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Original Article

Stability studies of the optimized oral metoclopramide hydrochloride tablet formulations prepared for IVIVC studies

Ahmad Khan[1], Baqir Shyum Naqvi[2], Muhammad Harris Shoaib[2], Jallat Khan[3], Rabia Ismail Yousaf[2], Muhammad Irfan[4], Kamran Hidayatullah[1], Maria Zafar[1]

[1]Department of Pharmacy, Quid I Azam University Islamabad, Pakistan
[2]Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Pakistan
[3]Department of Chemistry, Islamia University Bahawalpur, Bahawalpur, Pakistan
[4]College of Pharmacy, GC University Faisalabad, Pakistan

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ABSTRACT

To examine the influence of environmental factors on the quality of a drug product over time, in order to recommend storage conditions and establish shelf life for the product, the accelerated stability studies for optimized formulations (Immediate Release- F2, Intermediate Release-F10 and Slow Release-F18), prepared for IVIVC Study, were carried out for a period of six months using ICH guidelines (at 40±2 ^{o}C and 75±5% RH). All the formulations were tested for disintegration test, % drug content and % drug release over the entire period of testing. Observations showed no degradation of the drug throughout the six months periods as % content uniformity of the three optimized immediate, intermediate and slow release formulations at one, three and six month was found within the limits. Moreover the results of drug release profiles at pH 1.2, 4.5, 6.8 and distilled water was also remained unaffected throughout the test period under elevated conditions when the trial formulations were compared with those stored in refrigerator. Shelf lives were calculated by software *R Gui* and were found to be 24, 14 and 20 months for IR (F2), IntR (F10) and SR (F18) formulations respectively. These stable novel optimized formulations will then be used for In Vitro In Vivo Correlation (IVIVC) studies of Metoclopramide HCl. No such stability studies of three formulations of Metoclopramide HCl with varying release rates are conducted before.

Keywords: Metoclopramide Hydrochloride Tablet, Accelerated stability testing, Disintegration test, Drug content, Drug release.

INTRODUCTION

The product quality changes with change in time due to certain environmental factors such as humidity, temperature and light. The key objective of stability testing is investigation of those changes applicable to all future batches of the drug product tested. It also helps to establish a shelf life for the drug product. An ideal stability study should include the tests of all those attributes which are susceptible to change during storage condition [7]. The development and preparation of dosage form is critical for patient safety and drug effectiveness. The stability of compounds may influenced by physical and chemical parameters such as presence of additives, storage conditions, and the environmental factors such as temperature, humidity and light, these factors obtained major concern in the manufacturing of drugs [1,2]. Stability testing is an essential part of any drug development. The purpose of stability testing is to investigate changes; stability plays an essential role in the development of drug compounds. The assessment of the stability of compound requires an understanding of the features of drug compound. Lack of drug product stability may influence the purity, strength and safety. A well designed stability study should include testing of those attributes that are susceptible to change during storage and are likely to influence quality, safety and efficacy [2]. Compound will be exposed to degrading conditions mainly moisture, pH, oxygen, temperature and light during stability testing. Stability testing permits the establishment of suggested retest periods, shelf life for the drug product, expiration date of compounds, procedure development, and to recommend storage conditions, which will be appropriate for all future

***Corresponding Author Address:** Dr Ahmad Khan, Department of Pharmacy, Quaid I Azam University Islamabad, Pakistan; E-mail: ahmadkingsk@yahoo.com; Mobile: +923003543361*

batches of the tested drug product manufactured and packaged under similar conditions. Stability testing will also state the environment for the manufacturing and storage of drug compound [2]. Metoclopramide Hydrochloride is an antiemetic, gastroprokinetic agent; belongs to the group dopamine-receptor antagonist. It stimulates upper gastrointestinal tract motility, resulting in accelerated gastric emptying and intestinal transit, and increased resting tone of lower esophageal sphincter, its antiemetic property is due to antagonism of central and peripheral dopamine receptors. It is rapidly and almost completely absorbed orally with peak plasma concentration attained at 1-2 hours [3,5]. The optimization of formulations (F-2, F-10, F-18) work done comprised of following sections. Section I consists of formulation development and optimization of Metoclopramide HCl by Central Composite Rotatable Design using Design Expert® version 8.0.4 (Stat-Ease Inc). In section II three formulations with varying release rates i.e. immediate release, intermediate release and slow release were developed using crosspovidone as disintegrant in immediate release formulations. While HPMC K4M used as polymer in high concentration in intermediate and slow release formulation. These three best formulations (F-2, F-10 and F-18) were optimized on the basis of physicochemical and quality attributes. Model dependent approaches (Zero Order, First Order, Higuchi, Hixson-Crowell and Weibull models) and model independent approach (f_2) were used to compare the drug release among the formulations using DDSolver® software. The HPLC reported method was modified and validated for content assay is discussed in section III. In section IV swelling and erosion studies was performed for the three optimized formulations. The stability studies and shelf lives of the optimized formulations were determined by software *R Gui* presented in section V. The aim of the present study is to evaluate the quality of Metoclopramide Hydrochloride tablets by storing the three optimized formulations 40 ± 2°C/ 75 ± 5% relative humidity for 6 months accelerated stability testing.

