Assessment of Similarity between Dissolution Profiles of Ketotifen and Its Competitor Drug

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ABSTRACT: Release of drug after dissolution from solid pharmaceutical dosage forms is a crucial parameter to be studied to ensure fulfillment of requirements laid by the registration authorities. In this study we have used both independent model and dependent procedures to evaluate the alteration among dissolution profiles in which ketotifen, as tablet dosage form, has been utilized as model drug. The selection of an appropriate regression function, the significant predictable factors and the inspiration of the selection of points of dissolution in the evaluation of alterations was deliberated. The outcomes attained through mean dissolution times analysis.The f_1 and f_2 factors are also deliberated as a non-quantitative method. The obtained profiles were correlated with graphical illustration of concentration and rate. Profiles assessments using 0.1N HCL, phosphate buffer of pH 4.5 and 6.8 assessed by model- independent method. Ketofen 1 mg tablet were taken as a reference product against the ketofen t1 mg test product and their 12 units were analysed for the identification of similarity factor between them in all dissolution media (0.1 NHCl , 4.5 buffer and in 6.8 phosphate buffer). A comparison between dissolution profiles in different dissolution media (0.1 NHCl , 4.5 buffer and in 6.8 phosphate buffer obtained by using a dissolution apparatus at RPM 75 on different point intervals. Results obtained from the multipoint time interval at 120, 60, 45, 30 and at 15 minutes were analyzed by HPLC technique and it was revealed that the similarity between the test drug and reference drug i.e in 0.1 NHCl f_2 was 58.88, in 4.5 buffer f_2 was 83.71and in 6.8 buffer f_2 was 72.98 Results indicated that all the medium were produced similar results but buffer 4.5 produce more similarity as compared to the other dissolution mediums.
Keywords Model dependent methods, Model independent methods, Mean dissolution times**,** Dissolution profiles comparison, Correlation coefficients, Fit factors

I. INTRODUCTION

Drug release after dissolution from solid pharmaceutical dosage forms is an essential parameter to be studied to ensure fulfillment of requirements laid by the registration authorities, nowadays. [1][2][3]. The proper regression function and influence of the dissolution points are necessary for the evaluation of best dissolution profile [4]. There are many model-independent and model-dependent techniques mentioned in the methodical literature review. Present strategies principally endorse the request of a process established upon the f_2 statistic as an enumerate of the similitude of two dissolution curves, although this process has been frequently appraised lately[4][5]. Ketotifen ($C_{19}H_{19}NOS$) is a first-generation noncompetitive H_1-antihistamine is farthest vended as a salt with fumaric acid, it is an histamine H1 receptor blocker interfering with release of inflammatory mediators in allergic activity [6]. It has been offered for the management of anaphylaxis, skin allergy, rhinitis, and asthma. The mechanism of action of ketotifen is as a Histamine H1 Receptor Antagonist, selectively blocks histamine (H1) receptors and thwarts the archetypal indications triggered by histamine release. Ketotifen fumarate, obtain from two ways.[7] Thus called mast-cell stabilizer [8] It is used in the management of asthma in children and younger where inhaled management can be complicated and an oral drug like ketotifen presents prospective benefits to treat typical indications in such cases. This recommends that ketotifen has a place comparable to othr drugs : disodium cromoglycate or steroid aerosols to manage asthmatic condition related to steroid dependence. Ketotifen has the benefit of compelling twice-daily oral administration[9].Ketotifen is a exact beneficial medication for deterrence of asthma in children having atopic dermatitis and total IgE more than 50 IU/mL with insignificant

properties[10].The evaluation create that minor asthma indications were exact in the analysis of 4-32 week period with diminution in use of rescue oral steroids, rescue bronchodilator, and in exacerbations along with vibrant perception of usefulness from parents, children and physicians. [11].In current centuries, numerous mathematical models have been established for exploration of medicine dissolution data, and numerous diverse scientific tactics have been projected to evaluate the resemblance among two medicine dissolution profiles[12]. Nevertheless, until currently, no computer driver has been stated for abridging the computations elaborate in the modeling and valuation of dissolution summaries.DD Solver is an upright accumulation for such study [13].
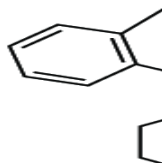
Figure 1 Structure of Ketotifen

