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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF TERBUTALIINE SULFATE

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Abstract:
The outcome of present work provides a concrete basis for development of fast dissolving tablets of Terbutaline sulphate. Various approaches explored in the present work can be applied to achieve quick disintegration, good mouth feel and adequate mechanical strength, which improve patient compliance. Further work can be focused on co processing of various diluents with superdisintegrant. Some herbal superdisintegrant in freeze dried form can be investigated to determine their effect on disintegration time and hardness. To evaluate the effects of fast dissolving tablets in stress conditions, pharmacokinetic study can be performed in diseased state, and to compare with the results obtained in non- diseased state. All the researchers working on Terbutaline sulphate concentrates their research on the disintegration behavior of the tablets using super disintegrants which does not full fill the basic requirements of the mouth dissolving tablets i.e. patient compliance. Industries who want to make a Terbutaline sulphate blindly incorporating insoluble taste masking resins, superdisintegrants for disintegration and trading as mouth dissolving tablet. Due to lots of limitations like hardness, mechanical strength, no ease of manufacturing and most important cost of manufacturing, that's why, industries concentrate whole emphasis on the use of superdisintegrants and make researchers not to work on mouth dissolving tablets instead moves on to mouth disintegrating tablets. Thus we concentrate on formulating mouth dissolving tablets giving complete dissolution of the formulation with minimum residue.

KEYWORDS- *Terbutaline sulphate, Migraine, Mouth Dissolving Tablet, Croscarmellose Sodium, Crospovidone, Superdisintegrants.*

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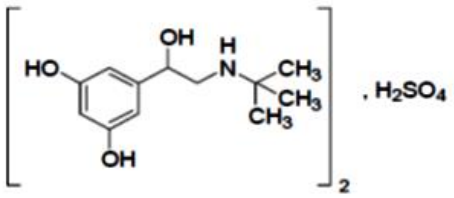
INTRODUCTION:

A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates quickly in the oral cavity upon the contact with saliva, and resulting in solution or suspension of the administered medicine. FDT dosage forms are also commonly known as fast melt, quick melt, orally disintegrating tablets, and or dispersible systems, have the unique property of disintegrating the tablet in the mouth in seconds (1).

Orodispersable tablets (ODTs), being best alternative of conventional tablets, defined as a solid dosage form containing medicinal substance that disintegrates within a matter of seconds when placed upon tongue. Two different types of dispersible tablets distinguished as one that disintegrates/dissolves instantaneously in the mouth and to be swallowed without the needs for drinking water, while the other tablet formulation can be readily to be dispersed in water to form a dispersion (Brown D *et al*, 2003) which is easy to ingest by the patients. The ODTs formulations have interesting features like exceptional taste masking ability, extremely low disintegration time, and pleasant mouth feel. Bioavailability and as result of reduced dosage, improved the clinical performance through a reduction of unwanted effects. Mouth disintegrating tablets are offering the combined advantages of both liquid and conventional dosage form but our aim of this review is to be provide the basic difference between mouth dissolving and mouth disintegrating tablet. One of the major problems with this drug is its very poor solubility in biological fluids that results into poor bioavailability after oral administration. The solubility enhancement of poorly soluble compound can be induced by changes in temperature, solvation properties using different cosolvent compositions, and by inclusion compound formation (1).

Terbutaline sulfate is Terbutaline Sulphate is (RS)-2-(tert-butylamino)-1-(3,5- dihydroxyphenyl) ethanol sulphate. The molecular formula is (C12H19NO3) 2 • H2SO4 and the structural formula is Terbutaline sulfate USP is a white to gray-white crystalline powder. It is odorless or has a faint odor of acetic acid. It is soluble in water and in 0.1N hydrochloric acid, slightly soluble in methanol, and insoluble in chloroform. Its molecular weight is 548.65 (2).



$(C_{12}H_{19}NO_3)_2.H_2SO_4$ Mol. Wt. 548.7

Description. A white or almost white, crystalline powder; odourless or almost odourless. When examined in the range 230 nm to 360 nm (2.4.7), the resulting solution shows a specific wavelength. In vitro and in vivo pharmacologic studies have demonstrated that terbutaline exerts a preferential effect on beta2-adrenergic receptors. While it is recognized that beta2-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta2-receptors in the human heart, existing in a concentration between 10% to 50%. The precise function of these receptors has not been established (see WARNINGS). In controlled clinical studies in patients given terbutaline sulfate orally, proportionally greater changes occurred in pulmonary function parameters than in heart rate or blood pressure. While this suggests a relative preference for the beta2-receptors in man, the usual cardiovascular effects commonly associated with other sympathomimetic agents were also observed with terbutaline sulfate (2).

