An investigation of an in vitro release pattern of Indapamide from Hypen SR matrix tablets

A research paper submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

Submitted by
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Abstract

Purpose*:** The purpose of this research work was to investigate the release pattern of Indapamide from Hypen SR matrix tablets. ***Method: Thirty tablets of Hypen SR were collected from the market and were characterized by physical parameters like hardness, thickness, weight variation and dissolution studies. Indapamide release was investigated using the method inscribed in Appendix XII B: Dissolution tests for tablets and capsules of British Pharmacopoeia. Hardness of the withdrawn samples from the market was measured by hardness tester (Veego, Germany). Thickness of the samples was measured by Vernier Calipers. Dissolution of the taken samples was investigated using dissolution tester (RC6, Vanguard Pharmaceuticals, USA) to evaluate release kinetics. ***Result*:** Mean hardness value of Indapamide tablets was found to be 54.03 N. Mean thickness value of Indapamide tablets was found to be 0.59 cm. Percentage difference of the weight variation test ranges from -4.17 % to 3.39 %. ***Conclusion:*** The release pattern of Hypen SR 1.5mg tablet did not fulfill its requirement to provide desired and optimum sustained release of the drug with the increase of time.

Keywords: Indapamide, Hypen SR, Release pattern, Hardness, Thickness, Dissolution.

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1.1 Introduction:

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 (≤90 mmHg), whereas the ability to control SBP (≤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]

1.2 Pathophysiological approach in reducing SBP:

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]

1.3 Guidelines in hypertension:

Several national and international organizations make recommendations for the choice of therapy for elevated BP. All agree that lowering BP per se is the primary goal of antihypertensive therapy. All acknowledge the need for multiple therapies in the majority of patients. **The European Society of Hypertension (ESH)** guidelines advise that all major classes of antihypertensive agents are suitable for the initiation and maintenance of antihypertensive therapy'. In common with all major guidelines, the **British Hypertension Society guidelines of 2004 BHS IV)** indicate conditions where specific drugs should be chosen. When none of these special conditions apply, **BHS IV** recommends that initial drug selection follows a treatment algorithm, with ACE inhibitor or angiotensin receptor blocker used in younger patients and thiazide diuretic in older patients. **The American joint national committee** report takes a less equivocal stance and recommends that: thiazide type diuretics should be used in drug treatments for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes'. **The World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines** recommend diuretics as the first-step antihypertensive treatment for **ISH. WHO-ISH, BHS-IV**, and **JNC-VII** also recommend using the lowest possible doses of long acting drugs, which are effective for 24 h with a single daily dose, in order to reduce metabolic disturbances and to improve the efficacy acceptability ratio. They acknowledge that at least two-thirds of patients with elevated BP are likely to require two or more therapies, one of which should be a diuretic. [5]

1.4 Pharmacology of Indapamide:

Indapamide is a thiazide-type diuretic with additional antihypertensive properties. Its molecular structure differs from thiazides by the presence of a 2-methyl indoline ring, which provides it with important lipophilic properties. Its diuretic effects are well demonstrated both in animals and humans, although their precise mechanisms and sites of action remain to be elucidated. Indapamide is likely to act predominantly on the cortical segment of the distal convoluted tubule, where it binds to a specific site family from which it can be displaced by hydrochlorothiazide, which suggests that at least part of Indapamide action involves the Na+–Cl) co-transporter of the distal tubule. The natriuretic and kaliuretic effects of Indapamide are dose dependent in rats and dogs. Interestingly, the maximum natriuretic effect seems to be reached with lower doses than the kaliuretic effect. As a consequence, and importantly from a therapeutic point of view, it was of interest to investigate the use of Indapamide at a dose sufficiently low to enhance natriuresis without significantly affecting the urinary excretion of potassium, which would increase the risk of hypokalemia. Besides its diuretic properties, Indapamide exhibits protective effects on the target organ damage in animal models of hypertension. It reduces left ventricle hypertrophy in spontaneously hypertensive rats (SHR) and limits the expression of the fetal isoform of fibronectin in the ventricle thus, potentially, preventing the development of cardiac fibrosis. Indapamide also reduces the appearance of nephrosclerosis in stroke-prone SHRs given NaCl, as well as in Dahl salt-sensitive rats. Finally, Indapamide significantly reduced the incidence of strokes in stroke-prone SHR receiving 1% NaCl. In addition to this ability to prevent end-organ damage in animal models of hypertension, Indapamide exhibits less prominent but potentially important pharmacological properties, including limiting sympathetic nerve activation, blocking voltage-operated calcium channels and promoting the production of prostacyclin. [5]

