In vitro release pattern of Indapamide from Indapa sustain release tablets

A research paper submitted to the Department of Pharmacy, East West University in the partial fulfilment of the requirements for the Degree of Bachelor of Pharmacy.

Submitted by:

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CONTENTS

Abstract:

Twenty tablets of Indapa matrix tablets were unruffled and then were characterized by physical parameters like hardness, thickness, weight variation and dissolution studies. Using the method adorned in Appendix XII B: Dissolution tests for tablets and capsules of British Pharmacopoeia, Indapamide release was explored.[8] Hardness of the withdrawn samples were calculated by hardness tester (Veego, Germany). Thickness of the samples was calculated by slide calipers. Using dissolution tester (RC6, Vanguard Pharmaceuticals, USA) dissolution of the taken samples were explored to assess release kinetics. Mean hardness value of Indapamide tablets were found to be 1.54 kg. Mean thickness value of Indapamide tablets were found to be 0.54 cm. Mean weight variation value of Indapamide tablets were found to be 0.07623 gm. We also performed dissolution test and that was the basis of our study. Various results were found from the tests and compared with the specification (British Pharmacopeias) and their standard was justified.

Introduction:

Indapamide is thiazide like diuretic. It contains the sulfonamide residue in their chemical structure. It is not truly thiazide. Indapamide is a lipid soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. Indapamide is metabolized and excreted by the gastrointestinal tract and the kidneys. It is therefore less likely to accumulate in patients with renal failure and may be useful in their treatment. [1]

Generally Indapamide is used in the treatment of hypertension, as well as decompensated cardiac failure.[2]

Indapamide is a diuretic (water pill) that is primarily used for the treatment of high blood pressure. It works by preventing the kidney from reabsorbing (retaining in the body) salt and water that is destined to be eliminated in the urine. This results in increased urine output (diuresis). Indapamide also is thought to reduce the salt in the smooth muscle of the walls of blood vessels. (The salt ultimately is eliminated in the urine.) The loss of salt from the muscle causes the muscle to relax, and the relaxation of the vessels results in reduced blood pressure. Indapamide was approved by the FDA in 1983.

It also is used to eliminate fluid when the body accumulates excess fluid, such as with edema and congestive heart failure. [3]

PHARMACOLOGICAL ACTION OF INDAPAMIDE:

Indapamide, an indole derivative of chlorosulphonamide, has an antihypertensive action causing a drop in systolic, diastolic and mean blood pressure. This antihypertensive action is maximal at a dose of 2,5 mg per day and the diuretic effect is slight, usually without clinical manifestation.

At higher doses, the diuretic effect becomes more prominent. The extra-renal antihypertensive action of 2,5 mg per day is demonstrated as a decrease in vascular hyperreactivity and a reduction in total peripheral and arteriolar resistance. The extra-renal mechanism of action has also been demonstrated by the maintenance of antihypertensive effect in functionally anephric patients. The extra-renal action is thought

to be due to the inhibition of transmembrane ionic influx, essentially calcic, and the stimulation of synthesis of the vasodilatory hypotensive prostaglandin PGE2.
Prolonged use of indapamide has been shown to be associated with a reduction in left ventricular mass in hypertensive patients.

Pharmacokinetics:

Indapamide is rapidly and completely absorbed after oral administration. Peak blood levels are reached after 1 to 2 hours. Indapamide is extensively metabolised and only 5-7% is found unchanged in the urine. The elimination half-life is 14-18 hours. Indapamide is 79% bound to plasma protein. The methyl-indoline portion of the molecule gives indapamide its lopiphilic character, and indapamide's lipid solubility is 5 to 8 times that of the thiazides. It is as a result of this characteristic that indapamide localizes in smooth vascular muscle.

INDICATIONS:

Indapamide is indicated in the management of mild to moderate hypertension.

CONTRA-INDICATIONS:

Severe hepatic insufficiency.
Safety in pregnancy has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults: Maximum dose is 2,5 mg per day. The dosage is one tablet containing 2,5 mg indapamide hemihydrate, daily, to be taken in the morning with breakfast. In more severe cases, Indapamide can be combined with other categories of antihypertensive agents.

Children: There is no experience of the use of this drug in children.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects include giddiness, headaches, anorexia, gastric irritation, nausea, vomiting, constipation and diarrhoea.

Indapamide given at 2,5 mg daily produces minimal diuresis. However, hyperuricaemia and hypokalaemia may occur and potassium supplementation may be required.

Serum potassium should be monitored in patients prone or sensitive to hypokalaemia (such as patients treated concomitantly with steroids, digitalis or laxative drugs). Uric acid should be monitored, particularly in patients with a history of gout, who should continue to receive the appropriate treatment.

