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Development of Sustained Release Tablet of Indapamide for the Treatment of Hypertension

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ABSTRACT
The aim of the study was to formulate and evaluate the indapamide SR tablet for the treatment of hypertension. Literature survey shows that indapamide is an anti-hypertensive and diuretic. The drug is been release up to 6 to 15 hours. after taken by orally these tablets are absorbed in blood level and shows the considerable peak of blood. It is been formulated as sustained releases for the betterment of therapeutic index and for blood level constant. Study concluded that HPMC may shows the best results for the maintain the release of drug.

Indapamidehemihydrate was the new class of drugs. It is used in the treatment of hypertension. These drugs show anti-hypertensive effect as well as used as diuretic. Studies shows that indapamide shows the high peak concentration in blood within 2 hours of administration.[1] Around 70 to 75% of dose is been eliminated by kidney and rest other is been eliminated by biliary route. The half-life is around 14 to 15 hours. The peripheral blood may reverse the taken up of indapamide from erythrocytes.[2,3]The concentration may be decreases after 8 to 9 hours of administration of drugs. The blood/plasma ratio is about 6:1 when administer the drug. Plasma proteins may bind the indapamide formulation. These are the metabolized drugs. Only 7 to 8% of drug is been recovered from the urine.[4,5]The pharmacokinetics of indapamide and metabolised are biphasic with the half-life of 24 to 26hours of radioactivity. 1.30mg to 10mg of daily dose may shows the antihypertensive effects.[6,7]

It is an indoline derivatives of chloro sulphonamide. It did not contain any thiazide groups and has only one sulphonamide group. These may produce anti-hypertensive effect which is used for the improvement of compliances in Wet granulation of is used for the preparation of these tablets. The compatibility study for optimized formulation shows satisfactory results.Evaluation of tablet was done for the hardness, friability, weight variation, thickness, drug content, in vitro buoyancy study, swelling index, In vitro dissolution studies and stability study.

KEYWORDS-Indapamide, sustained release, hypertension, in vitro dissolution, wet granulation

I. INTRODUCTION

atrial.[8,9] It is also used for the reduction of arteriolar peripheral resistance. it has two properties beyond diuresis. Vasodilation is been added and also has high concentration of antiarrhythmic effect.[10,11] These tablets lower the blood pressure within 24 hours.[12,13]these tablets are more lipid neutral. These tablets are also used for the overcome the problems like hypokalaemia, hyperglycaemia and hyperuricemia. These are effect on triglycerides serum, LDL cholesterol and glucose tolerance.[14,15]The major challenges are lack of sufficient bonding and adhesion at the interface.The adjacent compacted layers which is often the result of aninterfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may notalways be apparent immediately after compaction.[16,17]Sustained release matrix dosage forms are designed to achieve a prolonged therapeutic action by continuous releasing medication over an extended period of time after administration of single dose.[18,19,20]

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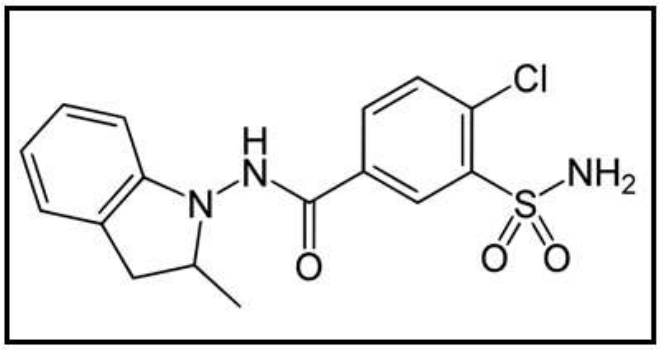

Figure 1. Structure of Indapamide

II. MATERIAL AND METHODS

Indapamidehemihydrate of pharmaceutical grade and all grades of polymers were obtained as a gift sample, respectively. Analytical grades chemicalsand reagents were used. Excipients which are used in this study are HPMC K4M, HPMC K100M, Magnesium stearate, Aerosil, Lactose monohydrate, Starch, Sodium bicarbonate, PVP K-30, Talc, Isopropyl alcohol.