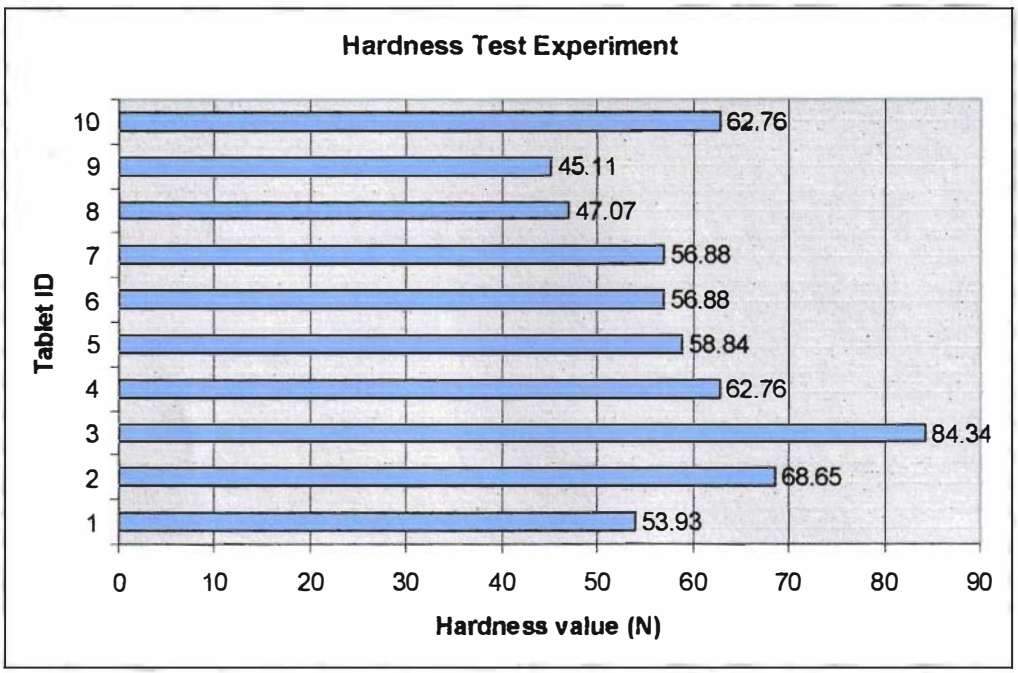
2.1 Study of Hardness:

Methodology: An acceptable hardness is required and tablet strength testing is necessary for both research and development of new formulations quality control and release pattern. The hardness of 10 Hypen SR tablets was determined using hardness tester (Veego). The sliding scale of the hardness tester was zeroed and each tablet was placed vertically between two jaws. Force was applied with a screw thread and spring until the tablet fractured. [8] Most materials testing is performed using the International System of Units. The Newton is the preferred unit of force as is recognized by the SI System. The average crushing strengths (hardness values) were determined and the data is presented as both in kilogram and Newton unit in **Table 1.**

2.2 Table 1: Hardness test of Hypen SR Tablets

Tablet ID	Hardness of Hypen SR in kg	Hardness of Hypen SR in Newton
1	5.5	53.93
2	7	68.65
3	8.6	**84.34**
4	6.4	62.76
5	6	58.84
6	5.8	56.88
7	5.8	56.88
8	4.8	47.07
9	4.6	**45.11**
10	6.4	62.76

2.3 Bar diagram 1: Hardness test of Hypen SR Tablets



Discussion:

Ideally all the different varieties of testing machines would give the same result if tablets of the same batch are used. In our research work we used hardness tester (Veego, Germany) to measure the harness of Hypen SR tablets and the measured values are found to be surprisingly of furthest range. The lowest value was found to be 45.11 N and the highest value was found to be 84. 34 N which is almost double compared to the lowest value. Again the dissolution of the tablets was also found to be retarded for the anomalies in crushing strength. [4]

Result:

The mean hardness value of Hypen SR is 54.03 N. The crushing strength rages from 45.11 N to 84.34 N.

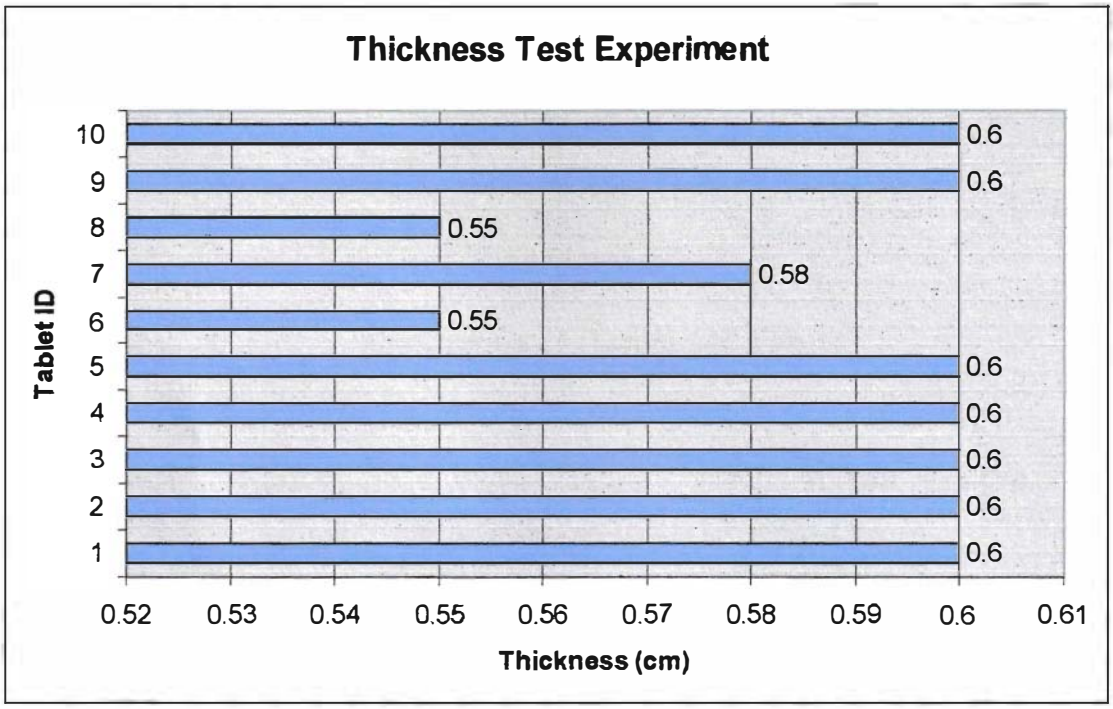
3.1 Study of Thickness:

Methodology: The objective of this experiment was to measure the thickness of table by using Vernier Calipers. Each Hypen SR tablets was placed horizontally between tw jaws. The screw of the caliper was run to hold the tablet and reading was taken in cr from the scale. [8] The average thickness was determined and the thickness determinatio procedure is presented in **Table 2.**

3.2 Table 2: Thickness test of Hypen SR Tablets

Tablet ID	Reading of cm Scale	Reading of Vernier Scale	Vernier constant	Vernier error	Thickness of Tablet (cm)
1	0.3	6	0.5	0	0.60
2	0.3	6.0	0.5	0	0.60
3	0.3	6.0	0.5	0	0.60
4	0.3	6.0	0.5	0	0.60
5	0.3	6.0	0.5	0	0.60
6	0.3	5.0	0.5	0	0.55
7	0.3	5.5	0.5	0	0.58
8	0.3	5.0	0.5	0	0.55
9	0.3	6.0	0.5	0	0.60
10	0.3	5.0	0.5	0	0.60

3.3 Bar diagram 2: Thickness test of Hypen SR Tablets



Discussion:

Seven out of ten randomly picked Hypen SR tablets (Indapamide) were found to have a thickness of 0.6 cm. Variation in thickness of the tablets of the same batch were less.

Result:

The average thickness was found to be 0.59 cm.

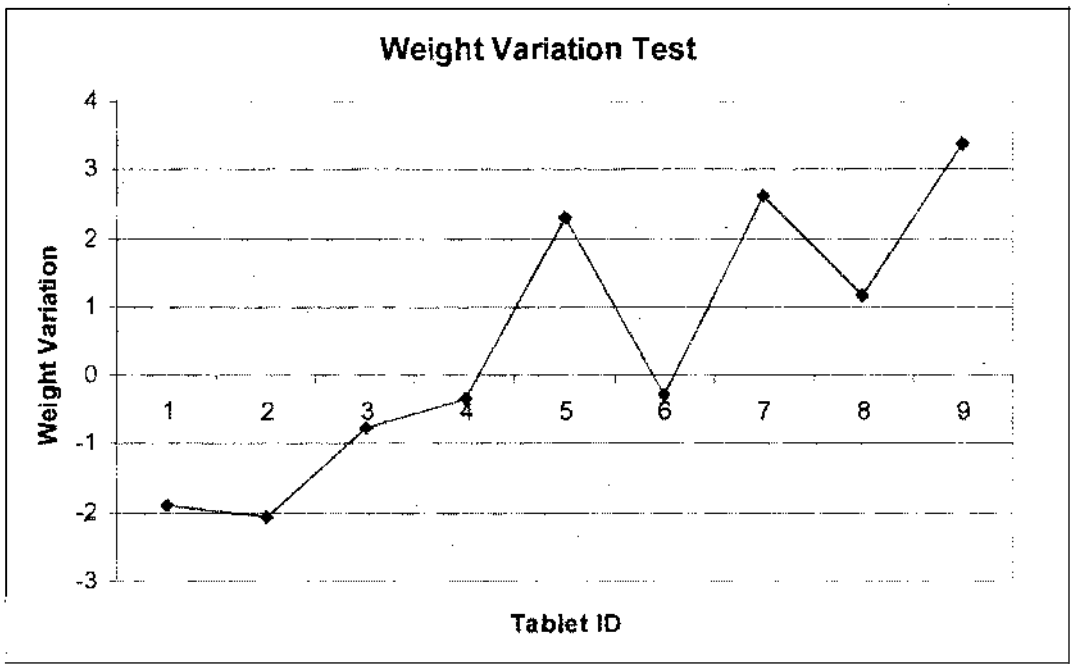
4.1 Study of Weight Variation:

Methodology: Objective of this experiment was to determine the uniformity of tab weights. Electronic weighing balance was used to weigh ten randomly withdrawn tab of Hypen SR (Indapamide). The average of the weight was calculated and considered an individual weight of the tablet. The weight variation test is presented in **Table 3** a showed graphically in **Line diagram 1.**

4.2 Table 3: Weight Variation test of Hypen SR Tablets

Tablet ID	Individual Weight (gm)	Average weight = sum of individual weight/10	Weight variation = (Avg Wt. - Ind. Wt.)*100/A Wt.
1	0.1735	0.16655	.-4.17
2	0.1697		-1.89
3	0.1700		-2.07
4	0.1678		-0.75
5	0.1671		-0.33
6	0.1627		2.31
7	0.1670		-0.27
8	0.1622		2.61
9	0.1646		1.17
10	0.1609		3.39

4.3 Line diagram 1: Weight Variation test of Hypen SR Tablets



Discussion:

Tablets are required to meet a weight variation test where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. [5] The variation from the average weight in the weights should be not more than ± 10 if the average weight is 130 mg or less. In my weight variation test of Hypen SR 1.5 mg tablet the average weight was found to be 0.16655 gm or 16.65 mg.