MATERIALS AND METHODS:

MATERIALS- Terbutaline sulphate was gifted by ZCL chemicals Ltd. Mumbai, Maharashtra, India. Croscarmellose Sodium and Crospovidone were purchased from Yarrow chemicals Mumbai, Maharashtra and are of AR grade.

METHOD

1. Scanning of Terbutaline Sulfate: Dilution data of stock solution for scanning of Terbutaline Sulfate in TABLE 1. Phosphate Buffer Saline (pH-7.4)

TABLE 1: Dilution data of stock solution for scanning of Terbutaline Sulfate in Phosphate Buffer Saline (pH-7.4)

Sr. No.	Dilution of stock Solution of Terbutaline Sulfate (1 mg/mL) with PBS (pH-7.4)	Concentration (µg / mL)	Maximum Wavelength (λmax) (nm)	Absorbance
1	10 times (1in 10 mL)	100	276.0	0.794
2	100 times(1 in 100 mL)	10	276.5	0.099
3	1000 times(1 in 1000 mL)	1	281	0.016

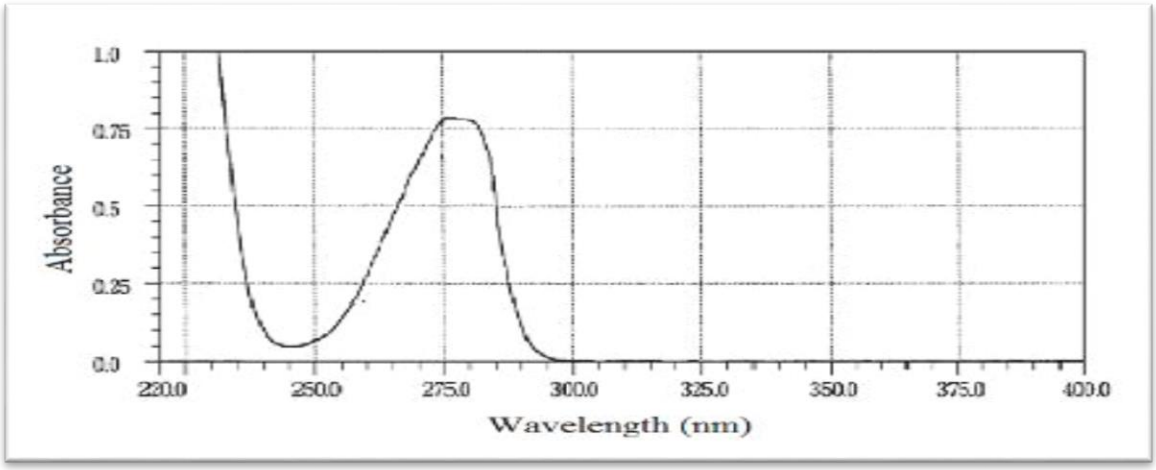


FIGURE NO 1. Wavelength of 276 nm. This wavelength is selected as λmax for the determination of absorbance of different Scanning of Terbutaline Sulfate concentration of solutions.

2. Preparation of Calibration Curve of Terbutaline Sulfate by U.V Spectroscopy Method

The calibration curve of Terbutaline Sulfate in Phosphate Buffer Saline (PBS) pH-7.4 was prepared to identify the linearity range of Terbutaline Sulfate. The calibration curve of Trebutaline Sulfate was prepared by examining the absorbance of Terbutaline Sulfate solutions of 10, 20, 40, 60, 80 and 100 µg / mL in Phosphate Bufer Saline pH-7.4 under UV Spectrophotometer at λmax of 276 nm. The results of absorbance of Terbutaline Sulfate solutions are shown in the Table 2 (3).

