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Original Research Article

Design and Development of Terbutaline Sulphate Fast Mouth Dissolving Tablet

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Abstract: Asthma is a chronic inflammatory disease that causes an associated increase in airway hyperreactivity leading to recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing, especially at night and early in the morning. Terbutaline sulfate is a selective beta2 adrenergic agonist. It is highly selective for β2 adrenergic receptors and has a long-lasting effect. It is given for symptomatic relief of bronchospasm and obstructive airway disease. Terbutaline sulfate is effective when taken orally, subcutaneously, or by inhalation. Although effects are rapidly observed after inhalation, the use of inhaled sympathomimetic drugs is initially associated with possible tachyphylaxis of resistance to beta-agonists, cardiac arrhythmias due to β1-adrenergic receptor stimulation, and Freon propellants. Raised concerns about hypoxemia and arrhythmia due to fluorinated hydrocarbons in many patient groups, including the elderly, children, the mentally ill, and uncooperative or nauseous patients, have difficulty swallowing conventional dosage forms such as tablets. Swallowing conventional tablets is further hampered by conditions such as water unavailability, allergic reactions, and coughing fits. These problems can be overcome by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration, as they dissolve in saliva and do not require water to be swallowed. When ingested, saliva serves to quickly dissolve the dosage form. A fast mouth dissolving tablet (FMDT) is an oral solid dosage form that dissolves rapidly when placed on the tongue, releasing a drug that dissolves or disperses in saliva and can be swallowed without the need for drinking water. Additionally, some of the saliva-soluble drugs from the mouth, throat, and esophagus are absorbed once saliva enters the stomach, increasing bioavailability by avoiding first-pass metabolism.

Keywords: Terbutaline Sulphate, Fast Mouth Dissolving Tablets (FMDT), super disintegrant, addition method.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways involving many cells and cellular factors. Chronic inflammation causes an associated increase in airway hyper responsiveness, with recurring episodes of wheezing, shortness of breath, chesttightness and coughing, especially at night or early in the morning. These episodes are usually associated with extensive airway obstruction. However, airway obstruction of ten resolves spontaneously or with treatment [1]. Asthma can develop with age, but children and young adults are the age groups most commonly affected. Although slight differences in prevalence between men and women have been reported, both sexes are affected almost equally. Contrary to popular belief, children are not always “asthmafree” and nearly two-thirds may continue to have symptoms into adolescence and adulthood [2]. Terbutaline is a β2 selective bronchodilator. It contains a resorcinol ring and thus is not a substrate for methylation by COMT. It is effective when take no rally, subcutaneously or by inhalation. Effects are observed rapidly after inhalation or parental administration. After inhalation its action may persist for 3 to 6 hours. With oral administration, the onset of effect may be delayed for 1 to 2 hours [3, 4].