II. METHODOLOGY

The instrument used for the research work were HPLC Agilent 1200, weighing balance Mettler Toledo Ag285, Dissolution apparatus DT70, ultrasonic water bath wu-203 korea and magnetic stirrer ab-009 galvano scientific and all the experimental work were performed at the lab facility of Jinnah university for women

Preparation of Reagents:
Preparation of 10 mMole disodium hydrogen phosphate Buffer:
Weighed **0.141gm** of disodium hydrogen phosphate and transfer into 1000 ml volumetric flask containing 800ml of distilled water, dissolve by stirring on magnetic stirrer until the material get dissolved. Adjust the pH to 6.5 by using 1% orthophosphoric acid and makeup the volume with distilled water.

Preparation of mobile Phase:
Prepare a mixture by adding 700ml of acetonitrile and 300ml of buffer. Filter the solution through 0.2 micron filter sonicates and degas the mobile phase.

Preparation of dissolution medium
0.1 N hydrochloric acid: Transfer 51 ml of hydrochloride acid (37% /w/w) to a flask calibrated to 6 liters that previously contain about 5 liter of distilled water. Dilute the solution to 6 liters with distilled water and mix

6.8 buffer medium
Transferred 40.83gm of monobasic potassium phosphate in 6 liter purified water, adjusted pH to 6.8 with sodium hydroxide or phosphoric acid..

4.5 acetate buffer medium
Transferred 17.84gm of sodium acetate trihydrate in 6 liter purified water, adjusted pH to 4.5 with glacial acetic acid.

Competitor Drug Information
Zatofen tablet 1mg core tablet was purchased from the pharmacy of gulshan area Karachi having batch number GLSAAC, manufacturing date 11-2017 and expiry date : 10-2019

Preparation of standard:
Weigh 20 mg of ketotifen fumarate working standard and transfer into 200ml Volumetric flask, add 150ml of dissolution medium, sonicate to dissolve, cool at room temperature and makeup the volume with dissolution medium up to the mark. Transfer 2ml of the overhead solution to 100ml volumetric flask, and finally make up standard volume with dissolution medium and mix.

Preparation of sample:
Upon completion of the dissolution time withdraw 10 ml of the dissolution sample separately from each of the vessel and filter through swirny filter paper use the filtrate as test solution.

Procedure
Dissolution Test: The drug release was measured in % using diverse formulations of Ketotifen were conceded out devouring USP dissolution test machine (II) Dissolution apparatus DT70, Germany), expending 500ml of buffer medium of phosphate, at $37^0C + 0.50C$ at a speed of 75 rpm. The drug release of Ketotifen was resolute by HPLC Agilent 1200 at 230nm [16] as shown in table1 .

Dissolution Profiles Comparison: The generated profiles of dissolution were related through USP dissolution test machine II Dissolution apparatus DT70 expending instantaneous released core tablet (Reference) at 75 rpm, consuming 500 ml of each of the following dissolution media: 0.1N HCL, phosphate buffer pH 4.5 and pH 6.8 at $37 + 0.5^0C$. Dissolution apparatus according to the test

conditions were maintained and the temperature has been equilibrated , by placing one tablet into each of the dissolution vessel and operated the apparatus for the specified time Almost 10ml of sample was introverted and clarified from each pot at 120, 60, 45, 30, and 15min and replaced with fresh medium of 10ml, dissolved Ketotifen

concentrations were resolute by HPLC Agilent 1200) at 230 nm. [14].

Analysis of data

Model-Independent Method Predominantly, similarity factor (f2) equation is widely recommended for comparision of the dissolution method data [15], expressed as f_2

$$= 50 \times \log\left(\frac{100}{1 + \frac{\sqrt{\sum(R_i - T_i)^2}}{N}}\right)$$

The profiles are found to be similar for test and reference when f2 is greater than 50, as shown in table 9

Table 1: Dissolution and chromatographic conditions

Conditions	Specifications
Medium	Buffer pH 6.8, 4.5 and 0.1 NHCl
Volume	500 ml
Apparatus:	USP-II (Paddle)
Speed	75 rpm
Units	12
Sampling times	15, 30, 45, 60 and 120 minutes
RSD	NMT 2.0
Tailing factor	NMT 2.0
Theoretical plates	NLT 1000
Wavelength	230 nm
Column	C18 BDS (150mmx4.6mm 5micrometer)
Volume	100 micro liter
Flow rate	1ml/minute
Limits	NLT 80%

