DEVELOPING AS DISCRIMINATIVE DISSOLUTION METHODS IN CORRELATION WITH *IN VITRO-IN VIVO* FOR QUETIAPINE FUMARATE FILM COATEDTABLETS 300MG

***A Bharath kumar , **Dr. Pabba Parameshwar**
*Research Scholar, School of Pharmacy, Career Point University, Kota Rajasthan, 9052637360, bharathranan@gmail.com

**Research Supervisor, School of Pharmacy, Career Point University, Kota, Rajasthan,

Corresponding authors: ***A Bharath Kumar , **Dr. Pabba Parameshwar**

Abstract

Discriminative drug dissolution profiles are testing can play an important role in predicating and estimation of in-vivo performance with bioequivalence studies for drug products development in pharmaceutical industry. The main objective of this study was to determine the Discriminative dissolution media enabling predicting *in-vivo* performance of Quetiapine Fumarate Tablets Discriminatory dissolution should provide the drug and dosage-form performance and should be used to formulation development, to identify and predicting on the bioavailability of orally drug product development, and to identify solubility limitations and stability issues. The importance of the development of predicting dissolution testing is increased by the fact that the majority of drugs currently in development. Biorelevant dissolution testing were performed and evaluation of Quetiapine Fumarate Tablets. Although *in-vitro* dissolution test findings showed the similarity of release profile of test product and reference drug products, the *in-vivo* results demonstrated that they may not be similar. The profiles based only on pharmaceutical attributes have also been described as discriminatory. This appears to have created confusion in properly defining and developing discriminating profiles. So, those proper discriminating profiles may be developed for improved evaluation of pharmaceutical products. Due to this reason, discriminating profiles was investigating the potential to be further used to establish *in-vitro in-vivo* correlation (IVIVC) during the development of Quetiapine Fumarate Tablets in solid dosage form.

Key words : Invitro-invivo, Quetiapine Fumarate, Film coated tablets.

INTRODUCTION

Quetiapine Fumarate is classified as BCS class 2 and is used for treat a typical antipsychotic conditions, schizophrenia and bipolar disorders. Studies shows the effect of the in vitro dissolution of ER formulation and the drug absorption, therefore, similar dissolution were carried out on quetiapine fumarate in the biorelevant dissolution media to check the competitive % drug release which can be predict the in vivo behavior of the test formulation and reference formulation[1,2,3,4].

Dissolution testing has emerged as a very important tool in the generic pharmaceutical industry. It is very widely used in formulation development, in monitoring the manufacturing process and as a quality control test. It can also be used to predict the in vivo performance of certain solid oral drug products.. Most recently, the use of dissolution testing has been extended to other solid generic dosage forms; in these cases it is generally called as in vitro release testing or simply drug release testing. Finally, dissolution testing plays significant role in identifying the need for the bioequivalence (BE) studies [4,5,6,7].

The main objective of drug product developing discriminating dissolution testing designed with appropriate dissolution media and hydrodynamics are useful from the early stages of drug development for identifying the bio- pharmaceutical performance of the compound (i.e. solubility problems, food effect, precipitation in the small intestine) through the later stages of development to assist in formulation strategies and the establishment of in vitro-in vivo correlations that will lead to reduction of the number of animal experimentation, bioavailability and bioequivalence studies [e.g. 7, 8]. The development of dissolution media in order to simulate the pre and postprandial states of the stomach, the small intestine and the colon is described. The second part deals with the description of compendial of different dissolution media and hydrodynamics used in dissolution experiments. At the last part applications of the biorelevant methods in the prediction of in vivo performance of oral formulations and the development of in vitro-in vivo correlations/relationships (IVIVCs/Rs) are presented.

Medium Selection

Unlike compendial media (conventional buffers, USP media), dissolution media should represent the gastric and intestinal environment in which different pH (0.1N HCL, pH 4.5 Acetate Buffer and pH 6.8 Phosphate Buffer). In these media, several properties such as pH, the presence of bile, the buffer capacity, and the surface tension of the GI fluids are taken into consideration. Bile salts and phospholipids may have a significant effect on the in vivo dissolution and transport in the small intestine of poorly soluble drug substances. For cases in which lipid-based formulations were characterized, lipolysis could be accounted for by the addition of lipolytic degradation products to the dissolution media to simulate the fed state, because they play an important role in the solubilization capacity of the medium [9,10,11,12,13,14].