MATERIALS AND METHODS

The accelerated stability study of the three optimized formulations i.e. immediate (F-2), intermediate (F-10) and slow release (F-18) was carried out for a period of six months by following ICH guidelines (40±2 ^{o}C and 75±5% RH). From each formulation 50 tablets were placed in ambered colored glass bottles. These samples stored at 40±2 ^{o}C and 75±5% RH for accelerated study were kept in humidity chamber. The drug content and dissolution were determined for each formulation at the end of each month. Shelf lives of the optimized formulations were determined by *R Gui* software (ICH QIA (R2), 2003).

RESULTS

The composition of the optimized formulations is mentioned in table 1. The results stability data and content assay are shown in the table 2 and 3 respectively. The figures 1-4 (a, b, c) depict the results of the combine release pattern at 0.1N HCl (pH 1.2), pH 4.5, 6.8 & distilled water of the optimized metoclopramide hydrochloride formulations after stability. The shelf life of the optimized formulations was also calculated by R Gui software (table 2).

DISCUSSIONS

The stability studies for optimized immediate, intermediate and slow release formulations of Metoclopramide HCl were performed by following ICH guidance under elevated storage conditions and control room temperature at 40±2 ^{o}C and 75±5% humidity for the period of 0, first, third and sixth months. Observations showed no degradation of the drug throughout the six months periods as % content uniformity of immediate release formulation (F2) for first, third and sixth months were 99.89 %, 99.58 %, 98.96 %, for intermediate release 99.06 %, 99.056 %, 99.02 % and for slow release are 99.13 %, 98.93 %, 98.75 % respectively (table 3). Moreover the results of drug release profiles (figures 1-4 (a, b, c) at 0.1N HCl (pH 1.2), phosphate buffer 4.5, 6.8 and distilled water was also remained unaffected throughout the test period under elevated conditions (table 2) and figures 1-4 (a, b, c). Similar findings were reported by Stosik et al in 2008 by determing the stability of immediate release oral 10 mg tablets of Metoclopramide HCl in pH 1.2 (gastric fluid) and pH 6.8 (intestinal fluid) with recovery rates of 102% and 99% at pH 1.2 and pH 6.8 respectively which confirms the Metoclopramide HCl stability throughout the pH range of the whole gastrointestinal tract [10].

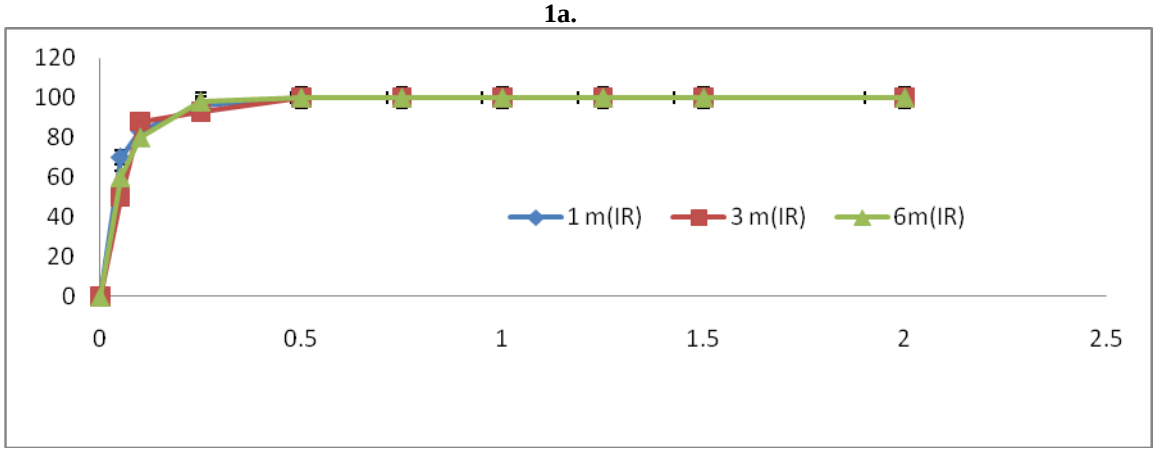
In another study Pitre and Stradi in 1987 studied the stability of Metoclopramide HCl and found conformity with the results of the present study and Stosik et al 2008 [9]. Shelf lives of Metoclopramide HCl tablets were calculated by software, R Gui and it was found to be 22.32, 13.56 and 20.33 months for optimized immediate (F2), intermediate (F10) and slow release (F18) formulations respectively (table 2). Fariya et al in 2012 also used stability software R Gui to perform the long term and accelerated stability studies of Ketoprofen tablets for the period of 12 and 6

