

A Research Article on: To Formulation & Evaluation of Anti-Hypertensive Drug of Indapamide Hemihydrate Sustained Release Tablet

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Abstract:

The end of the study is to formulate and to estimate the indapamide SR tablet for the treatment of hypertension. Literature check shows that indapamide is an anti-hypertensive and diuretic medicine. The medicine has been released up to 6 – 15 h, after taken orally. These tablets are absorbed into the systemic circulation and blood pressure shows the considerable peak of medicine. It has been formulated as sustained release form for the betterment of remedial indicator and for maintaining constant blood pressure situations. From the study, it has been concluded that HPMC shows the stylish results for the extending the release of medicine. Wet granulation system is used for the medication of these tablets. The in vitro study for optimized expression shows satisfactory results. The evaluation of tablets was done for the hardness, friability, weight variation, consistency, medicine content, in vitro buoyancy study, swelling indicator, in vitro dissolution studies, and stability study.

Keywords: Antihypertensive drugs, wet granulation, immediate release tablets, sustained release tablet, bilayer tablet, indapamide.

• Introduction

➤ Anti- hypertensive agents

• Hypertension

In the ultramodern period, hypertension is one of the most common health problems. It can do at any age. Now days, it has started being in youths also. Hypertension may lead to both coronary heart complaint and cerebrovascular accidents [1]. Cardiac hypertrophy, aortic aneurysm, and renal failure may also be caused by hypertension. As the blood pressure increases, the mischievous goods of blood pressure continuously increase. Threshold position of blood pressure can distinguish the threat and safety. If the systolic pressure increases up to 140mmHg and the diastolic pressure increases further than 90mmHg this is considered to be hypertension. A check programme shows that 25 of people in the whole world have hypertension [1,2]. With increase in age, these complications also increase. However, the death rate by heart failure and stroke will also reduce, If the blood pressure can be reduced. 90 to 95 of the population has idiopathic hypertension. It can produce long term cerebrovascular accidents, myocardial infarction and other complications. Renal complaint is benign hypertension. Reno- vascular hypertension narrows the renal roadway. Hypertension may affect the adrenal glands and beget pheochromocytoma, Cushing pattern, etc. However, it may beget death, If hypertension is n't treated in the right way. Severe hypertension is accelerated or nasty hypertension.

It causes renal failure, retinal hemorrhages and exudates. It occurs in normotensive persons. It may superimpose on secondary and pre-existing benign hypertension [2,3].

- **Types and causes of hypertension**

Essential and secondary hypertension are the two types of hypertension. The main causes of hypertension are as follows:

- 1. Renal**

Acute glomerulo-nephritis

Chronic renal disease

Polycystic disease, etc.

- 2. Endocrine**

Adrenocortical hyper-function

Exogenous hormones

Pheochromocytoma

- 3. Cardiovascular**

Contraction of aorta

Increased cardiac output

Rigidity of the aorta

- 4. Neurologic**

Psychogenic

Acute stress, including surgery

Sleep apnea

- **Pathogenesis of hypertension**

Cardiac output and total peripheral resistance are the two hemodynamic variables. Blood volume may affect the cardiac output. It also depends upon the body sodium homeostasis. Total supplemental resistance depends on the goods of neural and hormonal influences.

Juxta glomerular cells release renin, which transforms tube angiotensinogen to angiotensin I and also angiotensin- converting enzyme(ACE) convert into angiotensin II. Increase in both supplemental resistances may lead to increase in angiotensin II [4,5].

➤ **Classification of anti-hypertensive drugs**

- **Drug which acts on renin-angiotensin system-**
 - Angiotensin converting enzyme inhibitors- Enalapril, Benazepril, Trandolapril etc.
 - Angiotensin II receptor blockers- Losartan, Valsartan, Olmesartan etc. □Renin inhibitor- Aliskrin
- **Diuretics**
 - Loop diuretics- Frusemide, Bumetanide etc.
 - Potassium sparing diuretics- Amiloride, Triamterene etc.
 - Thiazides – Chlorthalidone, Indapamide etc.
- **Calcium channel blockers-** Nicardipine, Nimodipine, Verapamil etc.
- **Vasodilators**
 - Arteriolar dilators- Minoxidil, Diazoxide
 - Arteriolar and venular dilators- Sodium nitroprusside
- **Sympatholytic**
 - Centrally acting drugs – Methyldopa, Guanabenz etc.
 - Adrenergic neuron blockers – Reserpine etc.
 - Ganglion blockers – Trimethaphan
 - Adrenergic receptor blockers
 - α - blockers- Prazosin, Doxazosin, Phentolamine etc.
 - β - blockers- Acebutolol, Atenolol etc.
 - Mixed α and β blockers- Labetalol etc. [6,7]