Indapamide 2,5 mg (one tablet) daily can be administered to hypertensive patients with impaired renal function, and to those undergoing chronic haemodialysis, as there is no evidence of drug accumulation. However, the treatment should be discontinued if increasing azotemia or oliguria occur.

The co-administration of Indapamide with diuretics, which may cause hypokalaemia, is not recommended. [4]

Role of prostaglandins in the mechanism of action of indapamide:

The role of prostaglandins (PG) has been evoked in the mechanism of action of indapamide. Indeed, PG can act in the regulation of the blood pressure (BP) at different levels: vasodilatation, diuretic, natriuretic, antagonism of angiotensin II and vasopressin (VP), action on adrenergic system. To confirm this hypothesis, we studied the action of certain eicosanoids inhibitors on the antihypertensive action of indapamide in the SHR rat, anaesthetized with pentobarbital (40 mg/kg i.p.). Indapamide (3 mg/kg i.p.) induces significant decrease on BP over 60 min. Mepacrine (5 mg/kg i.p.), phospholipase A2 inhibitor, indomethacin (5 mg/kg i.p), cyclo-oxygenase inhibitor, and tranylcypromine (0,1 mg/kg i.p.), prostacyclin synthase inhibitor, antagonize the antihypertensive action of indapamide. In order to eliminate the importance of VP, we used Brattleboro rats (genetically depleted in VP): indapamide (3 mg/kg i.p.) maintains its hypotensive activity. To eliminate the role of kidney in PG synthesis, we have used cyclo-oxygenase

extrarenal inhibitor (sulindac) and the bilateral nephrectomy. Sulindac (1,25 mg/kg i.p.) and the bilateral nephrectomy do not remove the hypotensive action of indapamide. These results, demonstrating the PG extrarenal role and probably that of PGI2, localized in the vascular wall, could explain part of the antihypertensive mechanism of indapamide. [5]

Indapamide SR Versus Candesartan and Amlodipine in Hypertension:

1. Background

Reducing systolic blood pressure (BP) is of major benefit to patients with isolated systolic hypertension, but lowering normal diastolic BP may be harmful in terms of cardiovascular risk. Effects of different drugs on systolic BP, diastolic BP, and pulse pressure are therefore of interest.

2. Methods

The NatriliX SR (indapamide) versus Candesartan and amlodipine in the reduction of systoLic blood pressure in hypertensive patients study (X-CELLENT) was a randomized, double-blind, placebo-controlled study comparing the effects of three drugs on these BP components. Patients with systolic–diastolic or isolated systolic hypertension (n = 1758) received indapamide (1.5 mg) sustained release (SR), candesartan (8 mg), amlodipine (5 mg), or placebo once daily for 12 weeks.

3. Results

Compared to placebo all active treatments reduced all BP components significantly ($P < .001$). For the patients with isolated systolic hypertension (n = 388), the three treatments significantly reduced systolic BP, but only indapamide SR did not change diastolic BP and thus reduced pulse pressure significantly relative to placebo ($P = .005$). In an ancillary study using ambulatory BP monitoring (n = 576), all three treatments significantly reduced BP components during 24 h relative to placebo. Changes in systolic BP and pulse pressure were similar with the three treatments, but the reduction in diastolic BP was significantly smaller, and therefore more favorable, with indapamide SR

compared with candesartan (P = .039). In patients with isolated systolic hypertension (n = 106), indapamide SR reduced 24-h systolic BP significantly more than amlodipine (P = .037), and only indapamide SR reduced 24-h pulse pressure significantly relative to placebo (P = .03). All three drugs were well tolerated.

4. Conclusions

This distinctive BP-lowering profile of indapamide SR seems highly beneficial when compared to the either of candesartan or amlodipine.[6]

Evaluation of tablets:

***In vitro release studies*:**

Hardness test of Indapa:

Study of hardness: The hardness of 10 Indapa tablets were firmed using hardness tester (Veego). The average crushing strengths (hardness values) were determined and the data is presented in table 1.

Theory: Too 'soft' tablets can disintegrate in transport. An acceptable 'hardness' is required and tablet strength testing is necessary for both, research & development of new formulations, and for quality control. The test instruments should provide accurate results and output these results in n standard units.