2.1 Method of Preparation of tablet:

For the preparation of tablets indapamide hemihydrate and HPMC is mixed with other excipients. It should pour into porcelain mortar and stirrer about 10 mins. This preparation is used for the formation of mass by granulating fluid using isopropyl alcohol. Then these masses were passes through the sieve no 16 and put that into an oven with temperature 50^0C. After the completion of drying these granules are passes through sieve no. 12. Then around 5 to 8% magnesium stearate is mixed with this granule. By using flat-faced punch rotatory tablet machine is used for the compression of tablets.

Ingredient (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Indapamide hemihydrate	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65
HPMC K4M	85	-	-	-	60	54	44	44	34	-
HPMC K100M		86	-	-	60	54	44	34	32	30
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1
Lactose monohydrate	1	1	1	1	1	1	1	1	1	1
Starch	5	10	20	-	-	-	-	-	30	-
Sodium bicarbonate	5	10	20	30	40	50	-	60	-	-
PVP K-30	63	58	48	38	-	28	-	-	-	18
Talc	2	2	2	2	2	2	2	2	2	2

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Isopropyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Table 1.composition of indapamide hemihydrate (F1 to F10)

Ingredient (mg)	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**
Indapamide hemihydrate	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65
HPMC K4M	40	60	40	60	40	60	40	60	-	40
HPMC K100M	89	-	65	75	60	54	47	35	32	30
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1
Lactose monohydrate	1	1	1	1	1	1	1	1	1	1
Starch	-	5	10	20	30	-	40	-	30	35
Sodium bicarbonate	5	10	5	10	30	50	20	60	-	-
PVP K-30	66	59	48	36	-	28	-	-	-	19
Talc	2	2	2	2	2	2	2	2	2	2
Isopropyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Table 2.composition of indapamide hemihydrate (F11 to F20)

2.2 Standard curves of indapamide hemihydrate

Stock solution of indapamide hemihydrate was prepared. It was done by weighing 15mg of indapamide hemihydrate tablets in pH 1.2 HCl buffer and phosphate buffer with pH 7.2, transferred in 100 mL volumetric flask diluting with the same solvent. From this stock solution aliquots of 0.5-4.5 mL withdrawn. Different concentrations 4-46 µg/mL were prepared by diluting up to 10 mL with pH 1.2 HCl buffer and for phosphate buffer with pH 7.2. Absorbance was taken at λ_{max} 223 nm.

2.3 Precompression Parameter

2.3.1 Bulk density

A weighed powder was introduced in to the measuring cylinder and then the volume was noted.

2.3.2 Tapped density

A weighed powder was introduced in to the measuring cylinder. The cylinder was hit every 2seond from the height of 2.5 cm up to volume plateau.

2.3.3 Compressibility index

compressibility index helps to explain the flow properties of the powders. It was expressed in percentage.

2.3.4 Hausner's ratio

Hausner ratio is used for the measurement of powder flow.

2.3.5 Angle of repose

Fixed funnel method was used to measure the angle of repose. Drugs which contain different excipient were prepared and weighed it then transfer into a funnel. A funnel was just touching the apex of the heap of the drug. These powders now allow to flow on the surface freely.

2.4 Post compression Parameter

- **Weight Variation Test**

To study weight variation, 10 tablets were taken from each formulation and then weighted by electronic balance and mean ± SD was calculated.

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➢ **Hardness**

Hardness of the tablets indicated the with stand mechanical shocks while handling. Monsanto hardness tester were used to check the hardness of the tablets. These machines allow to measure the harness, thickness and diameters. Formulations of tablets were randomly picked and use to determine the hardness of the tablets.

➢ **Friability test**

Ten tablets were weighed and put into thefriabilator and continue for 4mins at 25 RPM. After that the tablets were then weighedagain. The two weights were used tocalculatefriability as follows:

$$\text{Friability test} = \frac{\text{Weig ht of tablets before test} - \text{weig ht after test}}{\text{weig ht of tablets after test}} / 100$$

Acceptance of tablet is done when the maximum loss of weight is not greater than 1.0 %.

