Quality control analysis of marketed metformin sample (glyciphage)

SUBJECT –PRACTICE SCHOOL
CODE –PT-781

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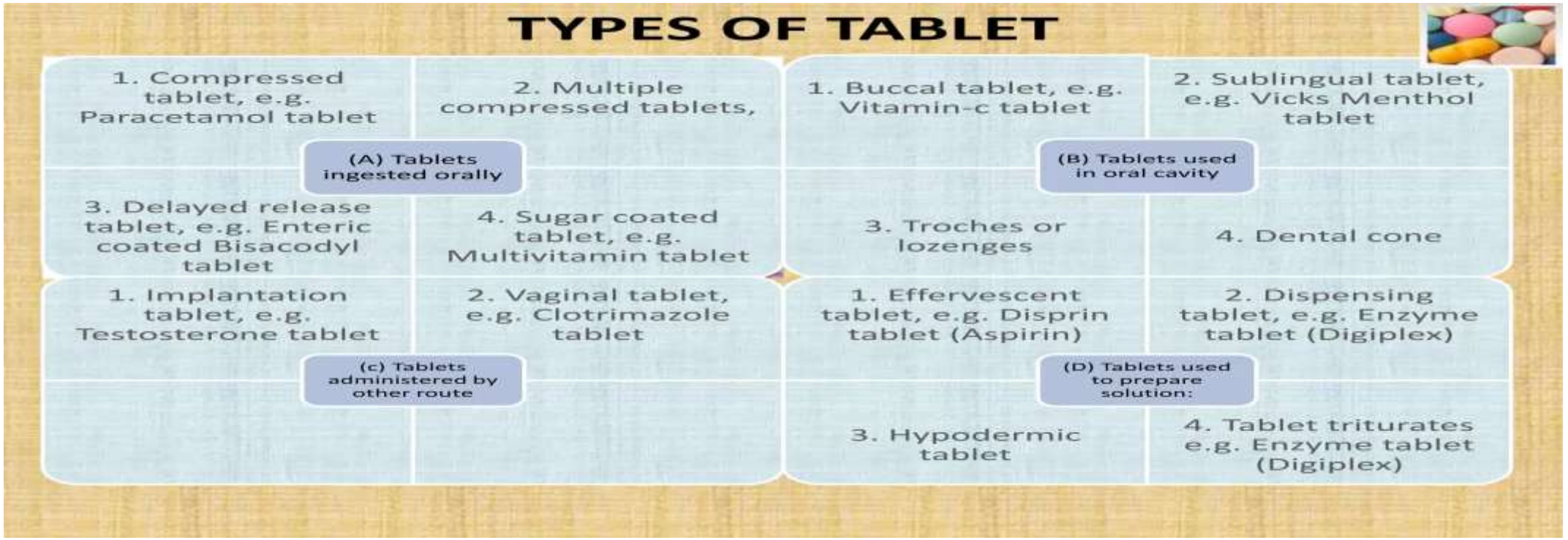
Introduction

Quality control (QC) is the part of GMP that is concerned with sampling, specifications, testing and with the organization, documentation and release procedures which ensure that the necessary tests are actually carried out and that materials are not released for use, sale or supply, until their quality has been judged to be satisfactory according to specification.[1] QC refers to the goodness or excellence of a Product. It increases output and reduces failure. QC emphasizes testing of products for faults and reporting to regulation that makes the decision to investigate or reject the release. Finished product controls (FPCs) are tests that are performed when the manufacturing process is completed in order to check qualitative and quantitative characteristics along with test procedures and their acceptance limits, by which the finished product must comply throughout its valid shelf-life.[2] Pharmacopoeias are called drugs standard. There are various types of pharmacopoeias such as Indian Pharmacopoeia (IP),British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt) and Japanese Pharmacopoeia (JP) indifferent parts of the world and they have laid down the specified limits within which the value should fall in order to be compliant as per the standards.