months respectively [2]. In another report Lee et al in 2010 provided software based calculations of shelf life of pharmaceutical products under ICH Tripartite Guidelines for QIE Evaluation [6]. He et al in 2007 and Ma et al in 2007 also reported the R package for the calculations of stability and shelf life and found it best solution of complex calculations of shelf life of pharmaceutical products [4,8].

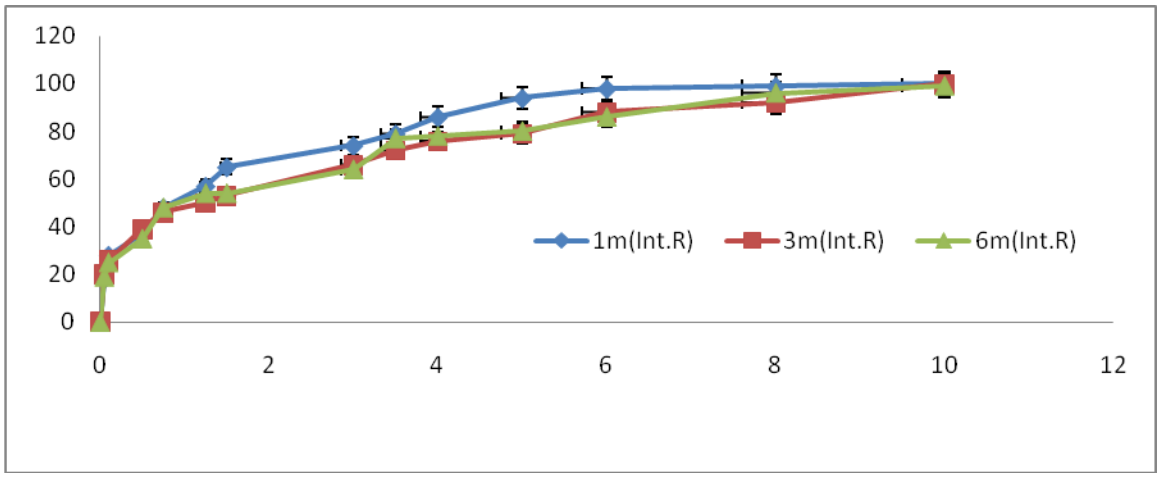
CONCLUSIONS

The accelerated stability studies was performed following ICH guidelines and the shelf life was calculated by software *R Gui* and were found to be unchanged during the entire period. Moreover the results of the present study also indicated that the formulations remained chemically and physically stable during the accelerated stability of 6 months.

1a.



Ib.



Ic.

