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Formulation and Evaluation of Mouth Dissolving Sublingual Tablets of Cimetidine to Treat Abdominal Cramps

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ABSTRACT: *The main objective of the current study is to formulate and evaluate the mouth dissolving sublingual tablets of H2 blockers by Direct Compression Method. All the Formulations were prepared by using three super disintegrants. All the formulations were evaluated for post-compression parameters like hardness, weight variation, friability, wetting time etc. The formulations were selected based on their disintegration time, hardness, wetting time and were subjected to in-vitro dissolution studies. The final results obtained showed that the disintegration time was less due to the use of super disintegrants and at the same time the tablets showed good hardness. This might be due to high wicking and capillary action with burst effects of Crosspovidone and more gelling tendency than sodium starch glycolate and CrossCarmellose sodium. Among all the six formulations F4 was selected as the best formulation.*

KEYWORDS: *Cimetidine, Disintegrants, Mouth dissolving sublingual tablet, Super disintegrants, abdominal cramps.*

I. INTRODUCTION:

Abdominal cramps are common symptoms associated with transient disorders or serious disease. Diagnosing the cause of abdominal pain can be difficult, because many diseases can cause these symptoms such as- Gastroenteritis, Diarrhea, Constipation, Irritable bowel syndrome, food poisoning, Heartburn, Indigestion, Gastro esophageal reflux Disease (GERD). Mouth Dissolving tablets are those which disintegrate or dissolve rapidly without water within few seconds in the mouth. According to the European pharmacopoeia these mouth dissolving tablets should dissolve or disintegrate in less than 3 minutes. Examples: Ibuprofen, Ketoprofin. Sublingual tablets are those which come in contact with the mucous membrane beneath the tongue and the drug diffuses through the sub lingual mucosa because the connective tissue beneath the epithelium contains a profusion of capillaries, the substance then diffuses into them and enters the venous circulation. Examples: Buprenorphine HCl, Abstral.

People frequently experience difficulty in swallowing conventional dosage forms such as tablet when the water is not available Example: In motion sickness, sudden incidence of coughing during the common cold and in allergic condition. For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity without the need of water have attracted the attention of the researchers. Mouth dissolving tablets are not only formulated for people who have difficulties in swallowing but also are best for active people. A solid dosage form that dissolves and disintegrates rapidly in the oral cavity, resulting in solution or suspension without the need of water are known as fast dissolving tablets. The quicker the drug gets dissolved, quicker will be the absorption and onset of clinical effect. Mouth Dissolving Tablets were introduced in the year 1980's since then this formulation has become popular in the pharmaceutical field. Fast dissolving tablets are an also known as mouth-dissolving tablet which melts-in mouth; Oro-dispersible tablets; porous tablets; rapimelts; quick dissolving etc. Their rising importance was underlined recently when the European pharmacopoeia had adopted the term "Orodispersible tablet" as a tablet to be placed in the mouth where it disperses rapidly prior to swallowing. According to the European pharmacopoeia, the oro- dispersible tablets should disperse/disintegrate in less than three minutes of time. The basic approach in development of fast dissolving tablets is the use of superdisintegrants like cross linked carboxymethyl (crosscarmellose), sodium starch glycolate (primogel, explotab), poly vinyl pyrollidone (polyplasdone) etc, which afford faster disintegration of the tablets after placing on the tongue, thereby releasing the drug in the saliva. The bioavailability of most of the drugs may be increased by the absorption of drug in the oral cavity and also due to pre-gastric absorption of saliva that contains dispersed drugs and that pass down into the stomach.

II. MATERIALS AND METHODS:

Cimetidine was obtained from Leo Chemicals Bangalore. Crosscarmellose sodium, Crosspovidone was gifted by BAL Pharma, Bommasandra, Bangalore. Sodium starch glycolate, Polyvinylpyrrolidone were obtained from Loba Chemie Pvt Ltd, Mumbai. Mannitol, Saccharine sodium, Magnesium stearate, Talc, Isopropyl alcohol was obtained from S.d. fine solution Ltd, Mumbai. All the Chemicals were used as received.

