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Research Article

Formulation and Evaluation of Terbutaline Sulfate Fast Dissolving Tablets

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Abstract

In the present fast dissolving tablets of Terbutaline sulfate are designed by novel co processing to disintegrate rapidly. The co-processed superdisintegrants were prepared by solvent evaporation method with blend of crospovidone and fenugreek seed mucilage. Fast dissolving tablets (FDT) were prepared by direct compression method. These tablets were evaluated for weight variation, hardness, thickness, disintegration time, water absorption ratio, friability and dissolution. It was found that the total maximum amount of drug from the optimized batch CPF5 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 fenugreek seed mucilage are superior to physical mixture and used in Terbutaline sulphate fast dissolving tablets formulation.

Keywords: Terbutaline sulfate, superdisintegrants, novel co processing, crospovidone and fenugreek seed mucilage

Introduction :

The development of an appropriate dosage form for older people, children, bed ridden patients, mentally retarded, uncooperative, nauseated patients been widely desired as it become difficult for these patients to swallow conventional tablets (Kremzar L. *et al*, 1998) Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration, leading to high level of patient compliance (Kremzar L *et al*, 1998, Hanawa T, 1995). To the make the best use of oral cavity we are going for ODTs production to ensure maximum absorption via mucous membrane.

Novel Co-Processing

Major challenge for tablets and capsule manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (> 70%) contain excipients at higher concentration than active drug.

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In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability. One such approach for improving the functionality of excipients is co-processing of two or more excipients

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. Co-processing excipients leads to the formulation of excipient granules with superior properties compared with physical mixtures of components or individual components5. The concept of formulating fast dissolving tablets (FDT) of metoclopramide hydrochloride (anti-emetic) using co-processed superdisintegrants which increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective (at low concentration of superdisintegrants) direct compression technique..[1-3]

Materials and Methods

Procurement of drug and excipients

The drug, excipients, chemicals/ reagents and equipments used for various experiments are enlisted as follows:

Terbutaline sulphate was gifted by ZCL chemicals Ltd. Mumbai, Maharashtra, India. fenugreek seed mucilage and Crospovidone were purchased from Yarrow chemicals Mumbai, Maharashtra and are of AR grade

Development of Analytical Method for Estimation of Terbutaline Sulfate

Scanning of Terbutaline Sulfate

Determination of maximum wavelength (λmax) of terbutaline sulfate was done by preparing three different dilutions of stock solutions (1mg/mL) and scanned those dilutions under UV-Vis Spectrophotometer.

Preparation of Calibration Curve of Terbutaline Sulfate in Phosphate

Buffer Saline (PH – 7.4)

Dissolved 50 mg of terbutaline sulfate in 50 mL of Phosphate Buffer Saline, PH-7.4(stock solution). The stock solution of terbutaline sulfate is diluted with Phosphate Buffer Saline(PBS), PH-7.4 to make solution

of 10, 20, 40, 60, 80 and 100 µg/mL. The prepared solutions were then examined under UV-Vis Spectrophotometer at λmax of 276 nm for absorbance and then calibration curve is plotted between absorbance and concentration[4] (Dobetti, L et al., 2000).

Preparation of Co-processed Superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and fenugreek seed mucilage (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use. 5-8

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). [5] (Gohel MC et al,2007)

Table-1: 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	55	55	55	55	55	55	55
Aspartame	10	10	10	10	10	10	10
Superdisintegrants (CP+FSM)	-	15	15	15	15	15	15
Aerosil	45	45	45	45	45	45	45
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 feugreek seed mucilage in different Ratios (1:1, 1:2, 1:3), **CP(F5,F6,F7)-** Co-processed Superdisintegrants of crospovidone and feugreek seed mucilage in different Ratios (1:1,1:2, 1:3), **CF F1-** Control formulation (without superdisintegrants), **CP –** Crospovidone, FSM : feugreek seed mucilage

Evaluation of Fornmulated fast dissolving Tablet [9-13]:

Hardness:. Hardness is amount of strength of tablet to withstand mechanical shocks of handling in manufacture, packaging and shipping and tablet should be able to withstand reasonable abuse when in the hand of consumer . Hardness of tablet was evaluated by Monsanto hardness tester or Pfizer tester. Hardness was measured in kg/cm^2 and for tablet it is above 4-6 kg/cm^2 .