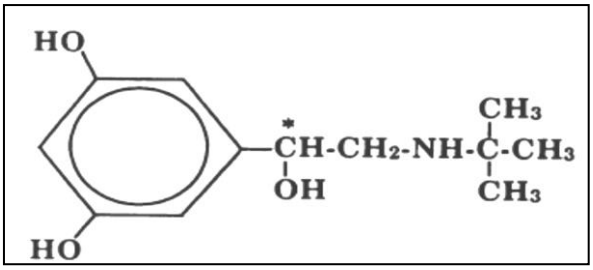

Figure: 1 Structure of terbutaline

A fast mouth dissolving tablet (FMDT) can be defined as an oral solid dosage form that dissolves rapidly when placed on the tongue and releases the drug to dissolve or disperse in saliva before beings wallowed. Some drugs are absorbed through the mouth, throat, and esophagus when saliva enters the stomach. The main problem with regular or all dosage forms is that they must be swallowed with water. Many patients find it difficult to swallow tablets, especially in older children, because of the physiological changes associated with these groups and lead to patient non-compliance. Other causes of patient non-compliance include sudden episodes such as all ergic attacks, motion sickness, coughing, and water unavailability. These problems can be addressed by fast-dissolving tablets that do not require water to facilitate swallowing [5, 6]. Various methods such as direct compression, freeze-drying, spray-drying, sublimation, and wet granulation processes are used to manufacture FMDTs [7]. A basic approach to developing FMDTs is to add super dis-integrant. The aim of this study was to formulate his FMDT with sufficient mechanical integrity to dis-integrate more rapidly in the oral cavity without water. To achieve this goal, mannitolis use dasadiluent and sodiums accharinis use dasasweetenerin tablet or mulations. Super disintegrants such as sodium starch glycolate (SSG), sodium carboxy methyl cellulose (SCMC) and poly vinyl pyrrolidone (PVP) K-30 have been used to improve dissolution rates and accelerate disintegration.

MATERIALS AND METHODS

MATERIALS

Terbutaline suphate was obtained as gift sample from Neuland Laboratories Limited Hyderabad.

Poly Vinyl Pyrollidone K-30 was obtained from Central Drug House (Delhi).

METHODOLOGY

Pre-Formulation Studies

Identification of Drug

The drug was identified by Ultraviolet spectroscopy (UV), Melting point, Solubility & FT-IR.

Solubility

Solubility of the drug was determined in different media (distilled water, ethanol, phosphate buffer pH 6.8, methanol, chloroform &Hexane. Accurately weighted drug was transferred in volumetric flasks containing different solvents and was shaken until saturation was achieved; the flask was sonicated for 30 min.

Melting Point

The melting point of Terbutaline sulphate sample was determined by melting point apparatus and compared with the melting point of reference sample of Terbutaline sulphate.

PREPARATION OF CALIBRATION CURVE

Calibration curve of Terbutaline sulphate in phosphate buffer solution, pH 6.8.From the standard stock solution of Terbutaline Sulphate (Stock I), 1ml was pipette out and volume was made up to 10 ml in a 10 ml volumetric flask (Stock II). From this stock II, again aliquots of samples pipette out ranging from volumes 1,2,3,4,5 and 6 ml into 10ml volumetric flasks and volume was made up using distilled water to produce concentrations 10, 20, 30, 40, 50 and 60 g/ml respectively. The absorbance was measured at276.0 nm against distilled water as blank. Plotted a calibration curve of Terbutaline Sulphate using concentration and absorbance on X and Y-axis respectively.

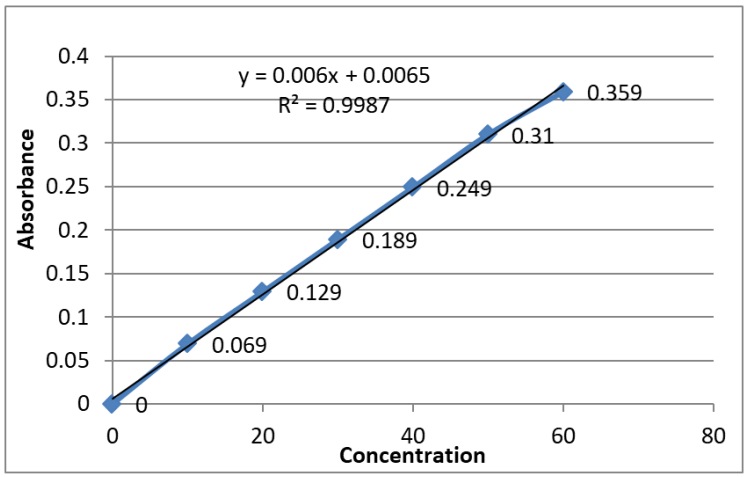

Figure 2: Calibration curve for Terbutaline Sulphate

Table 1: Solubility profile of Terbutaline Sulphate in different solvent

S.No	Solvent	Solubility
1	Ethanol	+
2	Chloroform	-
3	Methanol	+
4	Buffer solution pH6.8	+++
5	Water	+++
6	Hexane	+

+++ Freely soluble (1 to 10 of solvent), ++ Soluble (10 to 30 of solvent), + slightly soluble, -Insoluble (more than 10,000 of solvent)