Result:

The average weight of the Hypen SR (Indapamide) was found to be 0.16655 gm. The percentage difference or the weight variation did not exceed the ± 10% limit.

5.1 Study of Dissolution:

Preparation of the Dissolution Medium:

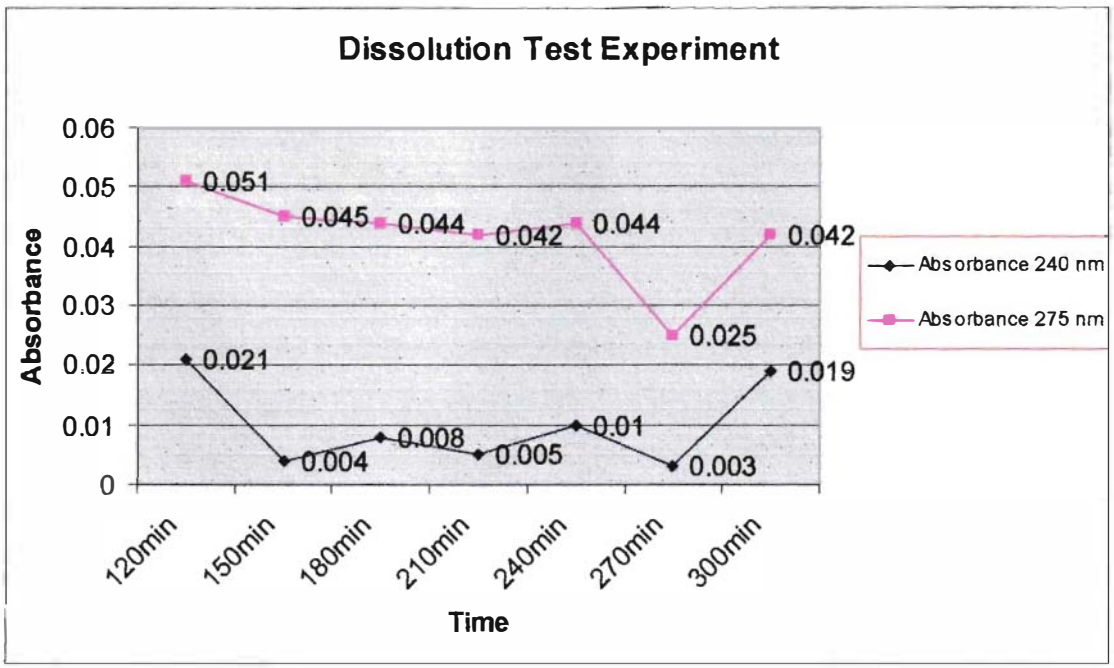
Methodology: The supplied HCL from the East West University laboratory of Pharmacy Department was 32% w/v. As the molecular weight of HCL is 36.5, the 1 M HCL solution contains 36.5 gm theoretically. So, from calculation it was found that 0.1 M HCL solution contains 3.65 gm of HCL and 11.4 ml of 32% w/v HCL is needed to prepare 1000 ml of 0.1 M HCL solution which was further used as dissolution medium. 1000 ml of 01 M HCL solution was required to be prepared as each of the two baskets is to be filled with 500 ml of 0.1 M HCL solution according to British Pharmacopoeia (BP). [3]

In vitro release studies: 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 revolutions per minute speed in accordance with BP. Dissolution studies were carried out by using 500 ml 0.1 M HCL solution as a dissolution medium in every vessel. Ten milliliter (ml) samples were taken 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 as directed by the BP. Reference Indapamide solution was prepared by diluting 1 volume of a .10% w/v solution of Indapamide. Then the absorbance of those solutions of different concentrations was observed with single beam spectrophotometer at 240 nm and 270 nm. [3] The data of absorbance at 240 nm and 270 nm are inscribed in **Table 4** and plotted graphically in **Line diagram 2.**

5.2 Table 4: Dissolution test of Hypen SR Tablets

Time	Absorbance	
	240 nm	275 nm
120min	0.021	0.051
150min	0.004	0.045
180min	0.008	0.044
210min	0.005	0.042
240min	0.010	0.044
270min	0.003	0.025
300min	0.019	0.042

5.3 Line diagram 2: Dissolution test of Hypen SR Tablets



Discussion:

Pharmacokinetics of Indapamide Sustained Release Tablets: Indapamide was first developed as 2.5 mg immediate release tablets. These were quickly absorbed leading to rapid and high plasma concentrations. The SR formulation offered dampening of the peak plasma concentrations while maintaining adequate concentrations for the next 24 h. In developing the SR form, a hydrophilic matrix was chosen as this presents several advantages including the lack of a requirement for special manufacturing technology, and no requirement for the use of organic solvents with their inherent risks of trace residues in the tablets and of toxicity for the environment. Hydrophilic matrices use polymers mostly cellulose derivatives which swell in contact with aqueous media such as, in vivo, the gastrointestinal fluids. The swollen matrix limits diffusion from the drug-containing core of the tablet, and therefore slows distribution into the gastrointestinal tract. For Indapamide SR a high molecular weight methylhydroxypropylcellulose is to be used. [5]

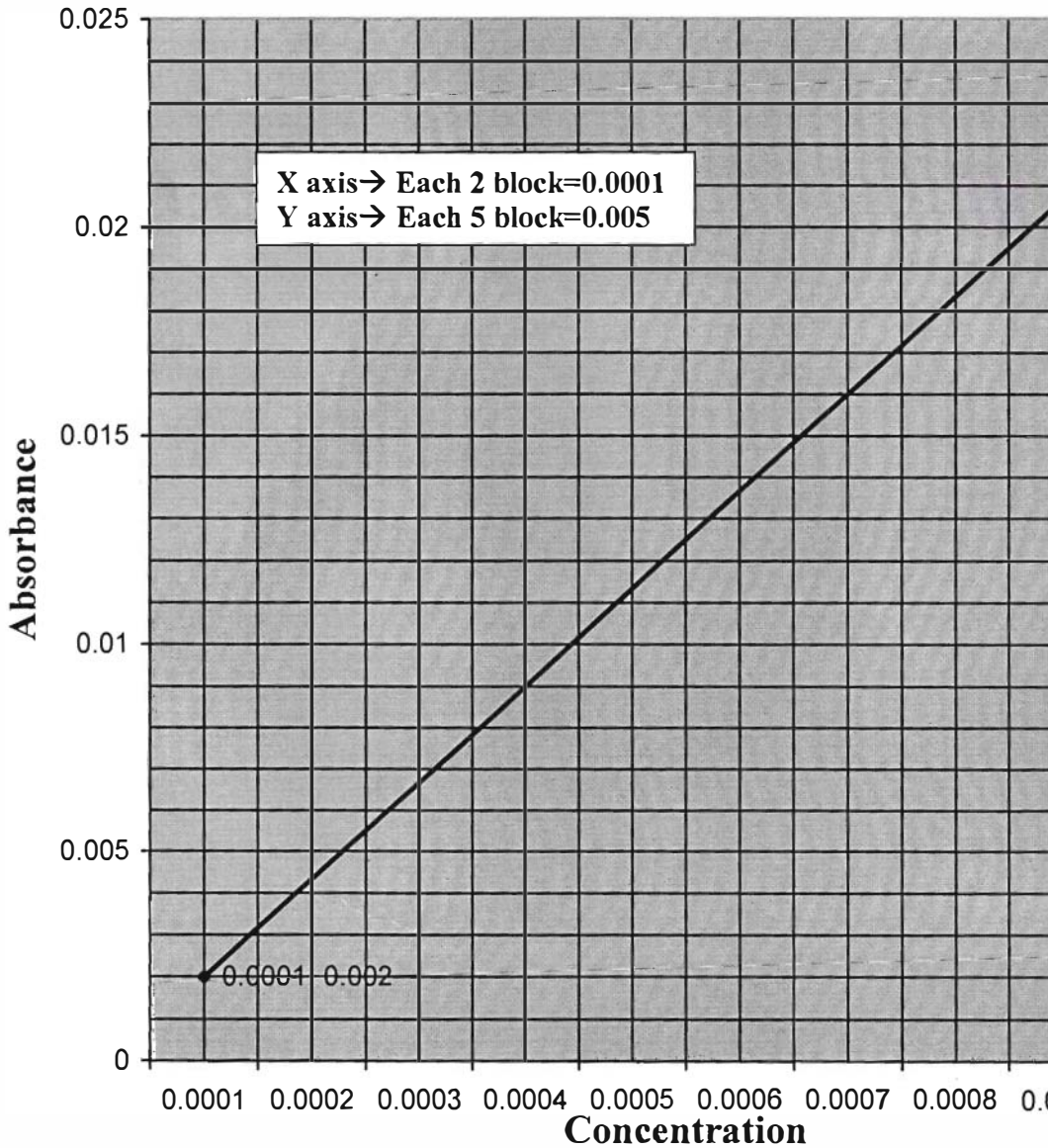
In my research work Hypen SR (Indapamide) 1.5 mg was chosen for study and it has been referred by a three month trial among 405 patients with moderate hypertension that Indapamide SR 1.5 mg had an identical effect to the 2.5 mg immediate release form. Ideally a sustained release Indapamide 1.5 mg tablet should maintain steady state concentration for prolonged period of time. [5]