Method: Fast dissolving tablets of Cimetidine were prepared by using different superdisintegrants like sodium starch glycolate (SSG), crosspovidone (CP) and crosscarmellose sodium (CSS) by direct compression method. Binders like Poly vinyl pyrrolidine (PVP), microcrystalline cellulose (MCC) were used for the preparation of the tablets. Sweeteners like sodium saccharine and mannitol were used. The composition of all the six formulations was made using different super disintegrants like CP, CSS, SSG. All the ingredients were uniformly blended in a porcelain mortar and were passed through sieve no.80 to get fine particles; the resultant mixture was compressed into tablets on a 10 station single punch rotary Tablet compression machine *Rimek minipress-11 MT, Karnavati eng.ltd*. A flat faced punch of 10mm in diameter was used for tableting, the compression force of the machine was adjusted to obtain the hardness of about 3.04 – 4.2 kg/cm^2. All the formulations F1 – F6 containing 200 mg of the drug were prepared and each tablet weighing approximately 450mg was punched.

Preformulation Evaluation: Fourier transform infrared spectroscopy (FT-IR) study was conducted using Shimadzu-IRFEINTY-1 to identify the purity of the drug and test the compatibility of the drug with the excipients. The melting point was carried out by capillary method using programmable melting point apparatus.

Pre-compression Evaluation: The flow properties of the blend were characterized in terms of Angle of repose, Carr's index and Hausner's ratio.

Evaluation of Cimetidine mouth dissolving sublingual tablets: The tablets were tested for its physical appearance, thickness and diameter using vernier callipers; weight variation using Digital weighing balance Sartorius- GE612; Hardness using Pfizer hardness tester; Friability using Roche friabilator. Drug content; Wetting time; In-vitro dispersion time; In-vitro disintegration and dissolution time were also determined.

Drug content estimation: 5 tablets from each of the formulations were triturated in a mortar. An accurately weighed powder equivalent to 10 mg of the drug was taken into a 50 ml volumetric flask and the volume made up with simulated salivary solution (SSS) pH 7.4. From the above flask 1 ml was pipette out into a100 ml volumetric flask and made up the volume using SSS pH 7.4. Absorbance of this solution was measured at 233 nm in UV-spectrophotometer. The drug content was determined using the following formula:
Drug content (in mg) = (Absorbance * Dilution factor)/ Slope * 1000

Wetting time: A piece of tissue paper doubly folded was placed in a Petri plate having an internal diameter of 8.5 cm containing 6ml of SSS pH 7.4. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds.

In vitro dispersion time:
The tablet was placed in 10 ml SSS pH 7.4. The time required for complete dispersion of the tablet was measured in seconds.

In-vitro disintegration time:
The in-vitro disintegration time of the tablet was determined using disintegration test apparatus. One tablet was placed in each of the 6 tubes of the basket a disc was added to each tube and the apparatus was run using pH 7.4 simulated saliva fluid maintained at 37±2°C as the immersion liquid. The time in seconds taken for complete disintegration of the tablet was noted when no palpable mass was remaining in the apparatus and recorded.

Dissolution test: The Dissolution was performed using USP II Paddle type apparatus maintaining 50 rpm using SSS pH 7.4 as dissolution medium at 37 ± 0.5°C. 1ml of the sample was withdrawn at regular intervals of 30 seconds and made up to 10 ml using SSS pH 7.4, filtered and analyzed for the amount of drug release maintaining sink condition.

Stability studies: The stability studies were carried out for a period of 3 months in the Stability chamber (Rimek). The tablets were packed in suitable packaging and stored under the following conditions as prescribed

by the ICH guidelines [40°C ± 2°C and 75 ± 5% RH (Q1C)]. The tablets were withdrawn periodically with an interval of 30 days and analyzed for Hardness, Disintegration, Dissolution, wetting time, drug content etc.