Preparation of FMDT of Terbutaline Sulphate by Super Disintegrant Addition Method

All the ingredients were sifted through sieve no. 40 and accurately weighed. Then moist granulation of the drug with dis-integrants and binders were done as per the formula using 2% solution of PVP K-30 in Isopropyl Alcohol. Then the remaining ingredients such as Mint flavour, Talc, Aerosil, Magnesium stearate were added to the dry granules according to the granule yield and compressed into tablets using the single punch CADMACH Tablet Machine with 8 mm punches. The prepared tablets were packed in an aluminium foil pouch. Using this procedure 4 batches of FMDT of Terbutaline Sulphate (100 nos+10 Placebo Tablets) in ratios 4:1(SD1), 1:1(SD2)[SSG:SCMC] and 4:1[SD3], 1:1 [SD4] [SSG:PVP] were prepared.

Table 2: Formulation Composition for FMDT by Super dis-integrant Addition Method

S. No	Tablet Ingredients (mg/tab)	Formulation code			
		SD1	SD2	SD3	SD4
1	Terbutaline Sulphate	5	5	5	5
2	Mannitol	100	112	100	112
3	Sodium Starch Glycollate (SSG)	16	4	16	4
4	Sodium Carboxy Methyl Cellulose (SCMC)	4	4	-	-
5	Poly VinylPyrollidone (PVP) K-30	-	-	4	4
6	Saccharine Sodium	0.050	0.050	0.050	0.050
7	MintFlavour Dried	2	2	2	2
8	Aerosil	2	2	2	2
9	Purified Talc	2	2	2	2
10	Magnesium Stearate	1	1	1	1

Figure 3: FMDT by Super disintegrant Addition Method

EVALUATION OF FMDT OF TERBUTALINE SULPHATE

Physical Parameters

Table 3: Micromeritic properties of different formulation

Formulation Code	Bulk Density	Tapped Density	Angle of Repose	Compressibility	Hausner Ratio
SD1	0.582	0.643	22.43	9.44	1.104
SD2	0.583	0.647	22.58	9.89	1.109
SD3	0.582	0.646	23.52	9.81	1.108
SD4	0.563	0646	21.85	10.2	1.148
Pure Drug	0.501	0745	23.25	24.52	1.482

Thickness of Tablets

Thickness of tablets was measured by Vernier calipers using the procedure described in Methodology Section3.A.(a). The crown diameters of all the formulations were found to be uniform (i.e. 8 mm).Thickness of all the formulations was in the acceptable range of1 mm to 1.2 mm (±5% of the average thickness of 10tablets).

Table 4: Thickness of FMDT Formulations of Terbutaline Sulphate

Formulation Code	Thickness* in mm± SD
SD1	1.00± 0.0547
SD2	1.00± 0.0552
SD3	1.00± 0.0547
SD4	1.00± 0.0552

Taste, Colour & Odour of Tablets

All the formulated FMDT of Terbutaline Sulphate were evaluated for their organoleptic properties such as taste, colour and odouras per the procedure in Methodology Section 3.A.(b).

Table 5: Evaluation of Taste, Colour, Odour of FMDT Formulations

Formulation Code	Taste	Colour	Odour
SD1	Sweet	White	Minty
SD2	Sweet	White	Minty
SD3	Sweet	White	Minty
SD4	Sweet	White	Minty

c) Hardness and Friability of Tablets

The hardness of all the formulations were checked using Monsanto Hardness Tester, by the method described in Methodology Section 3.A. (c). The average hardness of all the tablet formulations comes in the range of 2-3 Kg/cm^2 [8, 9].

The friability of all the formulations was checked using Roche Friabilator according to the method in Methodology Section 3.A. (c). the average friability for all the formulations comes in the range of0.22% to 0.95%.