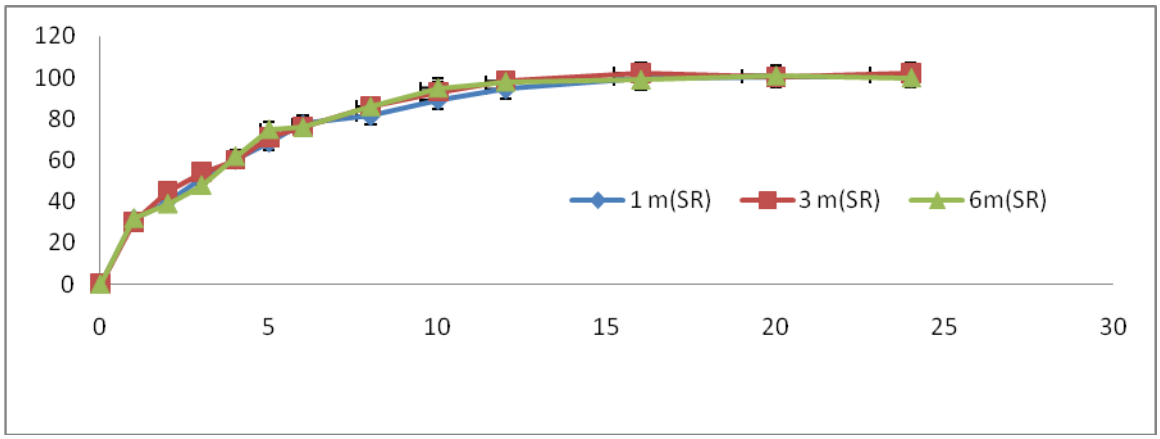
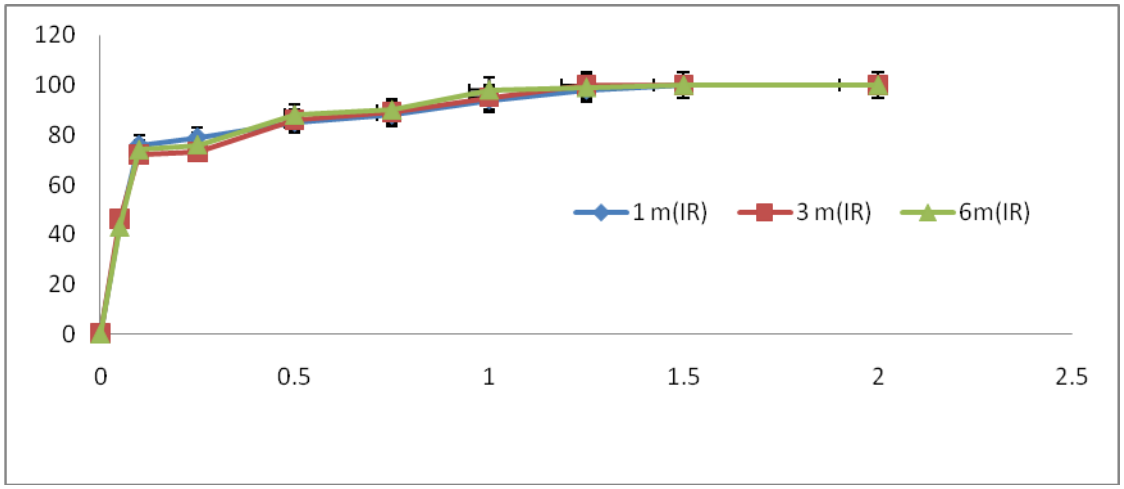
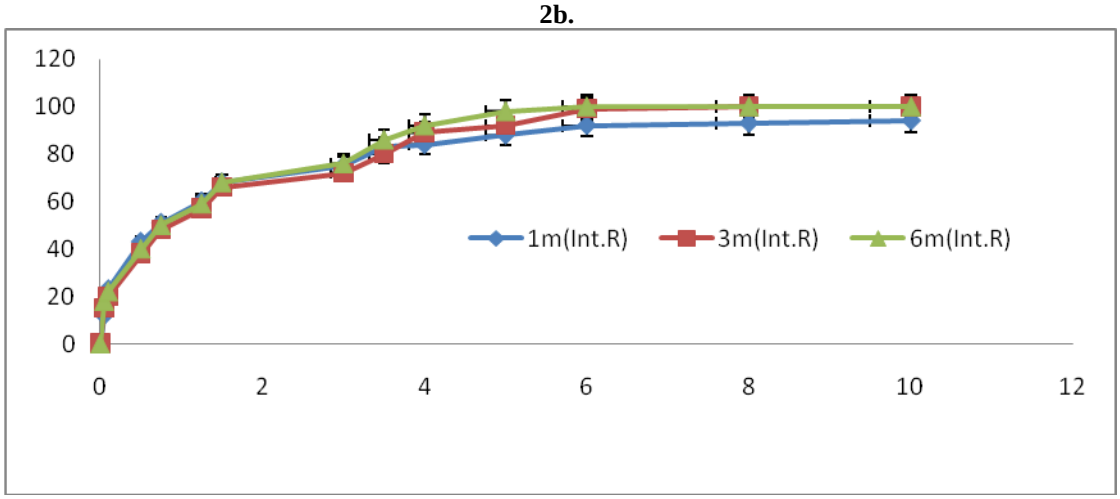


Fig. 1(a,b,c): Dissolution Profile (SD) of the Optimized IR (F-2), IntR (F-10) & SR (F-18) Formulation After Conducting Accelerated Stability at pH 6.8

2a.