III. RESULTS

Model independent and dependent procedures were used in this work to evaluate the alteration among dissolution profiles in which ketotifen, in the form tablet dosage form, is used as a model drug [2][3]Model - independent method Dissolution profiles were associated with the best using the similarity factor (f2). In all the three media, the profiles of reference product were analogous to the test product. Correspondingly,

dissolution profiles of the test product were also compared with immediate release (reference) product using the similarity factor (f2) in overhead media. Outcomes exhibited that the profile of reference formulation was comparable with in phosphate buffer pH 4.5 but given dissimilar results in 0.1N HCL and 6.8 buffer media as expressed in table 3,4,5,6,7 and 8. [4][15]

Table 3: Results of dissolution in 6.8 buffer for test product

Time intervals of dissolution profile in 6.8 buffer (test product)						
No	0 mints	15 mints	30 minutes	45 minutes	60 minutes	120 minutes
1	0.00	29.03	40.58	49.47	56.24	56.33
2	0.00	43.22	49.91	52.63	60.88	54.93
3	0.00	43.80	53.32	76.87	82.99	64.12
4	0.00	65.62	63.50	68.00	68.60	74.38

5	0.00	45.81	63.46	73.18	82.58	69.64
6	0.00	33.83	64.57	72.99	79.23	70.96
7	0.00	23.42	40.98	49.46	57.82	72.28
8	0.00	48.12	50.13	51.59	67.16	72.09
9	0.00	44.35	53.68	75.47	83.26	73.71
10	0.00	56.55	60.41	70.16	75.68	73.04
11	0.00	46.40	61.16	68.96	76.39	80.83
12	0.00	37.86	72.21	76.41	82.43	77.83
Average	0.00	43.17	56.16	65.43	72.77	70.01

Table 4: Results of dissolution in 6.8 buffer for reference product

Time intervals of dissolution profile in 6.8 buffer (reference product						
No	0 mints	15 mints	30 minutes	45 minutes	60 minutes	120 minutes
1	0.00	35.50	41.36	49.67	46.37	43.55
2	0.00	27.18	48.02	45.81	42.85	57.24
3	0.00	23.36	34.16	50.83	57.76	61.23
4	0.00	46.81	46.31	56.62	55.95	60.13
5	0.00	37.80	49.20	56.96	60.57	64.72
6	0.00	30.10	42.17	56.50	54.48	64.28
7	0.00	26.36	35.49	49.41	49.73	51.72
8	0.00	32.66	45.48	50.37	56.13	53.63
9	0.00	25.08	45.05	59.08	53.87	64.37
10	0.00	41.95	50.28	59.56	58.89	60.52
11	0.00	36.18	50.59	60.58	60.23	64.48
12	0.00	35.18	50.79	64.96	54.12	63.54
Average	0.00	33.18	44.91	55.03	54.25	59.12

Table 5: Results of dissolution in 0.1 NHCl buffer for test product

Time intervals of dissolution profile in 0.1 NHCl buffer (Test product)						
No	0 mints	15 mints	30 minutes	45 minutes	60 minutes	120 minutes
1	0.00	30.34	41.95	50.44	66.15	66.68
2	0.00	45.71	58.60	66.04	65.40	69.57
3	0.00	37.84	48.40	61.38	74.14	70.98
4	0.00	35.60	48.78	56.12	57.85	71.29
5	0.00	29.69	41.96	52.09	59.82	66.23
6	0.00	43.43	74.71	74.12	63.08	77.72
7	0.00	52.67	58.41	53.88	61.75	74.79
8	0.00	34.90	54.53	64.51	69.75	64.65
9	0.00	32.08	57.58	63.34	71.69	69.00
10	0.00	38.77	52.94	49.44	52.88	65.48
11	0.00	44.43	51.28	58.16	58.09	64.19
12	0.00	35.92	42.23	61.37	69.66	73.51
Average	0.00	38.45	52.61	59.24	64.19	69.51