TABLETS

Tablets are compressed solid unit dosage form containing medicament or medicaments usually circular in shape and may be flat or biconvex. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipient.

According to Indian Pharmacopoeia, pharmaceutical tablets are flat or bi-convex discs manufactured by compressing a drug or a mixture of rugs with or without suitable excipients.



Types of Tests to Evaluate the Qualities of Tablets

A. Non-Pharmacopeial or Non-Official Tests or In-House Tests of Tablet:

- Appearance/ Description
- Thickness and Diameter
- Hardness
- Organoleptic properties

B. Pharmacopeial or Official Tests of Tablets:-

- Identification Tests
- Friability Test
- Disintegration Test
- Weight Variation Test
- Uniformity of Dosage Unit Test
- Dissolution Test
- Assay Test
- Impurities Test.

METFORMIN TABLETS

Metformin is a biguanide antihyperglycemic used in conjunction with diet and exercise for glycaemic control in type 2 diabetes mellitus. It is also used off-label for insulin resistance in polycystic ovary syndrome (PCOS).

- It is a biguanide derivate
- First line oral therapy in the recent guidelines of the American Diabetes Association.
- Most widely prescribed drug to treat hyperglycemia, at least 120 million user worldwide.
- Monotherapy & in combination with all antidiabetic

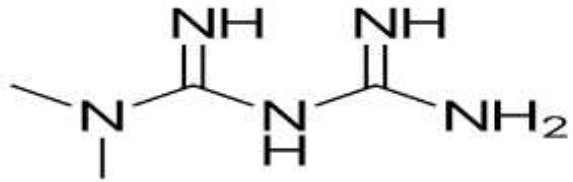


Fig. 1.-Chemical structure of Metformin.

Brands name available in markets are- Actoplus Met, Avandamet, Fortamet, Glucophage, Glucovance, Glumetza, Glycon, Invokamet, Janumet, Jentadueto, Kazano, Kombiglyze, Komboglyze, Qternmet, Riomet, Segluromet, Synjardy, Trijardy, Velmetia, Xigduo, glyciphage, etc .

We use GLYCIPHAGE – 500 MG as a test sample.

Fig.2.Glyciphage

AIM & OBJECTIVES

In tablet production, tablet production quality, quantitative evaluations and assessments of a tablet's chemical, physical, and bioavailability properties must be made. Not only that, during the compression of tablets, in process tests are routinely run to monitor the process, and as we all know that to control the quality as well as maintaining it is a severe concern nowadays. Therefore, in our practice school session we aimed to perform quality control test for marketed metformin tablets.

Our objectives to perform various quality control test for tablet such as hardness, friability, disintegration, dissolution, identifications and assay etc.

The quality control test, we performed discussed as follows :

Identification

Metformin was identified by chemical test as specified in IP. When 1-napthol solution and sodium hydroxide solution was added to metformin solution colour changed to orange-red colour, which darkened over time when kept. This result complied with the test as specified in IP.