2b.



2c.

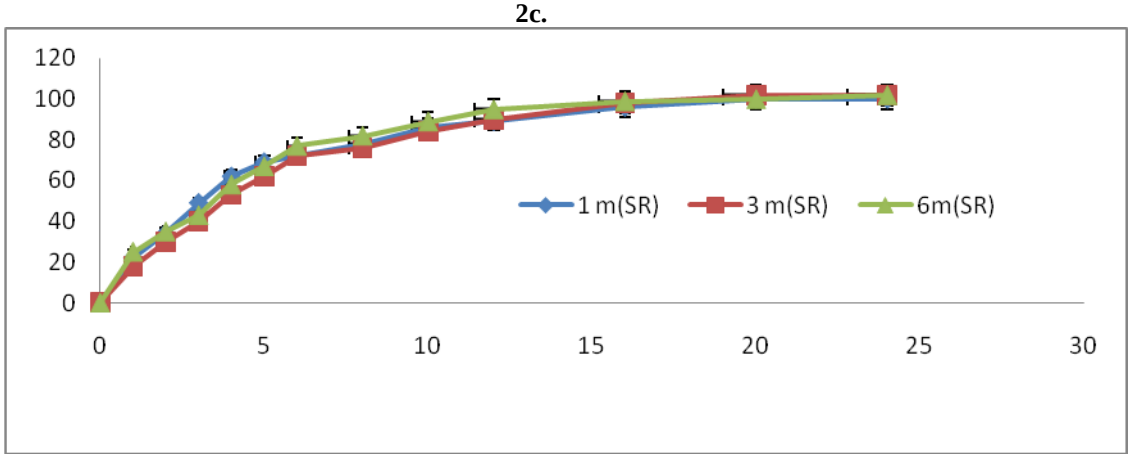
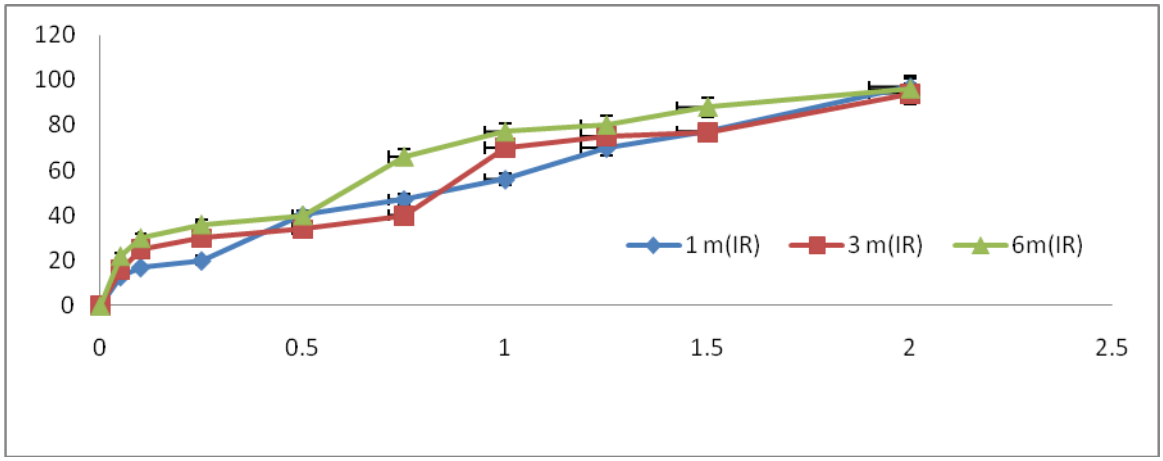
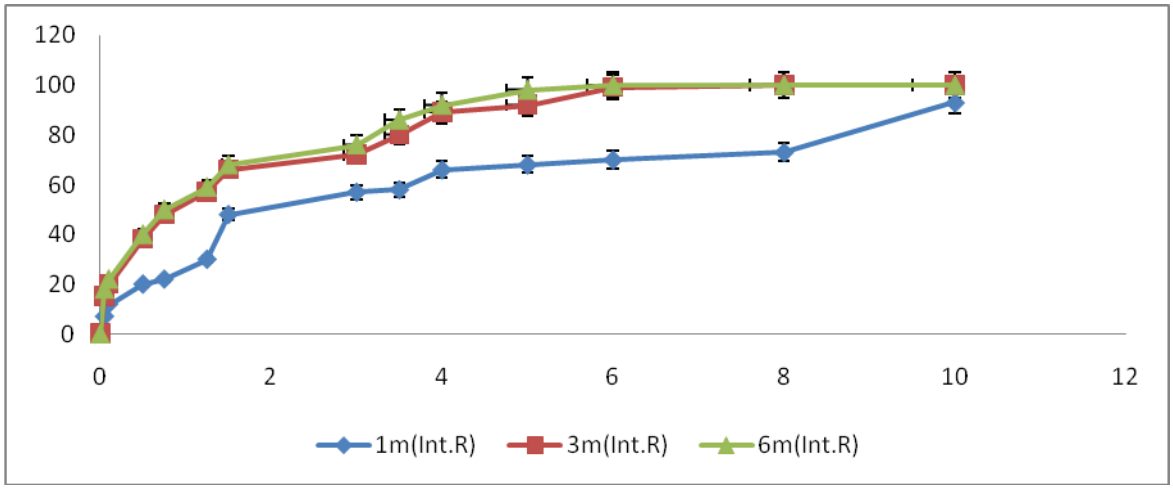


