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FORMULATION DEVELOPMENT AND EVALUATION OF ORO-DISPERSIBLE TABLETS OF TERBUTALINE

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ABSTRACT

The present work was concluded that to develop a stable, safe, fast release and convenient Oro dispersible tablets of Terbutaline for rapid therapeutic action. The formulations were optimized by using design expert software all the Five formulations (F1 to F5) of Oro dispersible tablets of Terbutaline were successfully prepared using Sodium Starch Glycollate as a super disintegrants and crospovidone by direct compression method. The Formulations were evaluated for parameters like thickness, hardness, friability, in- vitro disintegration time, wetting time, water absorption ratio, and in- vitro drug release studies. Based on the % of drug release at 15 minutes shows F1 maximum of 86.8 % and 60 minutes the maximum release of 95.5 %. The formulation (F1) was subject to stability studies for 3 months by storing them at 30°C/65%RH, 35°C/70%RH and 40°C/75%RH. The Results of physical appearance, hardness, friability, disintegration test, and % drug release have shown that there was no significant change at different storage conditions.

KEYWORDS: Oro dispersible tablets, terbutaline, stability, direct compression method.

INTRODUCTION

Fast disintegrating or Oro dispersible tablets (ODTs) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing. This novel type of delivery system offers convenience for treatment-resistant population who have difficulty in swallowing unit oral dosage form, namely tablets and capsules. These formulations are particularly beneficial to paediatric and geriatric patients, also during travelling where excess of water is not there. These fast-disintegrating tablets can also be designed in such a way that the drug is absorbed through the buccal and oesophageal mucosa as the saliva passes into the stomach. Due to this, the bioavailability of the drug is greater than that observed conventional dosage form. Furthermore, the side effects caused by first pass metabolism may be reduced.

These tablets dissolve, disintegrate or disperse in saliva within a few seconds. Super- disintegrants like cross-linked sodium carboxymethylcellulose (Croscarmellose), cross-linked polyvinylpyrrolidone (Crospovidone), sodium carboxymethyl starch (Sodium starch glycolate) etc. are used in this formulation.

Drugs released from ODTs get absorbed from the oral cavity, pharynx and oesophagus as the saliva passes down into the stomach. So as a result, the bioavailability of Oro-dispersible tablets is more than the other conventional oral tablets like film coated tablets, enteric coated tablets, multiple compressed tablets, sugar coated tablets, etc., Dispersion of therapeutic drug in the saliva in oral cavity causes pregastric absorption of drug which avoids first-pass hepatic or intestinal metabolism that increases bioavailability. The European Pharmacopoeia defined the term “Oro disperse” as that the tablet can be placed in the mouth where it disperses rapidly before swallowing.[5,6]

Terbutaline is a member of the class of phenylethanolamines that is catechol substituted at position 5 by a 2-(tert-butylamino)-1-hydroxyethyl group. It has a role as a beta-adrenergic agonist, an EC 3.1.1.7 (acetylcholinesterase) inhibitor, an anti-asthmatic drug, a bronchodilator agent, a sympathomimetic agent, a tocolytic agent and a hypoglycemic agent. It is a member of phenylethanolamines and a member of resorcinols.

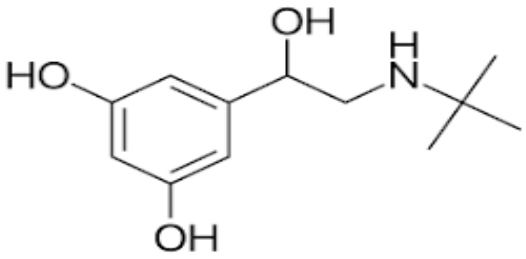

Figure 1: Chemical Structure of Terbutaline.

EXPERIMENTAL WORK

MATERIAL AND METHODS

Terbutaline sample collected from the Spira labs Hyderabad, all the polymers used in the formulations were purchased formth SD fine chemicals ltd. All the instruments used in the work was calibrated.

