Formulation and In Vitro Evaluation of Metoclopramide Fast-Dissolving Tablets

*Vinoda Manthati, Prabhakar Reddy Veerareddy**
Department of Pharmaceutics, University College of Pharmaceutical Sciences,
Palamuru University, Mahabubnagar, Telangana, India, 509001.
E-mail ID: headucpspu@gmail.com

ABSTRACT:
The objective of the study was to formulate and evaluate fast-dissolving tablets of Metoclopramide Direct compression method was used to formulate orally disintegrating tablets of Metoclopramide by employing different super disintegrates, polymers, and magnesium stearate (lubricant), Talc. These prepared formulations were then evaluated. Dissolution and drug content tests were performed using USP apparatus II and ultraviolet spectrophotometry, respectively. All formulations showed compliance with pharmacopeia standards. The effect of super disintegrates concentration and direct compression method on drug release profile was studied. Release profiles of F7 were found to be satisfactory compared to other formulations. F7 Formulation as processed excipient was found to be the best super disintegrates for the preparation of Metoclopramide fast dissolving tablet formulations. It has exhibited a faster disintegration time and best dissolution profile when compared to other formulations.
Keywords: Metoclopramide, Super disintegrates, Direct compression technique, in-vitro drug release studies.

I. INTRODUCTION

Oral administration is the most common route due to relief of ingestion, flexibility, pain elimination and most importantly.[2]Solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture.A tablet is well known among all oral dosage forms existing nowadays since of its comfort of self-administration, compactness and simple manufacturing.[2]Fast-dissolving tablets are useful in patients, such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active lifestyle.[3] Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients.[4] Metoclopramide is an antiemetic and gastroprokinetic agent. It gives quick relief to vomiting patients. It can diffuse and partition into the epithelium of the upper GIT. Moreover, chemotrigger zone (CTZ) is situated in the upper part of the body and ODT of metoclopramide can show quick action due to better and fast absorption from the upper part of GIT.[5]

II. EXPERIMENTAL WORK

MATERIALS

Metoclopramide was obtained from Hetero lab, HYD. Sodium starch glycolate and Croscarmellose sodium were procured fromSynpharma Research Labs, Hyderabad, and other chemicals, and the reagents used were of analytical grade.

METHODOLOGY

Drug excipient compatibility[6]

Compatibility studies of Metoclopramide and the super disintegrates were carried out by using Fourier Transform Infrared Spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450 cm-1 using a FTIR by the KBr disc method.

Formulation Development:

Table-1: Formulation table

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Metoclopramide	10	10	10	10	10	10	10	10
Cross povidone	10	20	30	40	-	-	-	-
Sodium starch glycol ate	-	-	-	-	10	20	30	40
Lactose Monohydrate	65	55	45	35	65	55	45	35
Micro crystalline cellulose	10	10	10	10	10	10	10	10

Magnesium stearate	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3
Total wt.	100	100	100	100	100	100	100	100

Procedure

Direct compression technique

Fast dissolving tablets of Metoclopramide were prepared by direct compression. All the ingredients were passed through 40- mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg using 6 mm round flat punches on 10- station rotary tablet machine (Rimek). [7]

Evaluation of tablet

Weight variation[8]

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness[9]

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness[10]

Hardness indicates the ability of a tablet to with stand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability[11]

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were deducted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity[12]

Powder equivalent of Metoclopramide was dissolved in phosphate buffer pH 6.8. Sufficient dilutions were made to obtain 10 mcg/ml solution. Absorbance of the resulting solution was measured using a T60 model UV/VIS spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated. Procedure was repeated by using four more tablets from the same formulation and the average value of all five tablets was calculated.

Wetting time[13]

A piece of tissue paper folded twice was placed in a small Petri dish containing ten milliliters of distilled water and water-soluble die. A tablet was placed on the paper and the time required for complete tablet wetting was measured. Complete wetting can be taken as the time at which colored water covered the entire tablet.

In- Vitro Release study[14]

The release rate of Metoclopramide from fast dispersible tablets was determined using dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 as a dissolution medium, at 37±0.5oC and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time interval (minutes). The samples were filtered through a 0.45m membrane filter. Absorbance of these solutions was measured using a instrument T60 model UV/VIS spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Kinetics of drug release studies [15]

The quantitative elucidation of the values obtained in the dissolution study is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related to the microspheres. For

understanding the mechanism of drug release and release rate kinetics of the drug 45 from dosage form, the Invitro drug dissolution data of optimized formulations obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix and Korsmeyer-Peppas models.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

Q0 - Qt = K0t

Arrangement of equation yields: Qt = Q0 + K0t

Where Qt is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution (most times, Q0 = 0)

and K0 is the zero-order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

First order Kinetics

The equation for first order release is given below

Log Qt = log Q0+ K1t/2.303

Where Qt is the amount of drug released in time t,

Q0 is the initial amount of drug in the solution

and K1 is the first order release constant.