➤ **Drug therapy approaches**

Both alone and in combination, antihypertensive agents are used in drug therapy for arterial pressure to normal level with minimum side effects. For elevated blood pressure, some therapeutic agents were chosen like spironolactone is used for the primary aldosteronism. These agents are used to normalize the blood pressure but have some side effects. An empirical approach is used in the absence of this information. It considers the efficacy, safety, value of life, comfort of administration, and economical. Combinations of the drugs are chosen for their synergistic action. When the specific therapy is absent, these are similar to respects, relying heavily on clinical trials and drug should used to initiate therapy. JNC started with diuretics and beta-blockers. It has the mortality trials which demonstrated with a positive effect of treatment. In WHOISH guidelines, therapy is being initiated with any six classes of agents. Some approaches are-

- I. Low dose is started and if this is not working, then moderate amount of dose is started.
- II. When the agent is started and it may treat or harm the coexisting condition.

- III. If the blood pressure is not controlled by the first agent, then the second agent from the different complementary class is introduced.
- IV. Long term tolerable drug is being used and given to the patients. [8,9].

➤ **Angiotensin- converting enzyme inhibitors**

Captopril was the first one in this category. C-terminal brace of amino acids is adhered by ACE from peptide substrates. Zinc atoms are present in its active sites. For the chemical knowledge of the target molecule, Captopril was the first successful drug designed. It has low potency and poor oral absorption that is why it is the weak inhibitor of enzyme and unsuitable drugs. It is designed to combine the steric properties of peptide antagonists in non-peptide molecules. For binding of zinc atom, it requires a sulfhydryl group. It couples with proline residue and binds with the active point of the enzyme. It accommodates the terminal leucine of angiotensin I. Enalapril, lisinopril, ramipril, perindopril andtrandolapril are some ACE inhibitors. These drugs are used in hypertension, myocardial infarction etc. [10, 6].

➤ **Hypertension in children:**

In children it is less common as compare to adults. It can lead to childhood obesity. In this treatment, life measures play the most important part. It's useful in less severe hypertension cases and no substantiation of organ damage. Some cases require drug treatment and it should be based on patient characteristics and physiology [11,12].

➤ **Non-pharmacological treatment**

- Excess amount of weight should be reduced
- Excess alcohol consumption must be reduced
- Sodium intake should be less
- Regular exercise
- Intake of less amount of fat
- Fruits and vegetable consumption should be more

➤ **Pharmacological treatment**

- Grade 3 patients of hypertension should be given prompt drug treatment.
- Grade 1 hypertension patients do not require any type of medication. If lifestyle modification is inadequate, and there are risk factors, then we should give the drug therapy.
- Patients with renal disease or diabetes may have lower thresholds. Prehypertension is controversial, whether there is any benefit in treating uncomplicated patients or not [13,14].

- **Materials & Method:** Indapamide hemihydrates, HPMC K4M, HPMC K100M, Lactose monohydrate, Magnesium stearate, Aerosil, Starch, Sodium bicarbonate, PVP K-30, Talc, Isopropyl alcohol.
- **Method of preparation of floating sustained release tablet**

For the preparation of tablets, indapamide hemihydrate and HPMC were mixed with other excipients. The powdered ingredients were mixed uniformly and subjected to wet granulation technique by using isopropyl alcohol. The wet mass was passed through the sieve no 16 and the resulting granules were dried into an oven at a temperature of 50⁰C. After the completion of drying, these granules were passed through sieve no. 12. Then around 5 to 8% magnesium stearate was mixed with these granules.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Indapamide hemihydrate	1.65	1.65	1.65	1.65	1.65	1.65	1.65
HPMC K4M	75	35	-	-	40	45	55
HPMC K100M	-	30	50	55	-	-	-
Lactose monohydrate	110	110	110	110	110	110	110
Magnesium stearate	1	1	1	1	1	1	1
Aerosil	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Starch	5	10	15	-	20	-	30
Sodium bicarbonate	5	10	20	30	25	40	-
PVP K-30	-	-	-	5	-	10	-
Talc	1	1	1	1	1	1	1
Isopropyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total Weight (mg)	200	200	200	200	200	200	200