Table 6: Hardness and Friability of FMDT Formulations of Terbutaline Sulphate

Formulation Code	Hardness* (Kg/cm^2) ± S.D.	Friability% (for 10 tablets)
SD1	2.580± 0.258	0.3016
SD2	2.630± 0.288	0.3765
SD3	2.280± 0.172	0.2247
SD4	2.230± 0.103	0.3734

*Each value is an average of 6 determinations

d) Wetting time of Tablets

All the formulations were evaluated for the wetting time using the procedure described in Methodology Section 3.A. (d). The average wetting time of all the formulations was obtained in the range of 30 to 137 seconds.

Table 7: Wetting time of FMDT Formulations of Terbutaline Sulphate

Formulation Code	Wetting time* (Seconds)± SD
SD1	85.00± 3.61
SD2	126.00± 1.73
SD3	70.66± 1.16
SD4	102.00± 3.00

*Each value is an average of6 determination

e) Moisture Uptake by the Tablets

Ten sample tablets from each batch were subjected to moisture uptake studies using the procedure described in Methodology Section 3. A.(e).

Table 8: Moisture Uptake by FMDT Formulations of Terbutaline Sulphate

Time (days)	Percentage increase in weight* of the formulations			
	Super disintegrant addition method			
	SD1	SD2	SD3	SD4
1	0.10	0.00	0.21	0.00
2	0.60	0.00	0.80	0.00
3	1.28	0.14	1.72	0.10
4	2.43	0.21	1.91	0.24
5	2.92	0.40	2.10	0.49
6	3.24	0.62	3.34	0.78
7	3.49	0.84	3.55	1.04
8	3.72	1.04	3.76	1.24
9	3.90	1.38	4.08	1.39
10	4.18	1.62	4.42	1.62
11	4.64	1.89	4.94	1.94
12	5.21	2.48	5.69	2.28
13	5.80	2.69	6.24	2.46
14	6.24	2.94	6.82	2.90

*Average value of 10 tablets

a) Drug Content and Release Studies) an Assay of Pooled Sample of Tablets

All the formulations were evaluated for the drug content using the procedure as Per Methodology Section 3.B.(a).The percentage drug content of all the formulations is shown in the table.

Table 9: Assay of FMDT of Terbutaline Sulphate

Formulation Code	Absorbance	Conc. From Std. Graph in mg	Conc. Dilution Factor(10) in mg	Amountin 50mlinmg	%Drug Content (Assay)
SD1	0.068	10.2727	102.7270	5.1364	102.7270%
SD2	0.061	9.1034	91.0335	4.5516	91.0335%
SD3	0.067	10.1057	101.0565	5.0528	101.0565%
SD4	0.071	10.7739	107.7385	5.3869	107.7385%

b) Weight Variation and Uniformity of Content

Uniformity of weight test for all the formulations were carried out using the procedure described in Methodology Section 3.B.(b).

Table 10: Weight Variation of FMDT Formulations of Terbutaline Sulphate

Formulation Code	Average Weight of one Tablet(mg)	%Weight Variation Range
SD1	131.8	-1.4279 to 0.9244%
SD2	132.1	-2.8710 to 2.2419%
SD3	132.3	-1.0408 to 1.7384%
SD4	133.8	-1.6440 to 2.092%

Table 11: Uniformity of Content of FMDT form Formulations of Terbutaline Sulphate

Formulation Code	Sample	% Drug Content	Compliane with the IP limit
SD1	5 tablets of each formulation	94.6285% to 103.1490%	Complies
SD2		91.4556% to 94.7965%	Complies
SD3		96.1412% to 104.8195%	Complies
SD4		94.4248% to 107.3252%	Complies

c) *In vitro* Dispersion Time

All the formulations were evaluated for *in vitro* dispersion time as per the procedure described in Methodology Section 3.B.(c). The average dispersion time for all the formulations comes in the range of 20 to 125 seconds.

d) *In vivo* Dispersion Time of Placebo Tablets

All the Placebo formulations were evaluated for *in vivo* dispersion time as per the procedure described in Methodology Section3.B.(d). The average dispersion time was in the range of 15 to 100 seconds.

