IN VITRO RELEASE PATTERN OF INDAPAMIDE FROM REPRES SR MATRIX TABLET

Prepared by:

A.T.M. Faiz Ullah Talukder

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Department of Pharmacy

East West University

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***Abstract*:**

Repres SR matrix tablets were collected from the market and those were characterized by physical parameters like hardness, thickness, weight variations and dissolution studies. Indapamide release was explored using the method adorned in Appendix XII B: Dissolution tests for tablets and capsules of British Pharmacopoeia. Hardness study of the withdrawn samples from the market was carried out by hardness tester (Veego, Germany). Thickness study of the samples was measured by slide calipers. Dissolution study of the taken samples was explored by using dissolution tester (RC6, Vanguard Pharmaceuticals, and USA) to assess release kinetics. Consequences of the physical tests are follows; Mean hardness value of Indapamide matrix tablets was found to be 10.5kg. Mean thickness value of Indapamide matrix tablets were found to be 0.69cm. Mean weight variation value of Indapamide matrix tablets were found to be 0.956. Beside this the release pattern of the samples was determined through dissolution test. And further discussion drawn on it which has been included at the following section of this paper. To conclude, the results obtained against different physical test for Repres SR matrix tablets were justified with the specification (British Pharmacopeias) whether they met the specified standard.

Introduction:

Indapamide is a non-thiazide sulphonamide diuretic drug, marketed by Servier generally used in the treatment of hypertension, as well as decompensate cardiac failure. The United State trade name for indapamide is Lozol. Indapamide is marketed as Natrilix outside of the US. Indapamide is an oral antihypertensive agent. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated; both vascular and renal actions have been implicated. The possible beneficial pharmacological effects of indapamide in the treatment of hypertension include a reduction in cardiac hypertrophy and a reduction in the thickening of arterial walls, a prevention of the accumulation of the embryonic isoform of fibronectin in coronary vessels, free radical scavenging leading to stimulation of vasodilator eicosanoid formation, and interaction with renal carbonic anhydrase. The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on kaliuresis or uric acid excretion. Only at doses greater than 1.5 mg indapamide sustained release tablet / day is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies. Significant hypokalemia (plasma potassium < 3.2 mili mol/L) has been reported in 4% of patients.

◎Absorption: The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract. Ingestion with food slightly increases the rate and extent of absorption. These changes are unlikely to be clinically significant. Peak serum level following a single dose occurs about 12 hours after ingestion; repeated Administration reduces the variation in serum levels between 2 doses.

◎Distribution: Indapamide is widely distributed throughout the body, with extensive Binding to some specific sites. In blood, it is highly bound to red blood cells (80 %) and, more specifically, to carbonic anhydrase (98 %) without having any significant inhibiting activity on this enzyme. Binding of indapamide to plasma proteins is 79 %. The plasma elimination half-life is 14 to 24 hours (mean 18 hours). The drug has a volume of distribution of approximately 60 L. Steady state is achieved after 7 days. Repeated administration does not lead to accumulation.

◎Metabolism: The drug is extensively metabolized in the liver, with only 5 to 7% of the dose excreted in the urine as unchanged drug.

◎Elimination: Elimination is essentially urinary (70% of the dose) and faecal (22%) in the form of inactive metabolites. [4]

The thiazide diuretics emerged from efforts to synthesize more potent carbonic anhdrase inhibitors. It subsequently became clear that the thiazide inhibits NaCl transport predominantly In Distal Convoluted Tubule (DCT).

Changes in urinary electrolytes patterns and body PH in response to diuretic drugs:

Groups	Urinary electrolytes			
	Nacl	NaHCO3	K+	Body pH
▪Thiazide	++	+	+	+
▪Carbonic Anhydrase inhibitor	+	+++	+	-
▪Loop Agents	+++	0	+	+
▪K+ sparing agents	+	+	-	-

+, increase; -, decrease; 0, no change [5]

Above chart confirms that thiazide diuretics are most preferable option in case of related physical consequences than other diuretics.

◎Indications: Repres® SR is indicated in the treatment of essential hypertension. It is effective in treating hypertension in patients with renal function impairment, although its diuretic effect is reduced. Repres® SR is also indicated for the treatment of salt and fluid retention associated with congestive heart failure.

Epidemiological studies have emphasized the close relationship existing between the increase in blood pressure (BP) and the incidence and prevalence of cardiovascular

disease. In the past, the severity of hypertension was classified principally on the basis of diastolic blood pressure (DBP). This was related to the haemodynamic characteristics of the disease, which was attributed to a reduction in the number of small arteries, with a resulting increase in peripheral vascular resistance and the fact that increases in peripheral resistance was the principal haemodynamic cause of high BP. Peripheral resistance is a determinant of mean blood pressure (MBP) close to the level of DBP. Nevertheless, many cross-sectional studies have shown that end-organ damage in hypertensive people is more strongly associated to SBP. Furthermore, recent prospective epidemiological studies have directed attention to SBP as a better guide than DBP to evaluate cardiovascular and all-cause mortality. A meta-analysis of outcome trials has confirmed the overwhelming importance of SBP as a determinant of risk. Studies have shown that drug treatment of hypertension frequently results in an adequate control of DBP ($\leq$90 mmHg), whereas the ability to control SBP ($\leq$140 mmHg) is achieved to a significantly smaller extent. Such studies have focused attention on the factors that determine the level of SBP and cardiovascular risk in hypertensive individuals, and on therapeutic interventions preferably reducing SBP. Several therapeutic trials have confirmed that SBP increases markedly with age while DBP becomes stable and even tends to fall spontaneously after the age of 50–60 years. In the Systolic Hypertension in the Elderly Program study involving elderly subjects with isolated systolic hypertension (ISH), the reduction in cardiovascular risk was associated with a decrease in SBP, whereas, in contrast, a decrease in DBP was associated with an increase in cardiovascular risk. In the past few years, several authors have clearly shown that brachial pulse pressure was also a strong cardiovascular risk factor for myocardial infarction in populations of individuals with hypertension. Furthermore, some studies have clearly indicated that cardiovascular risk is related not only to an increase in SBP but also to a decrease in DBP. Cardiovascular mortality was indeed substantially reduced but, at the end of the trial, the population was still characterized by a low DBP contrasting with an elevated SBP. Taken together, these findings indicate that, in elderly subjects treated for hypertension, the classic haemodynamic pattern of ISH is still present despite adequate drug treatment. In many diseases, the amount of sodium chloride reabsorbed by the kidney tubules is abnormally high. This leads to the retention of water, an increase blood