Fig. 2(a,b,c): Dissolution Profile (SD) of the Optimized IR (F-2), IntR (F-10) & SR (F-18) Formulation After Conducting Accelerated Stability in Distilled Water

3a.



3b.



3c.

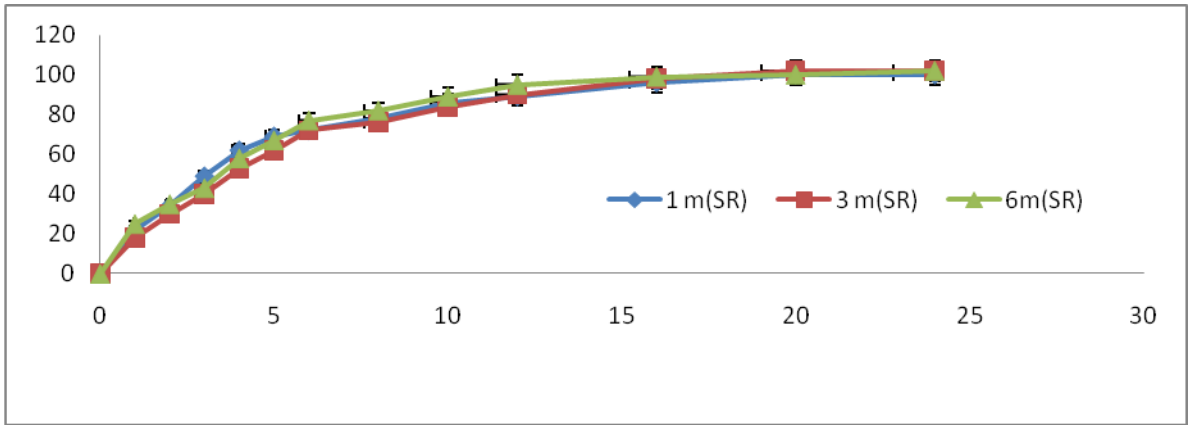
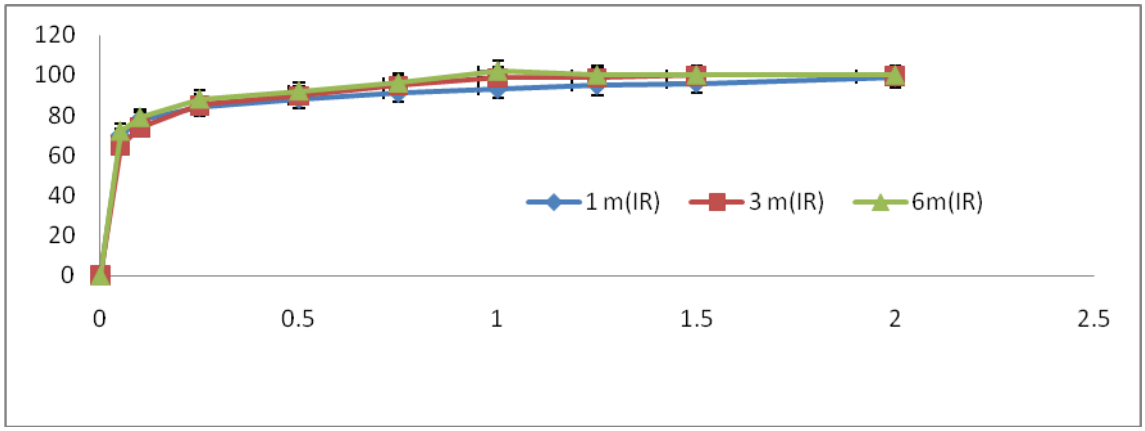