A graph of the decimal logarithm of the released amount of drug versus time will be linear. Microspheres following this dissolution profile release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

Higuchi described drug release as a diffusion process based on the Fick's law, square root time dependent. The simplified Higuchi equation is represented as

Qt=Kt ½

Where Qt = amount of drug released in time t,

K = Higuchi's constant

A linear relationship between amount of drug released (Q0 versus square root of time (t½) is observed if the drug release from the microspheres is diffusion controlled.

Korsmeyer-Peppas model

This mathematical model, also known as the Power Law, has been used, very frequently; to describe the drug release from several different pharmaceutical modified release dosage forms. The Korsmeyer-Peppas model relates drug release exponentially to time. It is described by the following equation

Mt/M∞ =atn

Where ‘a’ is a constant incorporating structural and geometric characteristics of microspheres, ‘n’ is the release exponent, indicative of the drug release mechanism, and the function of ‘t’ is Mt/ M∞ (fractional release of drug).

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared disintegration tablets of Metoclopramide were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2oc and refrigerator 2-8oc for a period of 90 days.[16]

III. RESULTS AND DISCUSSION

FT-IR Spectrum of Metoclopramide

All the formulations were uniform in drug content and the FTIR spectra of Metoclopramide and its fast disintegrating tablets are identical. The principle FTIR absorption peaks of Metoclopramide fast dissolving tablets were observed and found to be identical with the spectra of Metoclopramide pure drug. Thus from the spectra it was understood that there was no interaction between Metoclopramide and the disintegrates used in the preparation of tablets.

