Research Article

Formulation and Evaluation of Fast Dissolving Tablets of Terbutalin Sulphate

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ABSTRACT

In this investigation fast dissolving tablets of terbutalin sulphate were prepared using different superdisintegrants and different methods. Overall FDT prepared by sublimation method appears to be the best formulation. The order for the best methods is as follows FDT by sublimation method > direct compression method > intra & extra granulation method > wet granulation method. In this methods gradually deceased lactose ratio and increased to sodium starch glycolate crospovidone. FDTs were evaluated for physicochemical properties and *in vitro* dissolution. Effect of disintegrant on disintegration behaviour of tablet in artificial saliva, pH 6.8 was evaluated. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest percentage drug release.

INTRODUCTION

Fast dissolving tablets (FDTs) are solid single-unit dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provides a quick onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. FDTs are appreciated by a significant segment of population, particularly children and elderly, which have difficulty in swallowing conventional tablets or capsules[1,2, 3]. FDTs are prepared by various techniques, mainly direct compression, lyophilization and moulding. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies[4]. Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants[5].

Terbutalinesulphate is a β2 sympathomimetics used in the treatment of asthma. The mechanism of action of terbutalinesulphate is a beta (2)-adrenergic agonist and it stimulates beta (2)-adrenergic receptors in the lungs results in relaxation of bronchialsmooth muscles.[10] It is incompletely absorbed when administered through oral route and exhibits the bioavailability of about 15%, due to the high first pass metabolism in gut wall and short half life of about 3-4 hrs. On inhalation, only 10-20% of the inhaled dose reaches lungs and the remaining is swallowed. The drug is highly water soluble.[11]

The aim of the present investigation is to develop fast dissolving tablets, using terbutalinesulphate as a model drug to reduce the lag time and providing faster onset of action to relieve acute asthmatic attack.

MATERIALS AND METHODS

MATERIALS: Terbutaline sulphate obtained from Astrazeneca pharm Ltd, Bangalore, India. microcrystalline cellulose, lactose, sodium starch glycolate ,cross providone, camphore , Sunset yellow,pvp all chemicals obtained from S.D.Fine chem.ltd, Mumbai.

METHODS

Preparation of fast dissolving tablets

Direct compression method: Fast dissolving tablets were prepared by direct compression method. Each ingredient was weighed individually and passed through sieve no 60. After passing each ingredient, all ingredients were mixed using a glass mortar and pestle. Powder blend were then directly compressed using 8 mm, round-shaped tooling in a 8 station tablet compression machine (Riddhi Pharma instrument Ltd, Ahmedabad, India).

Sublimation Method: All ingredients were sifted through the sieve no 60 individually and weighed as per the formula displayed in Table. Weighed ingredients were mixed using a glass mortar and pestle. Finally, magnesium stearate and aerosil were added as lubricating agent. Powder blend were then directly compressed using 8 mm, round-shaped tooling in a 8 station tablet compression machine (Riddhi Pharma instrument Ltd, Ahmedabad, India). After compression tablets were heated in a hot air oven at 60°C until constant weight was obtained to ensure the complete removal of volatilizable component.

Wet granulation method: All ingredients were sifted through the # 100 mesh screen individually and weighed as per the formula displayed in Table. Weighed ingredients were transferred into Polythene bag and mixed vigorously for 15 minutes. The blend was taken in a stainless steel container, to which a sufficient volume of granulating agent, alcoholic solution of PVP (5% w/v) as granulating agent was added to form a damp mass. The damp mass was passed through the # 16 mesh screen to get wet granules. Wet granules were dried in a hot air oven for 1 hour at 60º C. After thorough mixing the dried resized granules with 10% fines, lubricated with magnesium stearate and aerosil. The uniformly mixed granules was compressed into tablets using 8 mm diameter, flat faced, round tooling set on 8 station rotary tablet machine (Riddhi Pharma instrument Ltd, Ahmedabad, India).

Extra granulation method: All raw materials were screened through the sieve no 100 separately and weighed as per the formula displayed in Table. In this method, 50% of super disintegrant (as intra) mixed with the other pre-weighed ingredients in a polythene bag for 15 minutes. The blend was transferred to a stainless steel container, to which a sufficient volume of granulating agent, alcoholic solution of PVP (5% w/v) as granulating agent added to form a damp mass. The damp mass is passed through the no 16 mesh screen to get wet granules. Wet granules were dried in a hot air oven for 1 hour at 60ºC. The dried resized granules were thoroughly mixed with 10% fines, remaining 50% of super disintegrant (as extra) and lubricated with magnesium stearate and aerosil. The uniformly mixed granules was compressed into tablets using 8 mm diameter, flat faced, round tooling set on 8 station rotary tablet machine (Riddhi Pharma instrument Ltd, ahmedabad, India).