Table 6: Results of dissolution in 0.1 NHCl buffer for reference product

Time intervals of dissolution profile in 0.1 NHCl buffer (reference product					
No	0 mints	15 mints	30 minutes	45 minutes	60 minutes	120 minutes
1	0.00	35.50	41.36	49.67	46.37	43.55
2	0.00	27.18	48.02	45.81	42.85	57.24
3	0.00	23.36	34.16	50.83	57.76	61.23
4	0.00	46.81	46.31	56.62	55.95	60.13
5	0.00	37.80	49.20	56.96	60.57	64.72
6	0.00	30.10	42.17	56.50	54.48	64.28
7	0.00	26.36	35.49	49.41	49.73	51.72
8	0.00	32.66	45.48	50.37	56.13	53.63
9	0.00	25.08	45.05	59.08	53.87	64.37
10	0.00	41.95	50.28	59.56	58.89	60.52
11	0.00	36.18	50.59	60.58	60.23	64.48
12	0.00	35.18	50.79	64.96	54.12	63.54
Average	0.00	33.18	44.91	55.03	54.25	59.12

Table 7: Results of dissolution in 4.5 buffer for test product

| Time intervals of dissolution profile in 4.5 buffer (Test product)					
No	0 mints	15 mints	30 minutes	45 minutes	60 minutes	120 minutes
1	0.00	51.25	55.88	62.18	82.58	84.89
2	0.00	49.99	71.29	84.40	91.05	87.88
3	0.00	52.40	61.00	70.75	77.60	86.23
4	0.00	39.61	60.24	76.85	86.06	86.57
5	0.00	39.57	44.16	54.21	56.83	65.07
6	0.00	61.35	73.07	77.69	88.78	96.78
7	0.00	42.53	62.86	73.10	81.80	84.22
8	0.00	45.71	53.20	69.43	74.69	85.36
9	0.00	43.02	51.18	65.08	71.87	82.58
10	0.00	47.78	48.39	67.20	69.43	71.75
11	0.00	37.70	43.10	48.71	55.14	63.40
12	0.00	54.35	56.07	74.13	83.49	86.12
Average	0.00	47.11	56.70	68.64	76.61	81.74

Table 8: Results of dissolution in 4.5 buffer for reference product

Time intervals of dissolution profile in 4.5 buffer (reference product					
No	0 mints	15 mints	30 minutes	45 minutes	60 minutes	120 minutes
1	0.00	49.78	50.17	57.23	91.11	80.99
2	0.00	42.42	61.89	82.99	96.86	90.55
3	0.00	48.81	62.46	61.97	77.56	77.51
4	0.00	42.42	66.87	63.81	75.77	93.54
5	0.00	45.07	42.56	62.49	69.98	65.92
6	0.00	57.73	56.97	74.77	90.41	89.19

7	0.00	45.37	57.90	65.10	88.14	73.74
8	0.00	50.80	53.02	64.64	74.70	75.94
9	0.00	48.73	42.97	64.42	67.71	77.00
10	0.00	37.30	41.26	67.30	70.77	70.47
11	0.00	42.42	39.37	70.74	44.13	70.51
12	0.00	44.02	56.24	65.40	85.00	79.16
Average	0.00	46.24	52.64	66.74	77.68	78.71