Materials required:

1. Hardness tester (veego).
2. Indapa matrix tablets.

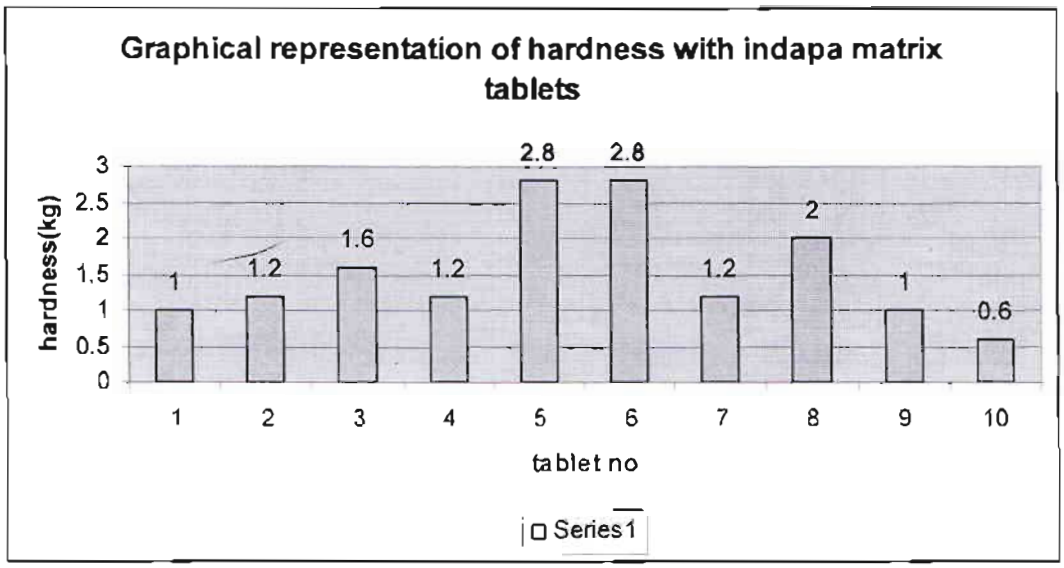
Procedure of hardness testing:

The sliding scale of the hardness tester were made zero. Tablets were placed vertically between two jaws (by one tablet). Force has been applied with a screw thread and spring until the tablet fractured. Readings were taken in kg from the sliding scale.

Table 1: Hardness test of Indapa matrix tablets

Tablet No.	**Indapa**
1	1 kg
2	1.2 kg
3	1.6 kg
4	1.2 kg
5	2.8 kg
6	2.8 kg
7	1.2 kg
8	2 kg
9	1 kg
10	0.6 kg

The mean hardness of indapa matrix tablets were 1.54 kg.



The hardness for the indapa matrix tablets were different at ranging from 0.6 to 2.8 kg at same pressure. The mean hardness value of Indapa matrix tablet was found 1.54 kg. For desired release pattern the specification for the hardness value of matrix tablet would be below 9.5 kg. So the Indapa matrix tablets follow the specification.

Thickness Test of Indapa:

The experiment was done to measure the thickness of Indapa matrix tablets by using vernier slide calipers.

Materials required:

1. Vernier calipers.
2. Indapa matrix tablets.

Procedure of thickness testing:

One tablet was placed vertically between two jaws. Run the screw of the caliper to hold the tablet. The reading was taken in cm from the scale.

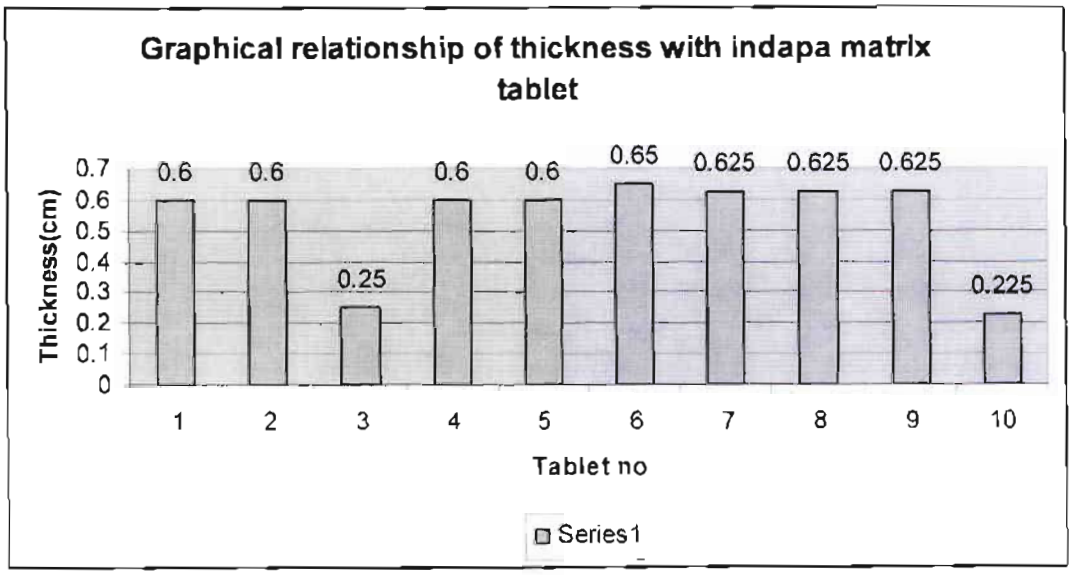
Thickness of the tablet is:

Reading of cm scale + Reading of vernier scale × Vernier constant – Vernier error

Table 2: Thickness of Indapa matrix tablets

No of tablet	Reading of cm Scale	Reading of vernier Scale	vernier constant	vernier error	Thickness of Tablet (cm)
1	0.2	8	0.5	0	0.60
2	0.2	8	0.5	0	0.60
3	0.2	1	0.5	0	0.25
4	0.2	8	0.5	0	0.60
5	0.2	8	0.5	0	0.60
6	0.2	9	0.5	0	0.65
7	0.2	8.5	0.5	0	0.625
8	0.2	8.5	0.5	0	0.625
9	0.2	8.5	0.5	0	0.625
10	0.2	.5	0.5	0	0.225

The average thickness of the tablets of indapa were 0.54 cm.



Weight variation Test of Indapa:

This experiment was done to determine the uniformity of Indapa matrix tablets.

Materials required:

1. Weighing balance.
2. Indapa matrix tablets

Procedure of weight variation test:

Ten Indapa matrix tablets were taken and weighed them. The average weight were taken and considered it as the standard weight of an individual tablet. Weighed all the Indapa matrix tablets individually and observed whether the individual tablets are within the range or not.

Table 3: Weight variation Test of Indapa matrix tablets

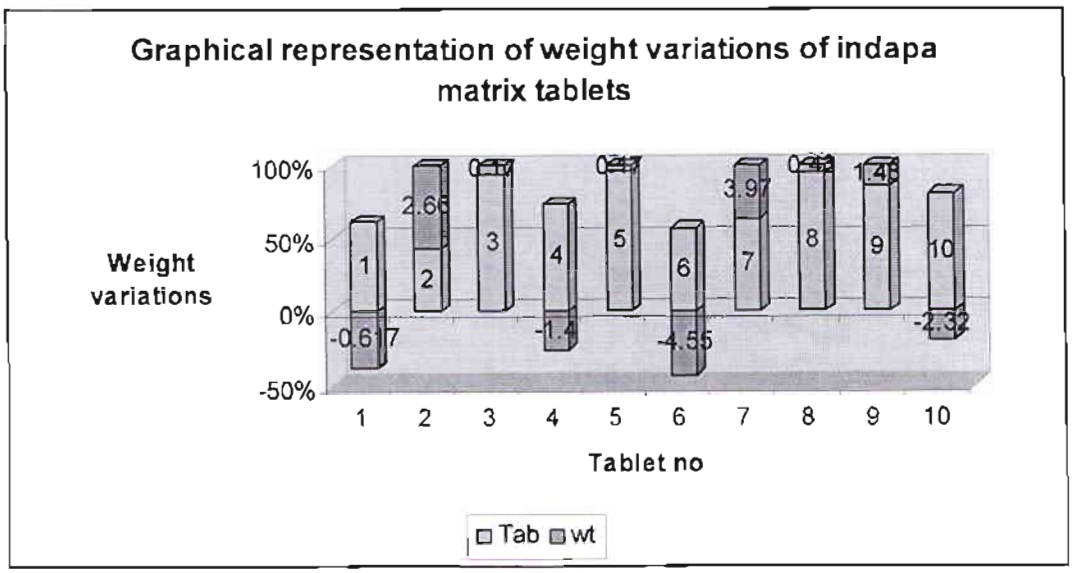
Table No.	**Intake weight (gm)**
1	0.0767
2	0.0742
3	0.0761
4	0.0773
5	0.0761
6	0.0797
7	0.0732
8	0.0759
9	0.0751
10	0.0780
Total weight	=0.7623

Average weight = 0.7623 / 10 = 0.07623 gm.

Table 4: Weight variation test for Indapa matrix tablets

Tablet no	**Individual Weight (gm)**	**Average weight = sum of individual weight/10**	**Weight variation = (A W. - Ind. W.)*100/A W.**
1	0.0767	**0.07623gm**	**-0.617**
2	0.0742		**2.66**
3	0.0761		**0.17**
4	0.0773		**-1.40**
5	0.0761		**0.17**
6	0.0797		**-4.55**
7	0.0732		**3.97**
8	0.0759		**0.43**
9	0.0751		**1.48**
10	0.0780		**-2.32**

The average weight variation of indapa matrix tablets were 0.07623 gm.



Dissolution test of Indapa:

In vitro drug release studies of the collected matrix tablet were conducted using BP XII D Apparatus 1 (Basket apparatus) by dissolution tester (RC6, Vanguard Pharmaceuticals, USA) at 37° C (± 0.5 °C) and 100 rpm speed. Dissolution studies were carried out by using 500 ml 0.1 M HCl as a dissolution medium in every vessel. Ten milliliter (ml) samples were taken by filtration at regular intervals of 120, 150, 180, 210, 240, 270 and 300 minutes. After each sampling the volume loss was added up by transferring the prepared media in each vessel. Absorbance was measured with single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 240nm and 270nm.