III. RESULTS AND DISCUSSION

TABLE 1: FORMULATION TABLE OF MOUTH DISSOLVING SUBLINGUAL TABLETS OF CIMETIDINE (F1-F6)

Ingredients (mg)	F_1	F_2	F_3	F_4	F5	F6
Cimetidine	200	200	200	200	200	200
SSG	8	12	-	-	-	-
CP	-	-	8	12	-	-
CCS	-	-	-	-	8	12
MMC	50	50	50	50	50	50
PVP	10	10	10	10	10	10
Sodium Saccharin	6	6	6	6	6	6
Magnesium Stearate	6	6	6	6	6	6
Talc	6	6	6	6	6	6
Mannitol	166	164	160	164	160	164
Total Weight(mg)	450	450	450	450	450	450

TABLE 2: POST-COMPRESSION STUDY DATA

Formulation code	Weight variation (mg) ±SD	Hardness (kg/cm2) ±SD	Friability (%loss) ±SD	Thickness (mm)	Drug content (%)
F1	452.5±7.68	4.20±0.31	0.302±0.04	5.16±0.15	96.02
F2	451.0±9.67	4.04±0.38	0.316±0.02	5.22±0.15	97.44
F3	449.0±5.22	4.08±0.17	0.303±0.00	4.16±0.05	98.72
F4	450.5±1.19	3.04±0.16	0.194±0.04	4.06±0.05	99.54
F5	450.0±9.01	3.64±0.38	0.303±0.04	4.43±0.11	96.77
F6	450.0±10.7	3.8±0.836	0.234±0.03	4.53±0.05	97.67

TABLE 3: RESULTS OF IN-VITRO EVALUATION OF MOUTH DISSOLVING SUBLINGUAL TABLETS OF CIMETIDINE

Formulation code	Wetting time (sec) ±SD	Disintegration time(sec) ±SD	Dispersion time(sec)±SD
F1	683.33±5.77	98.33±3.51	545.66±1.15
F2	726.66±1.52	92.33±2.51	528.33±4.04
F3	386.66±2.88	56.0±3.60	109±3.60
F4	356.66±2.88	44.66±2.15	96.66±1.52
F5	486.66±2.88	79.66±1.52	140.33±4.16
F6	471.66±2.88	73.66±1.52	116.66±3.05

TABLE 4: RESULTS FOR DISSOLUTION PROFILE OF MOUTH DISSOLVING SUBLINGUAL TABLET OF CIMETIDINE

Formulation code	%CDR after 30sec ±SD	%CDR after 60sec ±SD	%CDR after 90sec ±SD	%CDR after 120sec ±SD	% CDR after 150sec ±SD
F1	20.79±0.03	39.07±0.02	55.73±0.03	68.87±0.02	84.72±0.02
F2	23.23±0.03	41.23±0.01	58.84±0.02	71.46±0.03	86.88±0.03
F3	24.20±2.29	44.07±0.03	61.95±0.03	74.03±0.03	91.77±0.05
F4	26.75±0.02	45.30±0.05	63.72±0.03	79.31±0.04	99.48±0.06
F5	23.10±0.05	42.16±0.04	59.70±0.01	75.24±0.04	87.31±0.05
F6	24.58±0.02	45.94±1.14	62.36±0.05	78.21±0.05	90.29±0.06

TABLE 5: RESULTS OF STABILITY STUDIES OF BEST FORMULATION (F4)

Parameters	**Values at temperature (40° ± 2°c & 75 ± 5% RH)**		
	30 Days	**60 Days**	**90 Days**
Hardness	4 kg/cm^2	4.2kg/cm^2	3.8kg/cm^2
Drug content	98.34%	99.09%	99.39%
Wetting time	80 sec	79 sec	69 sec
Dispersion time	Sec	Sec	Sec
Disintegration time	16 sec	15 sec	12 sec
Dissolution	98.17% after	99.20% after	100.83% after
(% CDR)	150 sec	150 sec	150 sec