Table 6: Composition of indapamide hemihydrate SR tablet (F1 to F7)

➤ **Preformulation studies of drugs**

- **Calibration curve of indapamide hemihydrate in pH 1.2 HCl buffer and phosphate buffer pH 7.2**

A stock solution of indapamide hemihydrate was prepared by weighing 15mg of indapamide hemihydrate in pH 1.2 HCl buffer and phosphate buffer with pH 7.2 separately and transferred in 100 mL volumetric

flask by diluting with the same solvent. From this stock solution, aliquots of 0.5-4.5 mL were withdrawn. Different concentrations of 4-46 µg/mL were prepared by diluting up to 10 mL with pH 1.2 HCl buffer and phosphate buffer with pH 7.2 respectively. Absorbance was taken at λ_{\max} 240 nm.

- **Determination of Solubility**

Solubility is the most important parameter in pre-formulation studies. The solubility of indapamide hemihydrate it was determined at both pH 1.2 HCl buffer and phosphate buffer with pH 7.2. The temperature was maintained at $37.0^{\circ}\text{C} \pm 0.4^{\circ}\text{C}$ in a water bath and continually shaken into mechanical shaker to 18 to 24 hrs. The samples were withdrawn and filtered through a Millipore filter, and assayed spectrophotometrically [26].

- **Determination of Melting point**

DSC method was used to determine the melting point of both the drugs and was recorded and compared with the literature value.

Table 3: Reported melting points of indapamide hemihydrate

Method used	Literature value
DSC method	120 ⁰ C (MT) and 160 ⁰ - 162 ⁰ C (IH)

- **FTIR study**

Bulk drugs were identified by using FTIR Spectrophotometer. KBr pellet technique was utilized for sample analysis. Hydraulic pressure was used for preparing drug pellets. The wave number range of 400-4000 cm^{-1} was used.

- **Determination of particle size and particle size distribution**

For many active substances, particle size has an impact on powder flow, content uniformity and drug dissolution. In order to assure consistent product quality, the particle size of the API had been characterized. The particle size of indapamide hemihydrate was analyzed by Malvern Mastersizer, which was based on the principle of light scattering, by the dry method. Likewise, the particle size distribution of the powder of both the drugs was determined by electromagnetic sieve shaker apparatus [28].

➤ **Pre-compression parameters:**

- **Angle of Repose (θ):**

For measuring the angle of repose fixed funnel method was used. A weighed quantity of the drug (25 gm) was transferred into a funnel. The funnel was fixed in such a way that it just touched the apex of the heap of the drug. The powder was now allowed to flow on the surface freely. The height (h) and radius (r) were measured and angle of repose was calculated by the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1} \left(\frac{h}{r} \right)$$

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle.

Correlation of flow property and angle of repose has been depicted.

Flowability	Angle of repose (θ)
Very poor	More than 40
Passable	From 30 to 40
Good	From 25 to 30
Excellent	Less than 25

Table 4: Angle of repose (θ) and flow property characteristics

The same procedure was followed for evaluation of powder blend (granules) also.

- **Bulk density**

A weighed quantity of powder (25 gm) was introduced into the measuring cylinder and then the initial volume was noted. Bulk density was expressed in g/ml and determined by the following formula:

$$\rho_{\text{bulk}} = \frac{m}{V_{\text{bulk}}}$$

Where, ρ_{bulk} is bulk density, m is the mass of the powder and V_{bulk} is the volume of the powder [28].

The same procedure was followed for evaluation of powder blend (granules) also.

- **Tapped density**

A weighed quantity of powder (25 gm) was introduced into the measuring cylinder. Now this cylinder was put in the holder of USP tapped density apparatus, where it was tapped at an average rate of 300 drops/min., for 500 taps. After 500 taps, volume of powder (V_0) was noted and again tapped for another

750 taps. This gave a new volume (V_f). If the difference between V_o and V_f was more than 2%, another 1250 taps were given, until the difference was reduced to less than 2%. Tapped density was then calculated from the following formula:

$$\rho_{\text{tapped}} = \frac{m}{V_{\text{tapped}}}$$

Where, ρ_{tapped} is tapped density, m is the mass of the powder and V_{tapped} is the tapped volume of the powder [29].

The same procedure was followed for evaluation of powder blend (granules) also.