Materials required:

1. Dissolution tester
2. Analytical balance
3. filter paper
4. Beaker,Pipettes,Spatula,Funnel
5. Distilled water

***Operating parameters*:**

Medium: 1000ml 0.1 M HCl

Apparatus: 1

RPM: 100

Time: 300 minutes

λ Max: 240nm and 270nm.

Preparation of the Dissolution Medium: (0.1 M 1000ml HCl):

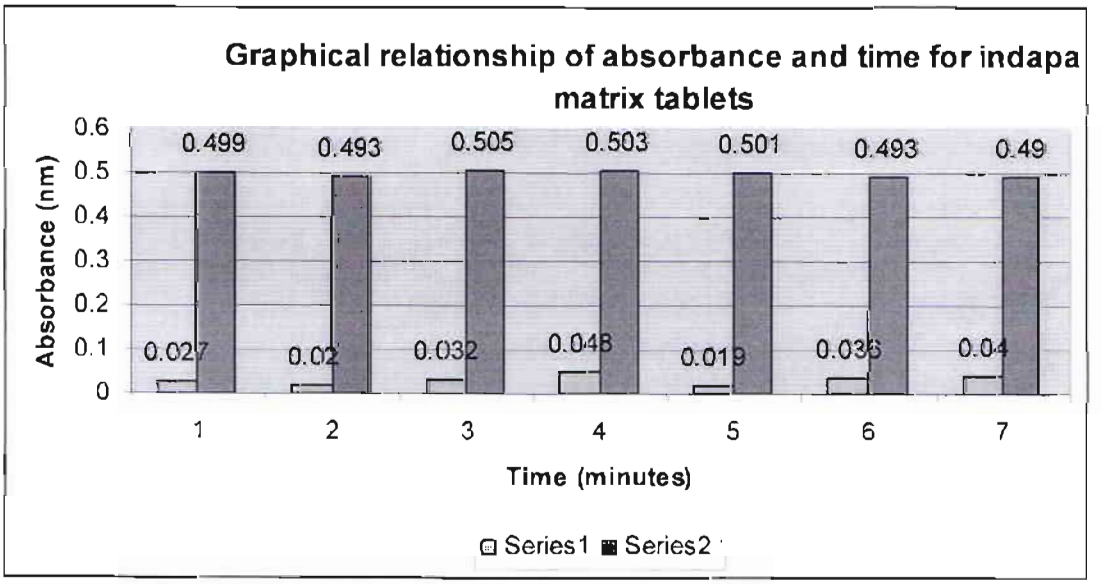
The supplied HCl from the East West University laboratory of Pharmacy Department was 32% w/v. As the molecular weight of HCL is 36.5, the 1 M HCl solution contains 36.5 gm HCl theoretically. So, from calculation it was found that 0.1 M HCl solution contains 3.65 gm of HCl and 11.4 ml of 32% w/v HCl is needed to prepare 1000 ml of 0.1 M HCl solution which was further used as dissolution. According to this the 250ml of 0.1M HCl will contain 2.85 ml of 32% w/v HCl solution.

Procedure of dissolution test of Indapa matrix tablets:

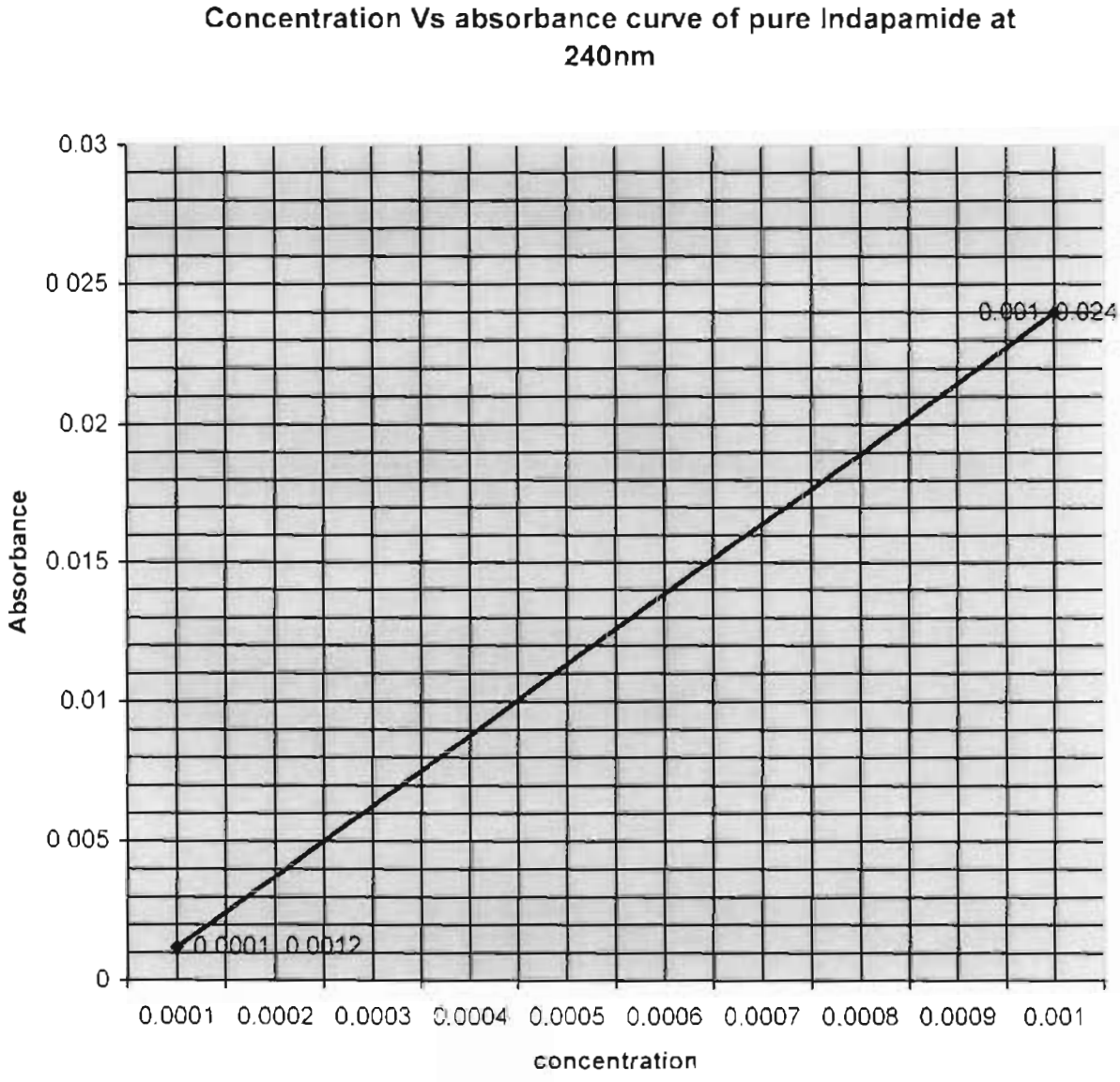
The Indapa matrix tablet were weighed. Water tank was filled and set the operating parameters on the dissolution test apparatus. 500ml of the 0.1m HCl solution was poured into one of the vessels and run the instrument till the set temperature was attained. 100ml of the medium was kept for using as blank. The Indapa matrix tablet was placed into the vessels and started the run. At the end of the time specified, 10ml of the sample was collected from the vessels and filtered it. With 10ml medium it was replaced and repeated it for other time interval set. Measured the absorbance of the solutions at 240 nm and 270 nm.