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Preparation of fast dissolving tablets

S. no	Ingredients(mg)	Formulation Code			Formulation Code			Formulation Code			Formulation Code		
		DC1	DC2	DC3	SB1	SB2	SB3	WG1	WG2	WG3	IEG1	IEG2	IEG3
1	TBS	5	5	5	5	5	5	5	5	5	5	5	5
2	MCC	100	100	100	100	100	100	100	100	100	100	100	100
3	Lactose	14	11	8	14	11	8	14	11	8	32	31	30
4	SSG+crospovidone	6	7	8	6	7	8	6	7	8	6	7	8
5	Saccharine sodium	1	1	1	1	1	1	1	1	1	1	1	1
6	Camphor	-	-	-	18	20	22	-	-	-	-	-	-
7	Sunset yellow	1	1	1	1	1	1	1	1	1	1	1	1
8	Orange flavor	1	1	1	1	1	1	1	1	1	1	1	1
9	Aerosil	2	2	2	2	2	2	2	2	2	2	2	2
10	Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2

Flow properties of blend

The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio7. For determination of angle of repose (□), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the (height of the pile/radius of its base) gave the angle of repose. Blends were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess blend was removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (_b) and tapped density (_t) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given below:

HR= _t/_b

IC = (_t_ _b)/_t * 100

Evaluation of fast dissolving tablets of TBS

Uniformity of weight

was followed for determining the water absorption ratio R was determined according to the following equation:

R = [(Wa – Wb)/Wb]× 100

where, Wb and Wa were the weights of the tablet before and after use8.

Disintegration time

Disintegration time was measured in 900 ml artificial saliva (pH 6.8) according to the USP 24 method without disc at 37 ± 0.5oC temperature. The disintegration time of 6 individual tablets were recorded and the average was reported 9.

Content uniformity

Twenty tablets were powdered, and 10 mg equivalent weight of Terbutaline sulphate in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of artificial saliva (pH 6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with artificial saliva (pH

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Hardness

Hardness was determined by taking six tablets from each formulation, using a MonsantHardness Tester.

Friability

The friability of sample of six tablets ware measured using a Roche Fribilator. Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fine's using 60 mesh screen and the percentage of weight loss was calculated.

% Friability = (Loss in weight / Initial weight) × 100

Wetting time and water absorption ratio

A piece of paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded. as the wetting time. The same procedure without Rosaline dye powder 6.8). The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 282 nm.

***In vitro* dissolution study**

The release of from FDT was determined using USP dissolution testing apparatus 2 (paddle method; Veego Scientific, Mumbai). The dissolution test was performed using 900 ml of artificial saliva, pH 6.8 at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to suitable concentration with artificial saliva, Ph 6.8. Absorbance of these solutions was measured at 276.50 nm using a Thermospectronic-1 UV/Vis doublebeam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Several Technologies are available to manufacture orally distintegrating tablets. The most common preparation methods are molding, lyophilization or freeze drying, direct compression, spray drying and sublimation. In the present investigation FDTs of terbutaline sulphate were prepared by four methods they are sublimation method ,direct compression method, intra & extra granulation method, wet granulation method.

Pre-compression Parameters

The pre-compression data's were shown in Table. The values for angle of repose were found in the range of 230.43' - 280.30'. This indicates good flow property of the mixed powder. Bulk densities and tapped densities of various formulations were found to be in the range of 0.45±0.01 to 0.50±0.05 (g/cc) and 0.49±0.006 to 0.67±0.00 (g/cc) respectively. Compressibility index of the prepared blends/granules fall in the range of 7.67%-12.33% indicating that the blends/granules have the excellent compressibility. Hausner's ratio of the prepared blends/granules fall in the range of 0.73-1.18 indicated that the blends/granules have the required flow property and strength for compression.