- **Carr's Index**

The compressibility of a powder was indicated by Carr's Index. It was expressed in percentage. It was determined using the equation below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Compressibility index helped to explain the flow properties of the powders. If the Carr's Index is below 15%, the flowability is good and if it is greater than 25%, then the flow ability will be poor.

Table shows the compressibility of powder based on Carr's Index and Hausner's Ratio. The same procedure was followed for evaluation of powder blend (granules) also.

- **Hausner's Ratio**

Hausner's ratio was used for the measurement of powder flow [27]. It was calculated by the following formula: -

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

If the Hausner's Ratio is greater than 1.25, the flow ability is poor.

Type of flow	Hausner's ratio	Carr's Index
Very very poor	>1.61	>38
Very poor	1.47 – 1.58	32 – 37
Poor	1.34 – 1.46	26 – 31

Passable	1.26 – 1.35	21 – 25
Fair	1.18 – 1.23	16 – 20
Good	1.13 – 1.17	11 – 15
Excellent	1.01 – 1.10	≤10

Table 5: Effect of Carr's Index and Hausner's Ratio on flow property

The same procedure was followed for evaluation of powder blend (granules) also.

➤ **Post compression parameters:**

• **Weight Variation Test**

The weight variation test was done by weighing 20 tablets individually, calculating their average weight and comparing the individual weights to the average weight obtained.

The following formula was used to calculate the % deviation [27]:

$$\% \text{ Deviation} = \frac{(\text{Average Weight} - \text{Individual Weight})}{\text{Average Weight}} \times 100$$

• **Hardness**

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. The Inweka hardness tester was used to check the hardness of random 20 prepared tablets [28].

• **Friability test**

The friability was determined by first weighing 10 tablets after dusting and placing them in a Roche friabilator, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablet was recorded and the percent friability was calculated using the following formula:

$$\text{Friability test} = \frac{\text{Weight of tablets before test} - \text{weight after test}}{\text{weight of tablets after test}} / 100$$

Acceptance of tablet was done when the maximum loss of weight was not greater than 1.0 % [29].

- **Thickness**

The thickness of the tablet was mostly related to the tablet hardness and was used as an initial control parameter. The thickness of the tablets was measured using vernier callipers. Twenty tablets were randomly selected [27].

- **Drug content**

Ten tablets were taken and crushed with the help of sonication, drug equivalent quantity was dissolved in 0.1N HCl and volume was made up to 100 ml. By using Whatman filter paper, drug solution was filtered. For obtaining the 10 μ g/ml concentration solution was treated with 0.1N HCl. By measuring the absorbance of the solution, the drug content was calculated [29].

- **Dissolution test**

USP dissolution apparatus type II was used for the dissolution of different batches of indapamide hemihydrate floating sustained release tablets. The dissolution study was performed out in pH 1.2 HCl buffer for the first 2 hrs, followed by phosphate buffer pH 7.2 for 3 to 16 hrs (900 ml). It was maintained at 37°C \pm 0.5°C of temperature with a 50 RPM stirring rate. Each sample was drawn at regular interval of time and the remaining volume was made up by fresh solvent. Whatman filter paper was used for filtration and by using UV-Visible spectrophotometer; observance was recorded against a blank.

- **Wetting time**

Randomly a tablet was taken and put it into 2 layers of absorbent paper. The absorbent paper was wetted by using pH 1.2 HCl buffer and the unused buffer was drained out from the petridish. The stopwatch was used to the record the time required for the buffer to diffuse from the wetted absorbent paper into the entire tablet. The test was executed three times and mean \pm Standard Deviation was calculated.

- **Swelling index**

In dissolution testing apparatus, previously weighed one tablet in each flask was placed to determine the swelling properties of tablet layer. It was conducted in a container capacity of 1000 ml containing 0.1N HCl at 37 \pm 0.5 °C. It was then rotated for 30 minutes at 50 rpm. Then the tablets were removed from the medium, excess water was removed and then final weight was recorded. The swelling index for the tablets was calculated using the following formula:

$$\text{Swelling Index} = \frac{(\text{Weight of swollen tablet} - \text{Initial weight of the tablet}) \times 100}{\text{Initial weight of the tablet}}$$

- **Floating property study**

The time taken by tablet to emerge on the surface of the medium is known as floating lag time (FLT) and duration of time the dosage form constantly remains on the surface of the medium is called total floating time [30].