METHODOLOGY

Drug-excipient compatibility studies

Compatibility of the drug and formulation is an important pre-requisite for formulation. Therefore, DSC and FTIR spectral analysis of pure drug Terbutaline and physical mixture of Terbutaline and super disintegrant were carried out. FTIR spectra of physical mixtures (1:1) of Terbutaline and various excipients, as well as the formulation were performed to find out any possible drug excipient interaction by ATR method using FTIR spectrophotometer.[72]

FTIR spectrum: The FTIR spectrum was recorded. Infrared Spectrophotometer (Shimadzu). The pellets were prepared on KBr press using mixture of sample and KBr in about1:10 ratio. The spectrum was recorded over the wave no. range of 4000 to 400 cm.

Pre formulation evaluation

Angle of Repose:
Bulk Density:
Tapped Density:
Carr's Index:
Haunser's ratio

STANDARD CURVE OF TERBUTALINE

Preparation of phosphate buffer pH 6.8

6.805 g of monobasic potassium phosphate was dissolved in water and to that solution, 22.4 ml of 0.2 M sodium hydroxide solution was added and the volume was made 1000 ml with water.

Stock solution

Terbutaline, 10 mg was accurately weighed and it was dissolved in 10 ml of phosphate buffer at pH 6.8.Then the volume was made up to 100 ml with phosphate buffer pH 6.8. The above solution is served as stock solution.

Dilutions

From the stock solution 1 ml was taken and it was diluted with phosphate buffer of pH 6.8 to 10 ml to get 10 µg/ml. Similarly, 2 ml, 3 ml, 4 ml, 5 ml and 6 ml was taken from stock solution and diluted with phosphate buffer of 10 ml of pH 6.8 to get 20, 30, 40, 50, 60 µg/ml respectively. The absorbance of the resulting solutions is determined at nm using UV-visible spectrophotometer.

DIRECT COMPRESSION

It is the simplest and most cost-effective tablet manufacturing technique for ODTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tableting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugar-based excipients.

The manufacture of tablets by direct compression involves comparatively few steps and they include

1. Premilling of formulation ingredients (active drug substance and excipients)
2. Mixing of active drug substance with the powdered excipients (including the lubricant)
3. Compression of the mixed powders into tablets.

Excipients used in the manufacture of tablets by direct compression method

The production of tablets by direct compression necessitates the inclusion of certain grades of excipients to achieve the correct powder flow and compression properties. These grades have typically been prepared by specific methods (such as spray-drying, wet granulation, slugging, crystallization) to achieve the correct physicochemical properties (e.g., particle size/distribution and flow properties).

Direct compression excipients used in the manufacture of tablets include

Diluents/fillers

Examples of diluents used in direct compression technology include
Spray-dried lactose (Lactopress Spray-Dried, Lactopress Spray-Dried 250, Pharmatose DCL 11, Pharmatose DCL 14)
Dicalcium phosphate (e.g., Encompress grades)Mannitol (granular or spray-dried grades, e.g., Pearlitol)
Sorbitol- Microcrystalline cellulose (e.g., Avicel pH-102)

Compression aid

Examples of commonly used compression aids include Microcrystalline cellulose (e.g., Avicel pH-102).

a. Super Disintegrants

- Pregelatinized starch (e.g., Starch 1500)
- Sodium starch glycolate (e.g., Explotab, Primogel)
- Croscarmellose sodium (e.g., Ac-Di-Sol)
- Crospovidone (e.g., Polyplasdone XL, Polyplasdone XL-10, Kollidon CL, Kollidon CL-M).

b. Lubricants and glidants

The types of lubricants and glidants used in the manufacture of tablets by direct compression method are similar to those used in other tablet manufacture methods and include:

- Lubricants (e.g., magnesium stearate, stearic acid, sodium stearyl fumarate)
- Glidants (e.g., talc, colloidal silicon dioxide).