volume and expansion of the extravascular fluid compartment, resulting in edema of the tissues. Several commonly encountered causes of edema including heart failure, hepatic ascites, nephritic syndrome and premenstrual edema and also nonedematous states including hypertension, hypercalcemia and diabetes insipidus can be well managed by diuretics. [1]

The thiazides are the most widely used diuretic drug in maintains of hypertension and also used to eliminate fluid when the body accumulates excess fluid, such as edema. They are sulfonamide derivatives and are related in structure to the carbonic anhydrase inhibitors. However, the thiazides have significantly greater diuretic activity than carbonic anhydrase inhibitor and they act on the kidney by different mechanisms. All thiazides affect the distal tubule and all have equal maximum diuretic effects, differing only in potency. [2] The thiazides like analogs lack the thiazide structure but like the thiazide it has the unsubstituted sulfonamide group and shares the mechanism of action. Indapamide is a lipid soluble thiazide like diuretic. It is a white or almost white powder and practically insoluble in water, soluble in ethanol (96 per cent). Indapamide contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 4-chloro-*N*-[(2*RS*)-2-methyl-2, 3-dihydro-1*H*-indol-1-yl]-3-sulphamoylbenzamide, calculated with reference to the anhydrous substance [3]

⊙Indapamide SR matrix tablets and Systolic Blood Pressure:

▪▪Three large double-blind clinical trials assessing the effect of Indapamide SR on SBP are reviewed. These studies have all been published and their methodology has already been thoroughly detailed. This review, therefore, mainly focuses on the results reported in various groups of hypertensive patients with major cardiovascular risk factors.

⊙Patho physiological approach in reducing Systolic Blood Pressure:

▪▪Medical treatment of hypertension usually results in parallel decline of SBP as well as DBP. Nevertheless, as already stated previously, an adequate control is frequently achieved on DBP and to a significantly smaller extent on SBP. In the case of ISH, the therapeutic goal is to obtain a preferential decrease in SBP while maintaining unchanged

DBP. In patients with essential hypertension, the International guidelines recommend the use of thiazide-type diuretics in monotherapy or in combination; they also highlight the need to select the lowest dosages. Other recommended pharmacological classes of antihypertensive agents include beta-blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and calcium antagonists.

While diuretics are still regarded as the treatment of choice in elderly patients and those with systolic hypertension, not all drugs in this class have the same efficacy. Indapamide SR, a thiazide-type diuretic, has shown activity in the elderly, as well as in patients with left ventricular hypertrophy (LVH) or type II diabetes mellitus. [1]

⊙Drug interactions:

Other Antihypertensive: Indapamide may add to or potentiate the action of other antihypertensive drugs. In limited controlled trials that compared the effect of indapamide combined with other antihypertensive drugs with the effect of the other drugs administered alone, there was no notable change in the nature or frequency of adverse reactions associated with the combined therapy.

Nor epinephrine: Indapamide, like the thiazides, may decrease arterial responsiveness to nor epinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

↳A subgroup of 187 patients aged over 65 years old was assessed. Indapamide SR reduced microalbuminuria by 46%. This effect was equivalent to enalapril (47%) with a similar decrease in MBP (-17.6±9.4 mmHg with Indapamide SR and -15.3±9.5 mmHg with enalapril). Additionally, 43% of the patients treated with Indapamide SR and 37% treated with enalapril had UACR normalization (<2.5 mg/mili mol for men and <3.5 mg/mmol for women) at the end point.

↳Both in the main and in the elderly subgroup of the Natrilix SR *vs* enalapril study on hypertensive type II diabetes with microalbuminuria (NESTOR), Indapamide SR and enalapril showed a similar reduction in microalbuminuria. The metabolic profile and renal function were unimpaired by the two treatments.

These results support the use of Indapamide SR as a first-line therapy in type II diabetic hypertensive patients with micro albuminuria.

↳Dosing can be, 1 tablet daily, preferably in the morning. In more severe cases, Repres SR can be combined with other categories of antihypertensive agents.

⊙Precautions:

The drug should be used cautiously in the following situations-disturbed water/electrolyte balance, diabetes, gout and kidney problems. Monitoring of potassium and uric acid serum levels is also recommended.

◎Evaluation of the Repres RS matrix tablets:

In vitro release studies

▪▪Study of hardness:

The hardness of 10 Repres SR matrix tablets was determined using hardness tester (Veego). Theoretically, too 'soft' tablets can disintegrate in transport. Too 'hard' tablets could damage 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:

- ▪Hardness tester (veego)
- ▪Repres SR matrix tablets

↳The following procedure was followed:

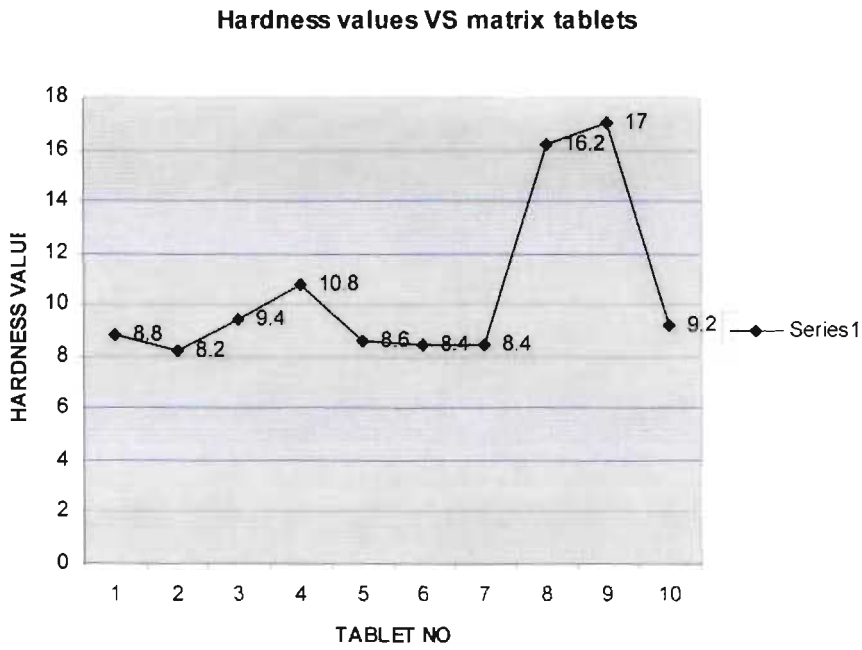
- ▪The sliding scale of the hardness tester were made zero.
- ▪Tablets were placed vertically between two jaws (by one tablet).
- ▪Force has been applied with a screw thread and spring until the tablet fractured.
- ▪Readings were taken in kg from the sliding scale.

Most materials testing are performed using the international system of units. Here kilogram (kg) is used.

The average crushing strengths (hardness values) were determined and the data is shown in **table 1**. The lowest value and the highest value are also shown at table 1:

Tablet No.	Hardness of Repres SR (kg)
1	8.8
2	**8.2 (lowest value)**
3	9.4
4	10.8
5	8.6
6	8.4
7	8.4
8	16.2
9	**17 (Highest value)**
10	9.2

*Table 1: Hardness test of Repres SR matrix tablets



*Graph 1: graphical show for relationship between hardness values with matrix tablets

◎Discussion about above tables and Graph

The mean hardness value of Repres SR matrix tablets was found 10.5kg. The result of hardness for the Repres SR matrix tablets were different at same pressure ranging from 8.2 to 17 kg. According to specification the hardness value for matrix tablet would be below 9.5kg for desired release pattern [6]. So it was found that the hardness was the highest for matrix tablets.

▪▪Study of thickness:

The experiment was carried to measure the thickness of Repres SR matrix tablets by using vernier slide calipers.

↳Materials required:

- Vernier calipers
- Repres SR matrix tablets

↳The following procedure has been followed:

- ▪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.

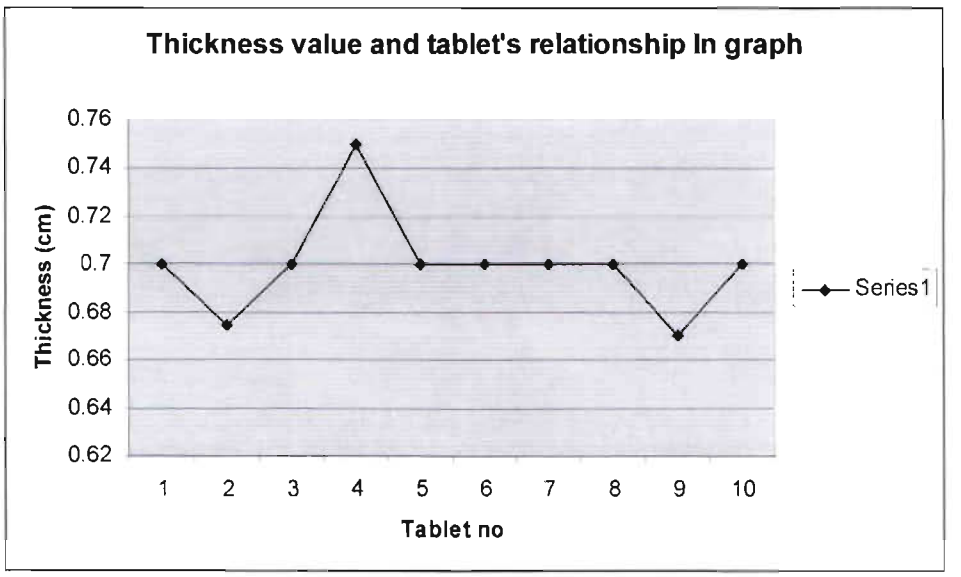
Formula assigned;

Thickness of the tablet = **Reading of cm Scale + Reading of Vernier Scale + Vernier Error.**

↳The thickness values of 10 Repres SR matrix tablets determined using vernier calipers Have been shown in table 2. The lowest value and the highest value are also shown at table 2.

No of tablet	Reading of cm Scale	Reading of vernier Scale	vernier constant	vernier error	Thickness of Tablet (cm)
1	0.4	6	0.5	0	**0.70 (Highest Value)**
2	0.4	5.5	0.5	0	0.675
3	0.4	6.0	0.5	0	0.70
4	0.4	7.0	0.5	0	0.75
5	0.4	6.0	0.5	0	0.70
6	0.4	6.0	0.5	0	0.70
7	0.4	6.0	0.5	0	0.70
8	0.4	6.0	0.5	0	0.70
9	0.4	5.5	0.5	0	**0.67 (lowest value)**
10	0.4	6.0	0.5	0	0.70

Table 2: Thickness values of Repres SR matrix tablets



Graph 2: graphical show for relationship between thickness values with matrix tablets

◎Discussion about above tables and Graph:

The average thickness of the Repres SR matrix tablets was found 0.69cm.It is well established that the thickness of the tablet could affect the release rate of the drug. Use of excess water insoluble coating agents or other excipients would cause changes in thickness and therefore release rate.

▪▪Study of Weight Variation:

This experiment was carried out to determine the uniformity of Repres SR matrix tablets.