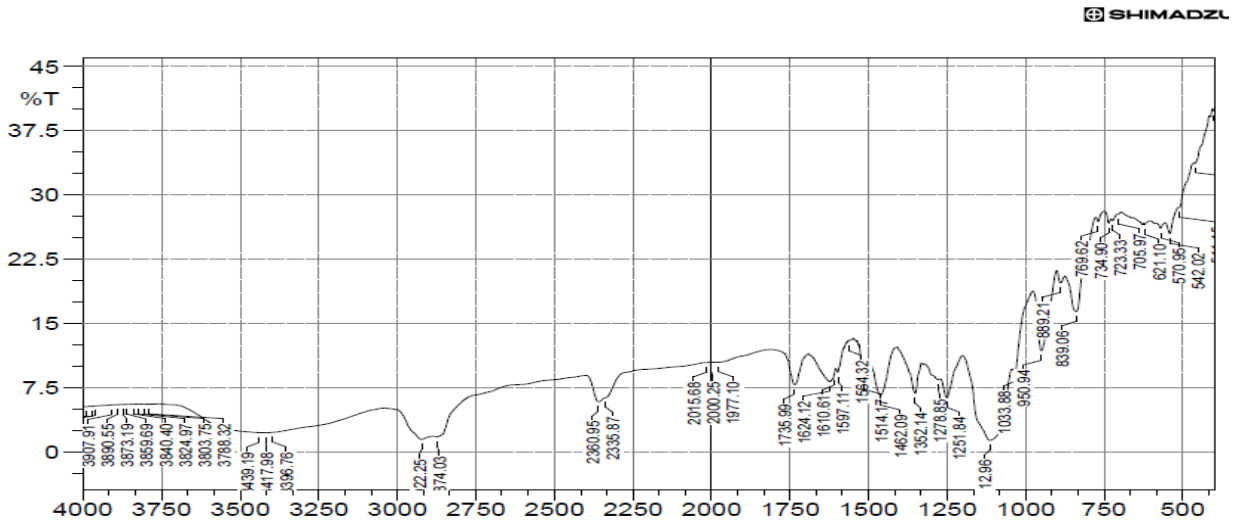

Fig-1: FTIR Studies of Metoclopramide

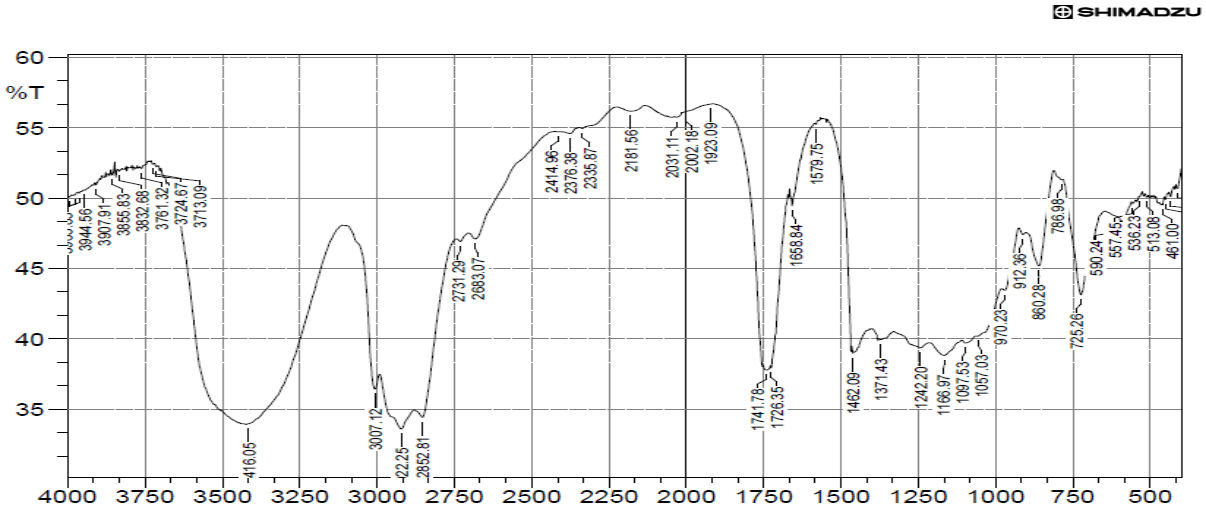

Fig-2: FTIR Studies of physical mixture of drug and sodium starch glycolate

Evaluation of tablet

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 2.1±0.36 mm to 2.7±0.43 mm.

Hardness:

The Measured hardness of tablets of each batch ranged between 3.9±0.28 to 4.4±0.39 kg/cm^2. This ensures good handling characteristics of all formulations.

Friability:

Tablets were evaluated by using Roche friabilator and friability of tablets was observed in the range 0.43±0.29-0.51±0.36%

Content Uniformity:

The Metoclopramide fast dissolving tablets were tested for drug content by UV method, the percentage drug content was found to be in between 83.59±0.31to 90.12±0.31%.

Disintegration Time:

Tablets were evaluated for disintegration time in the disintegration apparatus. The disintegration time was found in the range 18±1.49- 28±1.25 sec.

Wetting Time:

Tablets were evaluated for wetting time test. The wetting time was found in the range 156±1.37 – 164±1.31 sec.

Table-2: Evaluation parameters of Metoclopramide fast dissolving tablets

F. No.	Weight variation (mg)* Mean±SD	Thickness (mm)* Mean±SD	Hardness (kg/cm^2)* Mean±SD	Friability (%)	Drug content (%)	Disintegration time(sec)	Wetting time (sec)
F1	100±1.27	2.2±0.36	3.9±0.28	0.51±0.36	89.68±0.31	28±1.25	164±1.31
F2	100±1.39	2.5±0.39	4.1±0.30	0.49±0.22	88.23±0.31	25±1.20	161±1.34
F3	99±1.33	2.3±0.48	4.2±0.37	0.45±0.30	89.63±0.31	20±1.36	162±1.20
F4	100±1.38	2.4±0.47	4.0±0.42	0.43±0.29	83.75±0.31	19±1.40	160±1.25
F5	101±1.23	2.7±0.43	4.3±0.46	0.49±0.23	85.67±0.31	27±1.43	157±1.27
F6	100±1.25	2.1±0.36	4.4±0.39	0.50±0.26	83.59±0.31	22±1.50	156±1.37
F7	100±1.39	2.6±0.42	4.0±0.35	0.47±0.33	90.12±0.31	18±1.49	160±1.31
F8	99±1.31	2.2±0.31	4.3±0.31	0.49±0.25	89.36±0.30	26±0.31	162±0.31