Table 9: Results of similarity factor in all mediums

Dissolution medium	Dissolution Time	Similarity (f_2) factor
Buffer pH 6.8	120 minutes	58.88
Buffer pH 4.5	120 minutes	83.71
0.1 N Hydrochloric acid	120 minutes	72.98
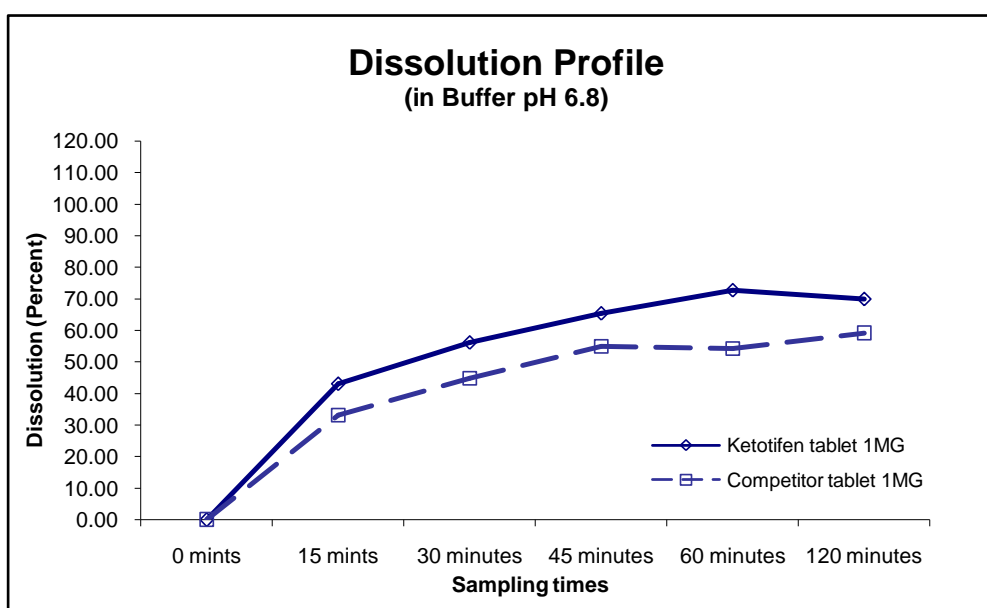
Figure 2: Dissolution profile in p H 6.8 Buffer medium
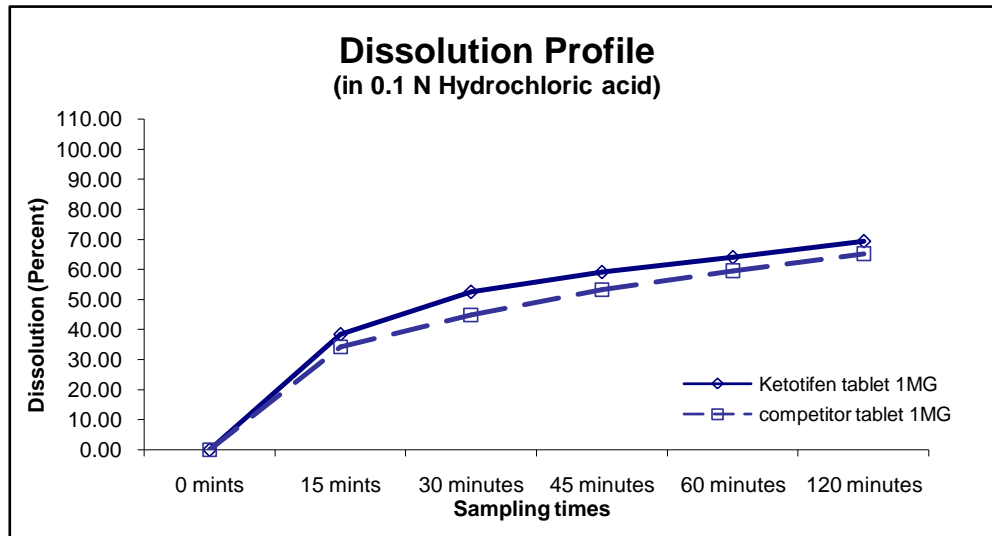
Figure 3: Dissolution profile in p H 0.1 NHCl Buffer medium
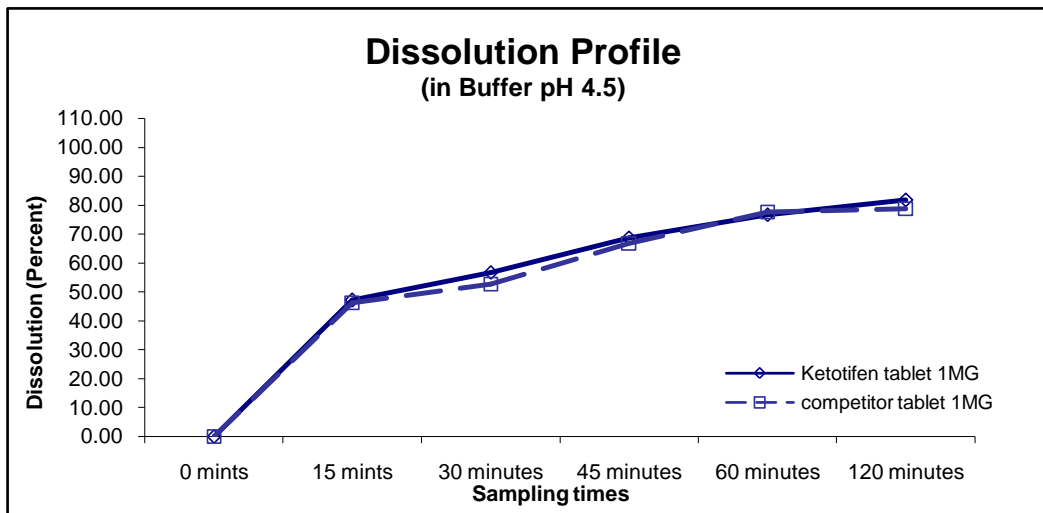
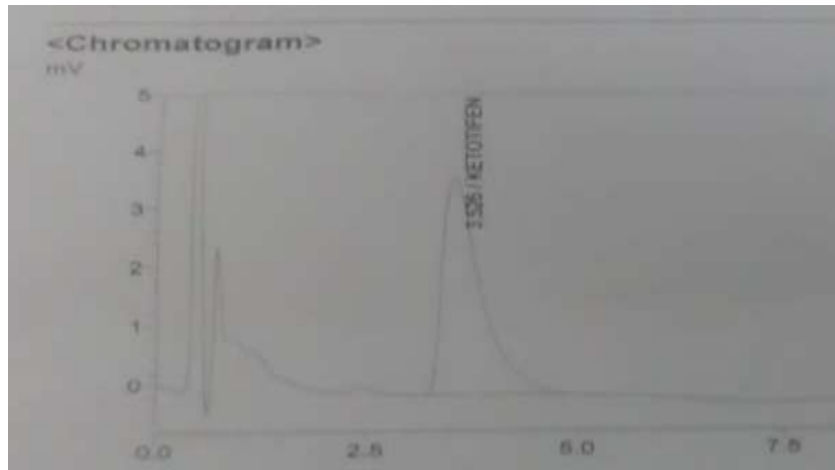**Figure 4: Dissolution profile in p H 4.5 Buffer medium**

