Table 8) indicate a good fit. Student *t* test was applied to perform significance test for regression coefficients and the coefficient is found to be significant if the calculated *t* value is greater than the critical value of *t*. From the results, $p<0.05$ indicates the formulations are statistically significant.

Table 8: Calculations for testing the model in portions for Terbutaline sulphate fast dissolving tablets *

For disintegration time						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	141.77	28.35	1.09	0.97	Significance F = 0.88
Error						
FM	2	52.07	26.03	-		
For wetting time						
	DF	SS	MS	F	R^2	
Regression						
FM	5	30.29	6.06	1.56	0.96	Significance F = 0.91
Error						
FM	2	7.78	3.89	-		

*DF, SS, MS, F, R^2, FM and RM indicates degree of freedom, sum of squares, mean of squares, fisher's ratio, regression coefficient, full model and reduced model.

In terbutaline fast dissolving tablets, formulation F3 and F7 containing 5% of crospovidone and plantago ovate husk powder seperately were found to be excellent batch with *in vitro* disintegration time of 10.17 seconds and 12.5 seconds and wetting time of 4.33 and 5.33 seconds, respectively. Taking into consideration of non-toxic, biocompatible, cheap in cost and easy availability of natural superdisintegrant, plantago ovate husk powder, formulation F7 for Terbutaline sulphate was considered as optimized formulation.

Accelerated stability studies

Accelerated stability studies were conducted at 40ºC / 75% RH for 1 month in stability chamber. Samples were collected at the end of one month and analyzed for hardness, friability, *invitro* disintegration time and uniformity of drug content and compared with that of initial results.

Table 9: Post compression parameters of optimized formulation of Terbutaline sulphate at the end of one month

Parameters	Initial	After one month
Hardness (kg/cm^2)	2.33	2.62
Friability (%)	0.92	0.78
In vitro disintegration time (seconds)	12.5	13.17
Drug content (mg)	99.36	99.28

From the above results, it was found that there is no drastic difference in optimized formulation before and after one month in stability studies in both Terbutaline sulphate fast dissolving tablets.

CONCLUSION

Geriatric and pediatric patients suffer from dysphagia to conventional oral dosage forms leads to high incidence of non-compliance and ineffective therapy which was overcome by formulating fast dissolving tablets. Fast dissolving tablet dissolves or disintegrates in the oral cavity rapidly without the need of water or chewing.

In the present study, an attempt was made to optimize the formulation of fast dissolving tablets of Terbutaline sulphate for the treatment of asthma using 3^2 full factorial design and compare the disintegrating efficiency of natural superdisintegrant, plantago ovate husk powder with synthetic superdisintegrant, crospovidone in two different concentrations of 2.5% and 5%.

Control formulation, F1 (without superdisintegrants) was compared with other formulations containing superdisintegrants. Drug excipient compatibility studies using FT-IR spectroscopy revealed that there was no chemical interaction between drug and excipients used. All the formulations prepared by direct compression had very good appearance without any chipping and cracking, weight variation, hardness, friability, fineness of dispersion, drug content were within limits. *In vitro* dissolution of formulations were compared using $T_{50\%}$ and $T_{90\%}$ where $T_{50\%}$ was the time at which 50% of the drug was released and $T_{90\%}$ was the time at which 90% of the drug was released.

The comparision of effect of natural and synthetic superdisintegrant was discussed here with respect to *in vitro* disintegration time and wetting time because these two are very important for quick and effective disintegration which leads to faster dissolution of a dosage form.

From the results of formulations F4 and F7 containing 2.5 and 5% concentration of natural superdisintegrant, plantago ovate husk powder, disintegration was nearly reduced to half when the concentration of superdisintegrant was doubled in F7 along with faster wetting than F4. From the results of formulations F2 and F3 containing 2.5 and 5% concentration of synthetic superdisintegrant, crospovidone, disintegration was reduced when the concentration of superdisintegrant was doubled in F3 along with faster wetting than F2. Formulations containing synthetic superdisintegrant (F2 and F3) disintegrated and wetted faster than formulations containing natural superdisintegrant (F4 and F7). Plantago ovate husk powder and crospovidone alone in 5% concentration disintegrated faster than these superdisintegrants alone in 2.5% concentration illustrates when the concentration of superdisintegrant is increased disintegration time is reduced. Disintegration time of formulations containing two different superdisintegrant in same concentrations showed very minor difference.

Combined effect of both superdisintegrants can be seen from the results of formulations, F5, F6, F8 and F9. Disintegration time was reduced to almost half in F6 when F5 and F6 was compared which is due to increase in concentration of crospovidone (from 2.5% to 5%) keeping the concentration of plantago ovate husk powder constant (2.5%). Formulation F9 containing both superdisintegrant (5% and 5%) in doubled concentration than F5 (2.5% and 2.5%) disintegrated and wetted in faster and also it has least disintegration time and wetting time in comparision with all formulations due to combined effect of highest concentration of two superdisintegrants.

From these results, it was concluded that plantago ovate husk powder alone in 5% concentration behaved almost same like crospovidone. Taking into considerations of other factors like toxicity due to synthetic method of preparation using chemicals, cost, availability, natural superdisintegrant had various advantages like non-toxic, biocompatible, cheap in cost and easy availability makes it better alternative option as superdisintegrant for designing fast dissolving tablet of Terbutaline sulphate suitable for administration to patients suffering from dysphagia for quick onset of action with pleasant taste. Accelerated stability studies of optimized formulation containing 5% natural superdisintegrant

revealed that there were no drastic differences in post compression parameters before and after one month of exposture to 45^{o}C and 75% relative humidity.

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