➤ **Results and Discussion.**

- **Calibration curve of indapamide hemihydrate in pH 1.2 HCl buffer and phosphate buffer pH 7.2**

Table 7: Readings of calibration curve of indapamide hemihydrate in pH 1.2 HCl buffer

Concentration (µg/mL)	Absorbance (240 nm)
0	0
0.5	0.11
2	0.233
4	0.354
6	0.475
8	0.55
10	0.711
12	0.825

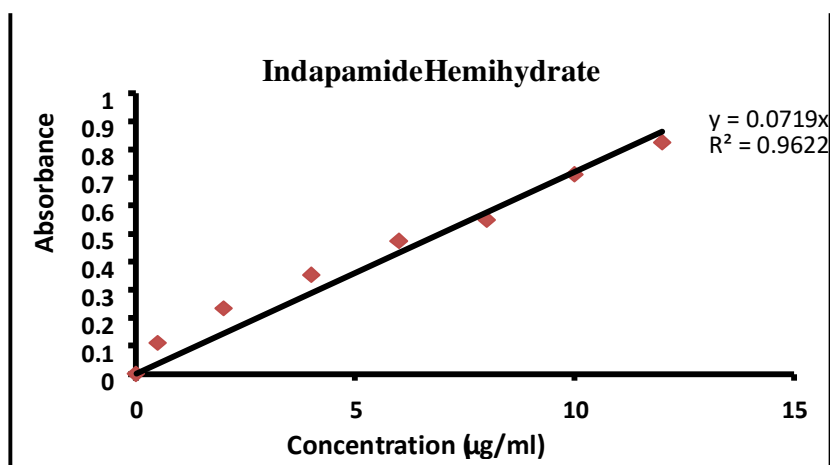


Figure 2: Calibration curve of indapamide hemihydrate in pH 1.2 HCl buffer

- **Determination of solubility**

Solubility of indapamide hemihydrate in pH 1.2 HCl buffer was determined to be 0.0360g/ml and in pH 7.2 phosphate buffer it was found to be 0.0580g/ml.

- **Determination of melting point**

Method used	Experimental value
DSC method	161 ^o C

Table 8: Melting point determination by DSC

- **FTIR study**

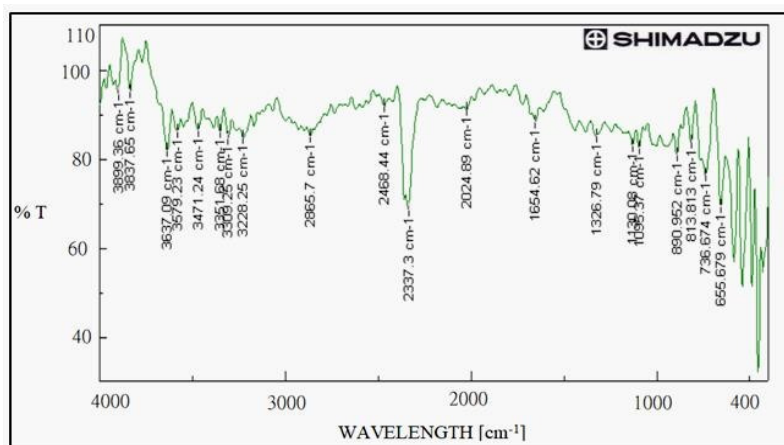


Figure 3: FTIR spectra of indapamide hemihydrate

- **Determination of particle size and particle size distribution**

The particle size of indapamide hemihydrate was analyzed by Malvern Mastersizer and the results are shown in table 9.

Table 9: Particle size analysis of drugs

Pre-compression parameters of powder blends of sustained release tablets of indapamide hemihydrate

The granules prepared were evaluated for their physical characteristics. The evaluation were carried out using the parameters such as bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose, as per the method described under preformulation studies [28]. The micromeritic properties of powder blends of preliminary batches are shown in Table 10.

Batch	Angle of Repose (°)	Bulk density (g/mL)	Tapped Density(g/ml)	Compressibility Index (%)	Hauser’s Ratio
F1	27.36±0.17	0.478±0.15	0.192±0.28	9.25±0.17	1.10±0.23
F2	27.25±0.16	0.480±0.13	0.168±0.26	13.59±0.16	1.15±0.15
F3	28.45±0.15	0.481±0.12	0.195±0.35	18.48±0.15	1.20±0.16
F4	27.65±0.13	0.489±0.11	0.165±0.33	9.45±0.12	1.21±0.17
F5	29.98±0.12	0.258±0.14	0.178±0.22	8.48±0.11	1.25±0.01
F6	27.75±0.15	0.148±0.15	0.156±0.28	8.49±0.11	1.09±0.03
F7	30.65±0.16	0.359±0.12	0.264±0.26	10.2±0.17	1.45±0.05