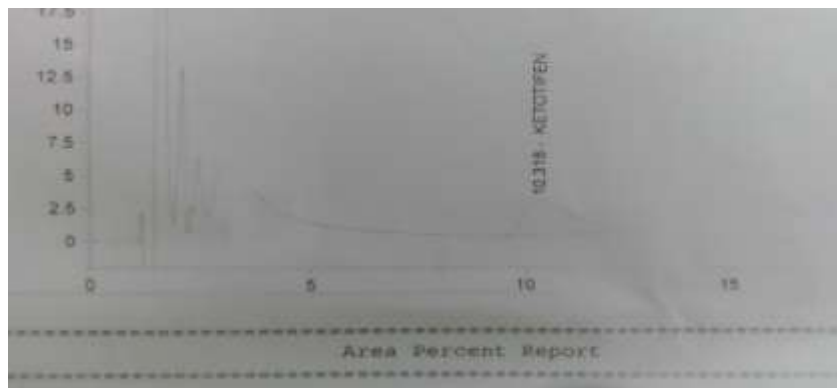**Figure 5: HPLC chromatogram of test standard.**

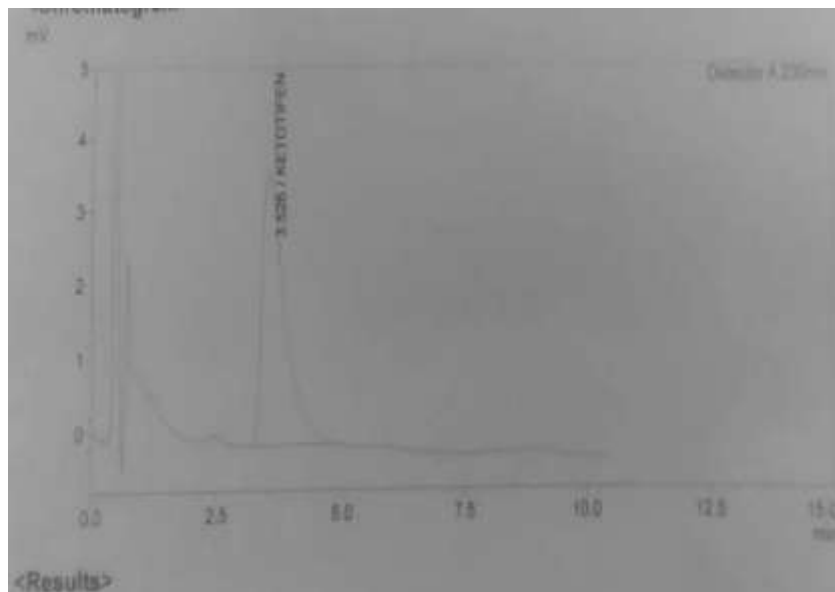**Figure 6: HPLC chromatogram of test sample in 0.1 NHCl.**