Table 12: *In- vitro* Dispersion Time and *in vivo* DispersionTime (Placebo tablet) of FMDT of Terbutaline Sulphate

Formulation Code	*In vitro* Dispersion Time* (seconds)± SD	*In vivo* Dispersion Time* (seconds)± SD
SD1	64.50± 7.34	50.62± 3.96
SD2	111.66± 9.69	100.16± 7.28
SD3	53.66± 7.91	40.83± 2.46
SD4	88.16± 4.21	81.66± 4.26

*Each value is an average of6 determination

e) *In vitro* Drug Release after Dispersion

All the formulations were evaluated for *in vitro* drug release after dispersion as per the procedure prescribed in Methodology Section 3.B.(e). The average drug release immediately after dispersion from all the formulations comes in the range of 72% to 91% [12] the results shown below.

Table13: *In-vitro* Drug Release after Dispersion of FMDT Formulations

Formulation Code	*In vitro* Dispersion Time* (seconds)± SD	*In vivo* Dispersion Time* (seconds)± SD
SD1	66± 7.18	87.6920± 3.6178%
SD2	114± 8.44	84.3520± 3.1398%
SD3	55± 7.12	91.0340± 2.1894%
SD4	94± 3.18	86.0220± 1.0742%

*Each value is an average of6 determination

f) *In vitro* Dissolution Studies

In vitro dissolution studies were performed as per the procedure describeding Methodology Section 3.B. (f) as per standard method.

Table 14: *In vitro* Dissolution Profile Data for FMDT Formulations

rmulation Code	Percentage Drug release*±SD of FMDT of Terbutaline Sulphate at the following time intervals			
	3minutes	6minutes	9minutes	12minutes
SD1	79.6671±2.8130%	81.5828±1.1129%	86.6740±1.1029%	94.7010±4.4285%
SD2	76.6602±0.9895%	80.6694±2.9613%	84.6786±4.1994%	85.6800±3.3139%
SD3	91.6860±1.4248%	94.6186±3.2416%	96.8064±4.1428%	97.7680±3.1628%
SD4	79.2582±2.2614%	86.6832±3.1020%	90.6924±4.9184%	93.6990±3.1625%

*Each value is an average of 3determinations formulation approach

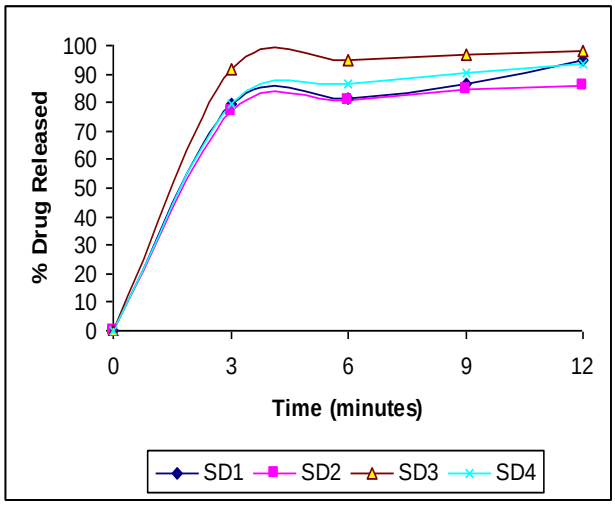

Figure 4: *In- Vitro* Dissolution Profile for FMDT Formulation

STABILITY STUDIES OF FMDT OF TERBUTALINE SULPHATE

Stability studies for all formulations were carried out as per the procedure in Methodology Section 4 the results shown below.

Table 15: Physical Appearance in Stability Studies of FMDT Formulations

Formulation Code	Physical Appearance Parameters					
	Taste		Colour		Odour	
	Sample in Deciccator	Sample # on Shelf	Sample in Desiccator	Sample# on Shelf	Sample in Desiccator	Sample# On Shelf
SD1	Sweet	Sweet	White	Off White	Minty	Odourless
SD2	Sweet	Sweet	White	Off White	Minty	Lightminty
SD3	Sweet	Sweet	White	Off White	Minty	Odourless
SD4	Sweet	Sweet	White	Off White	Minty	Lightminty

