Relationship of hardness and invitro release profile of different brands of Indapamide(SR) tablet available in Bangladesh.

A thesis report submitted to the department of pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

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Acknowledgement

First and foremost I would like to express my sincere thanks and gratitude to Mr.Atiqul Haque Pathan for supervising me and for his valuable guidance and support throughout the entire work. I am especially thankful to Sharif Md Tahsin Hassan, Sayem sadly, Maidul Islam, Abdullah al Masum and A T M Faiz Ullah Talukdar for their enthusiastic cooperation in this study. Many thanks also to all of my friends who helped me by giving advices from their experiences. I am also grateful to all of the official stuffs of Pharmacy Department, East West University. Specially I do like to give thanks to Incepta Pharmaceuticals Limited, Dhaka, for providing pure Indapamide and other supports to conduct the research work properly.

Contents

Abstract

Purpose: The objective of this research work was to evaluate the relationship between hardness and in vitro release profile of different brands of Indapamide(SR) tablet available in Bangladesh. **Method:** Three different brands of Indapamide(SR) tablets namely Repress(SR), Hypen(SR) and Indapa(SR) marketed by Square Pharmaceuticals Ltd. Opsonin Pharma Ltd and Drug International respectively were collected from the market and evaluated the hardness and dissolution profile of these tablets. The release profile of Indapamide(SR) was investigated by using the method inscribed in Appendix XII B: Dissolution tests for tablets and capsules of British Pharmacopoeia. Hardness of these tablets were measured by hardness tester (Veego, Germany) and dissolution of the taken samples were investigated using (RC6, Vanguard Pharmaceuticals, USA) dissolution tester to evaluate the relationship between the hardness of the tablet and the rate of dissolution. **Result:** The mean hardness value of the Indapamide(SR) tablets were found. Repress(SR) 110.37 N, Hypen(SR) 59.91 N and Indapa(SR) 15.09 N and the rate of dissolution of these different brands of Indapamide was found Repress(SR) 0.00016 mg ml , Hypen(SR) 0.00018 mg/ml and Indapa(SR) 0.0018 mg/ml when the absorbance was measured at 275 nm. **Conclusion:** There is a direct relation between the hardness of the tablet and the rate of dissolution. The dissolution rate was inversely proportional to the hardness of the tablet.

Keywords: Hardness, Dissolution, Compression force. Indapamide(SR), Diuretic, Hypertension.

Introduction:

Hypertension is also referred to as high blood pressure and is a medical condition in which the blood pressure is chronically elevated. It is the most common cause of different cardiovascular diseases all over the world. Hypertension can be classified as either essential (primary) or secondary. About 90-95% of hypertension is essential hypertension.[6]

The heart is a pump designed to force blood through our body. Blood is pumped from the heart through the arteries out to our muscles and organs. 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]

Drugs inducing a state of increased urine flow are called diuretics. Diuretics are inhibitors of renal ion transporter that decrease the reabsorption of Na^+ at different sites of nephron. As a result Na+ and other ions such as Cl^-, enter the urine in greater than normal amounts along with water which is carried passively to maintain osmotic equilibrium. [1]
Diuretics have been the standard antihypertensive drugs over the last four decades. Indapamide is a mild diuretic, which is one of the thiazides like analog. Unlike other thiazides diuretics, it lacks thiazides structure but share common mechanism of action. Indapamide is used to treat hypertension (high blood pressure) and also used to eliminate fluid when the body accumulates excess fluid, such as with edema and congestive hard failure. It is well absorbed orally and is taken as a single daily dose, generally in the morning before taking breakfast. It works by preventing the kidney from reabsorption of salt and water that is destined to the eliminated in the urine. This results in increase of urine output and also reduces the salt in the smooth muscle of the wall of blood vessels. The lost of salt from muscle causes the muscle to relax and the relaxation of the vessels results in reduced blood pressure. Indapamide is lipid soluble and it's protein binding is 71-79%. So the duration of action of this drug is high and is about 24-32 hours.[2]

Concept of sustain release dosage form:

The term "sustained release" has become associated with those systems from which therapeutic agents may be automatically released at predefined rate over a long period of time. Controlled release coating is designed to release drug at various rates on exposure to gastric or intestinal contents. Thus sustained release, sustained action, prolonged action, controlled release, extended action, timed release and repository dosage forms are terms used to identify drug delivery system that shows its action for longer period of time after administration of a single dose. [3]

