JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and Development of Fast Disintigrating Tablets using Cimetidine as a Model Drug

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ABSTRACT:

The present study was aimed towards the formulation and eveluation of fast disintegrating tablets by direct compression technology using Cimetidine as a model drug. Fast disintegrating tablet of Cimetidine was formulated using three Superdisintegrates in different concentrations i.e. 4%w/w, 6%w/w and 8%w/w and one disintegrates having concentration i.e. 4%w/w, 6%w/w and 8%w/w like Cross carmellose sodium, Crospovidone, Sodium Starch Glycolate. All the batches were prepared by direct compression method using the Cadmach Single punch tablet compression machine using 14X32 mm flat punch. Disintegration time and drug release were taken as the basis to optimize the immediate release tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study Selected formulation was subjected to stability studies for thirty days which showed stability with regards to release pattern.

KEYWORDS: Fast Disintegrating Tablet, Cimetidine, Superdisintegrants, Direct Compression Technology

Article history:
Received 17 March 2012
Accepted 26 May 2012
Available online 13 Jun 2012

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INTRODUCTION:

Recent advances in novel drug delivery systems (NDDS) aim to formulating a dosage form of drug molecules for convenient administration and to achieve better patient compliance.[1] One important innovation in this direction is the development of fast disintegrating oral dosage form that disintegrate fast/quickly before swallowing, upon contact with recipient tongue or buccal mucosa with little amount of water or with saliva.[2,3] The target of these new oral disintegrating dosage forms have generally been pediatric, geriatric, bedridden and developmentally disabled patients and also patients with persistent nausea, who are in traveling, or who have little or no access to water are also good candidates.[1]

Fast disintegrating tablets have all the advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients. Fast disintegrating tablets also have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form.[4,5,6]

Because the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention and increased bioavailability of drugs are possible. Because the pre-gastric drug absorption avoids the first-pass metabolism, the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.[7]

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste-masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the FDT formulations.[1]

Because FDTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.[1] H_2 receptor antagonist, Cimetidine occurs as a white to pale-yellow granular substance with a bitter taste and a sulfur-like odor.[8] It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of Cimetidine is 300 mg 4 time a day or 800 mg once daily. The effective treatment of erosive esophagitis requires administration of 300 mg of Cimetidine 4 times a day. [9,10,11,12] As we know Cimetidine is bitter in taste so to provide this drug in a more accessible and patient compliant form and to overcome such problems, in the present study it was decided to mask the bitter taste and formulate into a rapid disintegrating tablet. The physicochemical properties of Cimetidine are water soluble drug having plasma half life of 2 hrs, make it suitable candidate to formulate buccal disintegrating tablets.[13]

MATERIALS AND METHODS

Materials

Cimetidine, Crospovidone, Sodium, Starch Glycolate, Ac-Di-Sol, Aspartame were supplied by Aan Pharmaceuticals, Ahmedabad. All the ingredients received were of pharmaceutical grade and were used as received. Other materials and solvents used were of analytical grade.

Table.1 Formulation of fast disintegrating tablet of Cimetidine

Ingredients (mg)	A-01	A-02	A-03	A-04	A-05	A-06	A-07	A-08	A-09	A-10	A-11	A-12	A-13
Cimetidine	300	300	300	300	300	300	300	300	300	300	300	300	300
Crospovidone XL 10	10	20	30	-	-	-	-	-	-	10	10	-	10
Ac-Di-Sol	-	-		10	20	30	-	-	-	-	10	10	10
Sodium Starch Glycolate	-	-		-	-	-	10	20	30	10	-	10	-
Avicel PH112	167.5	157.5	147.5	167.5	167.5	147.5	167.5	157.5	147.5	165	165	165	165
Pineapple Flovour	5	5	5	5	5	5	5	5	5	5	5	5	5
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5	5
Aerosil	10	10	10	10	10	10	10	10	10	1	1	1	1
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	4	4	4	4
Total Weight	500	500	500	500	500	500	500	500	500	500	500	500	500