↳Materials required:

- ▪Weighing balance
- ▪Repres SR matrix tablets

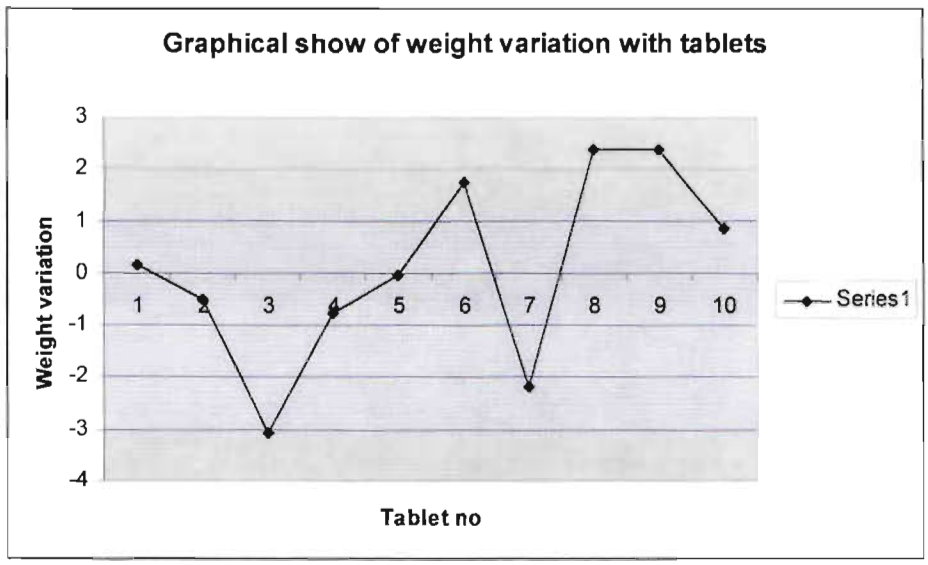
↳The following procedures were followed;

- ▪Ten Repres SR 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 Repres SR matrix tablets individually and observed whether the individual tablets are within the range or not.

↳The weight variation data of 10 Repres SR matrix tablets determined using weighing balance and it have been shown in table 3. The lowest value and the highest value are also shown at table 3.

Tablet no	Individual Weight (gm)	Average weight = sum of individual weight/10	Weight variation = (A Wt. - Ind. Wt.)*100/A Wt.
1	0.1982	0.1985gm	0.151
2	0.1995		-0.501
3	0.2046		**-3.07 (Lowest Value)**
4	0.2020		-0.76
5	0.1986		-0.05
6	0.1950		1.76
7	0.2028		-2.17
8	0.1938		**2.37 (Highest Value)**
9	0.1938		2.37
10	0.1968		0.856

Table 3: weight variation test for Repres SR tablets



Graph 3: graphical relationship for matrix tablets with weight variations.

◎Discussion about above tables and Graph:

The mean value of weight variation of repress SR matrix tablets was found 0.956.

▪▪Study of dissolution test:

In vitro, The BP XII D Apparatus 1 (Basket apparatus) by dissolution tester (RC6, Vanguard Pharmaceuticals, and USA) was used to conduct drug release studies of the collected matrix tablet. provided that the Temperature were maintained at 37° C (± 0.5 °C) and rotate the paddle at100 revolutions per minute(rpm) speed. Dissolution studies were carried out by using one liter distilled water 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. Standard Indapamide solution were prepared medium. Then the absorbances of those solutions of different concentrations were observed with single beam spectrophotometer at 240 nm and 270 nm.In analytical applications we often want to measure the concentration of an analyte independent of the effects of reflection, solvent absorption, or other interferences.

↳Materials required:

- ▪Dissolution tester
- ▪Analytical balance
- ▪Filter paper
- ▪Beaker, Pipettes, Spatula, Funnel
- ▪Distilled water

↳Operating parameters:

- ▪Medium: 1000ml 0.1 M HCl
- ▪Apparatus: 1
- ▪RPM: 100
- ▪Time: 300 minutes
- ▪λ Max: 240nm and 275nm.

↳The following procedures were followed:

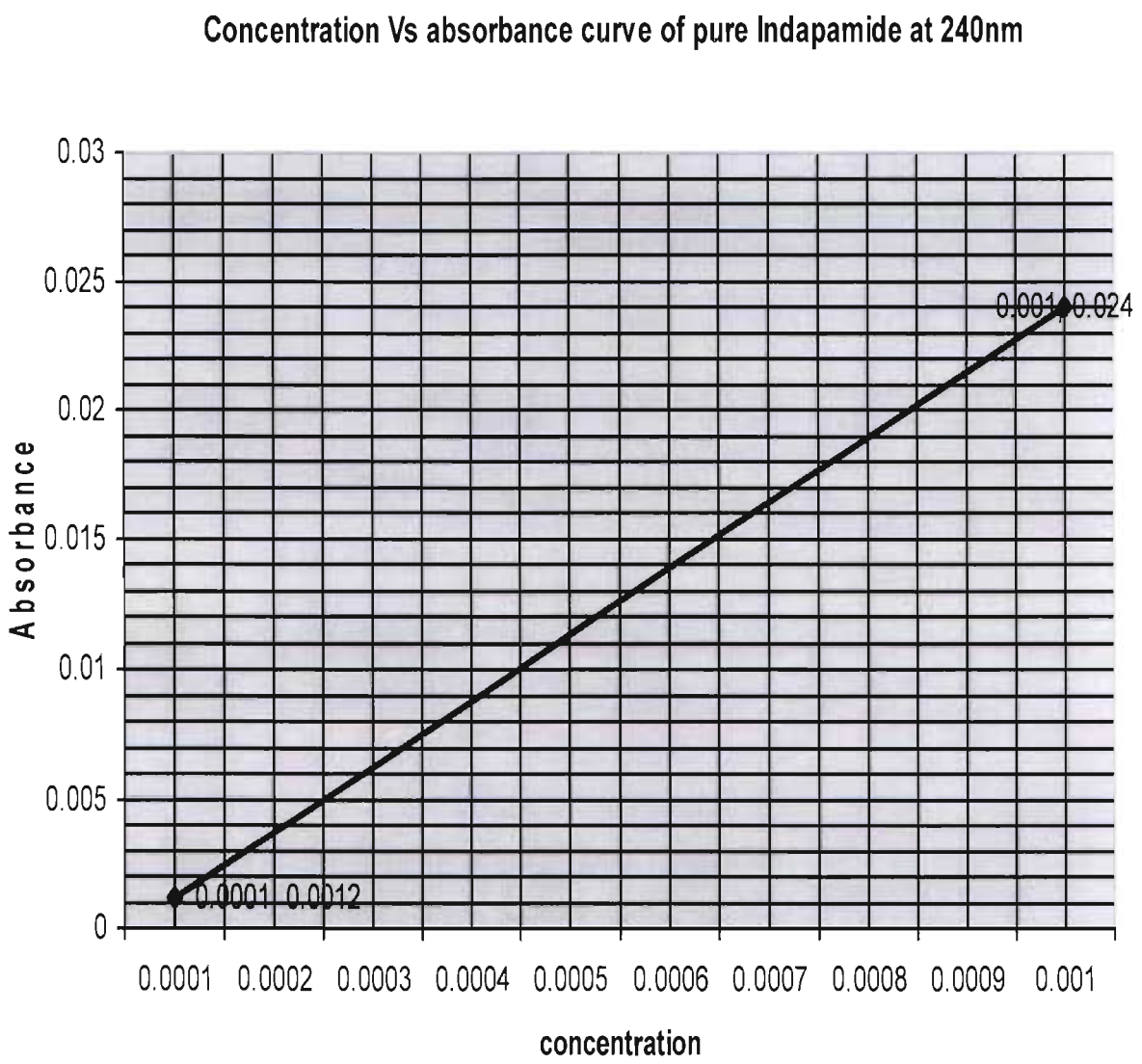
A. Preparation of the Dissolution Medium: (0.1 M 1000ml HCl)