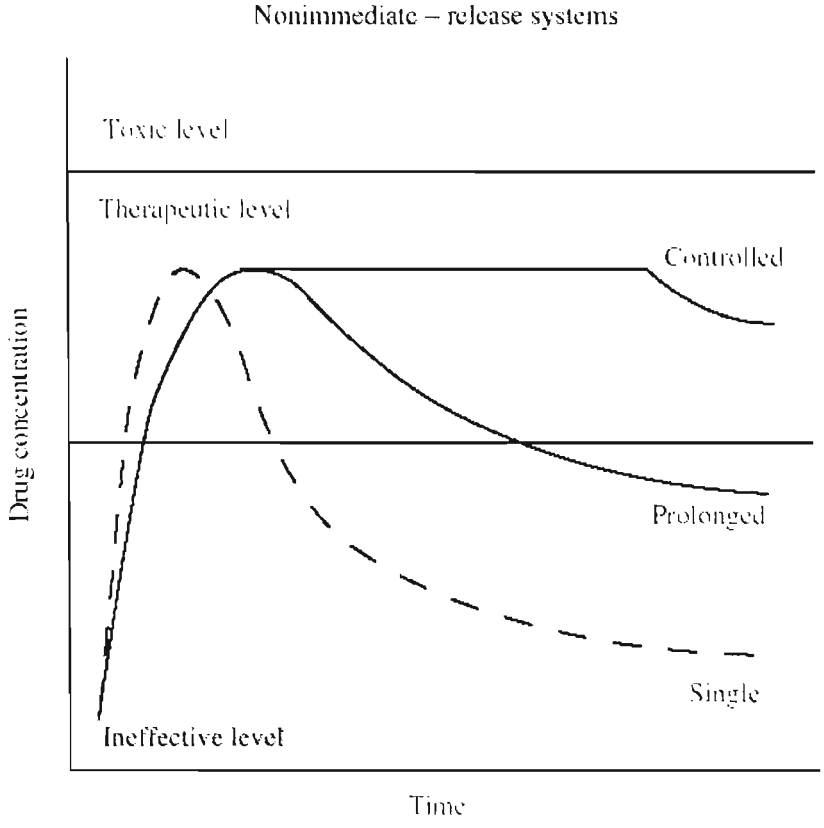


Figure-1. Drug concentration versus time for different release systems.

The pharmaceutical industry provides a variety of dosage forms and dosage levels of particular drugs, thus enabling the physician to control the onset and duration of drug therapy by altering the dose or mode of administration. Sustained release dosage form

design embodies several approaches to the control of drug action e.g., through a process of either drug modification or dosage form modification, the absorption process, and subsequently drug action can be controlled.[3]

Rational of sustain release dosage form:

Sustained release or controlled release products are designed to provide either the prompt achievement of a plasma concentration of drug that remains essentially constant at a value within the therapeutic range of the drug for a satisfactorily prolonged period of time or the prompt achievement of a plasma concentration of drug which, although not remaining constant, declines at such a slow rate that the plasma concentration remains within the therapeutic range for a satisfactorily prolonged period of time. To design an effective sustained release dosage form, one must have a thorough knowledge of the pharmacokinetic of the drug chosen for this formulation.[4]

Advantage of sustain release dosage form:

1. Sustained released drug delivery system provides improved treatment of many chronic illnesses where symptom breakthrough occurs if the plasma concentration of drug drops below the minimum effective concentration. For example: Asthma, depressive illness.
2. Improved maintenance of therapeutic plasma drug concentration.
3. SR drug delivery system maintains the therapeutic action of a drug during overnight no dose periods. For example: overnight management of pain permits improved sleep to ill or elderly patient.
4. Reduction of systemic side effects:
5. No overnight dosing.
6. This type of delivery system reduces the incidence and severity of untoward systemic side effects related to high plasma peak concentration.
7. Reduction of dosing frequency:

8. An improved patient compliance resulting from the reduction in the number and frequency of doses required to maintain the desired therapeutic response. For example: one peroral SR dosage form every 12-hour contributes improved control of therapeutic drug concentration.
9. Reduction in GI side effects:
10. SR delivery system reduces the incidence and severity of localized gastrointestinal side effects resulting from 'Dose dumping ' of irritant drugs e.g., potassium chloride.
11. It is more economical compare to the immediate release dosage form.

