Innovat International Journal Of Medical & Pharmaceutical Sciences, 2017; 2(4)

www.innovatpublisher.com

ISSN - 2456-8694

Research Article

PREPARATION AND *IN VITRO* CHARACTERSATION OF FAST DISINTIGRATING TABLETS OF CIMETIDINE

[1] N.M.VAGEESH [*], [2]RAMYA SRI SURA, [1]D RAFIAN , [1]U.GOVINDAMMA

[1]St.Johns college of pharmaceutical sciences, yerakota, yemmiganur , Kurnool (Dist) , Andhra Pradesh.[2]Department of Pharmaceutics, OU Ph.D Scholar, Osmania University, Hyderabad. *Email: vageeshpharma@gmail.com*

Received 2016.05.20-Accepted 2017.05.27

Abstract

Objectives: Oral administration is the most popular route while compared to other dosage forms due to ease of ingestion, pain avoidance, versatility and most importantly patient compliance but one important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in patients particularly pediatric and geriatric patients.

Method: The need for one of the non-invasive delivery system i.e., Fastly disintegrating tablets persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

Results: The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits

Conclusion: In the present work, an attempt has been made to develop Fast Disintegration Tablets of Cimetidine. Kollidon, Vivasol, Tulsion 330 were used to super disintegrants. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits

.

Key word: Cimetidine, Kollidon, Vivasol, Tulsion 330 and Fast Disintegration tablets.

INTRODUCTION

The Fast route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used Fast dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.

For these reasons, tablets that can rapidly dissolve or disintegrate in the Fast cavity have attracted a great deal of attention. Fast dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active.

An Fast disintegrating tablet (FDT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the.

US FDA defined FDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Recently European Pharmacopoeia used the term 'Fastdispersible tablet' as a tablet that is to be placed in the Fast where it disperses rapidly before swallowing.

Fast disintegrating tablets are also called as Fast-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, Fastdispersible tablets, rapimelts, pFastus tablets, quick dissolving tablet .

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Fast Disintegrating Tablets (Rosie et al., 2009).Three main points stand out in the final guidance:

- FDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the FDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an FDT for both patients and regulators.
- The guidance serves to define the upper limits of the FDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an FDT.

NEED TO DEVELOP FDT

The need for one of the non-invasive delivery system i.e., Fast disintegrating tablets persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

PATIENT FACTORS

Fast disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow tablets and capsules with an 8-oz glass of water. These include the following:

- Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.

A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic[3-4].

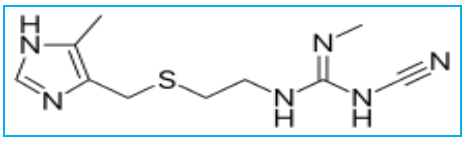
A patient with persistent nausea, who may be journey, or has little or no access to water

Pharmacodynamics

Cimetidine is a histamine H_2-receptor antagonist[5-13]. It reduces basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine,

insulin, betazole, or pentagastrin. It is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Cimetidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of Cimetidine include an increase in gastric bacterial flora such as nitrate-reducing organisms.

Chemical structure :



Chemical name: 1-cyano-2-methyl-3-[2-[(5-methyl-1H-imidazol-4-yl)methylsulfanyl]ethyl]guanidine

Adverse effects/Side effects: Headache, dizziness, somnolence, diarrhea**.**

Mechanism of action: Binds to an H_2-receptor located on the basolateral membrane of the gastric parietal cell, blocking histamine effects. This competitive inhibition results in reduced gastric acid secretion and a reduction in gastric volume and acidity.

Therapeuticefficacy/Indications: For the treatment and the management of acid-reflux disorders (GERD), peptic ulcer disease, heartburn, and acid indigestion.

Aim

The aim of the present study was Cimetidine Fast dissolving tablets formulated by employing Superdisintegrants

Objectives

Oral administration is the most popular route while compared to other dosage forms due to ease of ingestion, pain avoidance, versatility and most importantly patient compliance but one important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in patients particularly pediatric and geriatric patients.