➢ **Thickness**

Vernier caliper used to measure the thickness of each tablets. Calculation of average thickness of each tablet was done. If the tablets contain the deviated by ± 5% it passed the test.

➢ **Drug Content**

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

➢ **Disintegration Test**

Disintegration test apparatus is used for this test. It contains a basket rack as well as six glass tubes and the bottom of the glass it contains mesh sieve. 30 to 35 times per minutes this basket is raised and lowered in 950mL of water. It maintained 37 ± 2°C of temperature. In each tube 5 to 6 tablets were placed and recorded the time by which the tablet fragments are passes through the mesh this is known as the tablet disintegration time.

➢ **Dissolution Test**

By using USP dissolution apparatus type II are used for the preparation of different batches of the tablets. 0.1 N HCL is used for the dissolution medium for immediate release layer of tablets and other 0.01 N HCL with SLS of 0.5%w/v is used for the sustained release layer. It maintained 37 ± 0.5°C of temperature with 50 RPM stirring rate. Each sample were drawn at regular interval of time and the remaining volume is been make up by fresh water. Whatman filter paper is used for filtration and by using spectrophotometer observance is been recorded against a blank.

➢ **Wetting Time**

Randomly taken a tablet and put it into 2 layers of absorbent paper.By using pH 1.2 HCl buffer absorbent paper was wetted and the unused buffer is been drain out from the petri-dish. Stopwatch is used for the record of time required for the buffer to diffuse from the wetted absorbent paper into the entire tablet. This test was performed in triplicate and mean ± SD calculated.

➢ **Maximal Water Uptake Capacity**

Formulation of each tablets was weighed and put it into the Desiccator for 4hours. Desiccator contained activated silica gel. Percentage of Water contain were calculated by following equations: -

➢ $$\text{Water content} = \frac{\text{weight before drying} - \text{weight after drying}}{\text{weig ht before drying}} / 100$$

➢ **Swelling index**

In Dissolution Testing Apparatus tablet were placed for determining the swelling properties of tablet layer. It was conducted in a container capacity of 1000 ml of 0.1N HCl at 37 ± 0.5 °C.it was then rotated for 30 minutes on 50 RPM. Then the tablets were removed from the medium, to remove excess water and weighed. According to the equation, swelling characteristics were expressed in terms of percentage water uptake (WU %).

$$\text{Swelling Index} = \frac{(\text{Weig ht of dry tablet} - \text{weig ht of swollen tablet}) \times 100}{\text{Weig ht}}$$

2.5 DRUG RELEASE KINETICS

Dissolution data were calculated by different type of models such as zero-order, first order, Higuchi equations and Peppas equations.

2.6 DSC STUDY OF SUSTAINED RELEASE LAYER

DSC is used for the formation of thermogram of sustained release tablet (indapamide hemihydrate). For the calibration of DSC temperature and enthalpy Indium was used. Samples were accurately weight and use for DSC study. 10°C/min heating was done.

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III. RESULTS AND DISCUSSION

3.1 STANDARD CURVE OF INDAPAMIDE

3.1.1 Calibration curve of indapamide hemihydrate with pH 1.2 HCl buffer

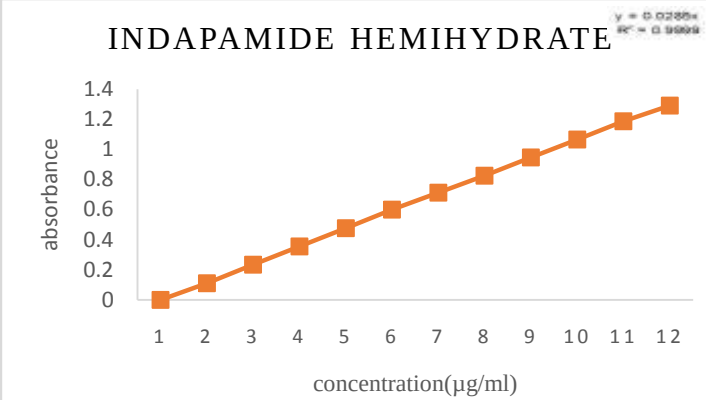

Figure 2. standard curve of indapamide at pH 1.2 HCl buffer

3.1.2 Calibration curve of indapamide hemihydrate with phosphate buffer pH7.2

Standard curve of indapamide hemihydrate is found to linear (1 to 6 µg/mL) in pH 7.2 phosphate buffer