Hydrodynamics

In-vitro experiments, hydrodynamics reflects the design of the apparatus; the agitation intensity; the flow, volume, and viscosity of the medium; and practical issues such as the position of the dosage form during the experiment. The choice of the most appropriate hydrodynamics is essential for the development of a discriminative dissolution method.

The current study mainly focuses on discriminative dissolution between the in vitro dissolution (Official dissolution media as per USP) and in vivo dissolution (Biorelevant dissolution medium) for poor water soluble drug with the necessary steps that need to be considered for in vitro dissolution Medium is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. These discriminative media can be used to assess the performance of different formulations for poorly water soluble compounds. discriminative media have been successfully applied over the past decade to obtain IVIVCs.[15,16]

In this study, we investigated Quetiapine fumarate Extended release test formulations. Since the Quetiapine fumarate can be affected by food and you should therefore take your tablets at least one hour before a meal or prior to bedtime. The dissolution behaviors in other media including simulated intestinal fluid. The obtained in vitro discrimination dissolution profiles were used to predict the absorption. The establishment of in vivo/in vitro correlations (IVIVCs) is discussed [17].

Material

Materials Quetiapine fumarate was provided as a gift sample by Aurobindo Research Center (Hyderabad, India). Microcrystalline cellulose (Avicel pH 101 & 112) and Lactose Monohydrate (Pharmatose 200M) from DFE Pharma Limited, Povidone (K30) is gifted from Balaji Amine, Mumbai, Sodium starch Glycolate Type A , Colloidal anhydrous silica ,Titanium dioxide, Macrogal-400, was received as a gift sample from Signet chemical Co-operation, Mumbai, Magnesium stearate were purchased from Nitika Pharmaceuticals Ltd.,.

Hydrochloric acid (sd Fine chemicals, India), potassium dihydrogen orthophosphate (sd Fine chemicals, India), sodium hydroxide pellets (Merck, India), and potassium chloride (Merck, India). The following chemicals were used to prepare buffers and HPLC mobile phase: sodium perchlorate monohydrate (Merck, India), acetonitrile (Fisher Scientific, India), methanol (Fisher Scientific, India), sodium acetate trihydrate (Qualigens, India/Merck, India), glacial acetic acid (Fisher Scientific, India), potassium biphthalate (Merck, India),. All other chemicals and reagents were of analytical grades.

MANUFACTURING PROCESS (METHODOLOGY):

The tablets are manufactured by wet granulation and followed by coating:

The process involves weighing of the starting materials, wet granulation and milling, drying and dry milling, mixing, compression, film coating.

Preparation of tablets were prepared by wet granulation method the composition of various formulations is given in Table 1. Quetiapine fumarate and the polymer grades used of Microcrystalline Cellulose, Sodium Starch Glycolate, Colloidal anhydrous silica and Lactose monohydrate were initially passed through ASTM #25 sieve. The drug and the polymer used were then proportionately mixed in Rapid Mixer Granulator 15 mins.

Binder solution:

Add Povidone K30 in Purified water under stirring and until clear solution is obtained. Granulation was done using Povidone Binder solution. The wet mass was dried in Rapid Dryer at 60^{o}C for 30-50 mins. The dried granules were again passed through ASTM # 20 sieve and blended with magnesium stearate (which is passed through ASTM # 60).

Tablets were compressed on 16.00 mm flat punch on a 5 station mini press tableting machine (Chanduma). And coating was done using the HPMC E6 polymer, Titanium Dioxide and

Macrogol 400. These tablets were evaluated for drug release and to study the effect of polymer concentration on drug release.

Table 1: Formulation development and composition of different formulations

Name of Ingredients	F1	F2	F3
Intragranular	**Quantity (mg) per Tablets**		
Quetiapine Fumarate	300.00	300.00	300.00
Lactose monohydrate	23.00	18.00	14.00
Microcrystalline cellulose (Avicel pH101)	26.00	21.00	15.00
Calcium Hydrogen phosphate Dihydrate	10.00	10.00	10.00
Sodium starch Glycolate Type A	10.00	15.00	15.00
Colloidal anhydrous silica	2.50	2.50	2.50
Granulating Solvent			
Povidone (K30)	10.00	15.00	20.00
Purified water	Q.S	Q.S	Q.S
Extra granular			
Microcrystalline Cellulose (Avicel 112)	30.00	30.00	30.00
Magnesium Stearate	3.50	3.50	3.50
Core Tablet weight	**415.00**	**415.00**	**415.00**
Film Coating			
HPMC E6	20.00	20.00	20.00
Titanium Dioxide	10.00	10.00	10.00
Macrogol 400	5.00	5.00	5.00
Purified water	Q.S	Q.S	Q.S
Total	**450.00**	**450.00**	**450.00**