Sr. No.	Concentration of Terbutaline Sulfate (µg / mL	Absorbance ± SD (n=3)
1	10	0.077±0.06
2	20	0.156±0.07
3	40	0.317±0.05
4	60	0.466±0.09
5	80	0.632±0.07

6	100	0.796±0.08

Table 2 Data for preparation of Calibration Curve of Terbutaline Sulfate in Phospahte Buffer Saline (pH 7.4) at λ_{max} of 276 nm

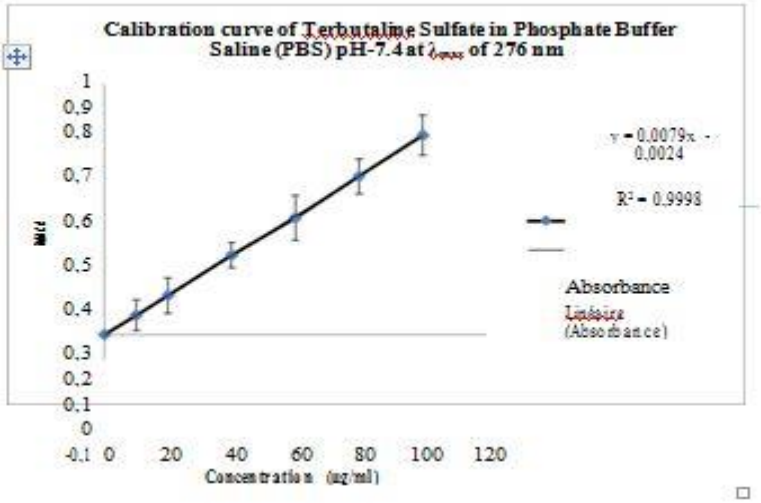


Figure 2: Calibration Curve of Terbutaline Sulfate in Phosphate Buffer Saline (pH-7.4) at λmax of 276 nm

3. Determination of Melting Point of Terbutaline Sulfate

The melting point of Terbutaline sulfate was determined to check the purity of the Terbutaline sulfate. The melting point of the Tebutaline sulfate was determined using Digital melting point apparatus. The results of the observed melting point of Terbutaline Sulfate are shown in the Table 3 (4).

TABLE NO 3: Data of Melting Point Determination of Terbutaline Sulfate

Sr. No.	Capillary Number	Observed Melting point (° C)
1	Capillary A	248
2	Capillary B	248
3	Capillary C	249

The results of the melting point determination showed that the drug is pure because it has melting point (248 °C) nearer to the reported melting point (i.e. 246-248 °C).

4. Determination of the Solubility of Terbutaline Sulfate

The solubility of the Terbutaline Sulfate was determined to find the extent to which Terbutaline Sulfate was soluble in different solvents such water, 0.1 N HCl, 0.1 N NaOH, Methanol, Ethanol and Acetone. The solubility of drug in different solvent assist in identifying the proper release medium for in-vitro release studies. The results for the determination of the solubility of Terbutaline Sulfate are shown in the Table 4. The solubility of the terbutaline sulfate found to be maximum in water. The solubility of terbutaline sulfate in 0.1 N HCl and 0.1 N NaOH were found to be less than water. The solubility of terbutaline sulfate in acetone was found to be more than methanol but less than 0.1 N HCl. The solubility of terbutaline sulfate found to be poorly soluble in methanol and ethanol (5).

Table 4: Data of Solubility Determination of Terbutaline Sulfate

Sr. No.	Name of solvents	Solubility at 25° C (mg/mL)
1	Water	30 ± 0.45
2	0.1 N HCl	26 ± 0.63
3	0.1 N NaOH	28 ± 0.87
4	Methanol	2.7 ± 0.52
5	Ethanol	1.2 ± 0.74
6	Acetone	10 ± 0.69

5. Preparation of fast dissolving tablets by direct compression method:

Fast dissolving tablets of Terbutaline Sulphate were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order. Powder blend was evaluated for bulk density, tapped density, Carr's index and Hauser's ratio.Compressed into tablets of 150mg using 8mm round flat punches on 10-station rotary tablet machine (Clit).(Gohel MC et al,2007)

Table-5: Formula for different batches of Terbutaline Sulphate tablets .

Ingredients	CF F1	PM F2	PM F3	PM F4	CP F5	CP F6	CP F7
Terbutaline Sulphate	5	5	5	5	5	5	5
Mannitol	110	101	101	101	101	101	101
Superdisintegrants (CP+CCS)	-	10	10	10	10	10	10
Aerosil	30	30	30	30	30	30	30
Pre-gelatinised Starch	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Where, **PM(F2,F3,F4) -** Physical Mixture of crospovidone and croscarmellose sodium in different Ratios (1:1, 1:2, 1:3), **CP(F5,F6,F7)-** Co-processed Superdisintegrants of crospovidone and croscarmellose sodium in different Ratios (1:1,1:2, 1:3), **CF,F1-** Control formulation (without superdisintegrants), **CP –** Crospovidone, **CCS–** Croscarmellose sodium.