#at Relative Humidity 80%

Table 16: Evaluation of parameters during stability studies of FMDT Formulations of Terbutaline Sulphate

Formulation Code	Physical Appearance Parameters					
	Hardness** (Kg/cm^2)		Weight Difference due to Moisture Absorption (%)		*In vitro* Dispersion Time**(Seconds)	
	Sample in Desiccator	Sample# on Shelf	Sample in Desiccator	Sample# on Shelf	Sample in Desiccator	Sample# on Shelf
SD1	2.55	2.21	1.28	9.47	66.25	50.19
SD2	2.62	2.41	0.61	5.16	114.72	91.24
SD3	2.25	1.94	1.70	10.18	58.70	39.16
SD4	2.22	2.00	0.52	5.42	92.62	80.08

*Average of5 determinations, **Average of3 determinations, #At Relative Humidity 80%

Table 17: *In-vitro* Dissolution Profile of FMDT formulations of during Stability Studies

Formulation code		Percentage Drug Release*±of FMDT of Terbutaline Sulphate at the following time intervals			
		3minutes	6minutes	9minutes	12 minutes
SD1	Initial	79.67%	81.60%	82.67%	94.70%
	1month	79.37%	80.94%	81.97%	94.00%
SD2	Initial	76.66%	80.67%	84.68%	85.68%
	1month	75.77%	80.28%	84.42%	84.79%
SD3	Initial	91.69%	94.70%	96.81%	97.71%
	1month	92.18%	93.16%	96.26%	97.04%
SD4	Initial	79.67%	86.68%	90.89%	93.90%
	1month	79.64%	86.49%	90.29%	93.02%

*Each value is an average of3 determination

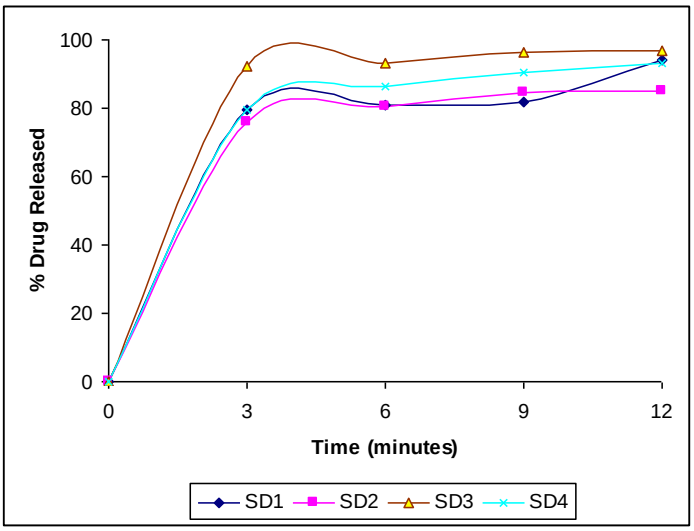

Figure 5: *In vitro* Dissolution Profile for FMDT by super disintegrant addition method after stability studies