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.

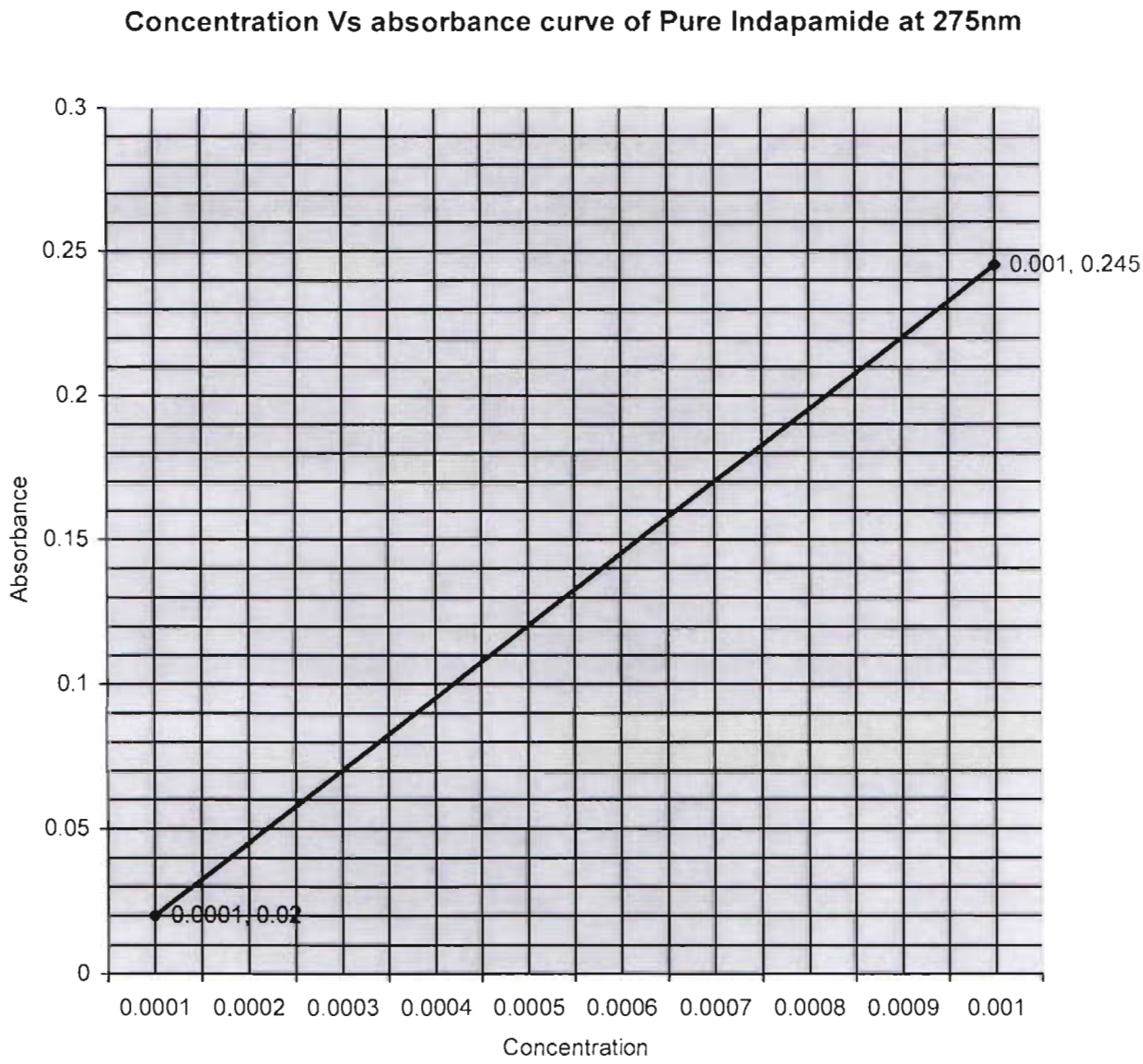
B. Study procedures:

1. The Repres SR matrix tablet were weighed.
2. Filled the water tank and set the operating parameters on the dissolution test apparatus.
3. Poured 500ml of the 0.1m HCl solution 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.
4. Placed the Repres SR matrix tablet into the vessels and start the run. At the end of the time specified, 10ml of the sample was collected from the vessels and filtered it. Replaced it with 10ml medium and repeated it for other time intervals set.
5. Measured the absorbance of the solutions at 240nm and 270 nm.