Sr.No.	Drug	Particle Size (µm)
1	Indapamide hemihydrate	24.88 µm

Table 10: Pre-compression parameters of indapamide hemihydrate SR tablets

Table 11: Post compression parameters of indapamide hemihydrate SR tablets

Formulation	Floating lag time (min:sec) n=6	Swelling index in 1hour (%) n=6	Wetting Time (seconds) n=6
F1	3:01	12.4±1.11	140.66±1.52
F2	0:92	13.8±0.59	77.33±3.05
F3	2:41	13.3±1.45	152.00±2.00
F4	2:19	13.4±3.12	224.33±8.64
F5	2:12	13.6±2.45	175.00±8.14
F6	2:06	13.35±0.99	332.00±2.02
F7	1:60	13.7±2.11	161.00±0.50

Table 12: Post compression parameters of indapamide hemihydrate SR tablets

• **Dissolution test results:**

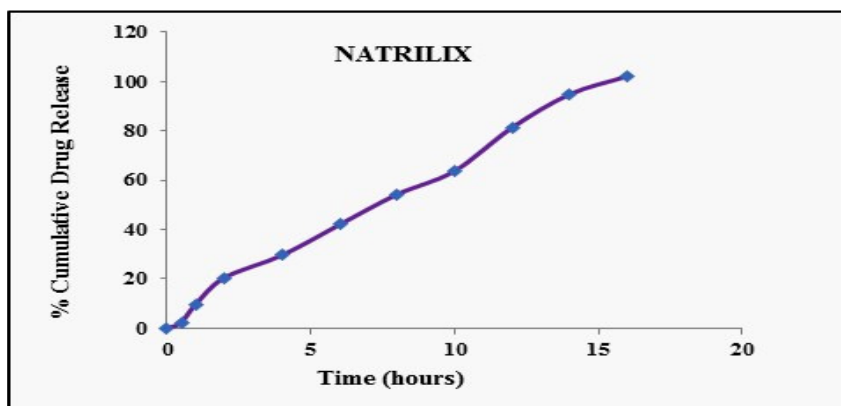


Figure 4: Dissolution test profile of Innovator (NatriliX)

Time (Hours)	Cumulative % Drug Release					
	NatriliX	F1	F2	F3	F4	F5
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	2.30±0.55	0.99±0.05	3.75±0.06	0.65±0.05	0.77±0.05	0.82±0.02
1	9.50±0.51	1.95±0.07	12.90±0.05	0.81±0.06	0.93±0.07	1.16±0.03

2	20.50±0.49	2.36±0.15	23.52±0.07	1.44±0.07	1.65±0.02	2.70±0.04
4	29.60±1.11	11.10±0.50	36.69±0.21	15.55±0.45	18.92±0.15	21.65±0.15
6	42.00±0.34	17.60±0.28	47.44±0.30	25.29±0.59	33.48±0.28	37.08±0.35
8	54.30±0.97	26.50±0.15	61.79±0.28	42.92±3.95	48.29±1.58	53.45±0.39
10	63.80±0.77	32.99±0.40	71.25±0.35	57.25±2.66	58.39±1.65	68.79±0.85
12	81.40±0.67	39.59±0.56	85.88±0.92	68.89±2.45	68.89±1.57	79.68±1.08

Table 13: Dissolution test results of indapamide hemihydrate SR tablets (F1 to F5)

➤ Conclusion.

The current research demonstrates that the controlled release of the drug (indapamide hemihydrate) within the matrix system of HPMC (sustained release polymer) plays a significant role. Findings from the pre-compression study indicate that F2 granules of indapamide hemihydrate exhibit excellent compressibility. The flow characteristic of power was determined to be strong and within an excellent range. The thickness and hardness were determined to be between 3–5 kg/cm² and 3–4 mm, respectively. In accordance with the ICH guidelines, the stability study was conducted and revealed that the batches remained stable for 6 months. The statistical analysis indicates that the optimized formulation exhibits enhanced bioavailability in comparison to the marketed formulation. The *in vitro* assessment of all batches indicates that the floating duration exceeded 23 hours, with a lag time of 4 to 8 minutes before floating began. These tablets were maintained for up to 16 hours.

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