The patient acceptability and compliance are important in design of the novel drug delivery system, one such drug delivery system is Fast dissolving tablets (FDTs) which has gained acceptance and popularity in the recent times.

The prime factor for the commercial success of Fast dissolving tablets is, because of its significant impact on patient compliance of all age groups. These dosage forms are designed in such a way that they disintegrate or dissolve in patient's Fast upon contact with saliva, within seconds without aid of water leading to faster onset of action.

The main objective of this study is to Fast dissolving tablets of Cimetidine using Super disintegrants.

Plan of work

1. Literature review
2. Selection of drug
3. Analytical method development
   a. Calibration curve (standard graph)
4. Preparation of Fast Dissolving Cimetidine tablet formulations
5. Characterization of micrometric properties
   - Angle of repose
   - Bulk Density
   - Tapped Density
   - Carr's Index (CI) (%)
   - Hausner's ratio
   - Characterization of tablets for the following parameters
   - Weight variation
   - Thickness
   - Hardness
   - Friability
   - Disintegration time
   - Content uniformity
6. *In vitro* dissolution studies
7. Drug- Excipients interactions
   - FT-IR

METHODOLOGY

Buffer Preparation

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Analytical method development for Cimetidine

Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 6.8 phosphate buffer UV spectrum was taken using Lab India Double beam UV/VIS spectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

Construction of standard graph

100 mg of Cimetidine was dissolved in 100 ml of pH 6.8 phosphate buffer to give a concentration of 1mg/ml (1000 µg/ml). From the above standard solution (1000 µg/ml) 1ml was taken and diluted to 100ml with pH 6.8 phosphate buffer to give a concentration of 0.01mg/ml (10µgm/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml,1ml were pipette out in 10 ml volumetric flask and the volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 2, 4, 6, 8 and 10 µg/ mL respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 238 nm.

Formulation Development

- Drug and different concentrations of super Disintegrates (Cross povidone **(CP)**, Crosscaramellose Sodium (**CCS)**, Sodium Starch Glycolate (**SSG)**) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar or 15 minutes.
- The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

The tablets were prepared by using Tablet Compression machine. The hardness of the tablets was maintained as 2.0 to 3.5 kg/cm2.Evaluation of tablets:

Pre compression parameters

Measurement of Micromeritic Properties of Powders

Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

Table 1. Formulation table showing various compositions

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cimetidine	200	200	200	200	200	200	200	200	200
Kollidon	16	20	24	-	-	-	-	-	-
Vivasol	-	-	-	16	20	24	-	-	-
TULSION 30	-	-	-	-	-	-	16	20	24
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Aerosil	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
Aspartame	2	2	2	2	2	2	2	2	2
Total weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Table 2. Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

Table 3. Scale of Flowability

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
Nov-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.

Bulk density = M/V_0 …….. (2)

M = Powder mass

V_0 = apparent unstirred volume

Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula.

Tapped density=M/V_f ..... (3)

M =weight of sample power taken

V_f =tapped volume

Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100 …….. (4)

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation.

Thickness

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Drug content

The content of drug carried out by five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 233 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

Dissolution test of Cimetidine tablets

Drug release from Cimetidine tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at a temperature of 37^0 C and at a speed of 50 rpm.

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15,20, 30, 45, 60minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies:

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

RESULTS AND DISCUSSION

Preparation Of Calibration Curve Of Cimetidine :

The Regression Coefficient was found to be 0.999 which indicates a linearity with an equation of y = 0.071x - 0.000. Hence Beer - Lambert's law was obeyed.