Table 5: Dissolution test for Indapa matrix tablets

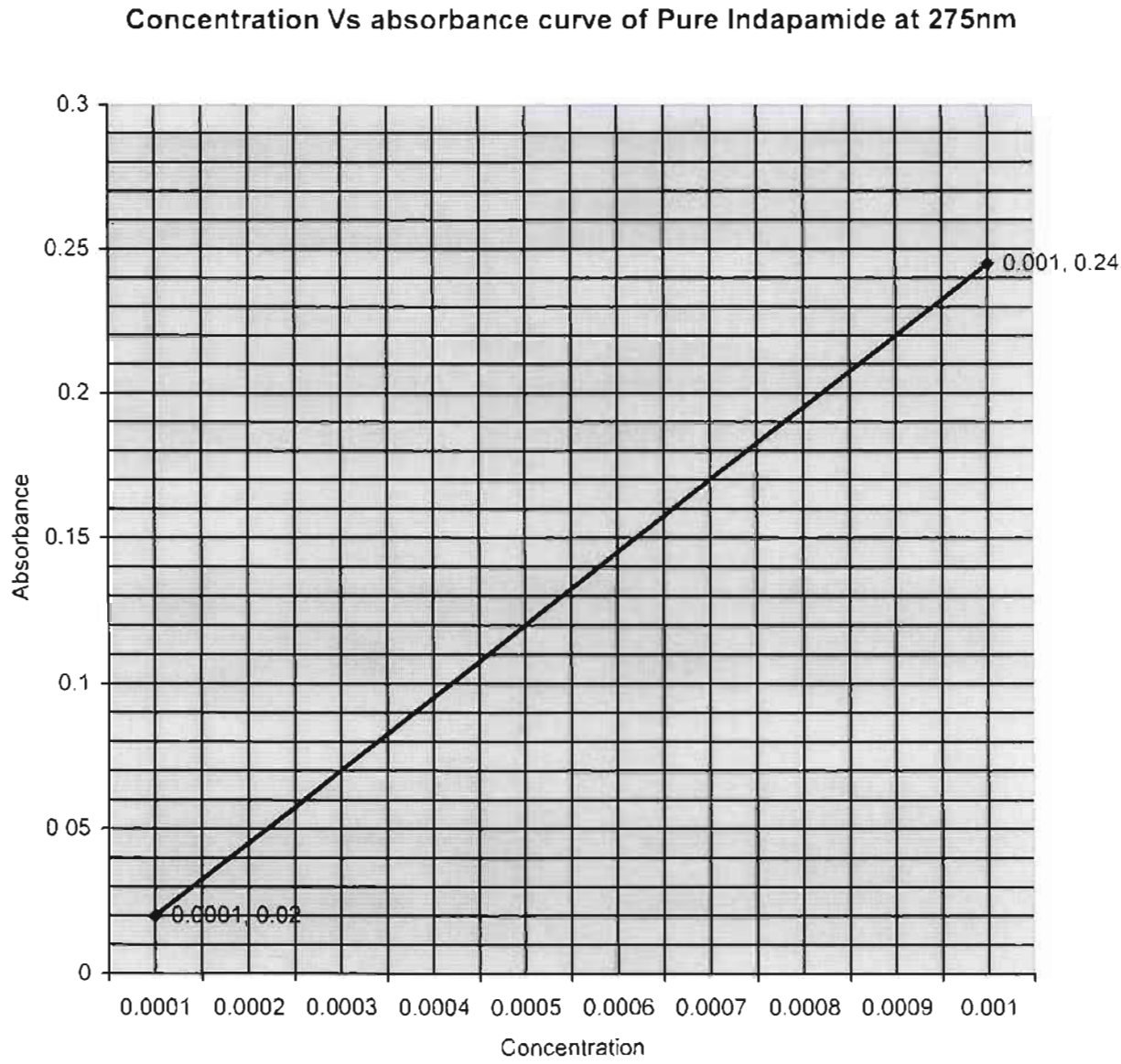
Time (min)	Absorbance(nm)	
	240 nm	275 nm
120	0.027	0.499
150	0.020	0.493
180	0.032	0.505
210	0.048	0.503
240	0.019	0.501
270	0.036	0.493
300	0.040	0.490



Standard curves of time vs concentration was found for crude Indapamide at 240 nm and 275 nm. These curves result straight line for showing Indapamide release from matrix tablets. The figure has been shown below:



Graph showing absorbance vs concentration relationship for pure Indapamide at 240 nm.



Graph showing absorbance vs concentration relationship for pure Indapamide at 275 nm

Procdure of graph scratching:

As the pure indapamide does not contain any excipients so it results straight line. Presence of excipients influences the drug release profile. What was the role of excipients were in Indapa matrix tablet that was found out by utilizing the above standard curve. First of all, we put the absorbance value at the 'y' axis and from every values straight lines were drawn towards the standard curve. Then from the standard curve again straight line were drawn towards 'x' axis. The 'x' axis reading was found has been considered as our desired concentration values. These were the amount of Indapa that released from matrix tablets at several time intervals. So the concentrations were found recorded in the following table 6 (containing results at 240 nm) and table 7 (containing results at 275 nm).

Table 6: The concentrations of the released drug were found at 240 nm has been documented at following table:

Time (min)	240nm
	Concentration (mg/dl)
120	0.000156
150	0.000126
180	0.000176
210	0.000238
240	0.000124
270	0.000190
300	0.000240

Graphical show of time and concentration relationship at 240 nm.