↳Standard curves of time vs. concentration were 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:



Graph5: showing absorbance vs concentration relationship for pure Indapamide at 240 nm.

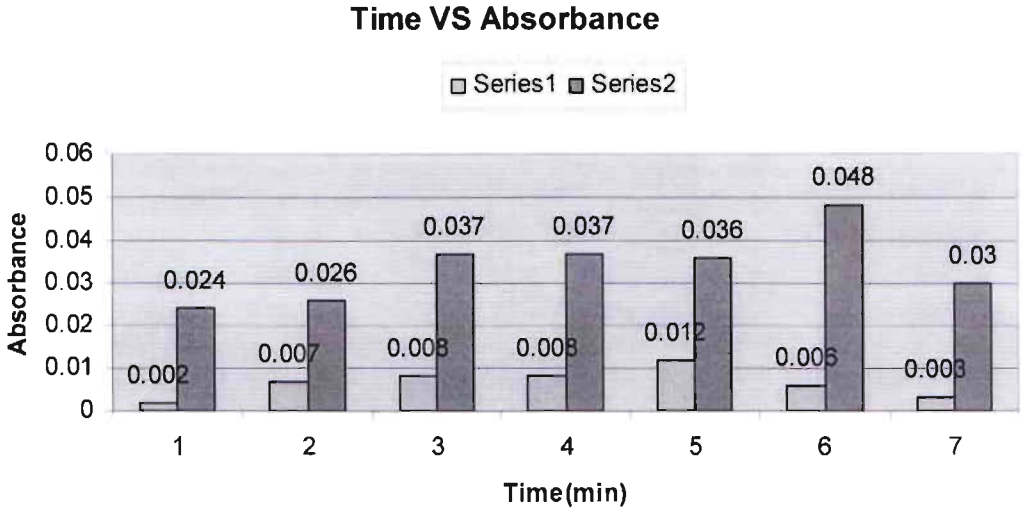


Graph 6: showing absorbance vs concentration relationship for pure Indapamide at 275 nm.

The Release pattern of repress SR matrix tablets determined by dissolution study gives following absorbance data shown in table 4. The lowest value and the highest value are also shown at table 4.

Time (min)	Absorbance	
	240(nm)	**275(nm)**
120	**0.002**	**0.024**
150	0.007	0.026
180	0.008	0.037
210	0.008	0.037
240	**0.012**	0.036
270	0.006	**0.048**
300	0.003	0.030

Table 4: Dissolution test for Repres SR matrix tablets



Graph 4: Graphical presentation of the relationship between the time and absorbance

The above data and graph shows that repress SR matrix tablet dissolved in 0.1M HCl And gives various absorptibity values in spectrophotometer at various time intervals.

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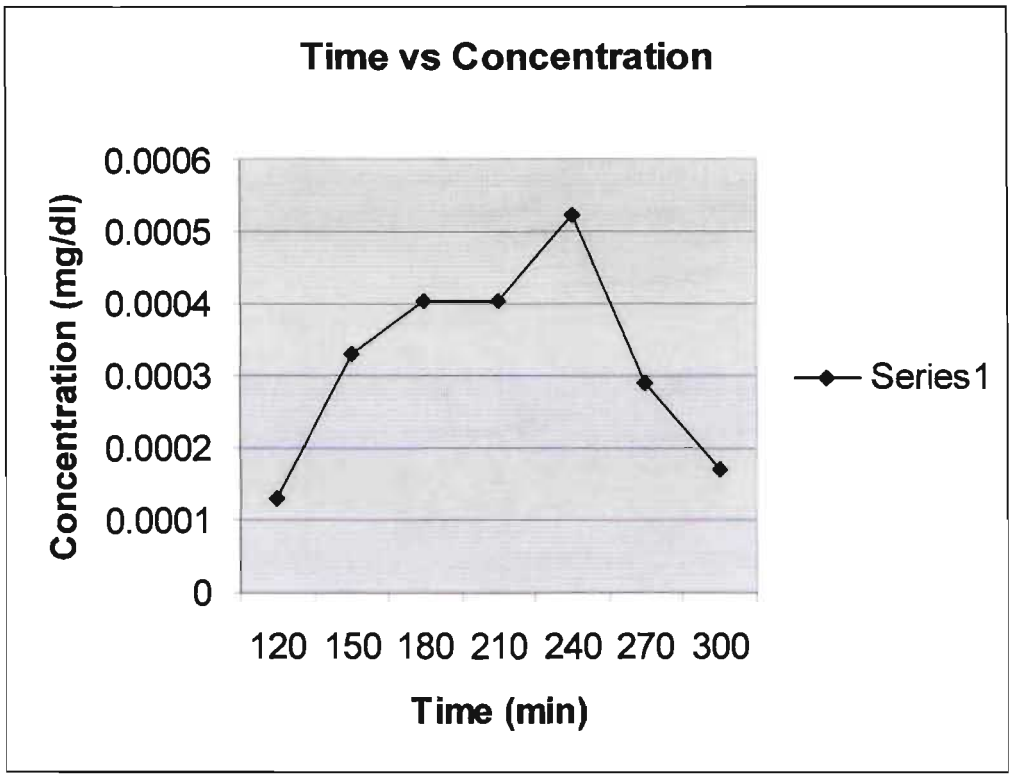
Time (min)	240nm
	Concentration (mg/dl)
120	0.000130
150	0.000330
180	0.000405
210	0.000405
240	0.000525
270	0.000290
300	0.000170

Table 5: The concentrations of released drugs were found at 240nm has been documented in the table.