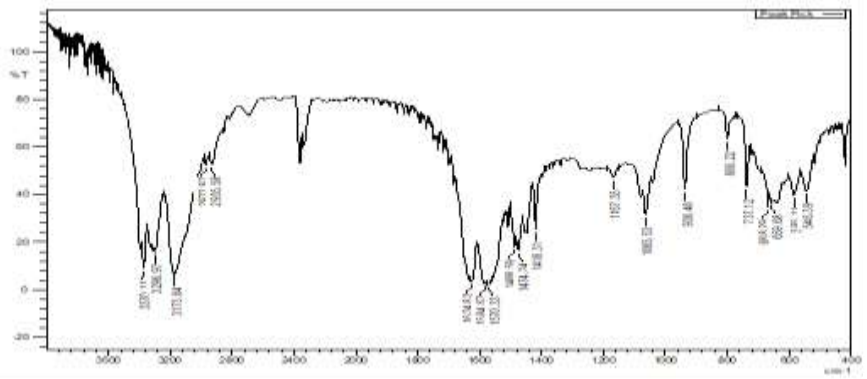


Fig.5 - FTIR spectra of metformin hydrochloride extracted from tablet

Fig.3 – initially orange colour produced

Fig.4 – darkness on keeping

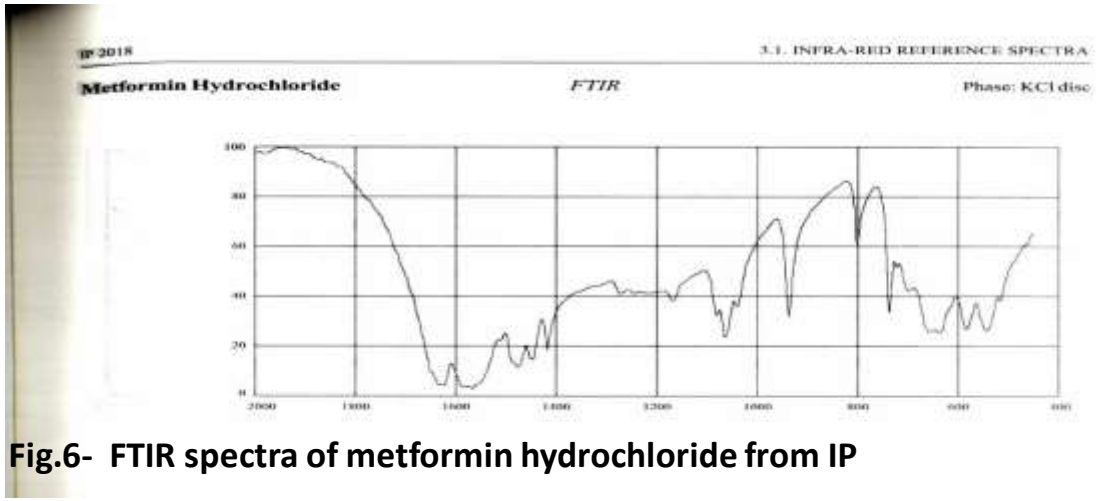


Fig.6- FTIR spectra of metformin hydrochloride from IP

Further, metformin in tablet dosage form was also identified by FTIR spectrophotometric method for that metformin was extracted with ethanol from tablet powder and after evaporating the solvent and further drying, FTIR spectrum was recorded by pressed pellet technique and compared with standard spectrum as specified in iP. FTIR spectrum of metformin extracted from tablet and standard metformin IR spectra as specified in IP were represented in Fig5 and fig6. Result of this study showed that finger print region of IR spectra of metformin extracted from tablet is exactly matched with the standard IR spectra indicated the presence of metformin in tablet dosage form.

Appearance:

Through visual identification, it was determined that the tablet was a white-coloured, oblong-shaped tablet with an average height of 5.5mm and a diameter of 11.8 mm. The brand name was engraved upon one surface of the tablet, and a dash mark was found on another surface, potentially providing unique identification for the tablet. The white colour appeared uniformly distributed on the product, which had a smooth surface and a slight characteristic odour. Through these tests, the tablet's level of flaws, such as chips, cracks, contamination from foreign solid substances, surface texture, and appearance, was found to have no defects compared to specifications.

Fig.7. Tablets

Size and shape study gives the following results-

Sl. No.	Thickness (mm)	Mean± stand. Dev.	Diameter(mm)	Mean± stand. Dev
1	5.7	55±0.196	11	11.8±2.058
2	5.2		10	
3	5.3		9	
4	5.4		12	
5	5.8		14	
6	5.7		11	
7	5.6		13	
8	5.5		16	
9	5.7		11.5	
10	5.6		10.5	

Table 1. Thickness

Hardness

A certain amount of strength, known as hardness, and resistance to friability were required by the tablets to withstand mechanical shocks during handling in manufacture, packing, and shipping. Adequate tablet hardness and resistance to powdering and friability were deemed necessary requisites for customer acceptance. Pfizer hardness tester was used for testing our sample. Hardness of the tablets is indicated in table2 . Mean hardness of tablet was found to be 3.8 ±0.2. The hardness test results of our sample (Glycyphage 500) were as follows:

Fig.8. Pfizer hardness apparatus.