Evaluation of tablets

Study of hardness: **Methodology:** From each brand of Indapamide(SR), 10 tablets were taken to determine the hardness by using manual hardness tester (Veego, Germany). The average crushing strengths (hardness values) were determined and the data is presented in the table-1.

Objective: The objective was to measure the hardness of Indapamide(SR) tablets and to find the relationship between the hardness and the in vitro release profile of these tablets.

Theory: Too soft tablets can disintegrate in transport and on the other hand too hard tablets can delayed the release of the drug from it's dosage form. So an acceptable hardness is required and thus the tablet's strength testing is necessary for both research and development of new formulations and also for quality control.

Materials required: 1. Hardness tester. 2. Tablets

Procedure: The hardness tester was taken and one tablet at a time was placed vertically between two jaws of the tester. Then the force was applied with a screw thread and the applying of force was continued until the tablet was fractured. Then the reading was taken in kg from the sliding scale. Then the reading of harness of 10 tablets from each brand of Indapamide(SR) tablet was taken by following the same procedure and the collected data was put into a table.

Measuring units: Most material testing was performed using the international system of units. The Newton is the preferred unit of force as is recognized by the SI system. However the kilogram can also be used. The kilogram is recognized by the SI system as the primary unit of mass. The Newton is the SI unit of force and it is the unit that should be used for the tablet hardness testing. Here 1 kilogram = 9.807 Newton.

Table-1: Hardness of different brands of Indapamide tablet.

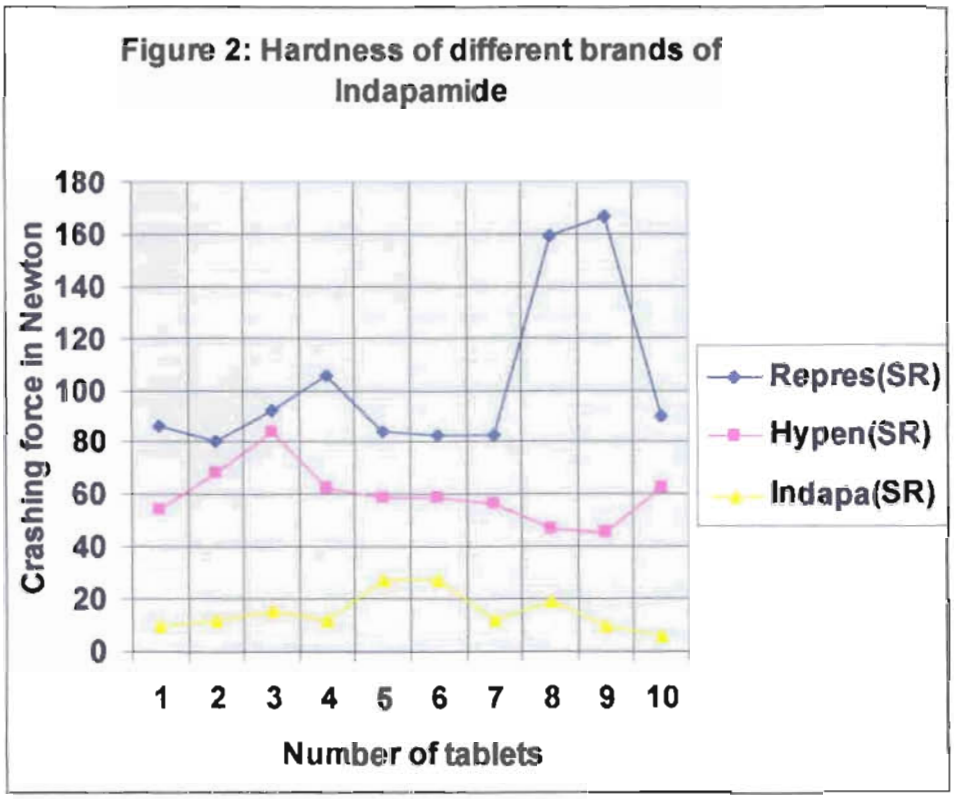
No	Hardness of Repress(SR)		Hardness of Hypen(SR)		Hardness of Indapa(SR)	
	in kg	in Newton	in kg	in Newton	in kg	in Newton
1.	8.8	86.3016	5.5	53.9385	1	9.807
2.	8.2	80.4174	7	68.649	1.2	11.7684
3.	9.4	92.1858	8.6	84.3402	1.6	15.6912
4.	10.8	105.916	6.4	62.7648	1.2	11.7684
5.	8.6	84.3402	6	58.842	2.8	27.4596
6.	8.4	82.3788	6	58.842	2.8	27.4596
7.	8.4	82.3788	5.8	56.8806	1.2	11.7684
8.	16.2	158.873	4.8	47.0736	2	19.614
9.	17	166.719	4.6	45.1122	1	9.807
10.	9.2	90.2244	6.4	62.7648	0.6	5.8842