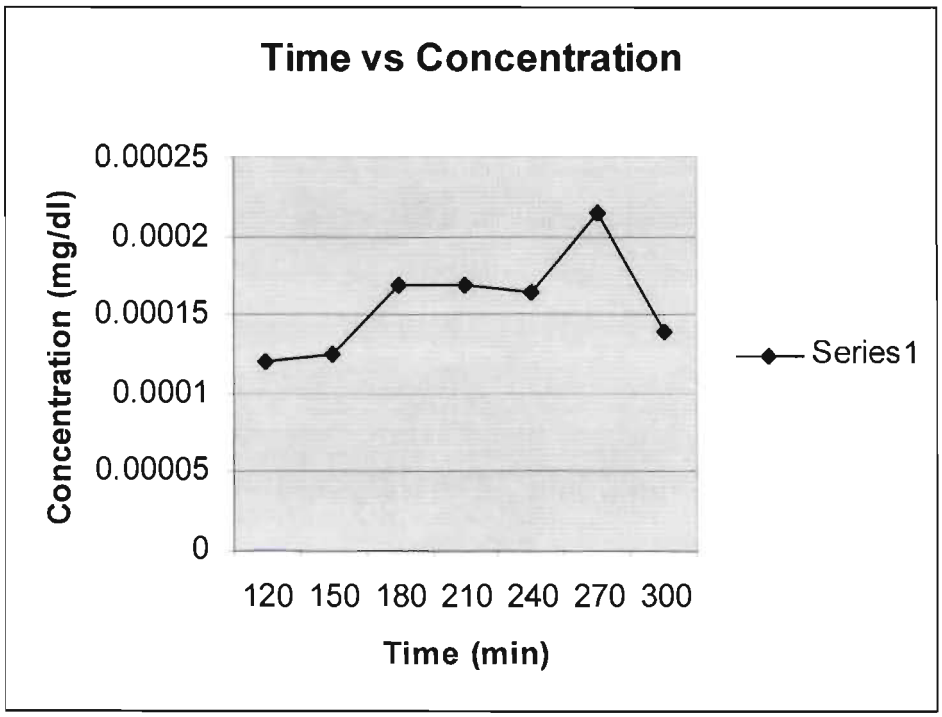


Graph 5: graphical show of time and concentration relationship. [240 nm]

↳The above graph results from the relationship between time intervals and of drug concentrations found at 240nm wave length by spectrophotometer. According to beer's plot the graph should results a linear relationship between these two parameters. But we found the plot which is deviates from its ideal relationship.

Time (min)	275nm
	Concentration (mg/dl)
120	0.000120
150	0.000125
180	0.000170
210	0.000170
240	0.000165
270	0.000215
300	0.000140

Table 6: The concentrations of released drugs were found at 240nm has been documented in the table.



Graph 6: graphical show of time and concentration relationship. [275 nm]

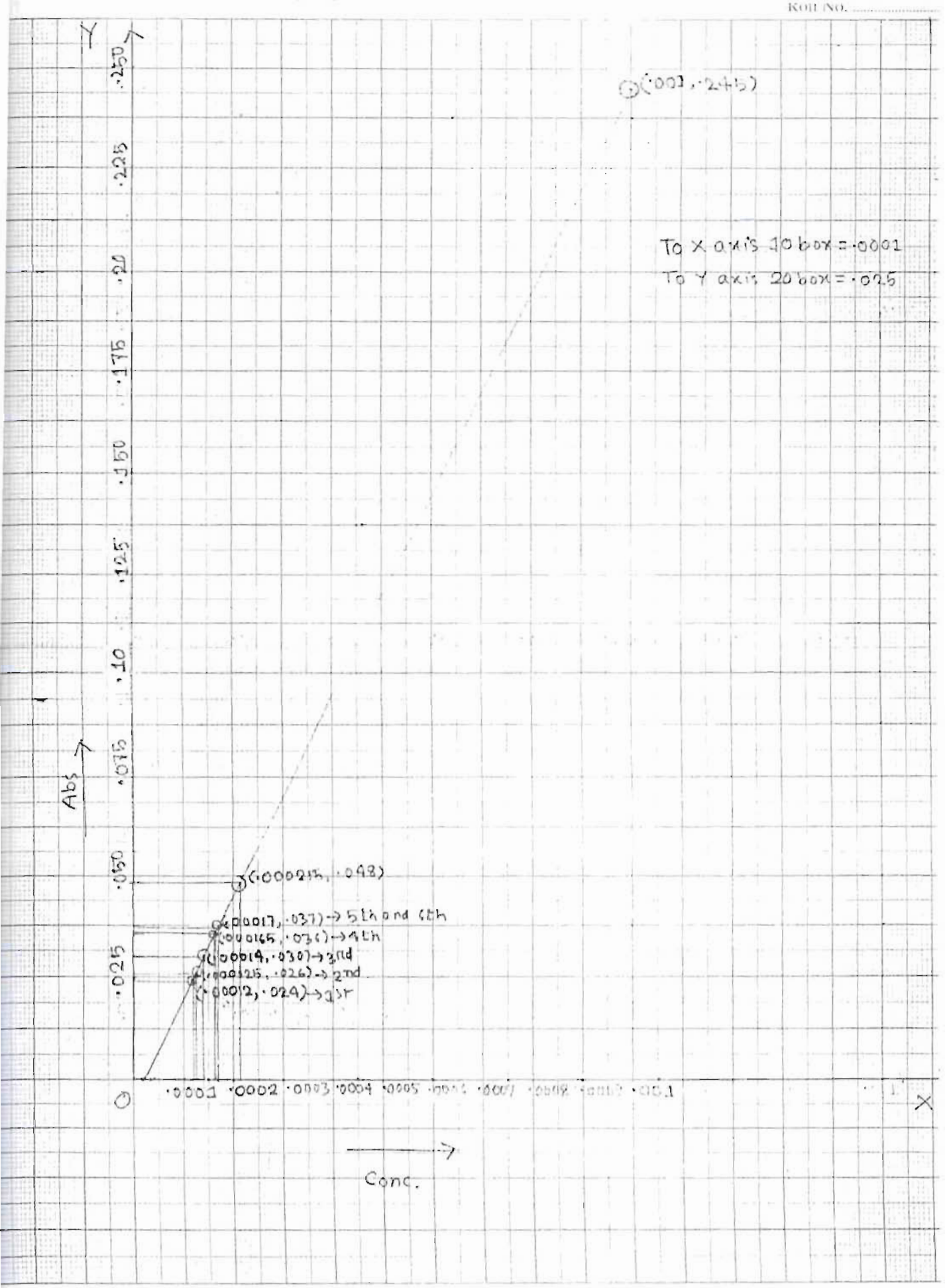
↳The relationship between time intervals and concentration from the above can be inscribed by a curvy line. But this should a straight line according to Beer's plot. So we can draw that the release patterns deviates from it ideal specification.

