

DEVELOPMENT AND EVALUATION OF FAST DISSOLVING DRUG DELIVERY SYSTEM

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Abstract

In the present fast dissolving tablets of Terbutalinesulfate 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.

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Keywords: Terbutaline sulfate, super disintegrate, Fast Dissolving Tablet.

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 coprocessed 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 Methods⁴⁻¹³

Preparation of Co-processed Superdisintegrant :

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 60° C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use.

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)

Evaluation of Formulated fast dissolving Tablet⁹⁻¹³:

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/cm² and for tablet it is above 4-6 kg/cm² .

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 was 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 $37 \pm 0.5^\circ\text{C}$ 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.

Results and Discussion

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 CP₀ (without superdisintegrant) were designed. As the blends were free flowing (angle of repose <30° 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/cm². 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 CSF2

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 CNF5, 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 CNF5 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, CNF5 is promising fast dissolving tablet formulation, CSF2 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, CCF is conventional commercial tablet formulation, Time₅ is percent drug released in 5 min, Time₁₀ is percent drug release in 10 min, Time₁₅ 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

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Table-1:Formula for different batches of Terbutaline Sulphatetablets.

Ingredients	CFF1	PM F2	PM F3	PM F4	CPF5	CPF6	CPF7
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+CS)	-	15	15	15	-	-	-
Superdisintegrants (HR+FSM)	-	-	-	-	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, CS(F2,F3,F4) - Physical Mixture of croscopvidone and croscarmellose sodium in different Ratios (1:1, 1:2, 1:3), CN(F5,F6,F7)- Co-processed Superdisintegrants of Hibiscus rosa and feugreek seed mucilage in different Ratios (1:1,1:2, 1:3), CF F1- Control formulation (without superdisintegrants), HR – Hibiscus rosa mucilage, FSM : feugreek seed mucilage, CP – croscopvidone, CS- croscarmellose sodium

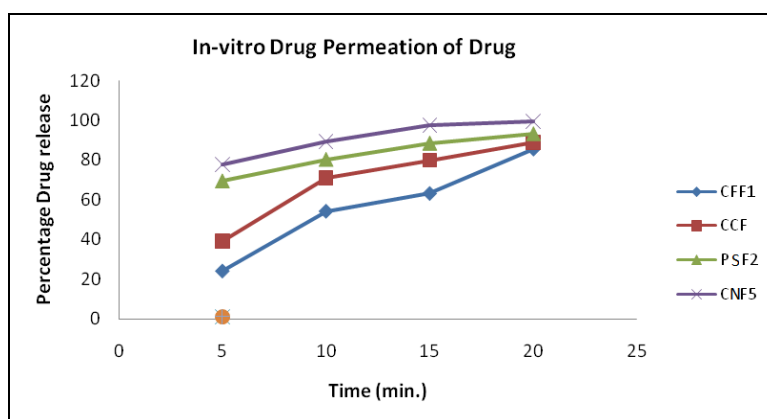


Figure 1 Dissolution rate profiles of Formulation

CFF1 control formulation, CCF conventional commercial formulation, CSF2 formulation containing 1:1 physical mixture of crospovidone and croscarmellose sodium, CNF5 promising formulation containing 1:1 physical mixture of Hibiscus rosa and fenugreek seed mucilage

TABLE 2. Evaluation of Terbutaline Sulphate FDT Formulations

Parameters	Formulation Code						
	CFF1	CSF2	CS F3	CS F4	CN F5	CN F6	CN 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
<i>In vitro</i> 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 3 *IN Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Formulation code	Parameters					
	Time ₅	Time ₁₀	Time ₁₅	t _{50%}	t _{70%}	t _{90%}
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