EVALUATION OF FAST DISSOLVING TABLETS
Weight variation
Friability
% Friability = 1- (loss in weight / Initial weight) X 100

Hardness (Crushing strength)
Wetting time: Determination of wetting time is also important. It also helps in studying the effect of various excipients in the disintegration of the tablet. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 ml of phosphate buffer pH 6.8. A tablet as put on the paper, and the time for complete wetting was measured.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation:

R= Wa – Wb/ Wb x 10

Where, Wb = weight of the tablet before water absorption Wa = weight of the tablet after water absorption

Disintegration time
Drug Content
Preparation of standard stock solutions: Terbutaline was weighed (100mg) and transferred to 100ml volumetric flasks and make up the volume up to the mark with distilled water and the final concentration of solution containing 1000 µg/ml of LSS.

Preparation of working solutions Aliquot from the stock solution of Terbutaline was appropriately diluted with distilled water to obtain working standard of Terbutaline.

Selection of detection
Wavelength Solution of drug was scanned over the range of 200-400 nm. It was observed that the drug showed considerable absorbance at 277 nm for Terbutaline was selected as the wavelength for detection.

$$\text{Drug content (mg)} = \text{concentration} \times \text{dilution factor}$$

$$\%\ \text{Drug content} = \frac{\text{drug content (mg)}}{\text{label claim (}-\text{mg)}}$$

In vitro dissolution test: In vitro dissolution study has to be performed by using USP type II Apparatus (paddle type at 50 rpm. Phosphate buffer pH 6.8, 900 ml is mainly used as dissolution medium which is required to maintain at 37±0.5°C. Aliquot of (10ml) dissolution medium is required to withdraw out at specific time interval (2min) and then it is required to subject for process of filtration. The amount of drug dissolved was determined by UV Spectrophotometer by measuring the absorbance of the sample. Three trials of each batch were performed and average % drug release with standard deviation was calculated and recorded.

RESULTS AND DISCUSSION
Drug excipient compatibility study
Standard curve of Terbutaline
Table 1: Standard curve of Terbutaline.

S NO	Concentration (µg/ml)	Absorbance (nm)
1	10	0.054
2	20	0.095
3	30	0.15
4	40	0.207
5	50	0.257
6	60	0.307
7	70	0.357

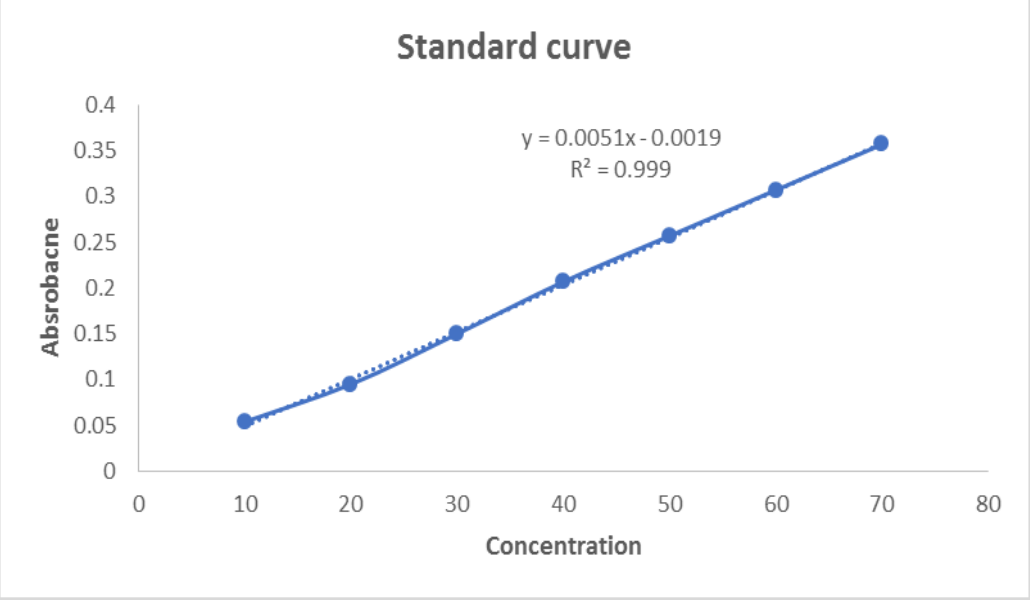

Figure 2: Calibration Curve For Terbutaline.