Figure 1: Comparison of wetting time

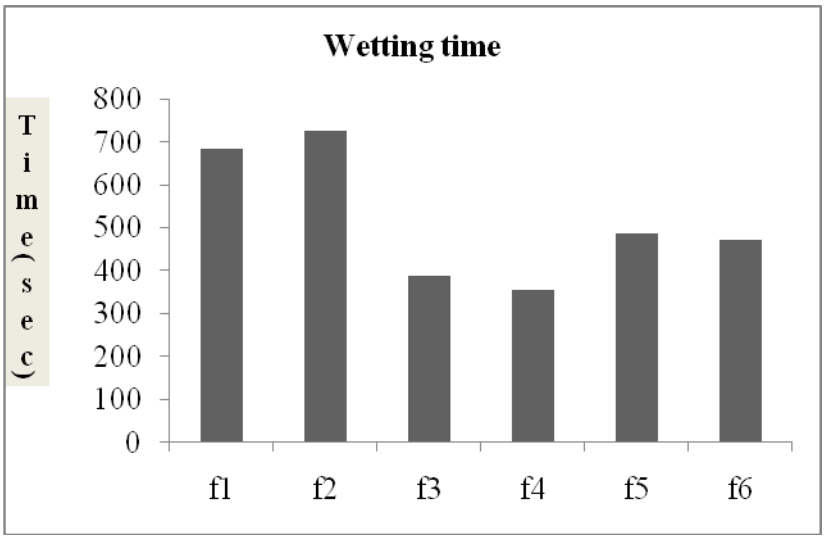


Figure 2: Comparison of disintegration time

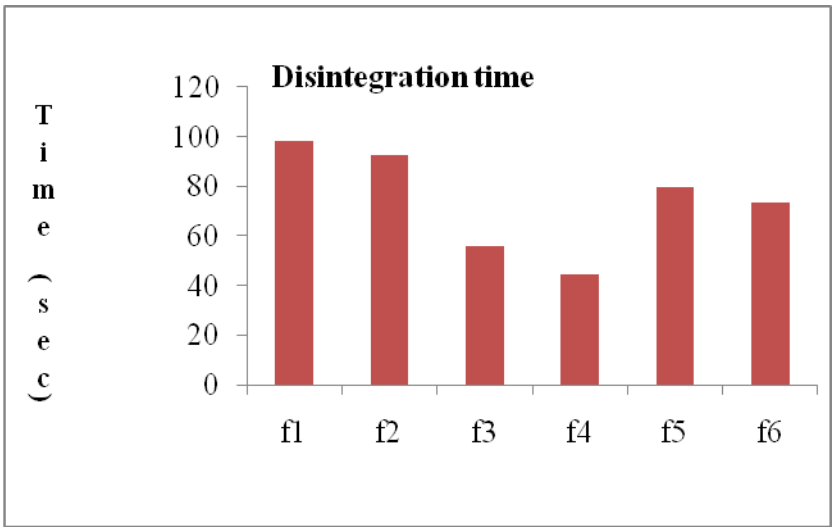


Figure 3: Comparison of dispersion time