Dissolution Studies

All dissolution runs were performed on six tablets using USP Apparatus 2 with a medium volume of 900 mL maintained at 37 °C unless otherwise indicated. Dissolution profiles were generated by sampling at 5, 10, 15, 20, 30, 45, and 60 min. were also generated in some profiles. Samples were filtered through 0.45- μm PVDF filters and analyzed for etoricoxib content by a validated HPLC method.

Preparation of In-vitro dissolution media (USP Official dissolution media Test 3)

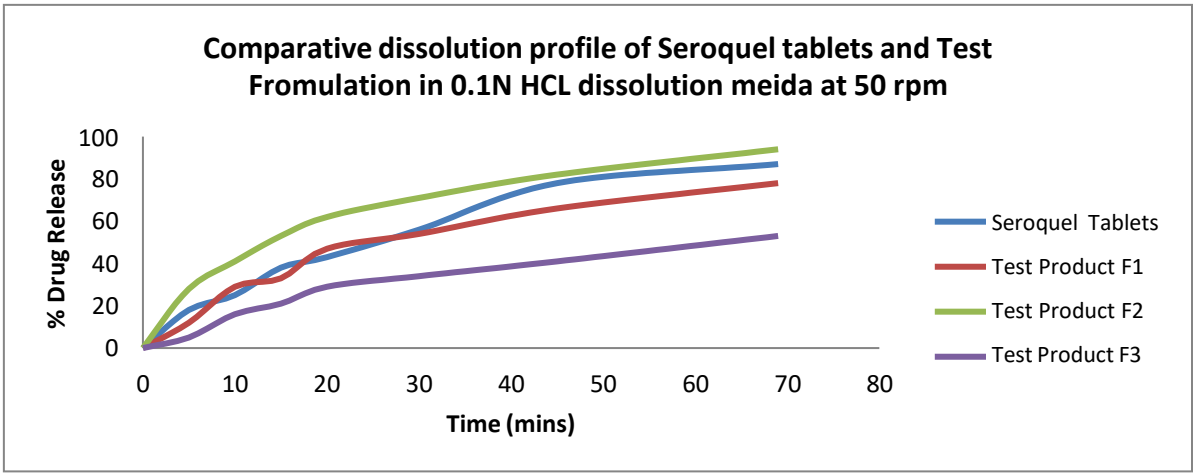
In vitro drug release studies [19]:

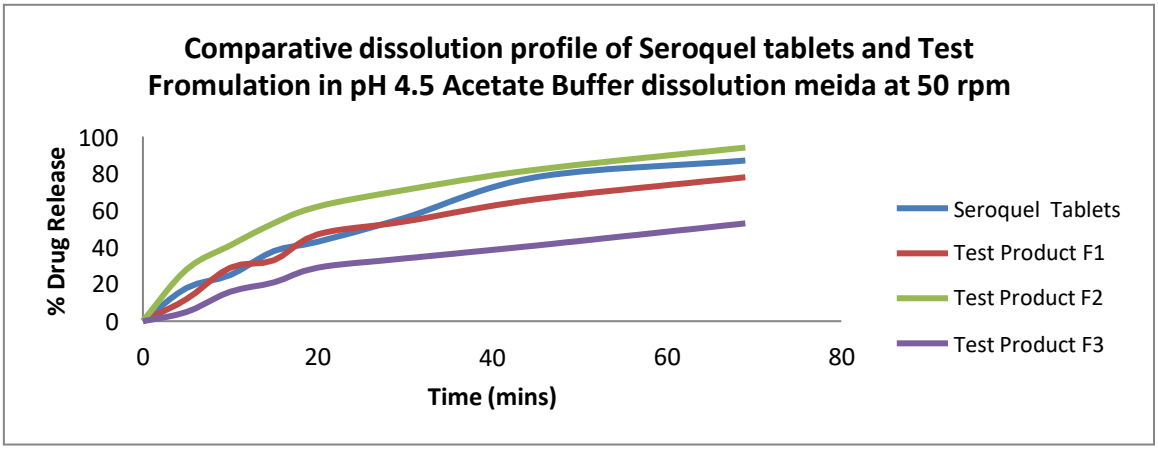
Dissolution studies were performed using the USP II, paddle-rotating method (Electrolab dissolution tester,TDT-08, India) at 37 °C ± 0.5 °C and 50 rpm using 0.1 N HCl/pH 4.5 Acetate Buffer and ph 6.8 Phosphate Buffer , 900ml as the dissolution media. Is solution studies were carried out in triplicate. A 2 ml aliquot of sample was withdrawn at regular time intervals, filtered and then these samples were diluted 10 folds with distilled water and then assayed spectrophotometrically at 246 nm. (Data tabulated in table no. 3 and graph 1 representing the comparative dissolution release between references and test product)