Tablet No.	Hardness(kg)	Mean±sd
1	3.5	3.8±0.223
2	3.7	
3	3.9	
4	3.8	
5	4.1	

Table 2. Hardness value.

Tablet hardness for oral tablets typically lies within the range of 3-10 kg, and our marketed Glyciphage, an uncoated metformin tablet, fell within this range. Therefore, it was inferred that it comply with specification.

Friability :

Fig.9. Roche Friabilator

The tablets underwent a tumbling action to test their resistance to abrasion and chipping. It was noted that tablet hardness did not serve as an absolute indicator of strength due to certain formulations, compressed into very hard tablets, tending to "cap" on attrition, resulting in the loss of their crown portions. Hence, another measure of a tablet's strength was considered, namely its friability. Roche Friabilator(fig.) was used to test friability. Six tablets were subjected to this test and after test weight loss was noted as 0.02 gm and percentage was weight loss was found to be 0.3%.

Friability test result of our sample was as follows :
Initial weight of tablets(W) – 6.46gm; Final weight of tablets(Wo) – 6.44gm.

so, Friability(f) =100(1-Wo/W)
= 100(1-6.44/6.46)
= 0.3%

So, friability of 6 sample is 0.3% of initial weight

Considering that a maximum mean weight loss from the three samples not exceeding 1.0% is generally deemed acceptable for conventional compressed tablets, the friability of our six tablets was measured at 0.3%. This value fell below the acceptable criteria, indicating that Glyciphage exhibited a positive result in the friability test.

Weight Variation test :

The weight variation test, a quality control measure for tablets assessing the consistency in their weight, was conducted. As per the IP guidelines, the weight variation limits are ±5% for tablets with a weight of 250 mg or more. Individual tablet weights were checked to ensure compliance with the specified weight range in this test. The obtained results of our weight variation test were given in table-

sl. No.	weight(g)	sl. No.	weight(g)	sl. No.	weight(g)	sl. No.	weight(g)
1	0.56	6	0.56	11	0.56	16	0.56
2	0.53	7	0.54	12	0.56	17	0.58
3	0.55	8	0.58	13	0.58	18	0.57
4	0.53	9	0.56	14	0.56	19	0.56
5	0.56	10	0.53	15	0.55	20	0.57
mean ± sd	0.5575±0.015						

Table 3.- weight variation test result

Upper limit = (Avg. wt. +limit) = (0.5575+0.0278) = 0.5853gm.

Lower limit = (Avg. wt. –limit) = (0.5575-0.0278) = 0.5297gm.

Therefore, it could be concluded that no tablets were found outside the specified limit range. This suggests a satisfactory outcome in the weight variation test, indicating uniformity in drug content throughout the tablets.

Disintegration test

Type of tablets	No. of tablets	Medium	Temp(oC)	Time(min.)
Film coated	1-3	0.1N HCl	37.3	13.28
	4		37.3	21.37
	5		37.3	24.42
	6		37.3	29.13

Table 4. **The results obtained from our disintegration test**

The time taken for the tablets to disintegrate into small particles was measured to ensure their ability to release the API.

The measurement of disintegration time was conducted using a device described in the USP/NF. This USP device for disintegration testing comprises 6 glass tubes, each 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. For the disintegration time test, one tablet was placed in each tube, and the basket rack was immersed in a 1-L beaker of water, simulated gastric fluid, maintained at 37°C ± 2°C.