6.1 Preparation of the Standard Curve:

As the concentration of the different withdrawn solution of Indapamide taken at different time intervals namely at 120, 150, 180, 210, 240, 270 and 300 minutes was unknown, it was decided to prepare a standard curve of pure Indapamide which was a kind gift from Incepta Pharmaceuticals Ltd. To begin with 1 g or 1000mg of the crude sample was weight in an electronic balance and was dissolved in 100 ml of the prepared medium of 0.1 M HCL in a volumetric flask where the concentration became 10 mg/ml. 10 ml of the solution was again diluted with the same medium of 0.1 M HCL to prepare a solution having concentration of 1mg/ml. Similarly it was diluted four times to a solution having concentration of 0.0001mg/ml. Both the solution having concentration of 0.001mg/ml

and 0.0001mg/ml were taken to measure the absorbance at 240nm in the single beam U spectrophotometer (HACH, Model no DR/400UV-VIS, USA). Absorbances w recorded as 0.023 for the solution having concentration of 0.001mg/ml and 0.002 for solution 0.0001 mg/ml. By plotting the value in Microsoft Excel 2003 application following **line chart 3** was found in which each 2 block of X axis was assumed to 0.0001 and each 5 block of Y axis was assumed to be 0.005.

6.2 Line Chart 3: Standard Curve of Crude Indapamide nm



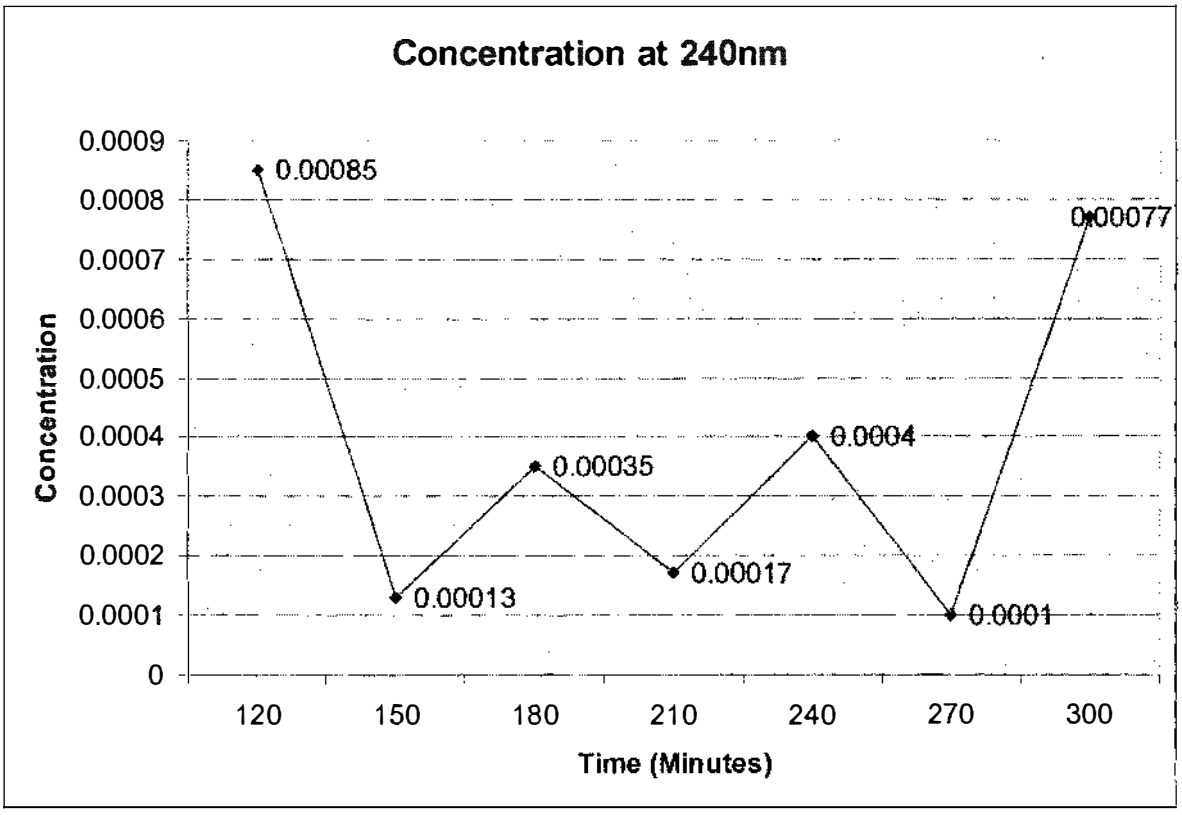
7.1 Calculation of concentration of Hypen SR 1.5mg:

Calculation of the concentrations of different solution of Hypen SR which was previously tested its absorbance at 240 nm were performed by plotting the absorbance data on the Y axis of the graph paper. All the absorbance found at several time intervals namely at 120, 150, 180, 210, 240, 270 and 300 minutes were plotted in the graph paper on the Y axis and a perpendicular was drawn from each of the absorbance value plotted on the Y axis. The point at which the perpendicular intersected was recorded and another perpendicular was drawn from the intercepted point on the slope previously drawn on the standard curve of the crude sample of Indapamide. The point at which the new perpendicular intercepted was found to be the concentration of Hypen SR. All the different absorbance of Hypen SR solution were plotted in similar way to get the concentration from the standard curve of crude Indapamide. The concentrations of the different solutions of Hypen SR are presented in **Table 5** and graphically represented in **Line Diagram 4.**