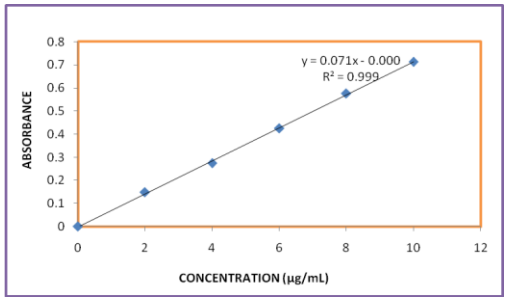


Fig.2: Evaluation of pre - compression parameters of powder blend

Table4: Calibration curve data of Cimetidine

Concentration (µg/mL)	Absorbance
0	0
2	0.148
4	0.275
6	0.425
8	0.576
10	0.712

Table 5: Evaluation of pre-compression parameters of powder blend

Formulation Code	Angle of Repose (°)	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	25.01	0. 59	0.57	14.03	1.16
F2	26.8	0. 46	0.67	16.41	1.19
F3	27.7	0. 32	0. 54	18.75	1.23
F4	25.33	0.54	0.64	15.62	1.18
F5	25.24	0.52	0.65	18.46	1.22
F6	28.12	0. 46	0. 56	15.15	1.17
F7	27.08	0.58	0.69	15.94	1.18
F8	25.12	0.48	0.67	15.78	1.18
F9	26.45	0.54	0.65	16.92	1.25

- For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters described earlier in methodology chapter.
- The bulk density of all formulations was found in the range of (0.32-0.59**)** and tapped density was in range of (0.54-0.69).
- The carr's index and hausner's ratio was calculated from tapped density and bulk density.

EVALUATIONS OF POST COMPRESSION PARAMETERS OF CIMETIDINE FDTs

Table6: Evaluation of post compression parameters of Cimetidine Fast dissolving tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (min)
F1	492	3.2	0.52	3.8	99.76	4.3
F2	500.1	3.1	0.54	3.9	99.45	4.4
F3	501.5	3.6	0.51	3.9	99.34	4.6
F4	499.4	3.4	0.55	3.9	99.87	4.8
F5	498.4	2.5	0.56	3.7	99.14	3.1
F6	497.3	2.7	0.45	3.6	98.56	3.3
F7	498.8	2.7	0.51	3.4	98.42	3.6
F8	499.7	2.8	0.49	3.7	99.65	3.7
F9	498.6	2.9	0.55	4.0	99.12	3.9

Weight variation and thickness

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above. The average tablet weights of all the formulations were noted down.

Hardness and friability

All the FDT formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown above. The average hardness for all the formulations was found to be between (2.5 to 3.6) Kg/cm^2 which was found to be acceptable.

Friability was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the FDT formulations were evaluated for their percentage friability using roche friabilator and the

results are shown above. The average percentage friability for all the formulations was between 0.45 to 0.56, which was found to be within the limit. Addition of Aerosil resulted in appreciable decrease in friability.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above. The assay values for all the formulations were found to be in the range of **(**98.42 to 99.87**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In vitro* disintegration time:** *In vitro* disintegration studies showed from 3.1 to 4.8 Minutes. The F5 Formulation showed Very Less *In vitro* Disintegration Time i.e., 3.1 Minutes.

***In Vitro* Drug Release Studies of Cimetidine**

Table7: Dissolution data of Cimetidine

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	24.50	29.37	28.96	27.68	32.37	33.41	39.36	37.79	36.83
10	33.58	38.70	35.86	35.28	49.55	39.36	55.77	45.48	46.83
15	42.18	53.47	47.10	48.61	52.97	44.63	67.78	58.01	52.31
20	47.92	63.76	58.20	52.50	59.13	65.67	72.35	67.35	59.04
30	57.22	72.56	62.30	67.13	71.70	74.74	87.43	74.64	66.04
45	64.68	79.09	68.82	72.74	81.46	77.50	92.65	80.35	79.71
60	78.17	91.22	84.84	75.73	93.66	88.98	98.62	89.65	87.43