Dissolution profiles of marketed product (Seroquel Tablets 300mg) vs. different formulation vs. Different dissolution media (The cumulative % drug release was calculated for the formulations and the drug release data were curve fitted)

Table 2: Dissolution profile using different dissolution media in 50 RPM

Formulation Type	In vitro dissolution using 0.1NHCL, 900ml, Apparatus 2, 50 rpm				In vitro dissolution using pH 4.5 Acetate Buffer, 900ml, Apparatus 2, 50 rpm				In vitro dissolution using pH 6.8 Phosphate Buffer, 900ml, Apparatus 2, 50 rpm			
Time (min)	Seroquel Tablets	F1	F2	F3	Seroquel Tablets	F1	F2	F3	Seroquel Tablets	F1	F2	F3
5	18	12	28	5	12	14	18	6	9	6	15	2
10	25	29	41	16	19	24	29	11	17	13	31	13
15	38	33	53	21	37	28	46	23	27	24	39	17
20	43	47	62	29	49	39	57	29	39	31	49	26
30	56	54	71	34	54	47	68	38	48	39	57	32
45	78	66	82	41	67	56	79	56	54	47	69	43
60	87	78	94	53	78	68	81	67	69	57	76	51
F2		59	45	33		55	52	45		58	49	47


Comparative dissolution profile of Seroquel tablets and Test Fromulation in 0.1N HCL dissolution meida at 50 rpm
% Drug Release
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Time (mins)
Seroquel Tablets
Test Product F1
Test Product F2
Test Product F3


Comparative dissolution profile of Seroquel tablets and Test Fromulation in pH 4.5 Acetate Buffer dissolution meida at 50 rpm
% Drug Release
100
80
60
40
20
0
0
20
40
60
80
Time (mins)
Seroquel Tablets
Test Product F1
Test Product F2
Test Product F3