7.2 Table 5: Concentration of Hypen SR calculated from the Standard Curve

Time (Minutes)	Absorbance at 240nm	Concentration
120	0.021	.00085
150	0.004	.00013
180	0.008	.00035
210	0.005	.00017
240	0.010	.00040
270	0.003	.00010
300	0.019	.00077

7.3 Line diagram 4: Concentration of Hypen SR Tablets at 240nm

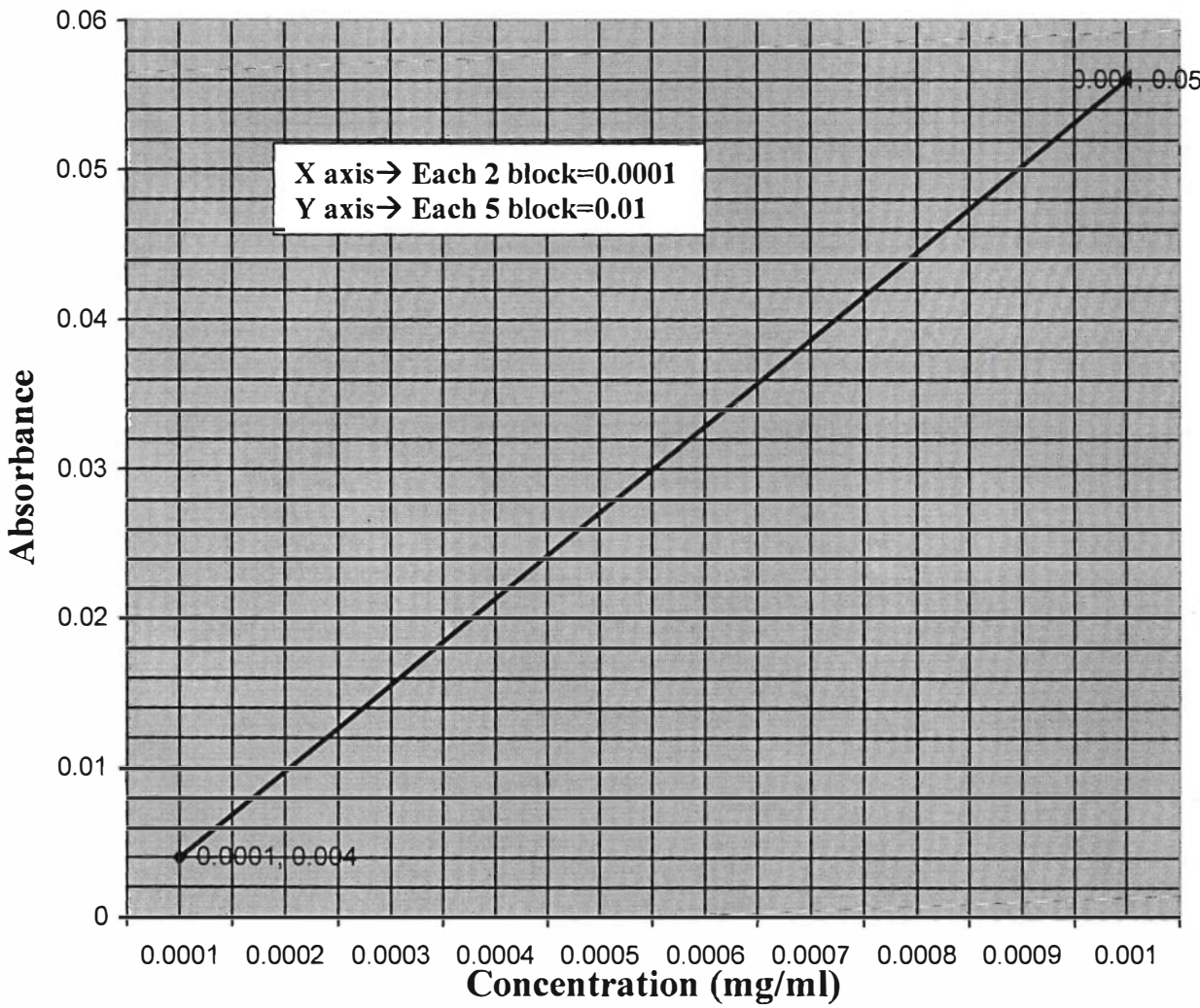


Discussion:

The concentration vs time profile graph of a sustained release preparation is supposed to maintain a steady state concentration for prolonged period of time. Unfortunately in my research work I had come to observe an abnormal graphical representation of the concentration plotted against time at 240 nm. As it is a single dose drug and designed in such a way to be released for 24 hours to give its optimum desired sustained release action, I have found the release pattern is not uniform and maintaining a sustained release. As the **mean steady state concentration is 0.005 mg/ml** four of the values are lying downward to it which was undesired and failed to prove its unique release pattern.