In accordance with the IP standards, the disintegration time for conventional uncoated tablets ranges between 5-30 minutes, with the majority of drugs having a maximum disintegration time of 30 minutes. Our film-coated tablets ultimately disintegrated at 29.13 minutes, showcasing a decent passable result for the disintegration test.

Dissolution Study in 0.1N HCl

The rate and extent of drug release from the tablets were tested to ensure conformity with the desired release profile. Dissolution tests have been developed for nearly all tablet products. The rate of drug absorption, especially for acidic drug moieties absorbed high in the GI tract, is often determined by the rate of drug dissolution from the tablet.

In accordance with the IP standard, the maximum dissolution time for uncoated metformin tablets is set at 45 minutes for phosphate buffer media. In our case(0.1N HCl), approximately 65% dissolution was observed after 45 minutes, which might indicate positive outcomes for the marketed metformin tablet (Glyciphage 500).

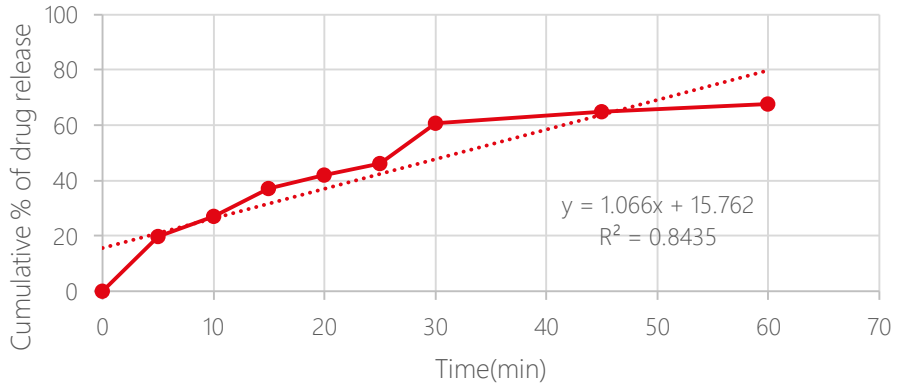


Fig.10. Drug release profile in 0.1 N HCL

Time(min)	Amount of drug in 900ml.(gm)	Drug in 2ml(gm)	Cumulative amt. of drug release(gm)	Cumulative % of drug release.
5	0.099	0.00022	0.099	19.80%
10	0.135	0.00030	0.13522	27.20%
15	0.185	0.00041	0.185	37.104%
20	0.2086	0.00046	0.2095	41.906%
25	0.230	0.00051	0.2314	46.278%
30	0.302	0.00067	0.3039	60.78%
45	0.3321	0.00066	0.3339	64.89%
60	0.3426	0.00067	0.3437	67.75%

Table 5. The results obtained from our dissolution test

Kinetics study from dissolution :

Time	Cumulative % drug released	% drug remaining	Square root time	Log Cumaulative % drug remaining	Log(time)	Log cumulative % drug released)	% Drug released	Cube root of % drug remaining(wt)	wt-w0
0	0	100	0	2	0	0	0	4.641589	0
5	19.8	80.2	2.236068	1.904174	0.69897	1.296665	19.8	4.312457	0.329133
10	27.21	72.79	3.162278	1.862072	1	1.434729	7.41	4.175328	0.466071
15	37.104	62.896	3.872983	1.798623	1.176091	1.569421	9.894	3.976866	0.664724
20	41.906	58.094	4.472136	1.764131	1.30103	1.622276	4.802	3.872967	0.768623
25	46.278	53.722	5	1.730152	1.39794	1.665375	4.372	3.773266	0.868324
30	60.78	39.22	5.477226	1.593508	1.477121	1.783761	14.502	3.397576	1.244014
45	60.89	39.11	6.708204	1.592288	1.653213	1.784546	0.11	3.394397	1.247193
60	60.75	39.25	7.745967	1.59384	1.778151	1.783546	-0.14	3.398442	1.243148