Friability: This test is applicable to compressed tablets and is intended to determine the physical strength of tablets. It was evaluated by Roche Friabilator with 100 revolution rotating 25 per minute for 4 min by using 6 tablets. According to USP tablet should have limit < 1%. for acceptance

Following formula was used to calculate the friability.

%F=1- (loss in weight/initial weight)100

Weight variation:

Weight variation was calculated as per method describe in USP.20 tablets was weighed individually and the average wias calculated.The requirements are met if the weight of not more then 2 of tablets differ by more then percentage listed in the tablet and no tablets differ by in weight by more then double that percentage.

Wetting Time and Water Absorption Ratio (R)

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$R = 100 \times (w_a - w_b)/ w_b$

Where w_b and w_a were tablet weights before and after water absorption, respectively.

Disintegration test

Disintegration test was measured using disintegration test apparatus. One tablet was placed in each of the six tubes of disintegration test apparatus. I.P. method was followed without using disc. The time required for complete disintegration of tablet in each tube was determined using stop watch.

Content of Active Ingredients:

Prepared tablets were accurately weighed and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to dose (250mg) of the prepared tablet was transferred in to a volumetric flask and the drug was dissolved in the solvent. The contents of the flask were sonicated for 10 min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 276 nm.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

In-vitro Dissolution studies of tablet using dissolution apparatus:

In vitro dissolution studies of the promising fast dissolving tablets of Terbutaline Sulphate, control and commercial conventional tablet formulations were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10, 15&30 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 mm membrane filter disc and analyzed for drug content by measuring the absorbance at 276 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

Results and discussion

Development of Analytical Method for Estimation of Terbutaline Sulfate

Scanning of Terbutaline Sulfate

The scanning of Terbutaline Sulfate was performed to determine the wavelength at which Terbutaline Sulfate absorb maximum of UV radiation when the solution of Terbutaline Sulfate was exposed to UV radiation. The Scanning of Terbutaine Sulfate was done by placing solutions of different dilutions (100, 10, 1 µg / mL) of stock solution (1 mg/mL) in Phosphate Bufer Saline pH-7.4 under UV Spectrophotometer. The results of scanning of Terbutaline Sulfate are shown in the Table 8.3.

The results of scanning of terbutaline sulfate at 100, 10, 1 µg / mL showed that the solution of the 100 µg / mL has maximum absorbance at wavelength of 276 nm. This wavelength is selected as λmax for the determination of absorbance of different concentration of solutions

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

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

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

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

The result of in-vitro drug release of Pure drug (Terbutaline Sulfate) shown in Table 3.

Table 3 : 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)

Evaluation of Formulated fast dissolving Tablet:

Fast dissolving tablets of Terbutaline Sulphate were prepared using co-processed superdisintegrants and physical mixture of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluents to enhance mouth feel. A total of six formulations and control formulation CP_0 (without superdisintegrant) were designed. As the blends were free flowing (angle of repose $<30^0$ and Carr's index <15% Table 3), tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 99 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.96-3.13 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 44-85% and 30-106 sec respectively. Among all the designed formulations, formulation, CPF5 was found to be promising and displayed an *in vitro* dispersion time of 22 sec, which facilitates their faster dispersion in the mouth.

Overall, the formulation CPF5 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and feugreek seed mucilage) was found to be promising and has shown an *in vitro* dispersion time of 22 sec, wetting time of 30 sec and water absorption ratio of 86% when compared to the formulation PMF2 containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) which shows 36sec, 38 sec, 76% and control formulation (CPF1) which shows 99 sec, 106 sec and 46% values respectively for the above parameters

In-vitro Dissolution studies of tablet using dissolution apparatus:

In vitro dissolution studies on the promising formulation CPF5, control (CFF1) 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 , $t_{50\%}$, $t_{70\%}$ 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)

Where, CFF1 is control formulation, CPF5 is promising fast dissolving tablet formulation, PMF2 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, CCF is conventional commercial tablet formulation, $Time_5$ is percent drug released in 5 min, $Time_{10}$ is percent drug release in 10 min, $Time_{15}$ is percent drug release in 15 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