Table 2 Evaluation of blend properties of Cimetidine fast disintegrating tablets

BATCH NO	B.D	T.D	H.R	C.I
A/01	0.47	0.57	1.20	16.12
A/02	0.54	0.68	1.23	17.79
A/03	0.52	0.67	1.26	20.49
A/04	0.43	0.62	1.30	22.24
A/05	0.50	0.69	1.27	17.81
A/06	0.57	0.61	1.28	21.17
A/07	0.49	0.52	1.21	20.89
A/08	0.41	0.60	1.35	22.22
A/09	0.46	0.55	1.32	22.28
A/10	0.58	0.67	1.28	18.47
A/11	0.46	0.43	1.1	12.29
A/12	0.42	0.58	1.22	16.08
A/13	0.51	0.66	1.17	11.40

Methods

Preparation of Tablet

Fast disintegrating tablets of Cimetidine was prepared according to Table No 1. All the excipients without magnesium stearate and Aerosil were mixed uniformly followed by addition of magnesium stearate and Aerosil[14]. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner ratio (Table 2). After evaluation of powder blend the tablets were compressed with Cadmach single punch compression machine using 12 mm flat faced punches.

Evaluation of Tablet

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, wetting time, drug content and in vitro dissolution study (Table 3).

Thickness: Thickness of tablets was determined using Vernier caliper. Five tablets from each batch were used and an average value was calculated.

Hardness: For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester (Cadmach).

Friability: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated, after revolution the tablets were dusted and weighed.

Uniformity of weight: Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.[15,16,17]

Table 3: Evaluation of Cimetidine fast disintegrating tablets

Batch No.	Avg. weight (mg)	Avg. Thickness (mm)	Avg. Hardness (N)	Disintegration Time (Secs)	% Assay (W/W)	% Friability
A/01	500.12	5.79	80.50	40-45	99.57	0.60
A/02	500.49	5.30	90.10	32-35	99.48	0.87
A/03	500.34	5.12	85.70	37-42	99.19	0.57
A/04	502.80	5.43	80.10	40-43	100.20	0.78
A/05	502.30	5.45	83.70	30-37	99.70	0.46
A/06	502.12	5.42	80.60	35-42	99.50	0.38
A/07	501.62	5.80	82.50	43-48	99.63	0.54
A/08	501.34	5.78	90.90	35-40	99.99	0.68
A/09	503.49	5.94	75.50	32-40	99.87	0.76
A/10	501.12	5.43	80.78	25-30	99.39	0.37
A/11	500.15	5.14	80.20	22-25	99.98	0.25
A/12	501.71	5.47	80.40	28-32	99.78	0.33
A/13	501.43	5.50	80.20	22-28	100.05	0.31

Disintegration test: The *in vitro* disintegration studies were carried out using Digital Tablet Disintegration Test Apparatus (Veego). One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±2 0C. The basket was then moved up and down through a distance of 5 to 6 cm. at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded [18].

Dissolution Studies: The release rate of Cimetidine from fast disintegrating tablets was determined using IP Dissolution Test Apparatus Type II (basket type). Tablets were placed in a dry basket at the beginning of each test. Lower the basket in the dissolution medium and apparatus was run at 50 rpm, The dissolution test was performed using 900 ml of 0.1 M HCL, at 37± 0.50C and 50 rpm. Ten-milliliter aliquots were withdrawn at time intervals of five minute. This was maintained at same temperature, was added to the bulk. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 343 nm using UV spectrophotometer Shimadzu 1700. Cumulative percentage drug release was calculated using an equation obtained from a standard curve [19].

RESULTS AND DISCUSSIONS

Evaluation of Blend Properties

Bulk densities of various formulations were found in between 0.41- 0.57 g/cm3. CI values varied from 16% to 22%. From these values it was evident that all these blends had excellent

flow properties. All the formulation shows the good blend properties for direct compression and hence tablets were prepared by using direct compression technology.

Evaluation of Rapidly Disintegrating Tablet

Tablet Thickness: Thickness values for of all tablets were in the range of 5.13-5.94 mm.

Uniformity of Weight: Weight variation values for prepared tablets were found within the specifications of I.P Limit.

Hardness: The hardness was uniformly maintained and it was found to be within 3-3.5 Kg/cm2.

Friability: Percent friability was less than 1% in the entire formulations and the values obtained lies within 0.394 to 0.525.