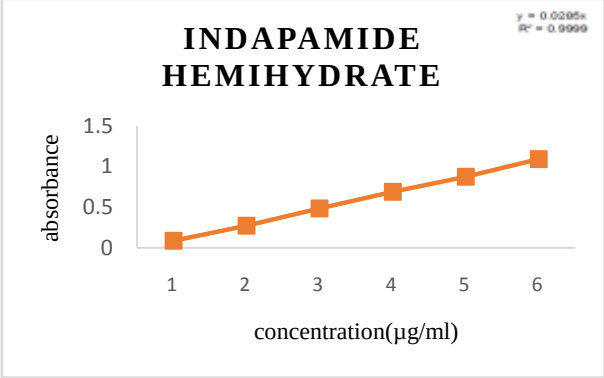

Figure 3. standard curve of indapamide at phosphate buffer pH 7.2

3.2 Precompression Parameter of Sustained Release Tablet

Precompression parameters like angle of repose, loose bulk density, tapped bulk density, compressibility index, and Hauser's ratio of all batches of indapamide hemihydrate.

Batch	Angle of Repose (θ)	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
F8	30.65±0.19	0.300±0.13	0.278±0.27	10.3±0.16	1.25±0.13
F9	29.34±0.17	0.245±0.14	0.233±0.29	10.56±0.15	1.35±0.12
F10	29.38±0.12	0.359±0.15	0.215±0.35	8.48±0.14	1.46±0.12

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F11	28.45±0.14	0.350±0.13	0.150±0.33	10.12±0.12	1.04±0.10
F12	27.55±0.16	0.470±0.18	0.166±0.32	12.14±0.13	1.00±0.18
F13	29.40±0.15	0.472±0.17	0.175±0.31	13.15±0.11	1.06±0.17
F14	30.10±0.15	0.365±0.12	0.189±0.30	16.15±0.12	1.02±0.19
F15	26.55±0.13	0.160±0.13	0.199±0.32	10.13±0.10	1.26±0.21
F16	27.45±0.14	0.490±0.12	0.233±0.26	9.12±0.12	1.39±0.12
F17	28.10±0.13	0.495±0.11	0.240±0.29	15.15±0.14	1.40±0.18
F18	29.20±0.10	0.255±0.15	0.265±0.31	16.17±0.16	1.56±0.13
F19	30.45±0.11	0.267±0.14	0.269±0.33	17.21±0.13	1.55±0.11
F20	30.85±0.12	0.489±0.15	0.271±0.34	18.02±0.15	1.50±0.14

Table 3.Precompression Parameters of indapamide hemihydrate

3.3 Post compression Parameter of Sustained Release Tablet

Tablet properties like weight variation, thickness, hardness, friability, swelling index, disintegration time, duration of floating and drug content of all batches.