6. In-vitro drug release of Pure drug (Terbutaline sulfate)

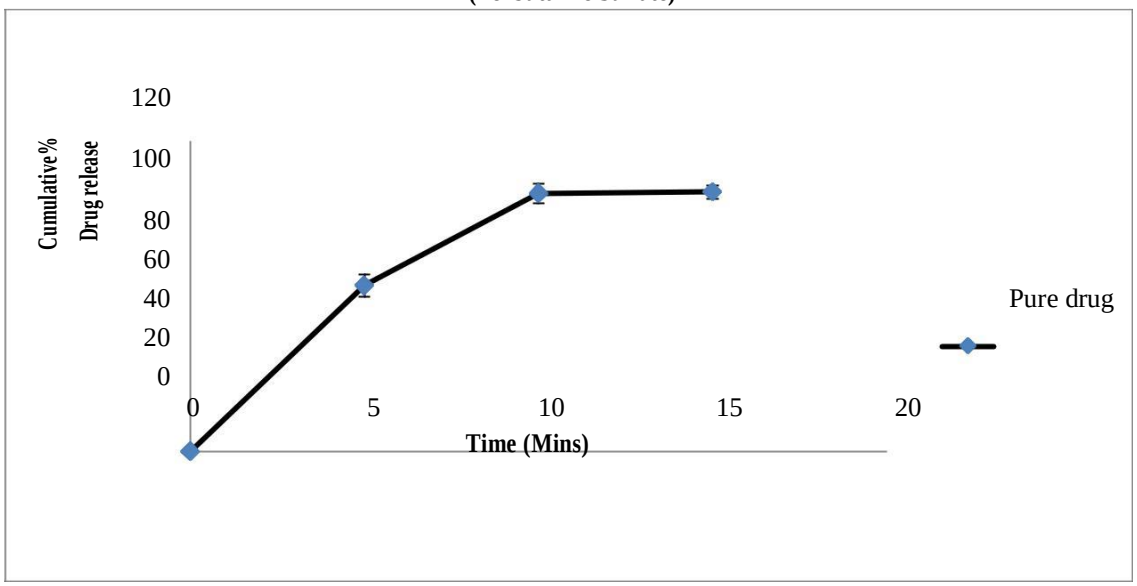
The result of in-vitro drug release of Pure drug (Terbutaline Sulfate) shown in Table 6 and the graph of in-vitro release of Pure drug shown in Figure 3 (6).

Table 6: In-Vitro Drug Release of pure drug (Terbutaline Sulfate) in Phosphate Buffer Saline pH-7.4

Sr.No.	Time (Mins)	Cumulative % drug release ± SD(n=3)
1	0	0
2	5	64.08 ± 4.35
3	10	99.68 ± 3.72
4	15	100.21± 2.65

All values are average of three determinations (n=3)

FIGURE 3 Plot of In-vitro drug release of Pure drug (Terbutaline Sulfate)



7. In-vitro Dissolution studies of tablet using dissolution apparatus:

In vitro dissolution studies on the promising formulation CPF5, control (CPF1) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 min, 10 min and 15 min (D_5, D_{10} and D_{15}), dissolution efficiency at 10 min (DE_{10} min), $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in Table 8.8 and dissolution profile depicted in fig. 8.4.. This data reveals that overall, the formulation CPF5 has shown nearly two and a half fold faster drug release ($t_{50\%}$ 2.41 min) when compared to the commercial conventional tablet formulation of Terbutaline Sulphate ($t_{50\%}$ 6 min) (7).