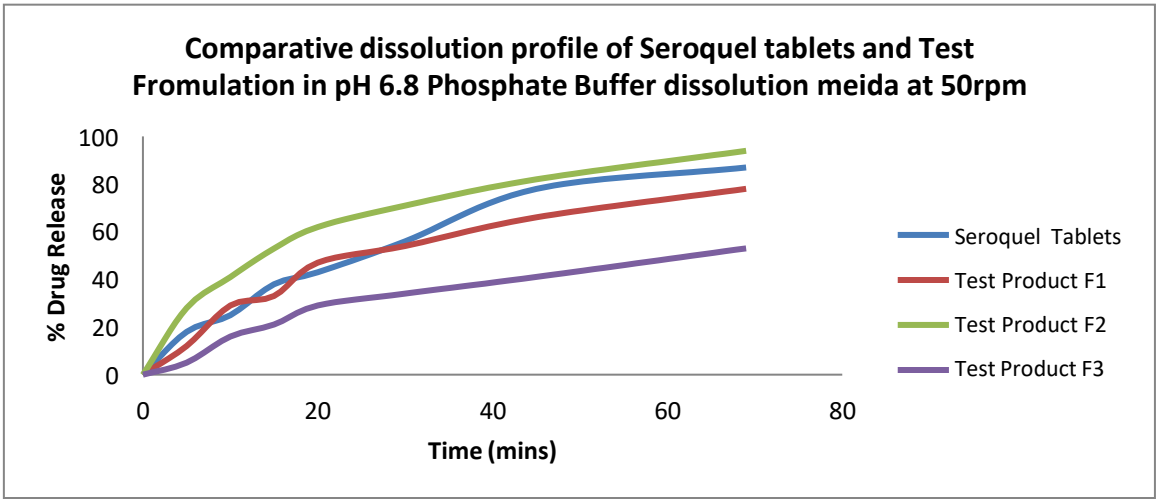
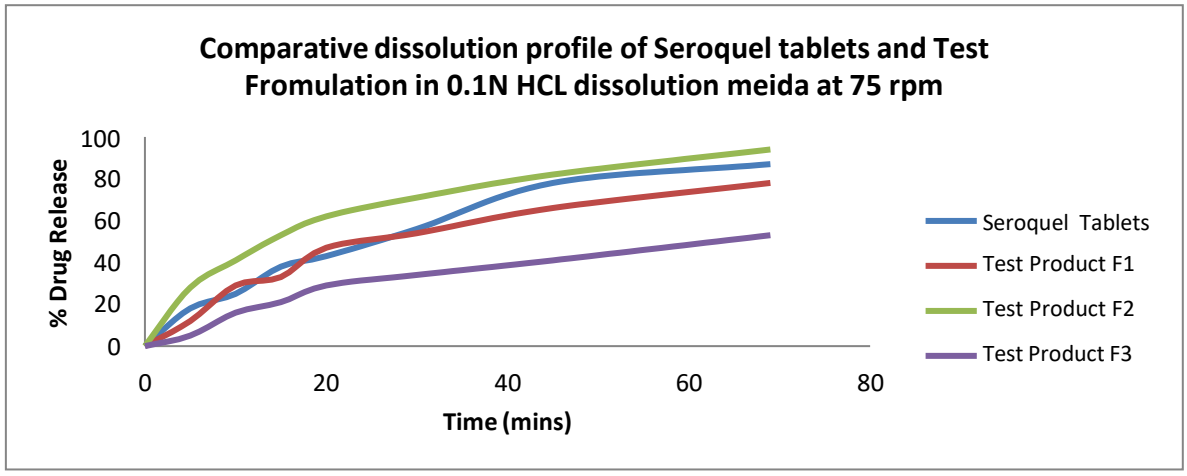
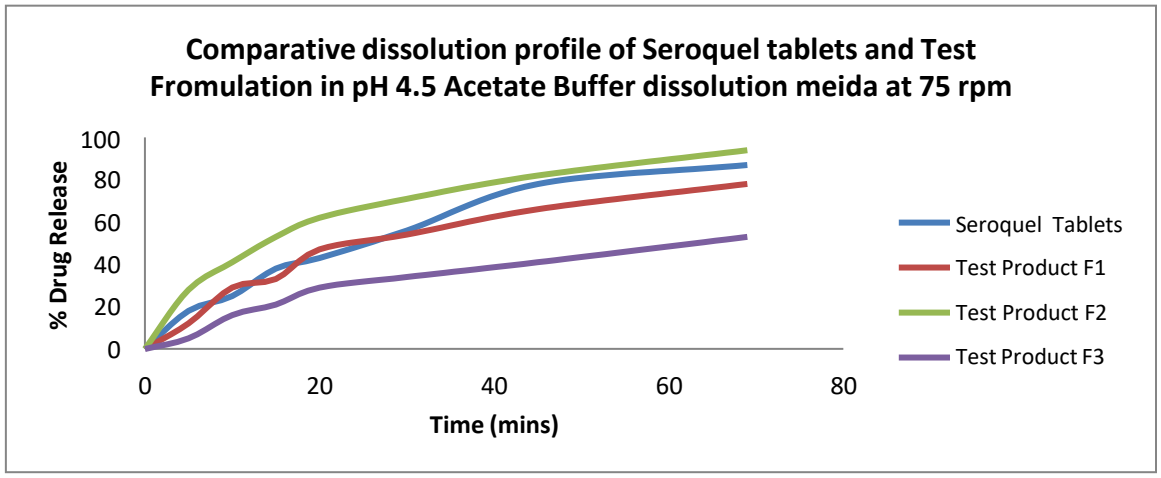

Comparative dissolution profile of Seroquel tablets and Test Fromulation in pH 6.8 Phosphate Buffer dissolution meida at 50rpm
% Drug Release
100
80
60
40
20
0
0
20
40
60
80
Time (mins)
Seroquel Tablets
Test Product F1
Test Product F2
Test Product F3