Procdure that followed during graph sketching :

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 Repres SR 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 value 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 Indapamide 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 275nm).

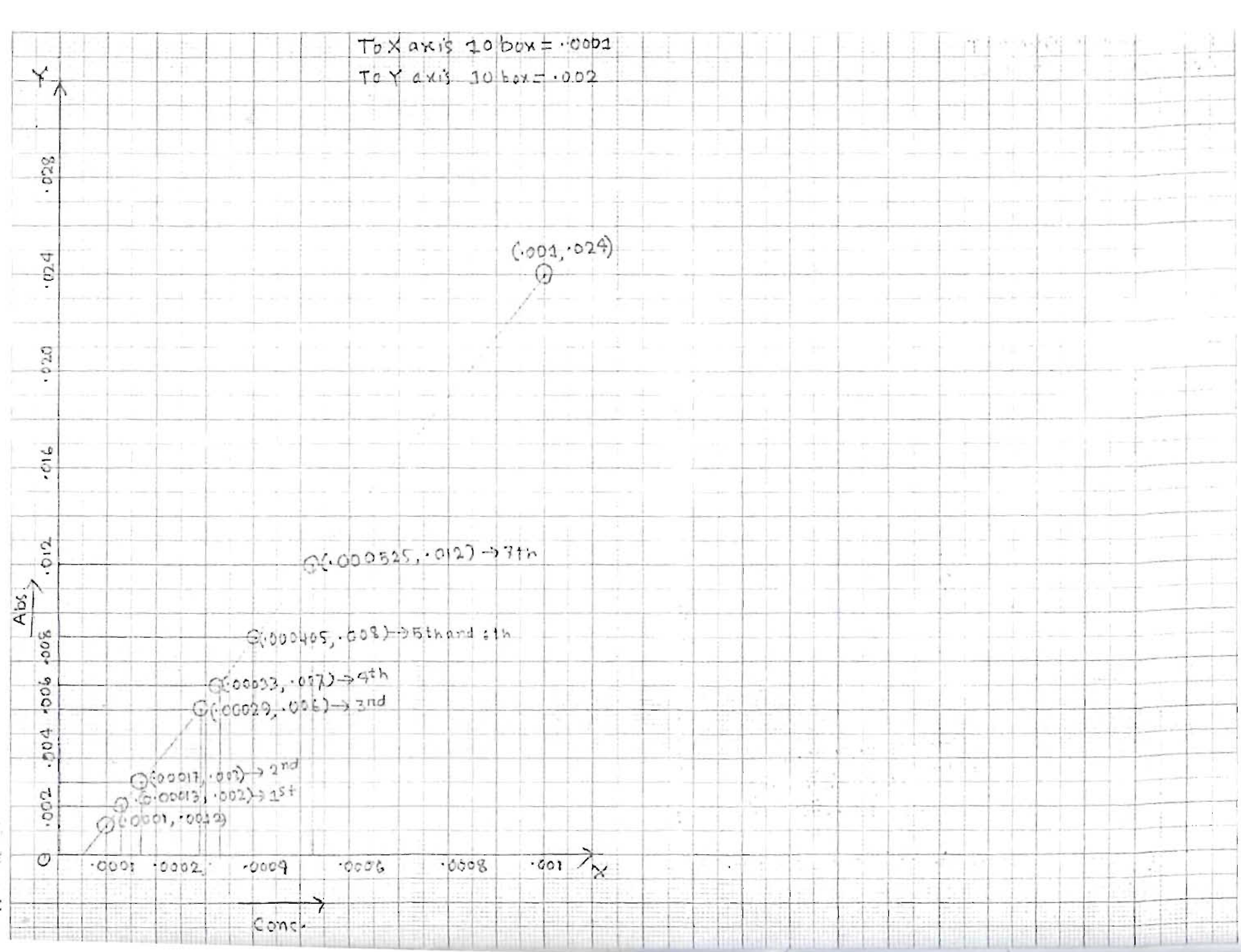
◎Discussion:

↳Sustained release drug delivery system has attracted a great deal of attention in pharmaceutical researches, mainly due to their therapeutic advantages. Because of the importance of indapamide in the treatment of essential hypertension and renal function impairment etc, the preparation of a sustained release dosage form could not only increase the efficacy of treatment and patient compliance, but also can produce desirable blood concentration and decrease the incidence of adverse effects. Manufacturing by high compression forces a continuous matrix is formed and change the tablet hardness causes relatively small change in porosity and therefore the release rate. The other reason of poor release rate could be due ton the use of water solubility nature of excipients.An ideal matrix formulation should contain polymers and diluents at amounts as little as possible, as well as releasing its content in a release profile over a reasonable length of time, and preferably zero order kinetic [8]. The zero order rates describe the systems where the drug release rate is independent of its concentration.



MICRO

NB 20 cm x 2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(·000405, ·008) → 5th and 6th
(·00033, ·007) → 4th
(·00029, ·006) → 3rd
(·00017, ·003) → 2nd
(·00013, ·002) → 1st
(·0001, ·0029)

Roll No.

Reference:

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