Disintegration test:

Among CIMETIDINE FDTs prepared using 2%, 4% and 6% Crospovidone XL 10, CIMETIDINE FDTs containing 4% Crospovidone XL 10 shows the faster disintegration time (32-35 Secs) and % drug release (78.3 % in 15 mins).

Among CIMETIDINE FDTs prepared using 2%, 4% and 6% Croscarmellose sodium, CIMETIDINE FDTs containing 4% Croscarmellose sodium shows the faster disintegration time(30-37 Secs) and % drug release (84.6 % in 15mins).

Among CIMETIDINE FDTs prepared using 2%, 4% and 6% Sodium starch Glycolate, CIMETIDINE FDTs containing 6% Sodium starch Glycolate shows the faster disintegration time (32-40 Secs) and % drug release (91.2 % in 15 mins).

Among CIMETIDINE FDTs prepared using different amount of Croscarmellose sodium, Crospovidone XL 10, Sodium starch Glycolate, , CIMETIDINE FDTs containing 2% Croscarmellose sodium and Crospovidone XL 10 shows the faster disintegration time (22-25 Secs) and % drug release (100.8 % in 15mins) as compared to other superdisintegrating agents. The decreasing order of superdisintegrating agents in term of disintegration time was as follows:

Croscarmellose sodium > Crospovidone XL 10 > Sodium starch Glycolate

The increasing order of superdisintegrating agents in term of % drug release was as follows:

Croscarmellose sodium > Sodium starch Glycolate > Crospovidone XL 10

When CIMETIDINE FDTs prepared using optimum concentration of both superdisintegrating agents, there was increased in disintegration time and increased in % drug release, so addition of two different superdisintegrating agents in one batch was shows effective results as compared to using one superdisintegrating agents in individual batch.

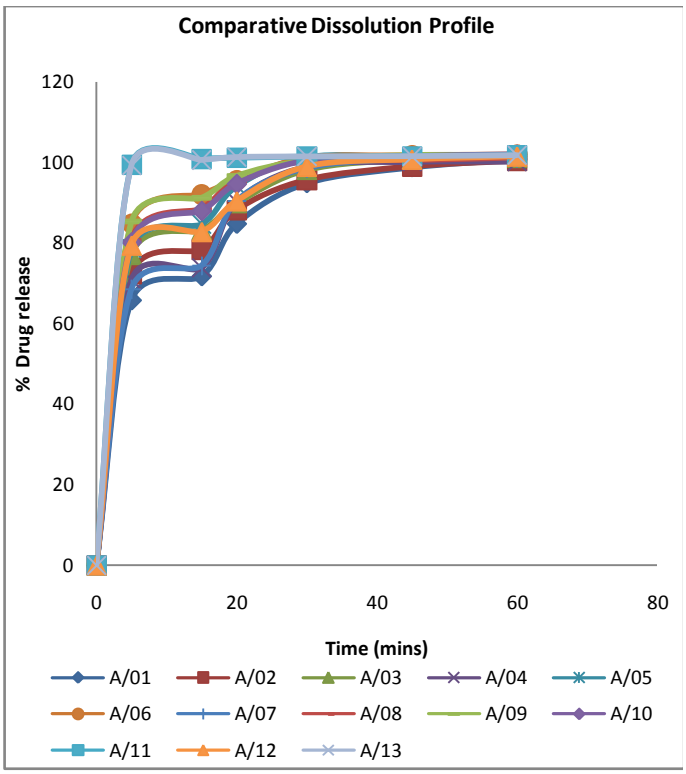

Figure 13 In-vitro Dissolution Study

CONCLUSION

From the above result it was concluded that for the preparation of CIMETIDINE FDTs, the combination of two different superdisintegrating agents were used to achieve maximum % Drug release and minimum Disintegration time

But the higher concentration of superdisintegrating agents in some batches was ineffective for the preparation of FDTs of CIMETIDINE.

Finally Crospovidone XL 10 and Croscarmellose sodium shows the better results as compared to the other superdisintegrating agents for the praparation of CIMETIDINE FDTs.

So, Fast disintegrating tablet of antipyretic, analgesic & inflammatory drug CIMETIDINE is prepared by wet granulation method. FDTs emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Disintegrating Tablet. Tablets prepared by DCPT040 used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and anti-inflammatory.

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