Dissolution studies

All the 8 formulation of Metoclopramide Fast dissolving tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-3: Drug release studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	25.93±1.49	27.65±1.51	29.21±1.47	30.18±1.30	28.10±1.27	24.58±1.50	20.19±1.17	24.93±1.27
10	35.42±1.40	37.89±1.23	38.91±1.28	42.82±1.27	40.39±1.30	39.85±1.46	38.46±1.50	37.86±1.30
15	53.56±1.37	54.59±1.48	59.43±1.30	52.95±1.32	52.34±1.25	53.17±1.47	50.27±1.44	57.42±1.46
20	70.42±1.23	69.86±1.26	75.82±1.43	71.53±1.26	73.69±1.28	75.10±1.37	74.96±1.37	75.96±1.42
25	81.93±1.36	82.63±1.40	85.75±1.27	83.91±1.30	80.30±1.33	81.39±1.29	83.21±1.29	85.42±1.39
30	95.19±1.42	94.98±1.43	95.26±1.26	93.05±1.24	95.50±1.24	92.50±1.33	96.52±1.30	93.46±1.30

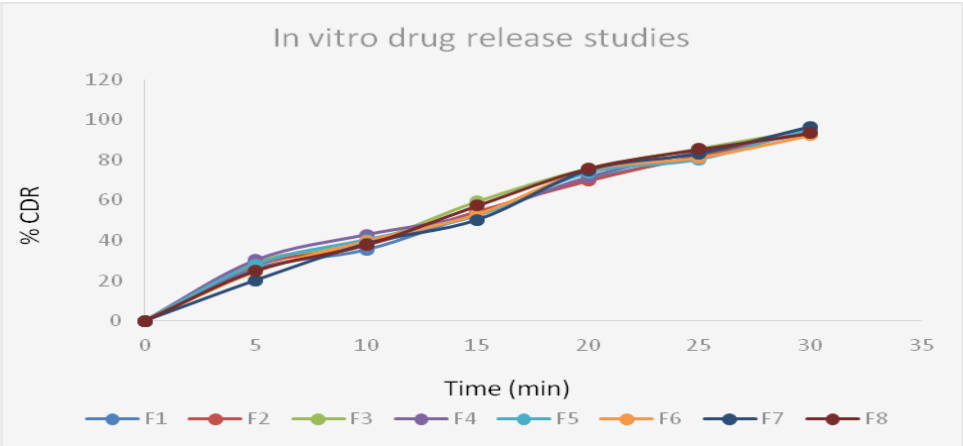

Table-3: Dissolution Profile of F1 to F4 formulation

Kinetic modelling of drug release

All the 8 formulation of prepared FDTs were subjected to in vitro release studies these studies were carried out using

dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Pappas Exponential Equation)