Discussion:

The hardness of different brands of Indapamide (SR) tablets were not same. The mean hardness of the Repress(SR) tablets was highest among these three brands and it was 110.37 N and the mean hardness of the Indapa(SR) tablets was lest and it was 15.06 N. The mean hardness of the Hypen(SR) tablets was 59.91 N.

Result:

The mean hardness of Repress(SR) was 110.37 N, Hypen(SR) was 59.91 N and Indapa (SR) was 15.09 N. The crushing strength rages from 5.88 N to 166.71 N.



Study of dissolution:

Dissolution of different brands of Indapamide tablet was determined by using electronic dissolution tester (RC6, Vanguard Pharmaceuticals, USA). The rate of dissolution helps to understand the release profile of the drug in vitro and thus it helps to determine the dose and dosing interval of any drug to achieve it's desired therapeutic action.

Objective: The objective was to determine rate and amount of the drug dissolved in different prescribed time when put into the dissolution media.

Theory: Dissolution is a process in which a solid substance sulubilizes in a given solvent i.e mass transfer from the solid surface to he liquid phase. Several theories to explain drug dissolution have been proposed. Some of the important one are:-

1.Diffusion layer model or film theory.

2.Danckwert's model or surface renewal theory.

3.Interfacial barrier model or limited salvation theory.

Diffusion layer model or film theory : This is the simplest and most common theory for dissolution. Here the process of dissolution of solid particle in aliquid, in the absence of reactive or chemical forces, consists of two consecutive steps.

a. Solution of the solid to form a thin film or layer at the solid liquid interface called as the stagnate or diffusion layer which is saturated with the drug . This step is usually rapid.
b. Diffusion of the soluble solute from the stagnant layer to the bulk of solution. This step is slower and is therefore the rate determining step in drug dissolution.

$$dC/dt = k(C_s - C_b)$$

Where, dC/dt = dissolution rate of drug,

K = dissolution rate constant,

C_s = concentration of drug in the stagnate layer,

C_b = concentration of drug in the bulk of the solution at time t.

Danckwert's Model: Danckwert did not approve of the existence of a stagnant layer and suggested that turbulence in the dissolution medium exists at the solid-liquid interface. As a result the agitated fluid consisting a macroscopic mass of eddies or packets reach the solid-liquid interface in a random fashion due to eddy currents. Then absorb the solute by diffusion and carry it to the bulk of the solution. Such solute containing packets are continuously replaced with packets of fresh solvent due to which the drug concentration at the solid liquid interface never reaches Cs and have a lower limiting value of Ci. Since the solvent packets are exposed to new solid surface each time , the theory is called as surface renewal theory.

The Danckwert's model is expressed by equation;

$VdC/dt = dm/dt = A(C_s-C_b)\sqrt{\gamma D}$

Where, m = mass of solid dissolve, γ = rate of surface renewal.

Interfacial barrier model: According to the interfacial barrier model, an intermediate concentration can exist at the interface as a result of salvation mechanism and is a function of solubility rather than diffusion. When considering the dissolution of a crystal, each face of the crystal will have a different barrier. Such a concept is given by the following equation;

$G = Ki(C_s-C_b)$

Where, G = dissolution rate per unit area,

Ki = effective interfacial transport.

Material required: Dissolution tester (RC6, Vanguard Pharmaceuticals, USA), tablets, 1000ml beaker, dissolution medium and distilled water.