Fig.11. Zero order Kinetics Model

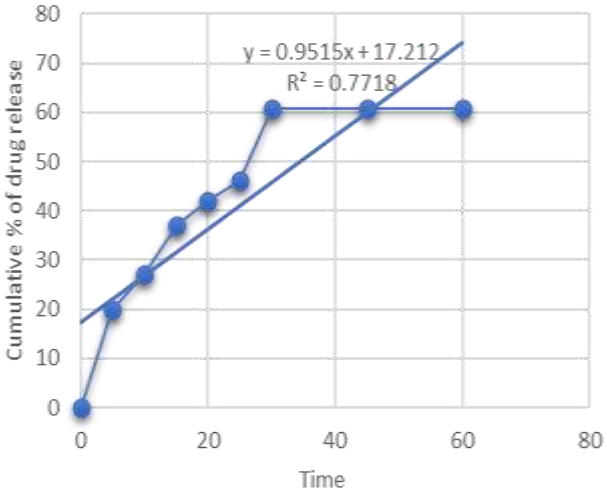


Fig.12.First order kinetics model

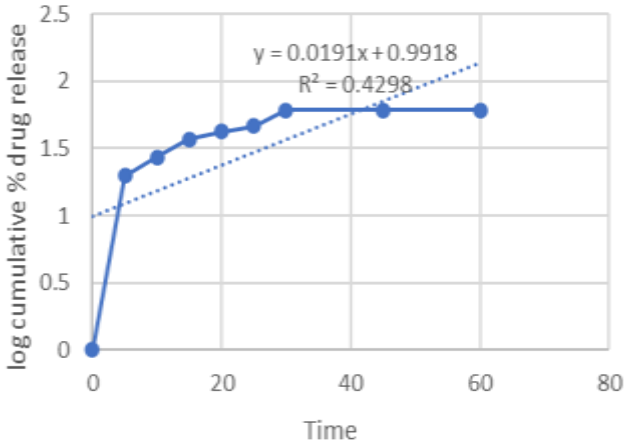


Fig.13. HIGUCHI Model

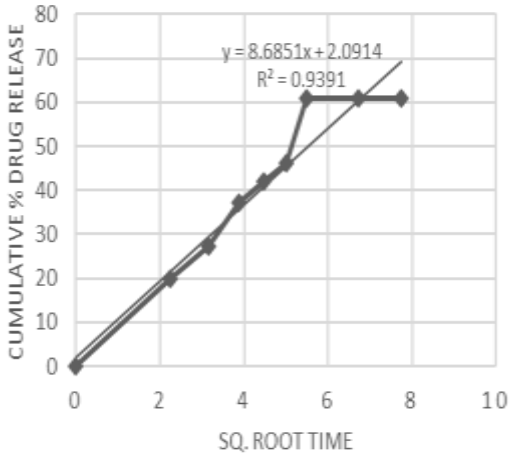
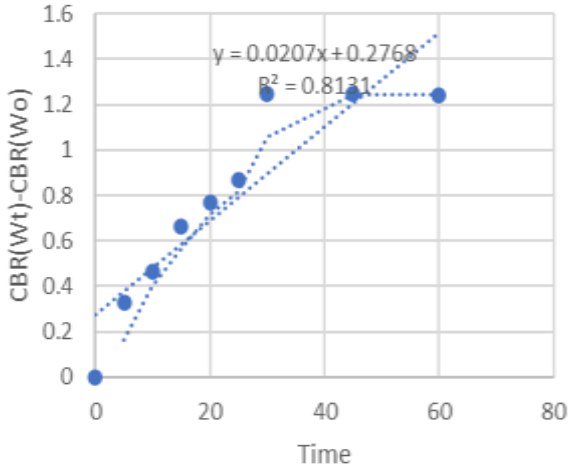


Fig.14 - Hixon-Coxwell method



ASSAY

The amount of active pharmaceutical ingredient (API) in the tablets is tested to ensure that it is within the specified range. assay is a process of analyzing a substance to determine its composition or quality. Tablet was assayed as per IP specification by UV spectrophotometric method.