Zero order kinetics

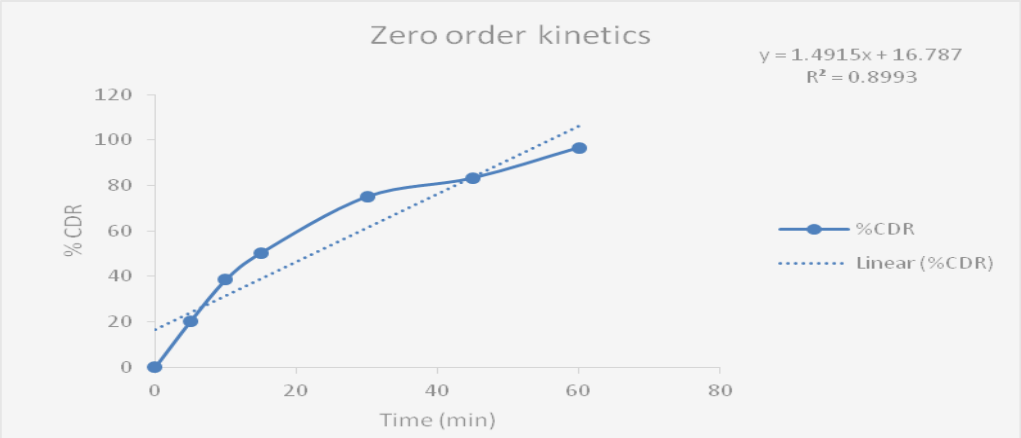

Fig-4: Zero order kinetics of optimized formulation

First order kinetics

Fig-5: First order kinetics of optimized formulation

Higuchi model

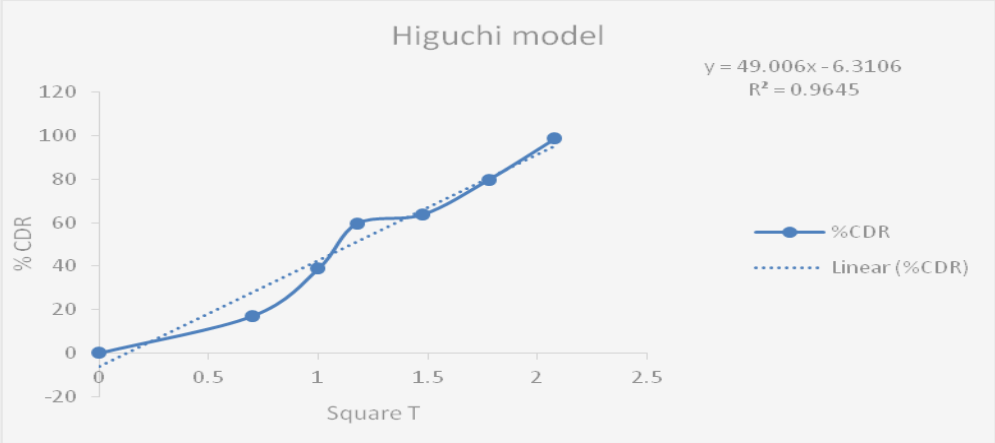

Fig-6: Higuchi model of optimized formulation

Korsmeyer peppas

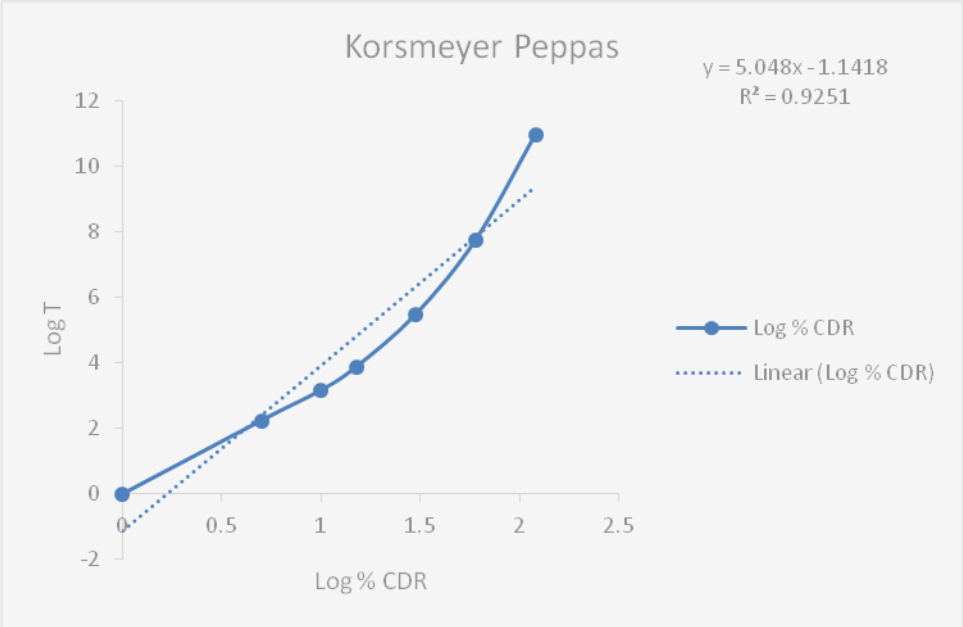

Fig-7: Korsmeyer peppas of optimized formulation

The kinetic values obtained for formulation F7 were shown. The values of in vitro release were attempted to fit into various mathematical models.
Regression values are higher with Zero order release kinetics. Therefore, all the Metoclopramide tablets Zero order release kinetics. Therefore, all the Metoclopramide tablets follow first order release kinetics.

Stability Study
There was no significant change in physical and chemical properties of the tablets of formulation F-7 after 3 months. Parameters quantified at various time intervals were shown.

Table-4: Stability studies of F7 formulations

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications (drug release)
F-7	25^{0}C/60%RH	96.52±1.30	95.87±1.54	94.68±1.36	93.61±1.25	Not less than (75%)
F-7	30^{0}C/75% RH	96.52±1.30	95.46±1.43	94.32±1.40	93.50±1.27	Not less than (75%)
F-7	40^{0}C/75% RH	96.52±1.30	95.30±1.39	94.28±1.42	93.08±1.22	Not less than (75%)

CONCLUSION

The aim of the present study was to develop an optimized formula for Fast dissolving tablet containing