Procedure: 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)

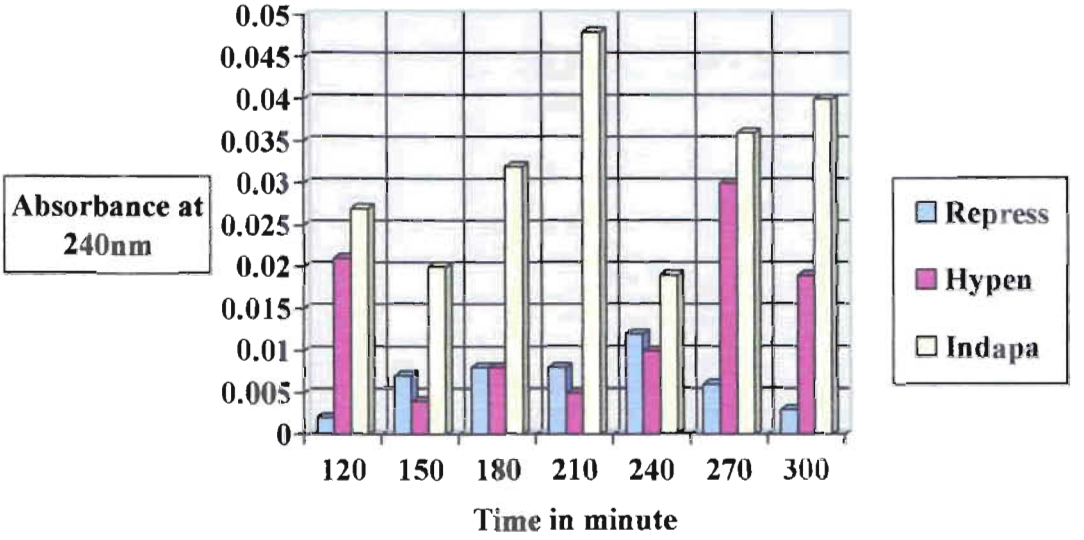
1. **Preparation of the dissolution medium**: Methodology: The supplied HCl was 32% w/v. As the molecular weight of HCl is 36.5, the 1 M HCL solution contains 36.5 gm theoretically. So, by calculating these we got that 0.1 M HCl solution contains 3.65 gm of HCl and 11.4 ml of 32% w/v HCl is needed to prepare 1000 ml of 0.1 M HCl solution which was further used as dissolution medium. 1000 ml of 0.1 M HCl solution was required as each of the two baskets was to be filled with 500 ml of 0.1 M HCl solution according to British Pharmacopoeia (BP).

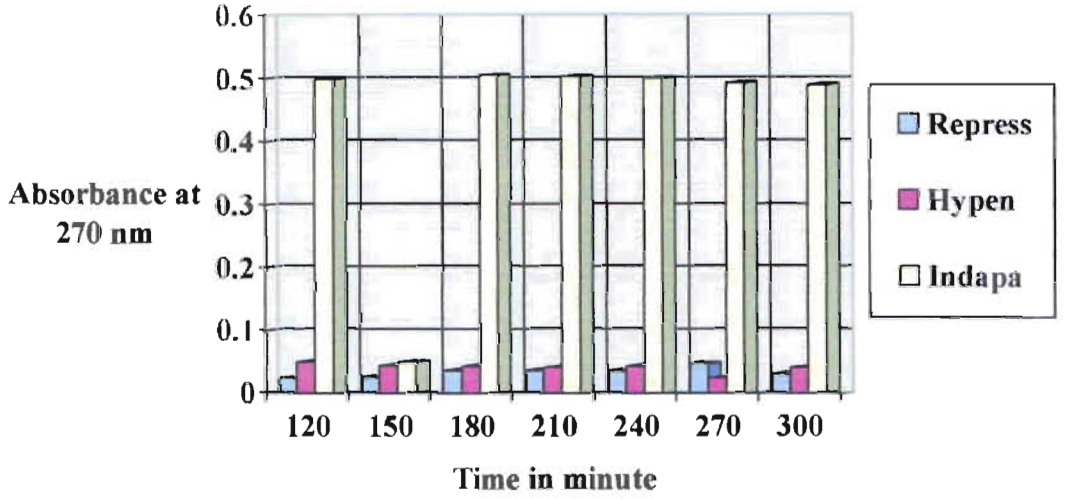
2. 500 ml of dissolution medium was taken into each basket of the dissolution tester and placed into their respective chamber.
3. Then one tablet from each brand of Indapamide were placed into the separate beakers of the dissolution tester and were started to run in a specific rotation of 100 rpm.
4. The operation was done at 37° C (± 0.5 °C) and the temperature was maintained carefully.
5. Then ten milliliter (ml) samples were taken at regular intervals of 120, 150, 180, 210, 240, 270 and 300 minutes.
6. After each sampling the loss of volume was filled up by transferring the prepared media in each vessel regularly.
7. Then the absorbance was measured with single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 240nm and 270nm.
8. Standard Indapamide solution prepared previously was used as the blank solution to measure the absorbance of each sample.
9. Then the data of absorbance of the different brands of Indapamide collected from the spectrophotometer and the data is presented in the table 2.