Fig. 3(a,b,c): Dissolution Profile (SD) of the Optimized IR (F-2), IntR (F-10) & SR (F-18) Formulation After Conducting Accelerated Stability at pH 4.5

4a.



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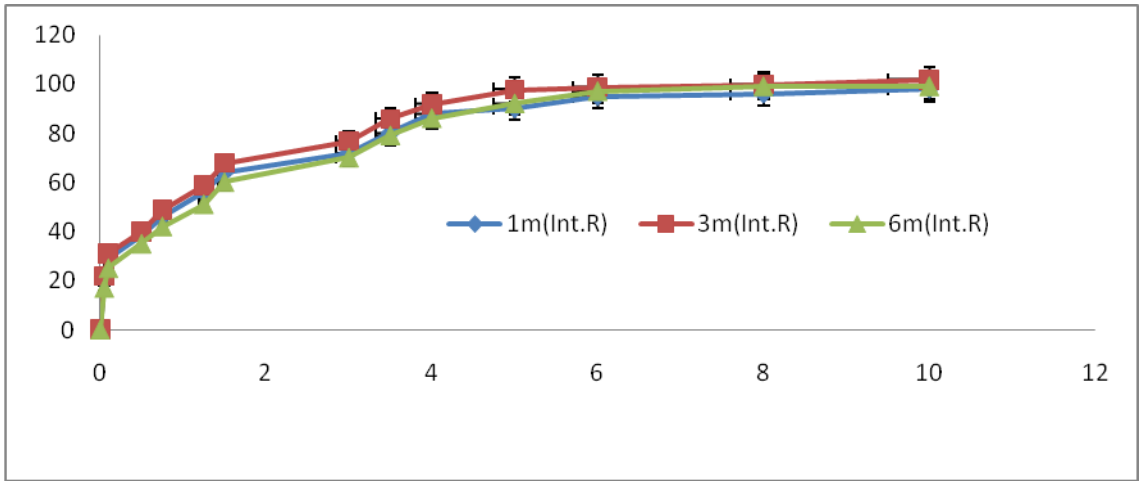

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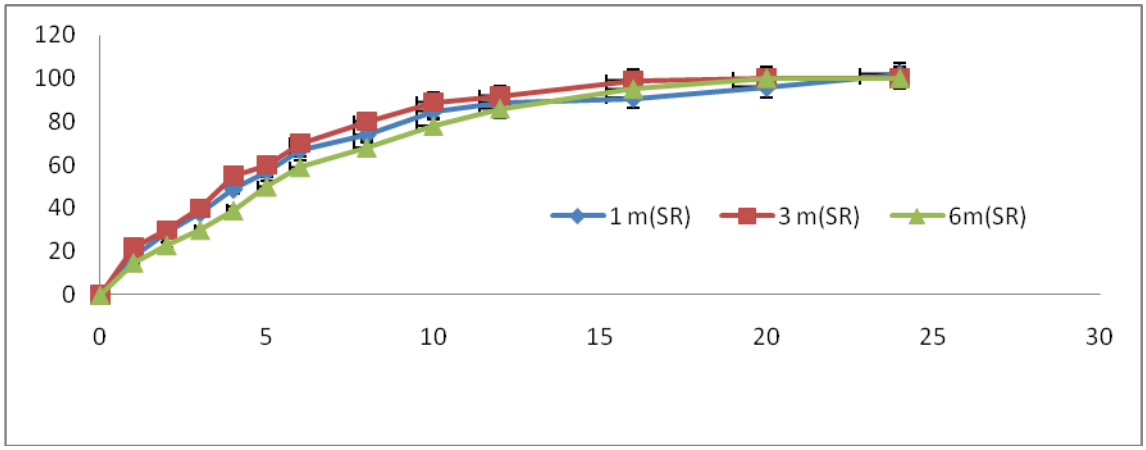