Table: Pre-compression Parameters of developed formulations

S.NO	Formulation code	Angle of repose(Ø)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio
1	DC1	25.03±0.81	0.49±0.06	0.59±0.05	10.00	0.83
2	DC2	23.43±0.58	0.47±0.05	0.49±0.06	9.00	0.73
3	DC3	24.57±0.64	0.45±0.22	0.59±0.05	11.33	1.18
4	SB1	24.27±0.64	0.45±0.01	0.63±0.06	12.33	0.90
5	SB2	24.40±0.68	0.49±0.06	0.60±0.07	11.00	0.93
6	SB3	27.40±0.87	0.47±0.01	0.59±0.05	9.67	0.90
7	WG1	24.33±0.68	0.50±0.05	0.59±0.05	10.00	0.93
8	WG2	23.97±0.64	0.47±0.01	0.55±0.01	11.33	0.97
9	WG3	23.97±0.92	0.46±0.01	0.67±0.00	8.67	0.90
10	IE1	28.30±0.35	0.46±0.01	0.59±0.05	8.33	0.93
11	IE2	25.23±0.58	0.49±0.06	0.52±0.06	9.00	0.90
12	IE3	24.90±0.69	0.48±0.05	0.58±0.06	7.67	1.00

Post compression Parameters

Visual examination of tablets from each formulation batch showed circular shape

Thickness

The dimensions determined for formulated tablets were tabulated in Table. Tablets mean thicknesses were almost uniform in all the formulations and were found to be in the range of 2.40 mm-2.80 mm.

Hardness test

Hardness of the three tablets of each batch was checked by Monsanto hardness tester and the data's were shown in Table . The results showed that the hardness of the tablets was in the range of 3.60±0.17 to 4.07±0.15 kg/cm2.

In vitro dissolution studies

Finally, the tablets were evaluated for *in vitro* dissolution studies in simulated saliva and the results were shown in the Figures. The highest dissolution rate and drug release was shown by FDT by sublimation method. The results shows that the order of drug release in dissolution studies is FDT by sublimation method > direct compression method > intra and extra granulation > wet granulation method. The sublimation method contain camphor as a subliming agent showed more than 96% of drug release with in 15 min, whereas direct compression method containing superdisintegrants showed more than 93% of drug release with in 15 min, and the remaining two methods showed more than 92% of drug release within 24 minutes.

Overall the FDT formulations of terbutaline sulphate showed the rapid dispersion and drug dissolution in sublimation method. It is mainly due to the highly porous nature of tablets. So rapid penetration of dissolution fluid to the tablets, which results in rapid bursting and dissolution of tablets.

Table: Post compression Parameters of developed formulations

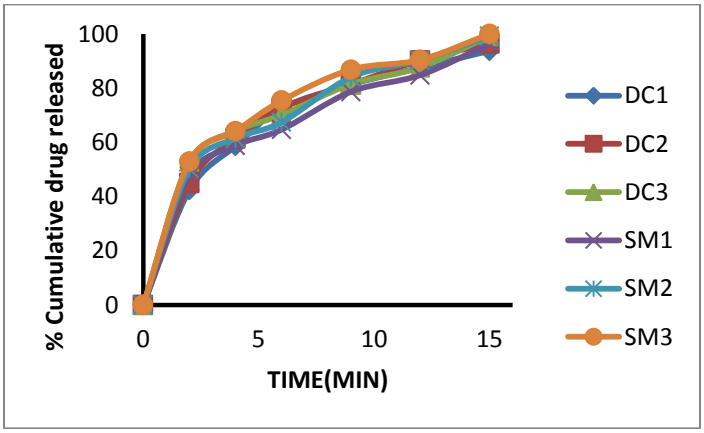
Formulation code	Weight variation (mg)	Wetting time (sec)	Water abs ratio (%)	Disintegration time (sec)	Drug content (%)
DC1	150.3±1.53	41.5±1.78	90.2±0.25	28.5±0.52	94.7±0.40
DC2	148.0±1.00	40.8±1.75	88.6±0.93	28.3±0.57	96.5±0.35
DC3	151.6±1.53	35.8±0.10	86.5±0.44	26.8±0.55	97.6±0.51
SB1	150.3±2.31	34.5±1.27	95.7±0.60	24.9±0.72	97.4±0.35
SB2	150.0±2.00	30.6±0.20	94.4±0.42	22.5±0.38	98.2±0.35
SB3	151.6±1.53	28.6±0.31	92.3±0.17	19.6±0.66	99.4±0.35
WG1	149.3±2.52	61.0±1.56	75.5±0.32	51.6±0.26	94.8±0.50
WG2	151.3±2.08	57.7±0.26	73.5±0.49	49.4±0.44	96.5±0.32
WG3	150.3±0.58	55.4±0.42	73.3±0.68	48.1±0.72	96.6±0.32
IEG1	154.0±2.65	52.8±1.42	77.5±0.31	45.7±0.40	94.8±0.50
IEG2	150.0±1.73	50.4±0.38	76.4±0.44	44.7±0.35	95.4±0.72
IEG3	150.6±2.08	49.1±1.40	74.4±0.36	43.3±0.36	96.5±0.35