The previously diluted crude sample of Indapamide solution was again taken to record the absorbance at 275 nm in the single beam UV spectrophotometer (HACH, Model no DR/400UV-VIS, USA). Absorbances were recorded as 0.056 for the solution having concentration of 0.001 mg/ml and 0.004 for the solution 0.0001 mg/ml. By plotting the value in Microsoft Excel 2003 application the following **Line Chart 5** was found.

7.4 Line Chart 5: Standard Curve of Crude Indapamide at 275 nm

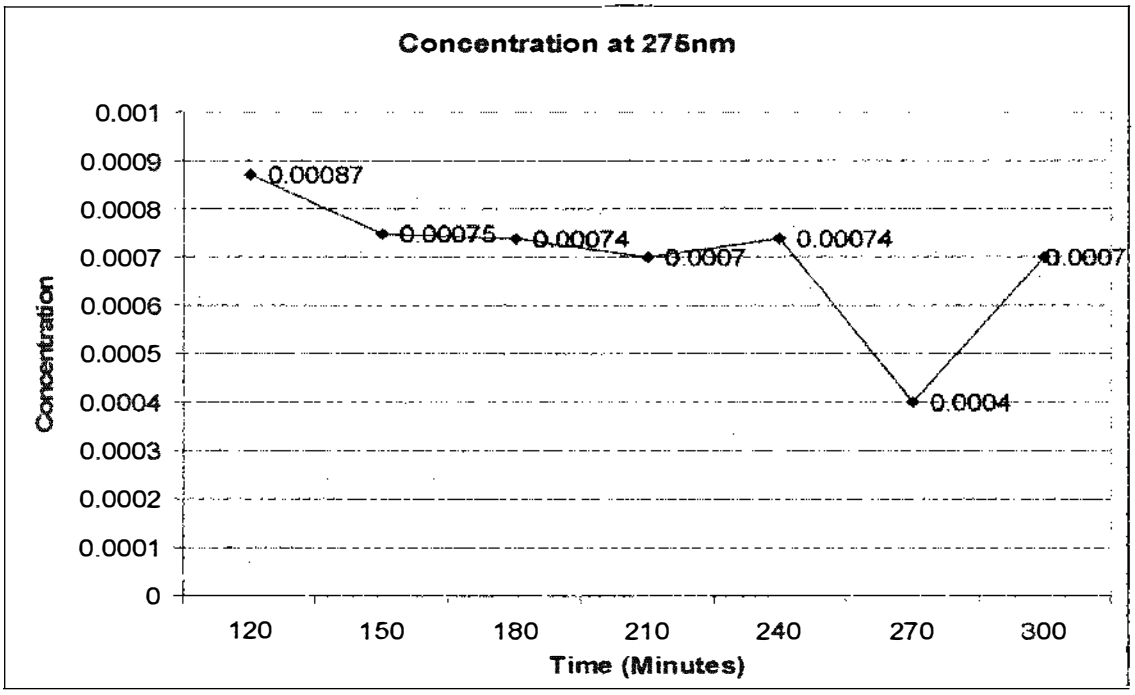


All the different absorbance of Hypen SR solution previously measured at 275 nm were plotted in similar way to get the concentration from the standard curve of crude Indapamide. The concentrations of the different solutions of Hypen SR are presented in **Table 6** and graphically represented in **Line diagram 6.**

7.5 Table 6: Concentration of Hypen SR calculated from the Standard Curve

Time (Minutes)	Absorbance at 275nm	Concentration
120	0.051	.00087
150	0.045	.00075
180	0.044	.00074
210	0.042	.00070
240	0.044	.00074
270	0.025	.00040
300	0.042	.00070

7.6 Line Diagram 6: Concentration of Hypen SR Tablets at 275nm



Discussion:

The concentration vs time profile graph at 275 nm was found satisfactory as it was observed from the graph that it maintained a steady state concentration. Five of its value maintained a concentration above the mean steady state concentration which was desired for a sustained release formulation. After 300 minutes the concentration was found as 0.0007 mg/ml. It is inscribed in the Appendix XII B: Dissolution tests for tablets and capsules of British Pharmacopoeia to measure the absorbance at two different wavelengths which was followed in this research and at 275 nm wavelength the recorded absorbance only indicated the above concentration which happened to be above the mean steady state concentration.

8.0 Conclusion:

In conclusion, the SR formulation of Indapamide is designed to epitomize the development of new drug formulations based on a solid pharmacological rationale. The SR formulation of Indapamide has to allow the same antihypertensive efficacy as that of immediate release form but at lower dose. This is accompanied by a significant improvement in the ratio wanted/unwanted effects which is of general concern in therapeutics, but is of specific importance in the long-term treatment of chronic diseases such as hypertension. Beyond antihypertensive efficacy particularly in the presence of elevated SBP, Indapamide 1.5 mg SR has been shown to protect two of the main target-organs of high BP: the heart through the regression of left ventricular hypertrophy, and the kidney through a decrease of microalbuminuria. [5] This whole research work leads to a conclusion that Hypen SR 1.5mg marketed by Opsonin Pharmaceuticals Ltd. did not have an unique release pattern as required by the specification of sustained release drug properties. Such release pattern would not let the thiazide type diuretic, Indapamide to provide an optimum therapeutic efficacy level for prolonged period of time.

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