By UV Visible spectroscopy :

The result we found at 232 nm the sample show absorbance 0.612.

So, % purity of metformin = (present amount/label claim)x100

= (0.478/0.5)x100

= 94%.

So, the % of drug present in glyciphage was found to be 94%

By HPLC :

High-Performance Liquid Chromatography (HPLC) is an analytical technique used to separate, identify, and quantify each component in a mixture. The mixture is separated using the basic principle of column chromatography and then identified and quantified by spectroscopy.

Assay by HPLC involves estimation of the content of active substance present in sample with respect to standard of known purity.

Content(mg/tab) = Test area x std wt. x dilution x purity of standard

Standard area x test Wt. x standard dilution.

=(117357798 x10x 10x99.89/35208334x 10x 10)

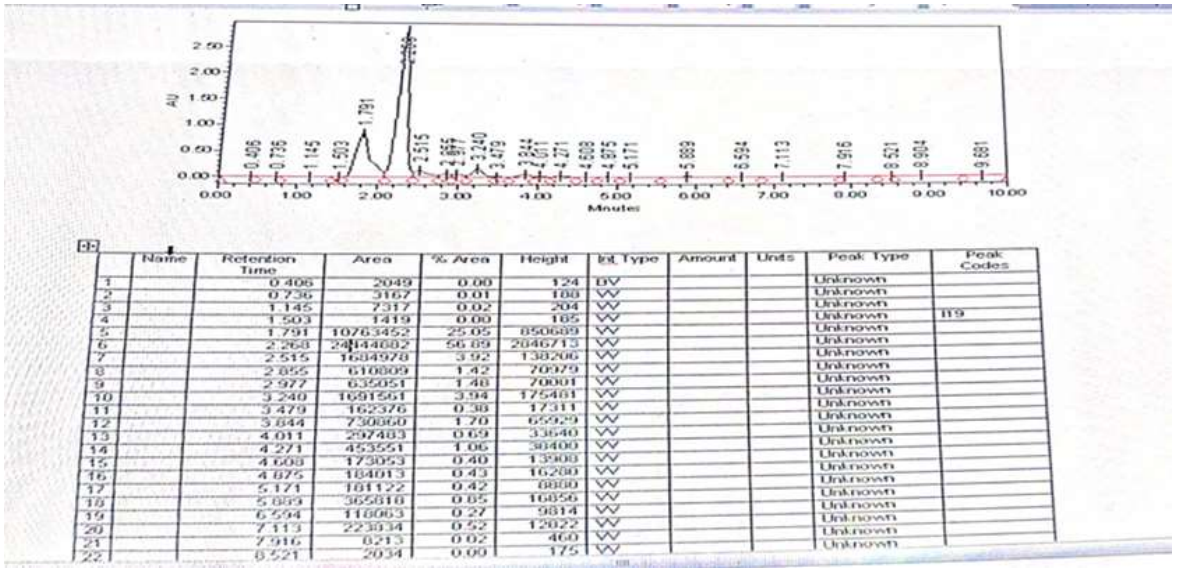
=333.329.

So, for pure drug 35208334 area covered by 1mg/ml drug.

So, as marketed drug cover 117357798 area its concentration will be 0.33mg/ml.