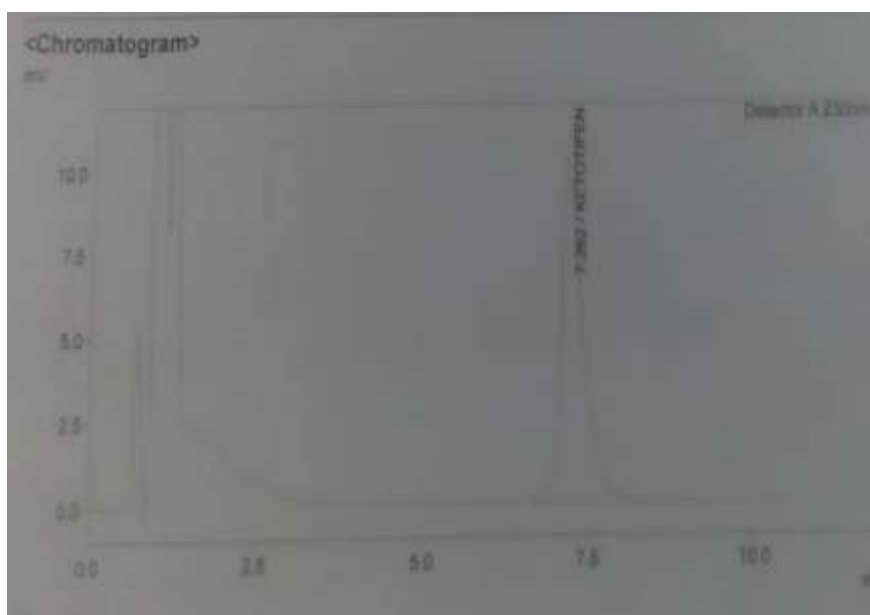**Figure 7: HPLC chromatogram of test sample in 4.5 buffer.**

Figure 8: HPLC chromatogram of test sample in 6.8 buffer

IV. DISCUSSION

Kinetics models are used to determine dissolution of drug from solid dosage form, in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f(t).Various methods are used nowadays to illustrate drug dissolution or drug release profiles such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), assay time ($t_{x\ min}$), similarity factor (f_2), Rescigno index (ξ_1 and ξ_2) and difference factor (f_1), [1]In the current analysis Ketotifen is chosen as a model drug which have pKa value of 4.6. Scientists have stated that in acidic media, Ketotifen exhibited low solubility and dissolution but as soon as the compound is squashed in to the basic environment i.e. upper small intestine, presence of bile salts and pH is increased, this progresses both the solubility and dissolution vividly [14][16] In the current examination, dissolution profiles were also connected in three diverse dissolution media i.e. 0.1N HCL, phosphate buffer pH 4.5 and pH 6.8. Outcomes showed that the % drug release of all the formulations after 120 min in pH 6.8 and 1.2 were less than 80% but in phosphate buffer pH 4.5, showed 81% drug release as articulated in Figure 2,3 and 4, the best dissolution medium for the analysis of dissolution profile of ketotifen 1 mg tablet was buffer p H 4.5 and its similarity factor f2 was also near to 100.

V. CONCLUSION:

The developed immediate tablet test product have appropriate properties that discriminate them from other solid dosage form . From the current investigation it has been explicated that Ketotifen tablets test product were similar to the reference product and their dissolution profile data proves that 4.5 p H medium was more suitable medium than other mediums. The mediums and methods of dissolution study was accurate, easy and rapid to use for analysis of dissolution of ketotifen 1mg tablet.

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