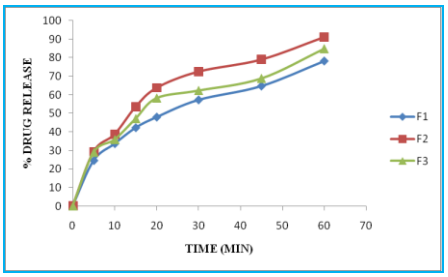


Fig.3: Dissolution profile of formulations F1, F2, and F3

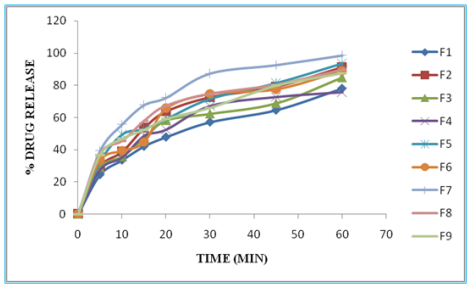


Fig. 6: Dissolution profile of all formulations F1- F9

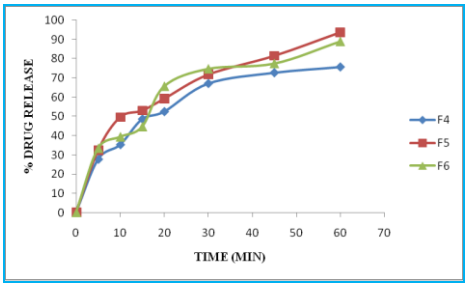


Fig. 4: Dissolution profile of formulations F4, F5, and F6

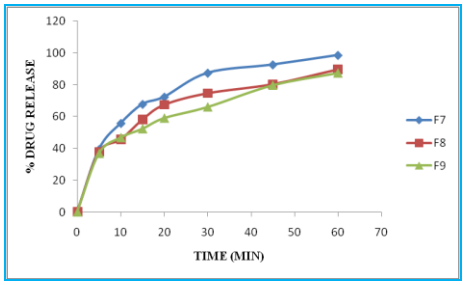


Fig. 5: Dissolution profile of formulations F7, F8 and F9

From the Table it was evident that the formulations prepared with Kollidon was showed good drug release i.e., 91.22% (F2 Formulation) in concentration of 20 mg. Formulations prepared with Vivasol showed good drug release i.e., 93.66% (F5 Formulation) in 20 mg concentration when increase in the concentration of Vivasol drug release retarded. Formulations prepared with TULSION 330 showed maximum drug release i.e., 98.62% (F7 Formulation) at 60 min in 16 mg of blend. Among all formulations F7 formulation considered as optimised formulation which showed maximum drug release at 30 min. i.e. 98.62%. TULSION 330 were showed good release when compared to Vivasol, Kollidon. Finally concluded that F7 formulation (Contains Tulsion 330) was optimised better formulation.

FTIR RESULTS

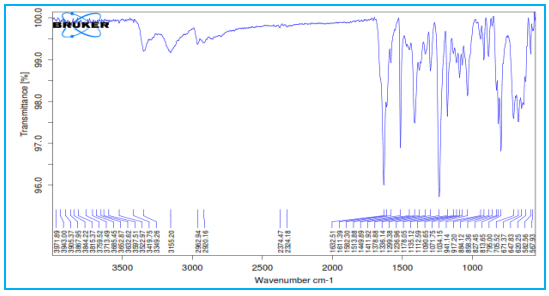


Fig.7:FTIR of Cimetidine Pure drug

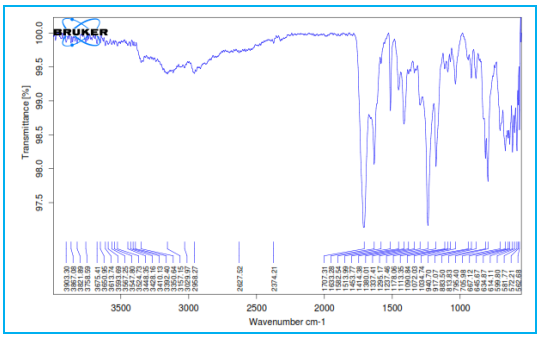


Fig. 8: FTIR of Cimetidine optimized Formulation

Cimetidine was mixed with various proportions of excipients showed no colour change, providing no drug-excipient interactions.

CONCLUSION

In the present work, an attempt has been made to develop Fast Disintegration Tablets of Cimetidine. Kollidon, Vivasol, Tulsion 330 were used to super disintegrants. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits.