TABLE 7: Evaluation of Terbutaline Sulphate FDT Formulations

Parameters	Formulation Code						
	CP_0	**PMF2**	**PM F3**	**PM F4**	**CP F5**	**CP F6**	**CP F7**
Hardness (kg/cm^2)*±SD	2.96±0.05	2.9±0.1	2.83±1.4	3.26±0.05	3.13±0.04	3.23±0.05	3.25±0.03
Thickness*(mm)	2.23±0.02	2.17±0.02	2.26±0.05	3.0±0.01	2.11±0.02	2.21±0.01	2.12±0.01
In vitro Dispersion time (s)*±SD	98±2	36.31±1.52	41.13±0.77	41.36±2.52	22±2	31.33±3.41	39±2.0
Wetting time (s)*±SDs	106±4.93	39.66±1.52	42±1	45.33±1.5	31±0.5	34.33±1.52	41.56±1.15
Water Absorption ratio (%)*±SD	46±1	76.33±1.15	71.66±1.52	64±1	86±1	78±2.08	71±2.14
Percent Drug Content (%)* ±SD	99.21±1.52	99.28±1.01	100±1.57	100±2.02	99.97±0.07	101±1.19	98.45±2
Weight Variation(%)	146-159 mg (IP limits ± 7.5%)						

TABLE 8 *In Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Formulation code	Parameters						
	D_5	**D10**	**D15**	**t50%**	**t70%**	**t90%**	**DE10min**
CPF 1	26 %	53.43%	62.81%	9.30 min	12.50 min	>30 min	27.02%
CF	40%	72%	81.77%	6 min	9.5 min	29 min	39.0%
PMF2	70%	80.86%	87.46%	3.88 min	5 min	16 min	61.39%
CPF5	76.5%	90.63%	99.27%	2.41 min	3.48 min	9.48 min	64.80%

Where, CPF1 is control formulation, CPF5 is promising fast dissolving tablet formulation, PMF2 is formulation containing physical mixture of superdisintegrants in1:1 ratio, CCF is conventional commercial tablet formulation, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, D_{15} is percent drug release in 15 min, DE_{10min} is dissolution efficiency at 10 min, $t_{50\%}$ is time for 50% drug dissolution, $t_{70\%}$ is time for 70% drug

dissolution, $t_{90\%}$ is time for 90% drug dissolution (9).

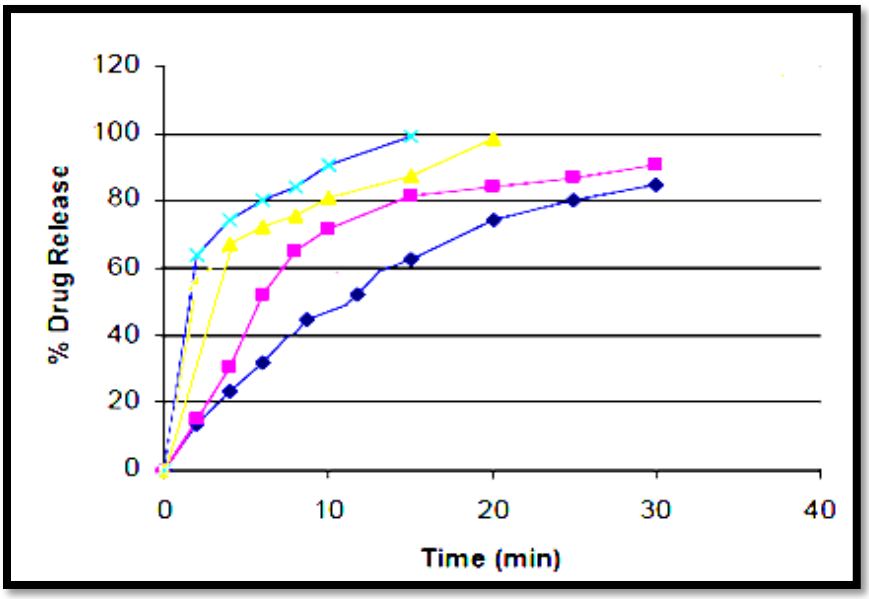


FIGURE 4: Dissolution Studies

CONCLUSION:

In the present research work an attempt has been made to optimize, formulate and characterize fast dissolving tablet (s) of Terbutaline Sulphate. Co-processed superdisitegrants consisting of crospovidone and croscarmellose sodium exhibited good flow and compression characteristics.

Terbutaline sulphate tablets containing co-processed superdisintegrants exhibited quick disintegration and improved drug dissolution. This formulation is more cost effective than aerosol inhalation pumps available. It was found that the total maximum amount of drug from the optimised batch was released in first 4 minutes of the dissolution study. The tablets disintegrated within 50 sec under experimental in vitro laboratory conditions. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and croscarmellose are superior to physical mixture of crospovidone and croscarmellose used in Terbutaline sulphate fast dissolving tablets.

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