Table 2: Absorbance of different brands of Indapamide.

Time	Repress		Hypen		Indapa	
	240nm	275nm	240nm	275nm	240nm	275nm
120min	0.002	0.024	0.021	0.051	0.027	0.499
150min	0.007	0.026	0.004	0.045	0.020	0.493
180min	0.008	0.037	0.008	0.044	0.032	0.505
210min	0.008	0.037	0.005	0.042	0.048	0.503
240min	0.012	0.036	0.010	0.044	0.019	0.501
270min	0.006	0.048	0.003	0.025	0.036	0.493
300min	0.003	0.030	0.019	0.042	0.040	0.490

Figure 3: Absorbance of different brands of Indapamide





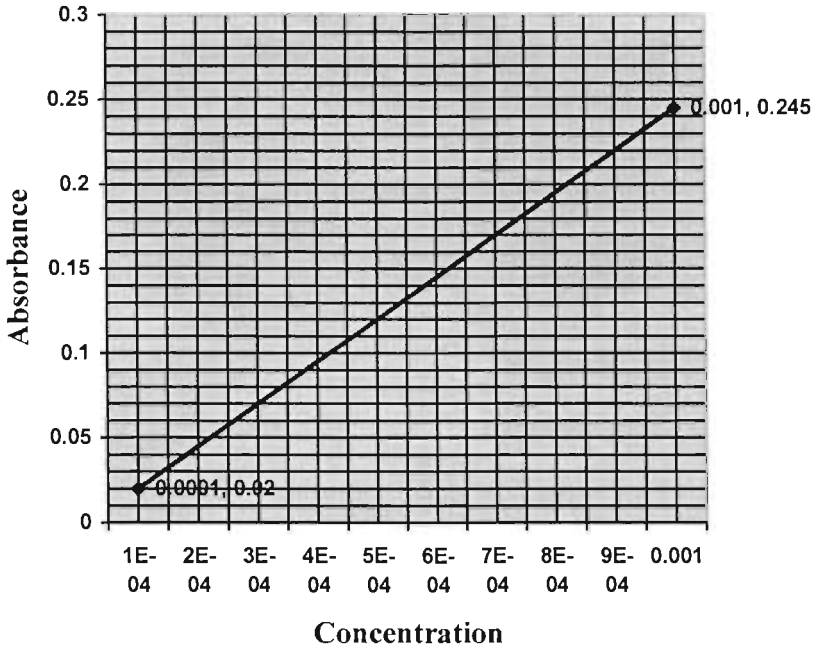
Drawing of the standard curve:

The standard curve was drawn by plotting the values of concentration of Indapamide and their absorbance determined by the single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 240nm and 270nm. The Indapamide solution was prepared by dissolving 10mg of pure Indapamide into 0.1M, 32% w/v HCl and then diluted it with the dissolution medium to get different concentrated solution. Then the absorbance of these different concentrated solution was measured by the single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 240nm and 270nm and the data is presented in the table-3.

Table-3: Absorbance of pure Indapamide against different concentrations of it.