PREFORMULATION STUDIES

Flow properties of the drug:

Table 2: flow properties of drug.

Bulk density	0.283	-
Tapped density	0.342	-
Angle of repose	45	Passable
Compressibility index (%)	23%	Passable
Hausner's ratio	1.33	Passable

Flow properties of the formulation

Table 3: flow properties of drug.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio	Flow ability
F 1	0.283	0.363	38.50	19.9%	1.25	Fair
F 2	0.289	0.357	39.59	19.7%	1.25	Fair
F 3	0.284	0.360	41.10	19.9%	1.25	Passable
F 4	0.286	0.356	39.88	20%	1.246	Fair
F 5	0.288	0.254	38.45	21%	1.26	Fair

EVALUATION OF ORO DISPERSIBLE TABLETS

Post compression parameters: Hardness and Friability

Table 4: Post compression parameters.

Formulation	Hardness (kg/Cm^2)	Friability (%)
F 1	3.83	0.63
F 2	3.99	0.75
F 3	3.91	0.88
F 4	3.90	0.69
F 5	3.96	0.81

Table 5: weight variation.

Tablet no	F 1	F 2	F3	F 4	F 5
1	0.107	0.1029	0.1043	0.1025	0.1089
2	0.1039	0.1025	0.1033	0.0997	0.1088
3	0.1083	0.0993	0.105	0.098	0.112
4	0.1046	0.1045	0.1056	0.1001	0.1025
5	0.109	0.0989	0.0996	0.1043	0.108
6	0.101	0.1112	0.1043	0.096	0.1073
7	0.103	0.1029	0.1113	0.1115	0.098
8	0.108	0.1027	0.1115	0.1109	0.1058
9	0.097	0.1055	0.1036	0.1078	0.1049
10	0.1075	0.1002	0.1099	0.1088	0.1949
11	0.1033	0.1036	0.1056	0.1008	0.1059
12	0.1045	0.1047	0.1023	0.1043	0.1994
13	0.0989	0.1089	0.1028	0.1056	0.0978
14	0.1085	0.0993	0.1112	0.1130	0.1025
15	0.1053	0.0996	0.1048	0.0986	0.1028
16	0.0999	0.1025	0.1013	0.1003	0.1078
17	0.1053	0.1089	0.1075	0.1027	0.0014
18	0.1044	0.1113	0.1081	0.1054	0.0019
19	0.1058	0.1029	0.0996	0.1027	0.1089
20	0.1003	0.0990	0.1088	0.1079	0.0973
Result	Pass	Pass	Pass	Pass	Pass

Table 6: Wetting time (secs), Water absorption ratio (%), Disintegration time (secs) % Drug content.

Formulation	Wetting time (secs)	Water absorption ratio (%)	Disintegration time (secs)	% Drug content
F 1	0.47	50	16	99.1
F 2	0.52	47	22	95.4

F 3	0.55	51	19	96.8
F 4	0.57	45	26	95.9
F 5	0.51	53	21	96.7

Dissolution profile of F1-F5

Table 7: Dissolution profile of F1-F5.