Metoclopramide After pre-formulation studies it was decided to prepare fast dissolving tablets prepared by direct compression method. In the formulation of sodium starch glycolate and crospovidone were used as super disintegrates. Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time and in vitro drug release. Fast dissolving tablet is a promising approach with a view of obtaining rapid action of the drug and would be advantageous in comparison to currently available conventional dosage forms. The selection of an ideal batch of Fast dissolving tablets was made after consideration of the evaluation parameters by dissolution study, disintegration time and wetting time. From the data obtained, it is observed from the formulation containing sodium starch glycolate in Formulation F7, shows Disintegration time in 18±1.49 seconds and the Percentage drug release is of 96.52±1.30 % at the end of 30 min which satisfied all the tablet evaluation parameters for Fast dissolving tablet Hence looking at all the satisfactory parameters F7 formulation is selected as the optimized formulation. The prepared fast dissolving tablets were found to stable after performing stability testing for three month. The optimized formulation followed zero order kinetics. Short term stability studies of optimized formulation as per ICH guidelines indicated that there is no significant change in physical appearance, drug content determination and in vitro drug release. So finally, it can be concluded that fast dissolving tablets of Metoclopramide could provide sustained delivery for prolonged period. A further clinical investigation has to be conducted to establish the safety and efficacy of the developed formulation.

REFERENCES

1. Aulton ME. Pharmaceutics: The science of dosage form design. 2nd ed. London; 2002.
2. Mahore JG, Wadhe KJ and Umekar MJ: Formulation and in-vitro evaluation of taste masked orodispersible tablet of metoclopramide hydrochloride. International Journal of PharmTech Research 2010; 2(3): 1827-1835. 3. Gupta DK, Agarwal DK, Tyagi S, Gupta R and Sharma KK: Natural & Synthetic Superdisintegrants in FDT: A Review. International Journal of Advanced Research, 2013; 1(6): 576-583. 4. Tripathi KD: Essentials of Medical Pharmacology, Jaypee Brothers Medical Publishers (P) Ltd., Edition 7 th, 2013: 659-660.
3. Banker GS, Rhodes CT. Modern pharmaceutics. 4th ed. New York: Marcel Dekker; 2002.
4. Wasay SA, Jan SU, Akhtar M, et al.: Developed meloxicam loaded microparticles for colon targeted delivery: Statistical optimization, physicochemical characterization, and in-vivo toxicity study. PLoS One. 2022;17(4 April):1–25
5. Bhowmik D: Fast dissolving tablet: An overview; Journal of chemical & pharmaceutical Research 2009; 163-177.
6. Deepak: Fast disintegrating tablets: A new era in Novel drug delivery system & new market opportunities. Journal of Drug Delivery & Therapeutics 2012; 2(3): 74-86.
7. Dinesh KV, Sharma I & Sharma V: A comprehensive review on Fast dissolving tablet technology. Journal of applied Pharmaceutical Science 2011; 01(05): 50-58.
8. Gupta A, Mishra AK, Gupta V, Bansal P, Singh R & Singh AK: Recent Trends of fast dissolving tablet- an overview of formulation technology, review article. Int J Pharma & Biological Archives 2010; (1): 1-10.
9. D. Shukla et al., Mouth Dissolving Tablets I: An Overview of Formulation Technology, Scientia Pharmceutica. 2009; 76; 309– 326.
10. H . Seager., Drug-delivery Products and the Zydis Fast-dissolving Dosage Form., J. Pharm. Pharmacol. 1998; 50: 375-382.
11. Kumar AH, Kavitha K, Kumar SA, Kumar MR, Singh SD. Novel approach of bilayer tablet technology-a review. Int J Pharm Chem Biol Sci 2013;3:887-93.
12. Prajapati BG, Patel B. Formulation, evaluation and optimization of orally disintegrating tablet of piroxicam. Int J Pharm Tech Res 2010;2:1893-9.
13. Basu B, Bagadiya A, Makwana S, Vipul V, Batt D, Dharamsi A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. J Adv Pharm Technol Res. 2011 Oct;2(4):266-73
14. Liji Jacob, Manju Salim S, Jilby Saju. Formulation and Evaluation of Transdermal Patches of Selegiline. Asian Journal of Pharmacy and Technology. 2022; 12(2):96-0.
15. Syed Muneer, Formulation and in vitro evaluation of Selegiline floating tablets , The Pharma Innovation Journal 2016; 5(1): 114-120
16. Eisa AM, El-Megrab NA, El-Nahas HM. Formulation and evaluation of fast dissolving tablets of haloperidol solid dispersion. Saudi Pharm J. 2022 Nov;30(11):1589-1602.