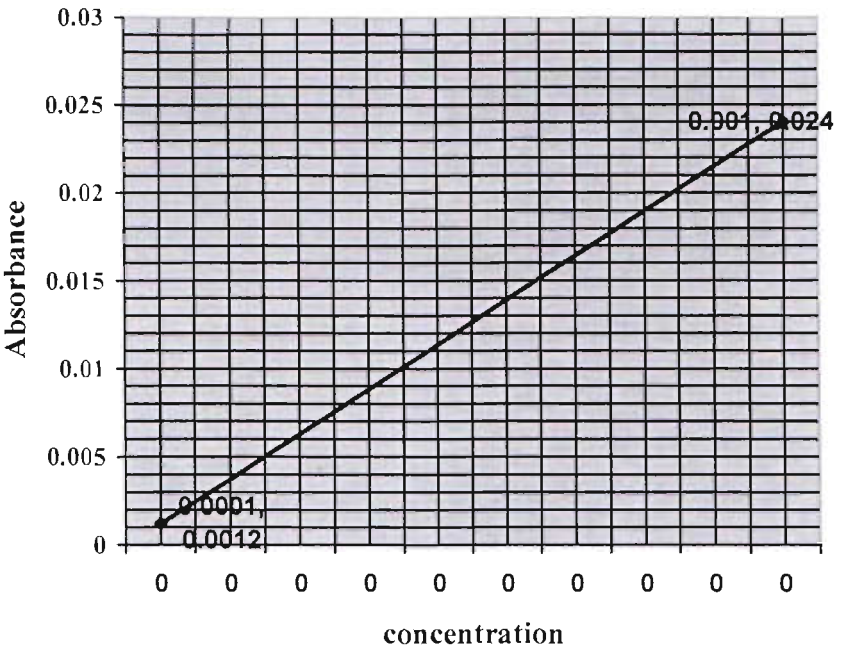
No	Concentration mg/ml	Absorbance at 240nm	Absorbance at 275nm
1.	0.001	0.024	0.245
2.	0.0001	0.0012	0.02

Figure 4: Concentration versus absorbance curve of Pure Indapamide at 275nm



Here, in 'X' axis 10 small square box was equal to 0.0002 and in 'Y' axis 20 small square box was equal to 0.1.

Figure 5: Concentration versus absorbance curve of pure Indapamide at 240nm



Here, in 'X' axis 10 small square box was equal to 0.004 and in 'Y' axis 20 small square box was equal to 0.1.

Determination of the concentration:

From these standard curve we can determine the concentration of the different brands of Indapamide dissolved at different times. If we plot the values of absorbance in the 'Y' axis and draw a horizontal line, it will intercept the standard curve at a particular point and then, if we draw a line vertically downward from that point, it will intercept the 'X' axis. The value of the particular point of 'X' axis will be the value of concentration of the particular drug with respect to it's absorbance

Table 4: Concentration of different brands of Indapamide

Time	Repress		Hypen		Indapa	
	240nm	275nm	240nm	275nm	240nm	275nm
120min	0.00012	0.0001	0.00028	0.00024	0.0018	0.002
150min	0.00024	0.00014	0.00024	0.0002	0.0024	0.002
180min	0.00028	0.00018	0.00024	0.0002	0.0028	0.0024
210min	0.00028	0.00016	0.0002	0.00018	0.0032	0.0024
240min	0.00046	0.00016	0.00012	0.00018	0.0024	0.0022
270min	0.00026	0.00022	0.00018	0.00014	0.0026	0.002
300min	0.00018	0.00016	0.0002	0.00018	0.0029	0.0018

Result: The rate of dissolution of these different brands of Indapamide was not same. At the time of 300 min the concentration of Repress(SR), Hypen(SR) and Indapa(SR) was 0.00016 mg/ml, 0.00018 mg/ml and 0.0018 mg/ml respectively when the absorbance was measured at 275 nm.

Factors affecting rate of dissolution:

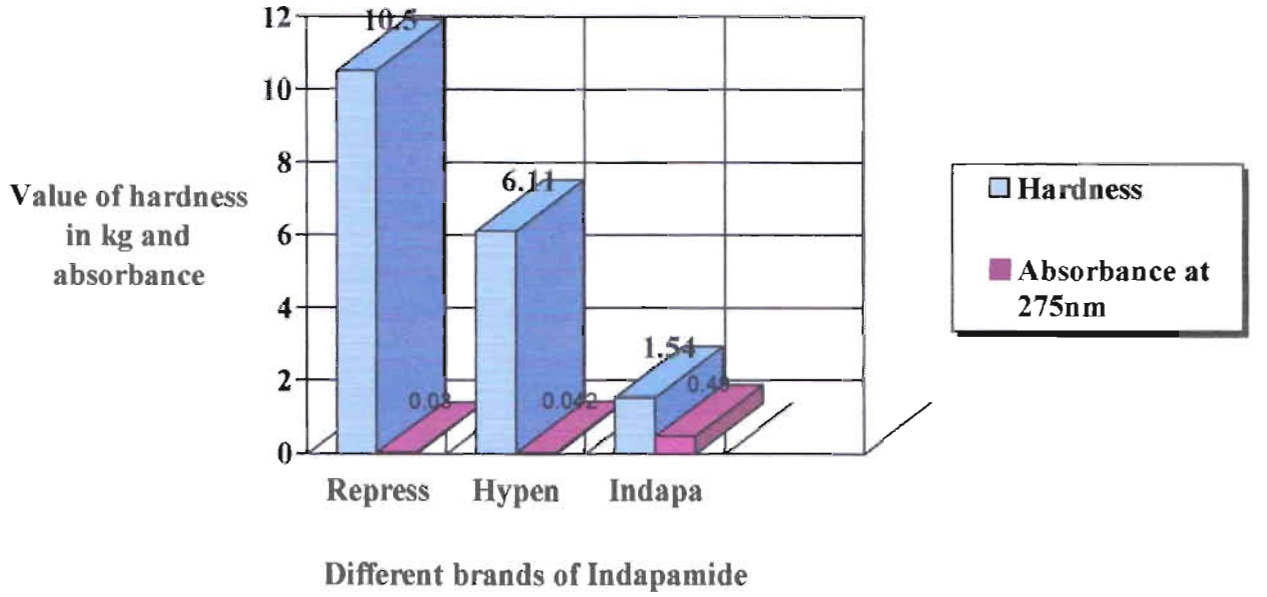
Many direct and indirect factors affect the rate of dissolution, such as-

- Effective surface area of undissolved solid
- Solubility of solid in dissolution medium
- Hardness of the tablet
- Compression force and speed of compression
- Amount and type of the binder and the disintegrant and method of incorporating these
- Humidity during manufacturing
- Amount and type of diluents of filler
- Granule size and size distribution

Relationship between the hardness of the tablet and rate of dissolution:

Among the different factors that affect the rate of dissolution, hardness of the tablet is one of the direct factor that affect the dissolution. The rate of dissolution is inversely proportional to the hardness of the tablet. And the hardness of the tablet mainly depends on the compression force and amount and type of binder and disintegrant used in the formulation. In here we measured the hardness of different brands of Indapamide(SR) tablets and got the mean hardness of Repress(SR) 110.37 N , Hypen(SR) 59.91 N and Indapa(SR) 15.09 N. On the other hand we also measured the rate of dissolution of different brands of Indapamide and got the extend of dissolution in different times. From these data we can see the hardness of the Repress(SR) was highest and it's rate of dissolution was lowest among these three brands. At the same time the hardness of Indapa(SR) was lowest and it's rate of dissolution was highest among these brands.

Figure 3:Relationship between hardness of the tablet and rate of dissolution



Conclusion: The SR formulation of Indapamide allows the same antihypertensive efficiency 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.[11] The efficacy of the drug formulated as SR form, depends on release pattern or rate of dissolution of the drug. The dissolution rate of a drug depends on many factors. Hardness of the tablet is one of the important factors that affects the rate of dissolution. There is a direct relation between the hardness of the tablet and the rate of dissolution. The dissolution rate is inversely proportional to the hardness of the tablet.

Reference:

1. Lipincot, Pharmacology 3rd edition.
2. KD Tripathi, Essentials of Medical Pharmacology, 5th edition.
3. Lachman, L.,Liberman,H.A., & Kanig, J.L., (1991);pharmaceutical dosage form(sustained release dosage form),2nd edition, pp.430-432
4. Aulton, M.E., (2002); Pharmaceutics(modified release Peroral dosage form), 2nd edition, pp. 289-305
5. D.M Brahmankar and Sunil B. Jaiswal (2005), Biopharmaceutics and pharmacokinetics
6. Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright (1993). Human Biology and Health
7. Leon Shargel, Aplied Biopharmacetics and Pharmacokinetics, 5th edition.
8. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical chemistry, 11th edition.
9. Leslie G . Chatten, Pharmaceutical Chemistry, volume 1.
10. British Pharmacpoea-2007
11. An overview of the pharmacology and clinical efficacy of indapamide sustained release J. Sassarda*, A. Bataillarda, H. McIntyreb.
12. Ashutosh Kar, Pharmaceutical Drug Analysis, Second edition.