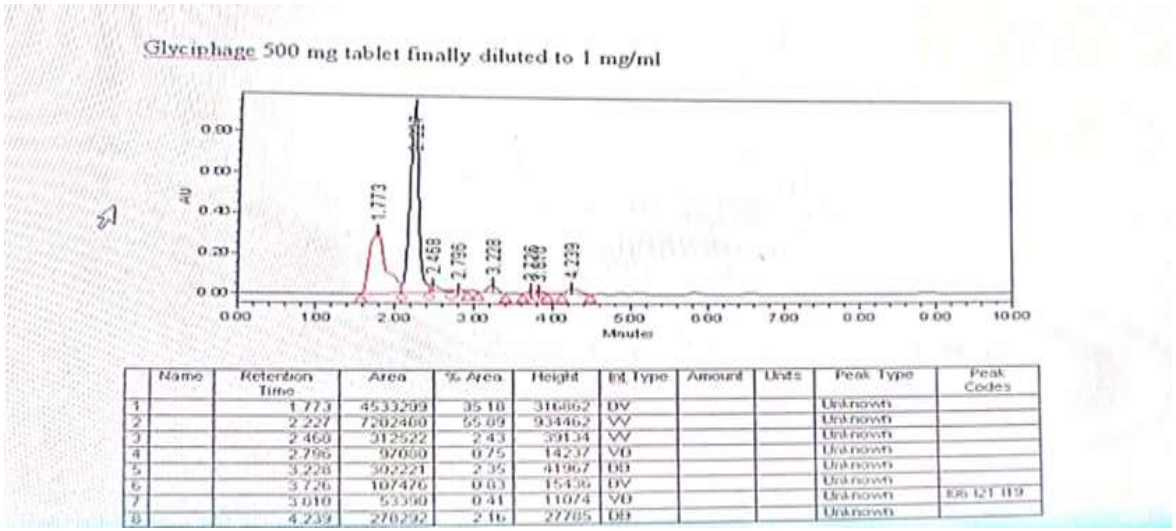
Content of metformin was - (333.329/ 500)x100 =66.67%

Fig. 15 - HPLC Instrument



	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1		0.406	2049	0.00	124	BV			Unknown	
2		0.736	3167	0.01	188	VV			Unknown	
3		1.145	7317	0.02	204	VV			Unknown	
4		1.503	1419	0.00	185	VV			Unknown	119
5		1.791	10763452	25.05	850689	VV			Unknown	
6		2.268	24144682	56.09	2046713	VV			Unknown	
7		2.515	1684978	3.92	138206	VV			Unknown	
8		2.855	610809	1.42	70979	VV			Unknown	
9		2.977	635051	1.48	70801	VV			Unknown	
10		3.240	1691561	3.94	175481	VV			Unknown	
11		3.479	162376	0.38	17311	VV			Unknown	
12		3.844	730860	1.70	65929	VV			Unknown	
13		4.011	297483	0.69	33640	VV			Unknown	
14		4.271	453551	1.06	38400	VV			Unknown	
15		4.608	173053	0.40	13983	VV			Unknown	
16		4.875	184013	0.43	16280	VV			Unknown	
17		5.171	101122	0.42	8809	VV			Unknown	
18		5.889	365818	0.85	16856	VV			Unknown	
19		6.594	116063	0.27	9814	VV			Unknown	
20		7.113	223934	0.52	12022	VV			Unknown	
21		7.916	8213	0.02	460	VV			Unknown	
22		8.521	2034	0.00	175	VV			Unknown	

Fig .16 - Standard metformin sample.



	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1		1.773	4533289	35.18	316862	BV			Unknown	
2		2.227	7202460	55.89	934462	VV			Unknown	
3		2.468	312522	2.43	39134	VV			Unknown	
4		2.796	97000	0.75	14237	VB			Unknown	
5		3.228	302221	2.35	41967	BB			Unknown	
6		3.726	107476	0.83	15436	BV			Unknown	
7		3.810	53390	0.41	11074	VB			Unknown	105 121 119
8		4.239	270292	2.16	27785	BB			Unknown	

Fig.17 - Marketed metformin sample (Glyciphage)

CONCLUSION

In this study various parameter like Appearance, Identification, Hardness, Friability, Weight variation, Disintegration Time, Dissolution Study, Assay of market metformin table (Glyciphage 500) were evaluated. Our results indicate that these tablets comply with all tests as recommended in IP. Hence, based on above study it can be concluded that glyciphage 500 mg have maintain all standard as per IP.

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Thank You