Sampling time	% Amount of drug Release (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	18	13.5	12.8	14.1	12.5
4	27.2	24	28.2	26.46	26.6
6	40	39.9	44.2	40.5	37.6
8	51.2	52.3	54.9	47.3	46.5
10	62.26	62.6	58.53	54.3	51.06
15	86.8	77.2	81.2	77	74.8
30	91	85.33	86.16	84.5	78.9
45	93.8	91	91.13	88.4	81.03
60	95.5	92.1	95	92.2	87.5

n = 3

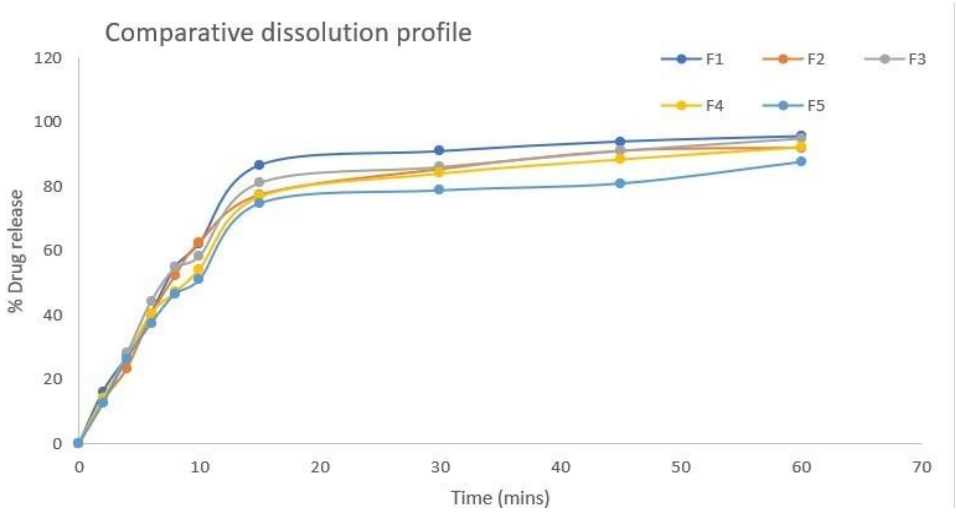

Figure 3: Comparative Dissolution profile of F1 to F5.

Summary

The present study is an attempt to develop and formulate fast dissolving tablets of Terbutaline with super disintegrants which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action and to prevent the first pass metabolism of Terbutaline .

In this system direct compression was used, sodium starch glycollate (SSG), were used as super disintegrants, talc is used as flow promoter, magnesium stearate was used as lubricant, mannitol as sweetener and diluent.

The drug- polymer compatibility was confirmed by FTIR studies. The results obtained by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients.

Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps.

The post-compression parameters like the thickness, hardness, friability and in vitro disintegration time, wetting time, water absorption ratio and in vitro drug release were carried out and the values were found to be within limits.

The Formulation F1 shows the maximum dissolution rate and % of drug release was found to be 95.5%. The other Formulations shows F2 - 92.1% F3 – 95% F4 – 90.9% and F5 shows the lesser release 87.5%

Based on the % of drug release at 15 minutes shows F1 maximum of 86.8 % and 60 minutes the maximum release of 95.5 %.

CONCLUSION

The present work was concluded that to develop a stable, safe, fast release and convenient Oro dispersible tablets of Terbutaline for rapid therapeutic action. The formulations were optimized by using design expert software all the Five formulations (F1 to F5) of Oro

dispersible tablets of Terbutaline were successfully prepared using Sodium Starch Glycollate as a super disintegrants and crospovidone by direct compression method. The Formulations were evaluated for parameters like thickness, hardness, friability, in- vitro disintegration time, wetting time, water absorption ratio, and in- vitro drug release studies. Based on the % of drug release at 15 minutes shows F1 maximum of 86.8 % and 60 minutes the maximum release of 95.5 %. The formulation (F1) was subject to stability studies for 3 months by storing them at 30°C/65%RH, 35°C/70%RH and 40°C/75%RH. The Results of physical appearance, hardness, friability, disintegration test, and % drug release have shown that there was no significant change at different storage conditions.

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