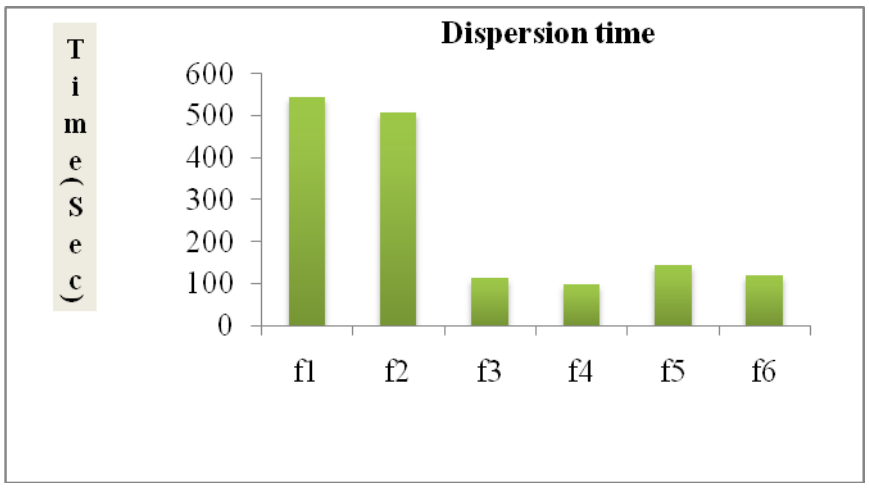


Figure 4: Comparison of Dissolution profile of the tablets of Cimetidine F1-F6.

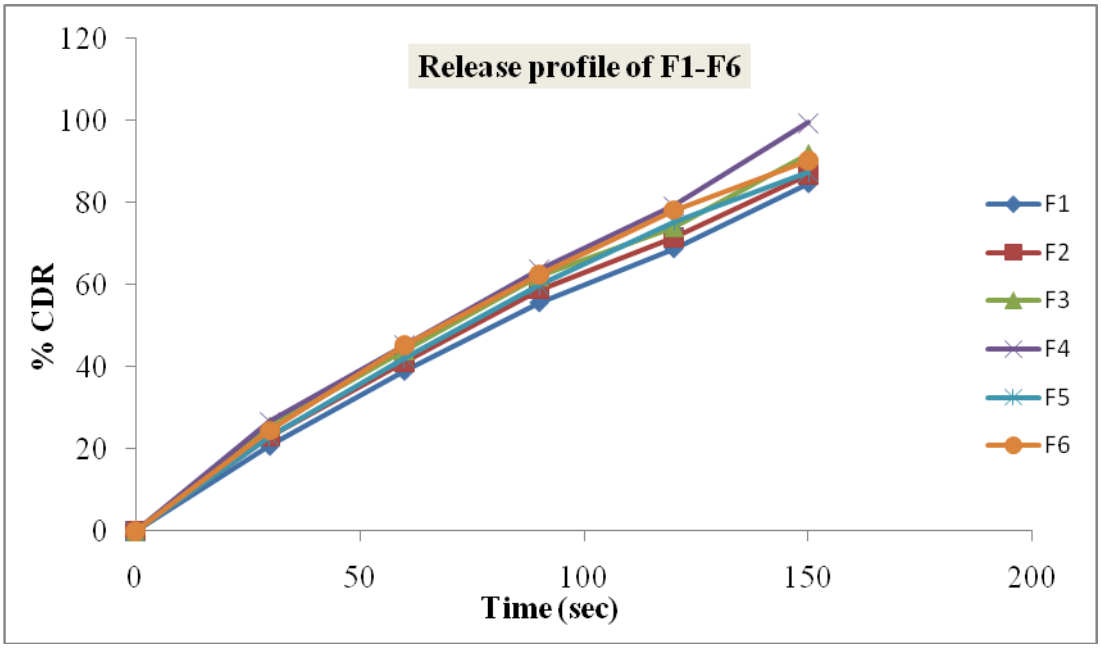
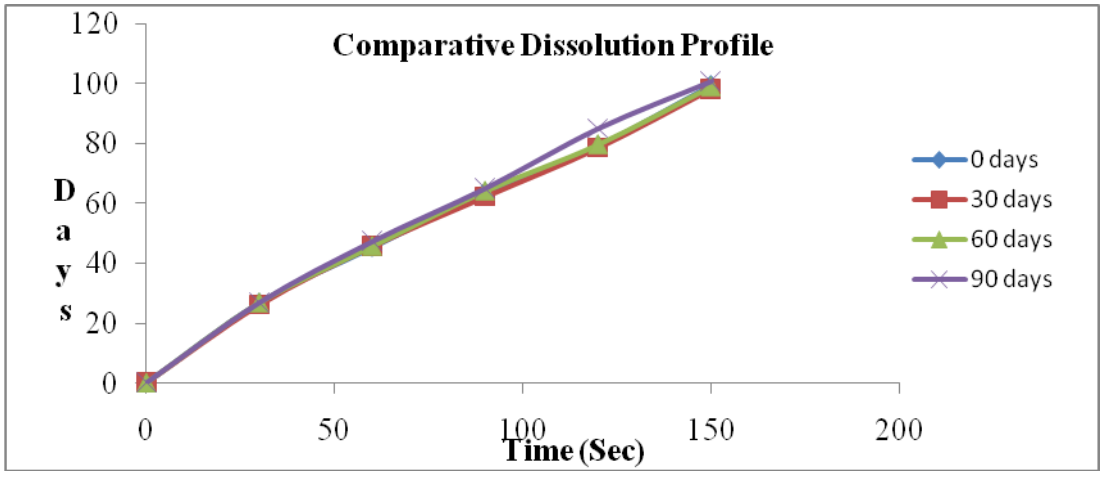