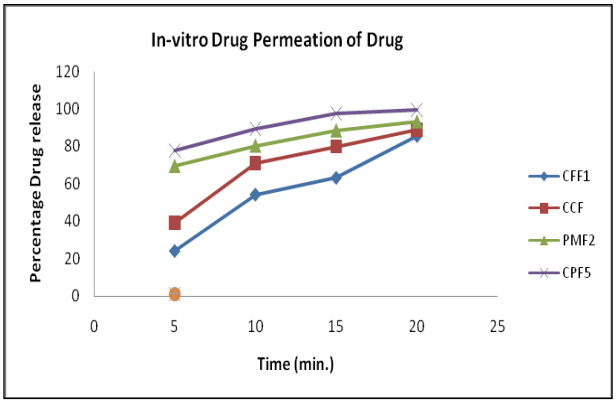

FIGURE 1 Dissolution rate profiles of CFF1 control formulation, CCF conventional commercial formulation, CMF2formulation containing 1:1 physical mixture of

crospovidone and fenugreek seed mucilage,CPF5 promising formulation in pH 6.8 phosphate buffer

TABLE 4 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 5 :*IN Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Formulation code	Parameters					
	$Time_5$	**$Time_{10}$**	**$Time_{15}$**	**t50%**	**t70%**	**t90%**
CFF 1	24.34 %	54.23%	63.12%	9.32 min	13.10 min	>30 min
CCF	39.00%	71.07%	80.05%	6.65 min	9.5 min	29 min
PMF2	69.56%	80.34%	88.43%	4.01 min	5.21 min	16 min
CPF5	77.56%	89.34.63%	99.45%	2.32 min	3.48 min	9.48 min

Reference

1. Allen, LV. And Wang, B. 2001. Process for making a particulate support matrix for making a rapidly dissolving dosage form. US Patent 6207199.
2. Ammanage A., et al ; Taste Masking of Dicyclomine Hydrochloride by Polymer Carrier System and Formulation of Oral Disintegrating Tablets; Asian J Pharm Clin Res, 2011, 4(1), 35-40
3. Anand, Vikas., kataria, Mahesh., kukkar Vipin., Saharan, Vandana. and Choudhary, Kumar. Pratim. 2007. The latest Trends in the taste assessment of pharmaceuticals. Drug discovery today. 12(5/6): 257-265.
4. Dobetti, L., Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug Dev. Ind. Pharm., 2000; 25: 571–581.
5. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets of salbutamol sulphate: A novel drug delivery system. Indian Drugs.2004; 41:592-8.
6. Gohel MC et al. Preparation and Assessment of Novel Co-processed Superdisintegrant Consisting of Crospovidone and Sodium Starch Glycolate: A Technical Note. AAPSPharmSciTech. 2007;8(1):Article 9:p.E1-E7
7. Habib, W., Khankari, RK. and Hontz, J., Fast-dissolve drug delivery systems. Crit Rev Ther Drug Carrier Sys., 2000; 17:61–72.
8. Kalpesh G., et al, Formulation and characterization of fast disintegrating tablet of aceclofenac by using sublimation method, Int J Pharm Sc Drug Res; 2011; 3(1), 19-22
9. Microemulsion-basedmedia as novel drug delivery systems. Adv.Drug Deliv. Rev., 2000; 45; 89–121.
10. Ravi K., et al, design and characterization of Aceclofenac Mouth Dissolving Tablets by effervescent formulation approach, Der Pharmacia Lettre; 2010; 2(1); 220-236
11. Sanoferjan AM, Nanjundaswamy NG., Formulation and evaluation of β-cyclodextrin complexes of tenoxicam. Ind. J. of Pharm. Sci., March 2000; 62(2): 119-121.
12. Yoshio k., et al, Effect of preparation method on properties of orally disintegrating tablets made by phase transition, Int. J. Pharm, 2008; 355; 87-92
13. Yoshio k., et al, Effect of type of lubricant on the characteristics of orally disintegrating tablets manufactured using by phase transition, Eur. J. Pharm. Bio., 2008; 69; 986-992