From the Dissolution data it was evident that the formulations prepared with Kollidon was showed good drug release i.e., 91.22% (F2 Formulation) in concentration of 20 mg. Formulations prepared with Vivasol showed good drug release i.e., 93.66% (F5 Formulation) in 20 mg concentration when increase in the concentration of Vivasol drug release retarded. Formulations prepared with TULSION 330 showed maximum drug release i.e., 98.62% (F7 Formulation) at 60 min in 16 mg of blend. Among all formulations F7 formulation considered as optimised formulation which showed maximum drug release at 30 min. i.e. 98.62%. TULSION 330 were showed good release when compared to Vivasol, Kollidon. Finally concluded that F7 formulation (Contains Tulsion 330) was optimised better formulation.

ACKNOWLEDGEMENT

I take this opportunity to express my deep sense of gratitude to all teaching and non-teaching staff of St.Johns college of pharmaceutical sciences, yerakota, yemmiganur , Kurnool (Dist) , Andhra Pradesh India for his encouragement, guidance and inspiration to write this article and also thankfull to Sura Lab,Hyderaad,Telangana for providing necessary facilities for research work.

REFERENCES

1. Jaysweh J Harani, Dhaval A Rathod, Kantilal R Vadila, Orally disintegrating tablets, A review, *Tropial Journal of Pharm.Sciences*, 2009, 8(2), 161-172.
2. V.B.Yadav, A.V.Yadav, Liquisolid granulation technique for tablet manufacturing, an overview, *Journal of Pharmacy Research*, 2009, 2(4), 670-674.
3. Spireas S, Bolton M, Liquisolid systems and methods of preparing same, U.S. Patent 5,968,550, 1999.
4. Ellsworth AJ, Witt DM, Dugdale DC, Medical Drug Reference, Elsevier science, Missouri, 2003, 610-612.
5. Subrahmanyam, C. V. S. Dissolution. In *Textbook of Physical Pharmaceutics*, 2nd ed.; Jain, M. K., Ed.; Vallabh Prakashan: Delhi, India, 2000; pp 1, 92.
6. Ahmad Zaheer et al., Solubility enhancement of poorly water soluble drugs, a review *IJPT*, 2011, 3(1), 807-82.
7. Brahamankar D. M; Jaiswal S. B; Bioavailability and Bioequivalence, *In Biopharmaceutics and Pharmacokinetics*, A Treatise, 1st edition, Vallabh Prakashan: Delhi, India, 1995, 298-299.
8. Sekiguchi K, Obi N, Studies on absorption of eutectic mixtures, I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, *Chem. Pharm. Bull*,1961, 9, 866–872.
9. Fahmy RH, Kassem MA, Enhancement of famotidine dissolution rate through liquisolid tablet formulation: *In vitro* and *In vivo* evaluation, *Eur. J. Pharm. Biopharm*, 2008, 69, 993-1003.
10. Spiras S, Liquisolid systems and methods for preparing same, United States patent, 6,423,339 B1, (2002).
11. Ajit S. Kulkarni, Nagesh H. et al., Liquisolid Systems: A Review. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 2010, 3(1), 795-802.
12. Spireas SS, Jarowski CI, Rohera BD. Powder Solution technology, Principles and Mechanism, *Pharma Research*, 1992, 9, 1351 – 1358.
13. Liao CC, Physicochemical properties of selected powdered drug solutions, Ph.D. thesis, St.John's university, Jamaica, NY, 1983.
14. Martin AN, Swarbrick J, Cammarata A, Physical Pharmacy, Lea & Febiger, Philadelphia, 1983; 445-468.
15. Frizon Fernando, Josimar de Oliveira Eloy, Carmen Maria Donaduzzi, Márcia Lina Mitsui, and Juliana Maldonado Marchetti. "Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods." *Powder Technology* 235 (2013): 532-539.
16. Noushin Bolourchian, Mohammad Mehdi Mahboobian, and Simin Dadashzadeh. "The effect of PEG molecular weights on dissolution behavior of Simvastatin in solid dispersions." *Iranian journal of pharmaceutical research: IJPR* 12, no. Suppl (2013): 11.
17. Javadzadeh Y, Mussalrezaei L, Nokhodchi A, Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices, *Int J Pharm*. 2008, 362, 102-108.