Figure 5: Comparison of dissolution profile of F4 before and after stability studies.



IV. DISCUSSION

Mouth dissolving sublingual tablet were prepared by direct compression method using Cimetidine as the model drug to relief abdominal cramps. The bindners used were poly vinyl pyrrolidone; fast disintegrants were sodium starch glycolate, crosspovidone, micro crystalline cellulose; diluents used were micro crystalline cellulose; glidant used were talc, magnesium stearate; sweetners used were sodium saccharine and mannitol. The pre-compression parameters like Carr's index, Hausner's ratio and angle of repose were determined. The post-compression parameters were determined for all the formulations F1-F6 and the values were found to be within the limits. The tablet thickness ranged between 4.066 – 5.166 mm, hardness ranged between 3.04- 4.2 kg/cm^2,the friability ranged between 0.194- 0.302 %, the drug content was found to be in the range of 96.02 - 99. 54%. The stability studies for the optimized formulation F4 was performed for three months, at 40 ± 2°C, 75 ± 2% RH and the results showed that the formulation was found to be stable.

V. CONCLUSION:

Cimetidine belongs to the class of drugs used in the treatment of gastric ulcers, peptic ulcers, and gastro-esophageal reflux disease. Orally it is rapidly absorbed within half an hour, but within 10 minutes after i.m. and 2 minutes after i.v. injection and its action lasts for about 4-6 hours. In the present study an attempt was made to formulate cimetidine as mouth dissolving sub lingual tablets to obtain a quick relief from the abdominal cramps using different superdisintegrants. Six formulations each containing 200 mg of the drug and 3 different super disintegrants in different ratios were prepared. The results of pre formulatory and post formulatory studies obtained were satisfactory. The study also showed that, the super disintegrant crosspovidone showed better disintegrating property than crosscarmellose sodium and sodium starch glycolate. Further the formulation no.F4 was found to be optimum and was subjected to 3 months stability studies. The results of the stability studies showed that the formulation was stable. The Mouth dissolving sublingual tablets of Cimetidine show quicker action, instant release, maximum absorption, better bioavailability at pH 7.4 and quick relief from the stomach cramps. They offer more compliance for patients who are unable to swallow, the elderly, stroke victims, comatose patients and patient who refuse to swallow such as paediatric, geriatric & psychiatric patients. However a Good mouth feel property is an essential criteria in the formulation of this dosage form which was obtained by using sweeteners.

VI. ACKNOWLEDGEMENT:

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