***In vitro* drug release profile of TBS FDTs by direct compression method and sublimation method**:

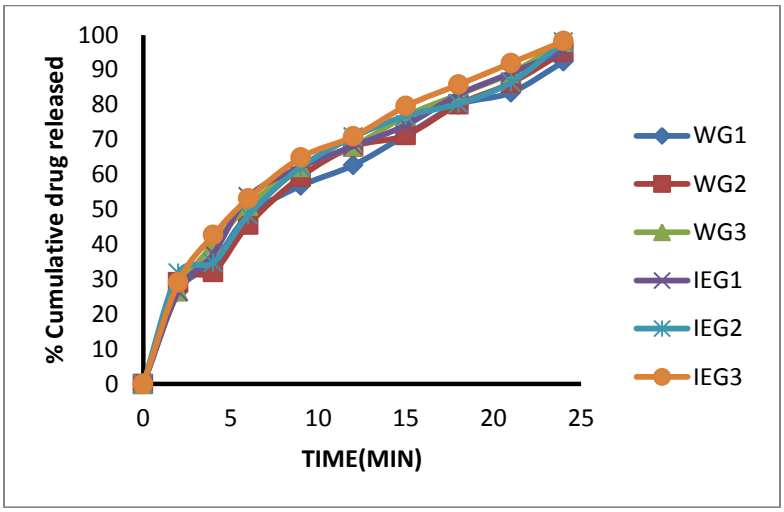
Time (min)	% Cumulative drug released					
	direct compression			sublimation method		
	DC1	DC2	DC3	SM1	SM2	SM3
0	**0**	**0**	**0**	**0**	**0**	**0**
2	42.35±0. 52	45.03±0.07	52.94±0.55	47.65±0.48	50.29±0.17	52.94±0.24
4	58.71±0.72	61.38±0.34	64.12±0.37	58.77±0.41	61.44±0.76	64.12±0.22
6	72.59±0.02	72.65±0.71	70.12±0.13	64.71±0.09	67.41±0.44	75.41±0.25
9	81.32±0.42	81.36±0.18	81.47±0.27	78.65±0.64	84.03±0.22	86.82±0.46
12	87.50±0.31	90.21±0.49	87.65±0.29	84.79±0.14	90.24±0.85	90.41±0.26
15	93.74±0.70	96.47±0.16	99.18±1.78	96.29±0.05	99.15±0.12	99.95±0.35

***In vitro* drug release profile of TBS FDTs by intra and extra granulation method and wet granulation method**

Time (min)	% Cumulative drug released					
	wet granulation method:			intra and extra granulation method		
	WG1	WG2	WG3	IEG1	IEG2	IEG3
0	**0**	**0**	**0**	**0**	**0**	**0**
2	26.48±0.01	29.12±0.01	26.47±0.02	26.47±0.14	31.76±0.27	29.12±0.20
4	34.71±0.02	32.09±0.03	40.01±0.01	37.35±0.58	34.76±0.22	42.68±0.69
6	48.32±0.03	45.68±0.01	51.03±0.03	53.65±0.35	48.38±0.26	53.13±0.51
9	56.79±0.03	59.41±0.03	62.18±0.03	62.18±0.03	62.18±0.03	64.91±0.70
12	62.71±0.02	68.01±0.01	68.15±0.02	68.15±0.07	70.76±0.19	70.91±0.16
15	71.32±0.01	71.32±0.01	76.82±0.03	74.18±0.6	76.82±0.53	79.62±0.49



***In vitro* drug release profile of TBS FDTs by direct compression method and sublimation method**



***In vitro* drug release profile of TBS FDTs by intra and extra granulation method and wet granulation method**

CONCLUSION

In the present study it can be concluded from the characterization of fast dissolving tablets of Terbutaline sulphate that formulation containing Crospovidone is most acceptable. It was also observed that to further increase the drug release from FDTs, solubility enhancement of Terbutaline sulphate is required and is under investigation. Further *in vivo* studies in human volunteers are required to correlate *in vitro* release data.

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