Table 3: Dissolution profile using different dissolution media in 50 RPM

Formulation Type	In vitro dissolution using 0.1NHCL, 900ml, Apparatus 2, 75 rpm				In vitro dissolution using pH 4.5 Acetate Buffer, 900ml, Apparatus 2, 75 rpm				In vitro dissolution using pH 6.8 Phosphate Buffer, 900ml, Apparatus 2, 75 rpm			
Time (min)	Seroquel Tablets	F1	F2	F3	Seroquel Tablets	F1	F2	F3	Seroquel Tablets	F1	F2	F3
5	27	22	38	12	23	19	25	11	13	9	21	6
10	38	32	51	28	31	23	44	18	23	17	39	12
15	46	39	59	31	39	36	61	20	29	21	46	19
20	59	49	71	46	46	41	79	31	41	31	54	29
30	67	57	79	51	55	51	86	39	49	37	63	37
45	78	71	89	59	69	62	92	43	62	56	78	43
60	91	87	98	67	81	73	99	51	76	62	89	56
F2		58	48	40		63	34	36		53	44	44





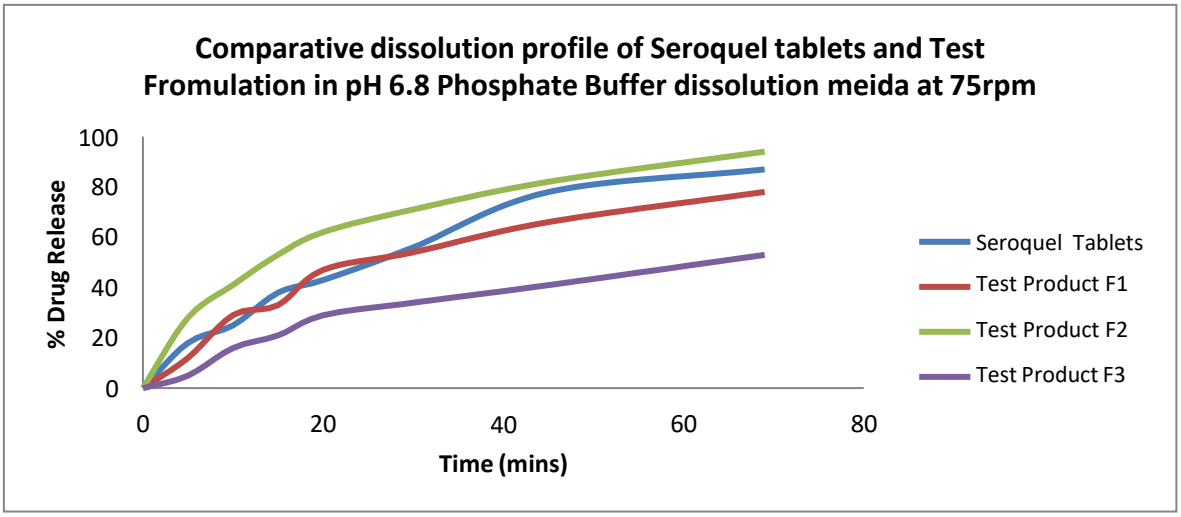
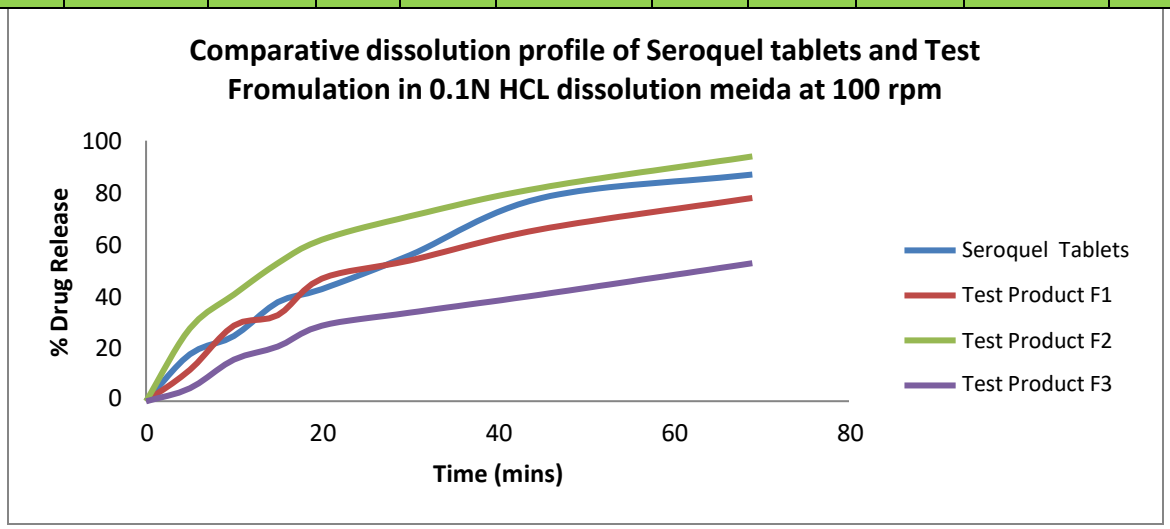
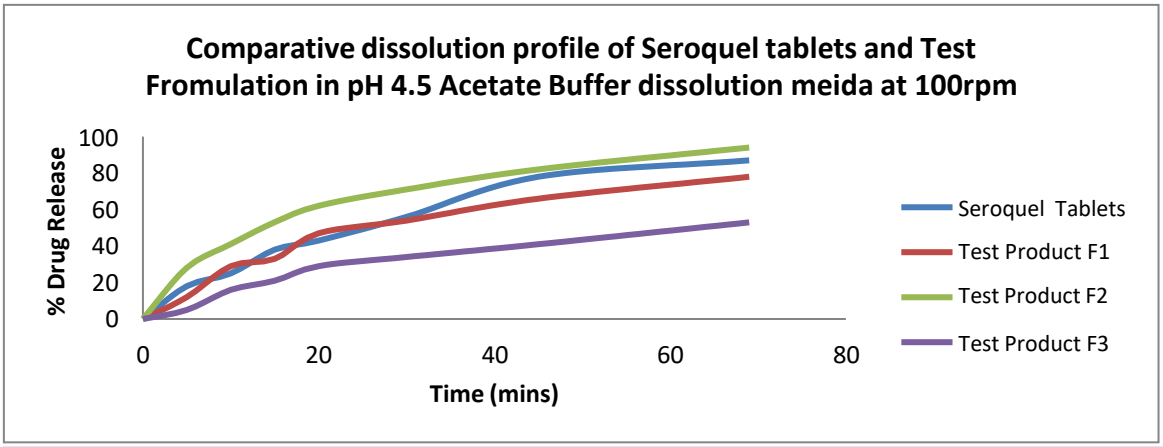
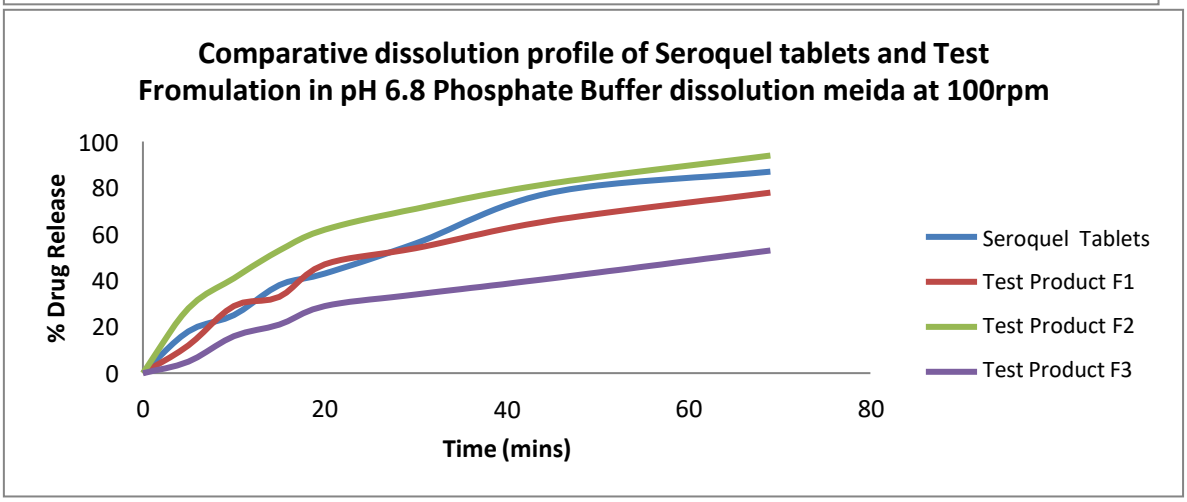