RESULT AND DISCUSSION

In this study, a total of four formulations of rapidly orally dissolving terbutaline sulfate tablets were prepared using the super disintegrant addition method. To select the optimal formulation, we checked various parameters, performed *in vitro* dissolution studies, observed and compared their release profiles. Evaluation of physical parameters, active substance content and release studies were performed according to official methods and using modified official methods. Stability studies were conducted according to a modified method for 1 month and evaluated parameters such as physical appearance of the formulation, hardness, weight change due to moisture absorption, *in vitro* dispersion time, and *in vitro* dissolution test. The drug was identified by ultraviolet spectroscopy (UV), Melting point& Solubility. The λ max was found to be 276 nm against distilled water as blank. The calibration curve and the data were obtained by the procedure described in pre-formulation studies section. The melting point of the drug was found to be 246^0C. The solubility profile of drug was tabulated in table 1. Four formulations (SD1, SD2, SD3 & SD4) of FMDT of Terbutaline Sulphate were prepared by super disintegrant addition approach. The figures of the prepared tablet were shown in Figures 3. The prepared formulations were evaluated by various parameters. The angle of repose and compressibility values was tabulated in table 3. The result showed that blend has excellent flow properties. All the FMDT formulations were evaluated for their thickness, using vernier Calipers and the results were shown in Table 4. The average thickness for all the formulations was found to be with in the allowed limit of deviation i.e.± 5%of the standard value. All the FMDT formulations were evaluated for their taste, colour, odour and recorded in Table 5. The average hardness in between 2 Kg/cm^2, which was found to be acceptable; because these formulations have to be dispersed or disintegrated on the tongue between 15 seconds to 3 minutes Table 6. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tissue paper in a petridish. Moisture uptake studies for the FMDT formulations were performed according to the procedure in micromeritic Properties and the results were shown in Table 7. The maximum moisture uptake was shown by the SD3. The moisture uptake by FMDT formulations using super disintegrant addition method is due to the water uptake and the swelling behavior of the sodium starchglycollate (table 8). From the evaluation it is proved that, higher the concentration of super disintegrant higher is the moisture uptake. All the formulation was evaluated for their uniformity of weight the results were shown in Table 10. The maximum allowed percentage weight variation for tablets weighing 80–250 mg by I.P is 7.5%, and no formulations are exceeding this limit. Thus all the formulations were found to comply with the standards given in IP. The test for uniformity of drug content should be carried out only after the content of active ingredient (assay) in a pooled sample of tablets has been found to be within the accepted limit of the stated amounts, (i.e. limit of not less than90% and not more than 110%of Terbutaline Sulphate). Formulations were checked for their *in vitro* dispersion time and the results were shown in Table 12 & 13 and Figure 4. Formulation SD_3 shows the rapid dispersion in 53.66 ± 7.91 seconds followed by SD_1 in 64.50±7.91 seconds. Formulations SD_4 (88.16±4.21 seconds) and SD_2 (111.66 ± 9.69 seconds) takes comparatively more time to get completely dispersed. This is due to the difference in the ratios of SSG and the other disintegrants (SCMC and PVP). Because SD_1 and SD_3 contain higher concentrations of super disintegrant. So the amount of water up take and swelling will be more for these formulations, which results in the rapid dispersion or disintegration. Placebo formulation SD_3 shows the rapid dispersion in 40.83 ±2.46 seconds followed by SD_1 in 50.62 ± 3.96 seconds. Placebo formulations SD_4 (81.66± 4.26 seconds) and SD_2 (100.16±7.28 seconds) take comparatively more time to get completely dispersed. This is due to the concentration difference of SSG in these formulations. Higher the concentration ratio of super disintegrants and other disintegrant, higher will be the saliva absorption of the tablet and rapid will be the swelling and further bursting

or dispersion of tablet on tongue. The results of *in-vitro* drug release after dispersion of the formulations were shown in Table 13. This test was an attempt made for better *in vitro in vivo* correlation. The highest drug release of 91.0340 ± 2.1894 % was obtained from formulation SD_3, which get dispersed in 55 ± 7.12, seconds. Result of *in- vitro* dissolution studies showed that the highest dissolution rate and drug release at the end of 12 minutes SD_3 (97.7680 ± 3.1628%) followed by SD_1 (94.7010± 4.4285%), SD_4 (93.6990 ± 3.1625%) and SD_2 (85.6800 ± 3.3139%). Stability study was conducted for all the FMDT formulations in both desiccator and shelf storage conditions, and the results were shown in Tables 16 & 17. There was no significant reduction in drug release profile of any tablet formulation, no significant taste, colour and odour changes for desiccator stored samples. But the formulations exposed to shelf storage have shown some minor colour and odour change with significant increase in weigh and decrease in hardness.

CONCLUSION

The current study concludes that the FMDT of terbutaline sulfate can be successfully designed and the availability of different technologies and the multiple advantages of fast-dissolving oral tablets will certainly increase patient compliance and their popularity in the near future. Based on *in vitro* release studies, the FMDTs prepared in this study released more drug than conventional tablet form drug release.

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