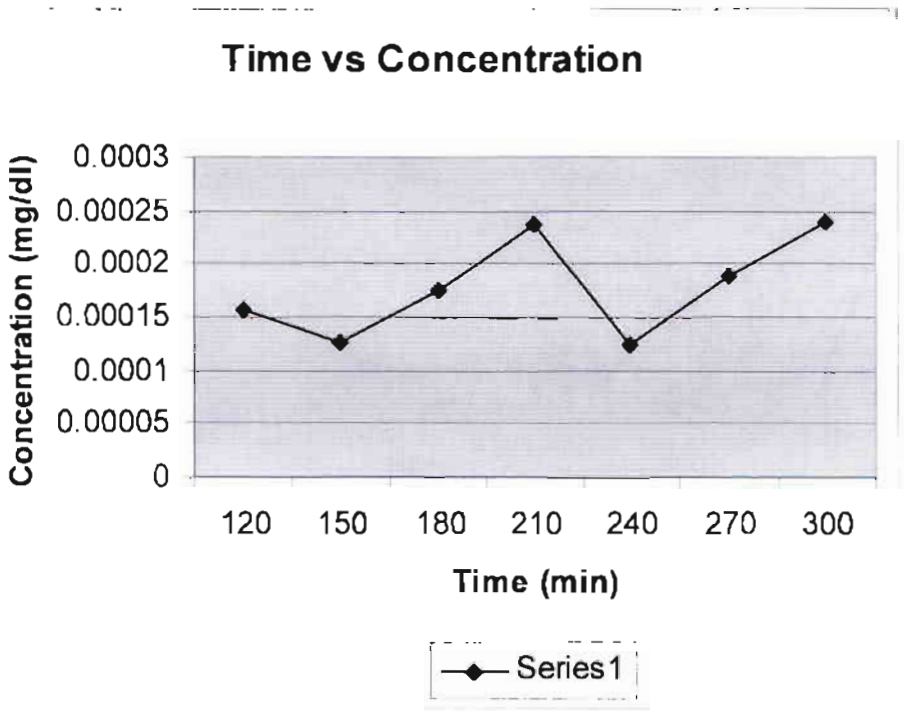
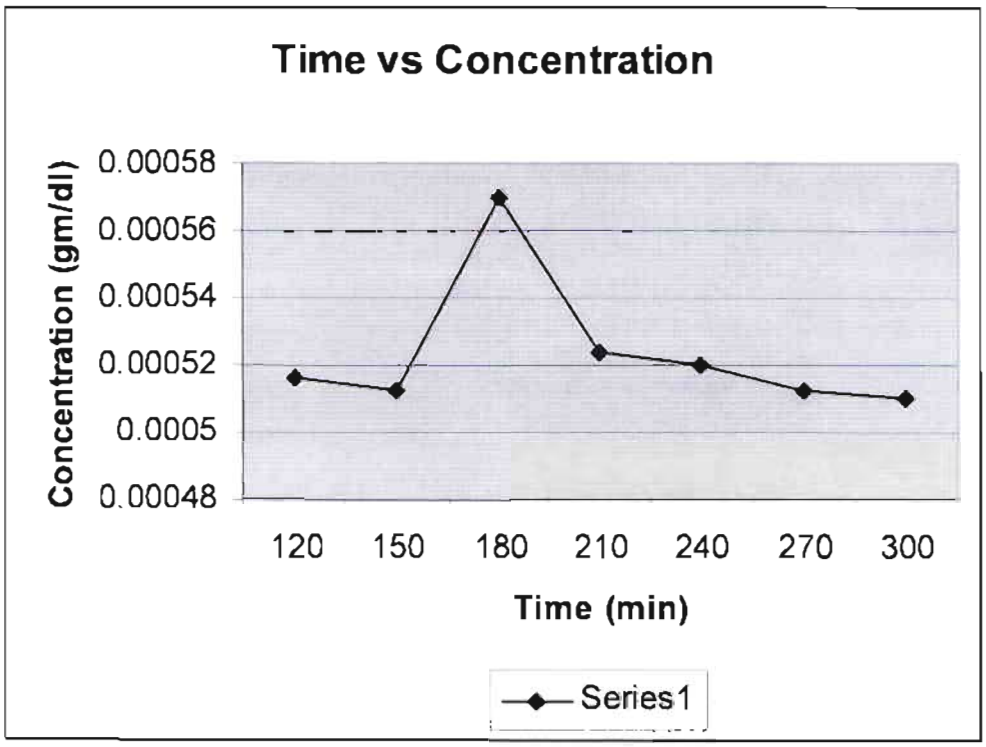


Table 7: The concentrations of released drugs were found at 275nm has been documented in the following table:

Time (min)	275nm
	Concentration (mg/dl)
120	0.000516
150	0.000512
180	0.000570
210	0.000524
240	0.000520
270	0.000512
300	0.000510

Graphical show of time and concentration relationship at 275 nm.



According to standard curve, the time vs concentration relationship should give standard line in case of both 240 nm and 275 nm. But both the above graphs show wavy line. That means the drug release from matrix tablets does not follow continuity with specified range.

Discussions:

Indapamide, a loop diuretic used to treat edema associated with congestive heart failure, hepatic cirrhosis, and renal disease. It is a good choice for these relative pathophysiologic conditions.

Granulation is the key process in the production of many dosage forms involving the controlled release of a drug from coated or matrix-type particles. A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation

The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter, uniformity of weight, drug content, hardness, friability, and in vitro dissolution. The pharmacopoeial limit for the percentage deviation for tablets were monitored carefully. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability. [7]

Concentration vs Resistance calculations

On 'x' axis 5 Boxes = .0001

On 'y' axis 5 Boxes = .012

(.001, .024)

(.0001, .002)

Absorbance (nm)

.028
.024
.020
.016
.012
.008
.004

.0001 .0002 .0004 .0006 .0008 .001

Concentration (mg/dl)

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