Table 4: Dissolution profile using different dissolution media in 50 RPM

Formulation type	In vitro dissolution using 0.1NHCL, 900ml, Apparatus 2, 100 rpm				In vitro dissolution using pH 4.5 Acetate Buffer, 900ml, Apparatus 2, 100 rpm				In vitro dissolution using pH 6.8 Phosphate Buffer, 900ml, Apparatus 2, 100 rpm			
Time (min)	Seroquel Tablets	F1	F2	F3	Seroquel Tablets	F1	F2	F3	Seroquel Tablets	F1	F2	F3
5	35	32	49	16	29	21	37	16	19	15	37	9
10	48	43	61	27	38	29	49	21	27	23	49	16
15	56	51	72	37	45	38	65	31	35	35	58	23
20	68	61	79	49	59	48	75	38	47	45	69	38
30	76	69	91	58	68	62	81	43	58	58	74	47
45	89	81	97	67	79	73	96	49	73	69	89	53
60	99	91	101	77	91	86	99	61	81	76	97	59
F2		61	47	36		57	44	45		74	37	43







CONCLUSIONS

This study showcased the systematic and sequential design of experiments in the development of a discriminatory dissolution method for a BCS Class 2 drug exhibiting highly pH-dependent solubility. The parameters for the robust and discriminatory dissolution method for Quetiapine Fumarate Tablets are 900 mL of pH 6.8 phosphate buffer in Apparatus 2 at 50 rpm. Significant variations in drug release profiles were observed in the different dissolution media. The method can be used in the formulation development studies, as well as for the selection of biobatch for the bioequivalent study. The proposed of studying the effect of the physiological properties of GI fluids on the rate of drug release from tablets prepared using different types of binder and Disintegrants attaining similar release profiles in a compendial- or FDA-recommended dissolution medium and help predict more accurate in vitro–in vivo correlations for pharmaceutical dosage form.

REFERENCES

1. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and invivo bioavailability. Pharm. Res. 12, 413–420.
2. Blume, H., Ali, S.L., Siewert, M., 1993. Pharmaceutical quality of glibenclamide products: a multinational postmarket comparative study. Drug Dev. Ind. Pharm. 19 (2), 713–2741.
3. Blume, H., Mutschler, E., 1989. Bio ¨aquivalenz. Govi-Verlag, Eschborn. Budavari, S., O'Neil, M.J., 1996. The Merck Index. Chapman &Hall.Costa, P., Lobo, J.M.S., 2001.
4. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.
5. Dressman, J.B., Amidon, G.L., Reppas, C., Shan, V.P., 1998.
6. Dissolution testing as a prognostic tool for oral drug absorption immediate release dosage forms. Pharm. Res. 15(1), 11–21.
7. Kalantzi, L.; Goumas, K.; Kalioras, V.; Abrahamsson, B.; Dressman, J. B., Reppas, C. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. Pharm. Res. 2006, 23 (1), 165–176.
8. Siewert M, Dressman J, Brown CK, Shah VP. FIP/AAPS guidelines to dissolution/in vitro release testing of novel/special
9. dosage forms. AAPS PharmSciTech. 2003;4(1):1.
10. Shah VP, Tymes NW, Skelly JP. In vitro release profile of clonidine transdermal therapeutic systems and scopolamine patches. Pharm Res. 1989;6:346–51.
11. Food and Drug Administration. Guidance for industry: immediate release solid oral dosage forms: scale-up and post-approval changes.
12. Rockville, MD: US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research; November 1995.
13. Food and Drug Administration. Guidance for industry: modified release solid oral dosage forms: scale-up and post-approval changes. Rockville, MD: US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research; October 1997.
14. Chapter 711: Dissolution. In: United States Pharmacopeia 31 (USP 31): National Formulary 26 (NF 26). 2008. p. 267–274.2010.
15. Chapter 724: Drug release. In: United States Pharmacopeia 31 (USP 31): National Formulary 26 (NF 26). 2008. p. 275–278. 2010.
16. Chapter 1092: The dissolution procedure. Development and validation. In: United States Pharmacopeia 31 (USP 31):
    National Formulary 26 (NF 26). 2008. p. 573–678.
17. Food and Drug Administration. Guidance for industry: dissolution testing of Immediate Release Solid Oral Dosage Forms.