Fig. 4(a,b,c): Dissolution Profile of the Optimized IR (F-2), IntR (F-10) & SR (F-18) Formulation After Conducting Accelerated Stability at pH 1.2

Table. 1: Composition of the Optimized Formulations

Optimized Formulation	Metoclopramide HCl	HPMC	MCC PH-102	Lactose DC	Cross Povidone	Magnesium Stearate
	%	%	%	%	%	%
F-2	8.3	0.14	17.50	30	0.5	5
F-10	8.3	22	17	30	-----	-----
F-18	8.3	35	25	30	-----	-----

Table. 2: Stability Data of Optimized Metoclopramide HCl Formulations at 40±2 °C and 75±5% RH					
Parameters	**Unit**	**Periods (month)**	**Optimized Formulations**		
			F2	**F10**	**F18**
Disintegration Test (n=6)	min	1	2±0.32	84±0.29	257±0.44
Dissolution Test (n=6)	%		101.02±0.06	102.34±0.12	101.22±0.17
Shelf Life (n=5)	(months/weeks)		22.32881	13.56218	20.33182
Disintegration Test (n=6)	min	3	2±0.25	80±0.33	250±0.31
Dissolution Test (n=6)	%		99.98±0.021	99.75±0.15	102.41±0.23
Shelf Life (n=5)	(months/weeks)		21.4321	13.3223	21.1321
Disintegration Test (n=6)	min	6	3±0.11	81±0.24	260±0.31
Dissolution Test (n=6)	%		101.87±0.09	102.23±0.06	100.39±0.20
Shelf Life (n=5)	(months/weeks)		22.7685	13.9576	20.4721

Table. 3: % Content Assay (95-105%) of three Optimized Formulations According to Accelerated Stability Studies (40±2 °C and 75±5% RH)				
Formulation		**1(month)**	**3(month)**	**6(month)**
F-2	1	99.86	99.43	99.98
	2	99.86	98.26	99.87
	3	99.87	100.37	99.99
	4	99.88	99.42	99.99
	5	99.87	100.44	99.95
	Mean	99.89	99.58	98.96
	RSD %	0.042	0.79	0.045
F-10	1	99.07	99.27	99.03
	2	99.05	99.55	99.01
	3	99.08	99.68	99.01
	4	99.06	99.56	99.05
	5	99.05	99.78	99.03
	Mean	99.06	99.56	99.02
	RSD %	0.01	0.19	0.01
F-18	1	99.02	98.45	99.67
	2	99.13	99.14	99.75
	3	100.10	100.00	99.78
	4	99.20	98.55	99.8
	5	99.20	98.51	99.79
	Mean	99.13	98.93	98.75
	RSD %	0.66	0.59	0.05

REFERENCES

1. AL-GOHARY, O. M. N, AL-KASSAS, R. S. Stability studies of aspirin–magaldrate double layer tablets. Pharmaceutica Acta Helvetiae 2000; 74:351–360.
2. FARIYA Z et al. Stability studies of fast dispersible Ketoprofen 100 mg tablets. International Journal of Pharmaceutical Sciences Review and Research 2012;13:58-60.
3. GOODMAN L S, GILMAN A. Goodman and Gilman's the Pharmacological Basis of Therapeutics, New York: McGraw-Hill Professional, 2001.
4. HE S G et al. Formation, Detection and Stability Studies of neutral vanadium sulfide clusters. Journal of Chemical Physics 2007;126:194315-194315.
5. KASIM N A et al. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Molecular Pharmaceutics 2004;1:85–96.
6. LEE H Y et al. An R package for drug stability data analysis. Comput. Methods Prog. Biomed 2010;100: 140-148.
7. LUSINAA M et al. Stability study of losartan/hydrochlorothiazide tablets. International Journal of Pharmaceutics 2005;291:127–137.
8. MA N et al. Determination of duloxetine in human plasma via LC/MS and subsquent application to a pharmacokinetic study in healthy chinese volunteers. Clinica chimica acta 2007; 380.
9. PITRE D, STRADI R. Metoclopramide Hydrochloride: Academic Press, San Diego ,USA 198.
10. STOSIK A G et al. Biowaiver monograph for immediate release solid oral dosage forms: Metoclopramide Hydrochloride. J Pharm Pharmaceut Sci 2008; 97:3700-3708.