Formulation	**Weight* (mg)**	**Thickness* (mm)**	**Hardness* (Kg/cm2)**	**Friability† (%)**	**Disintegration Time* (Seconds)**	**Drug content* (%)**	**Swelling index in 1hour (%)**
F1	815.7±7.8	6.32±0.06	4.5±0.30	0.584	35.38±6.55	100.60±0.68	12.4
F2	818.4±6.5	6.25±0.05	5.0±0.05	0.623	53.18±13.99	101.9±0.58	12.8
F3	819.9±7.75	6.34±0.06	5.2±0.35	0.789	36.67±5.60	101.8±0.44	13.3
F4	813.7±6.9	6.45±0.05	5.3±0.45	0.654	55.52±35.25	102.6±0.56	13.4
F5	808.5±7.9	6.65±0.08	5.1±0.65	0.357	79.69±24.38	101.7±1.48	13.6
F6	815.6±4.3	6.35±0.06	4.1±0.35	0.458	54.85±16.19	100.8±0.50	13.8
F7	804.7±6.7	6.45±0.05	5.2±0.45	0.036	55.52±14.30	101.3±0.56	13.7
F8	819.9±6.9	6.36±0.08	4.6±0.25	0.458	55.56±34.2	100.9±0.67	13.5
F9	817.5±7.8	6.74±0.04	6.4±0.35	0.369	60.25±33.56	101.8±0.86	12.6
F10	809.3±5.9	6.63±0.06	4.4±0.65	0.753	65.89±33.86	101.9±0.82	12.7
F11	810.5±1.5	6.96±0.08	4.2±0.36	0.449	78.36±34.26	100.15±0.85	12.9
F12	802.8±1.4	6.25±0.09	3.5±0.35	0.552	75.25±33.52	101.59±0.83	12.5
F13	806.2±1.5	6.29±0.05	2.2±0.11	0.724	70.45±32.25	100.45±0.84	13.3

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F14	815.3±1.4	6.29±0.07	3.6±0.22	0.706	75.20±29.45	101.15±0.80	13.4
F15	819.4±1.5	6.29±0.06	4.5±0.32	0.552	80.25±30.15	100.17±0.78	13.6
F16	820.45±1.6	6.19±0.05	3.4±0.31	0.451	82.10±29.45	101.1±0.75	13.4
F17	804.29±1.7	6.29±0.07	5.0±0.40	0.305	86.13±21.25	100.18±0.56	13.5
F18	810.30±1.6	6.60±0.08	3.4±0.15	0.203	84.25±19.45	101.20±0.42	12.2
F19	816.70±1.3	6.30±0.06	4.2±0.20	0.155	72.15±25.10	100.16±0.59	12.3
F20	819.29±1.2	6.31±0.02	3.1±0.30	0.683	74.36±24.59	101.25±0.65	13.4

Table 4.post compression parameter of indapamide hemihydrate

3.4 Dissolution test of indapamide hemihydrate

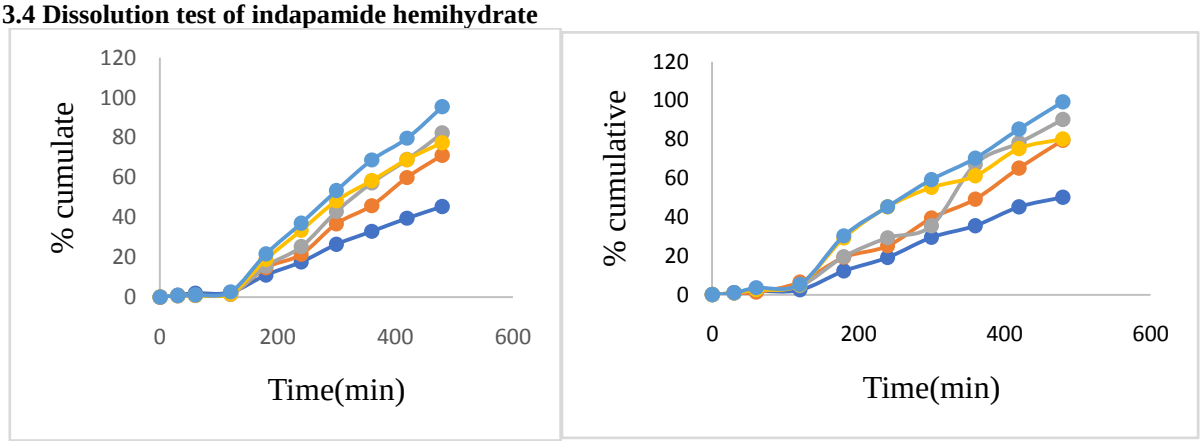

Figure 4. Dissolution test of indapamide hemihydrate (F1 to F10)

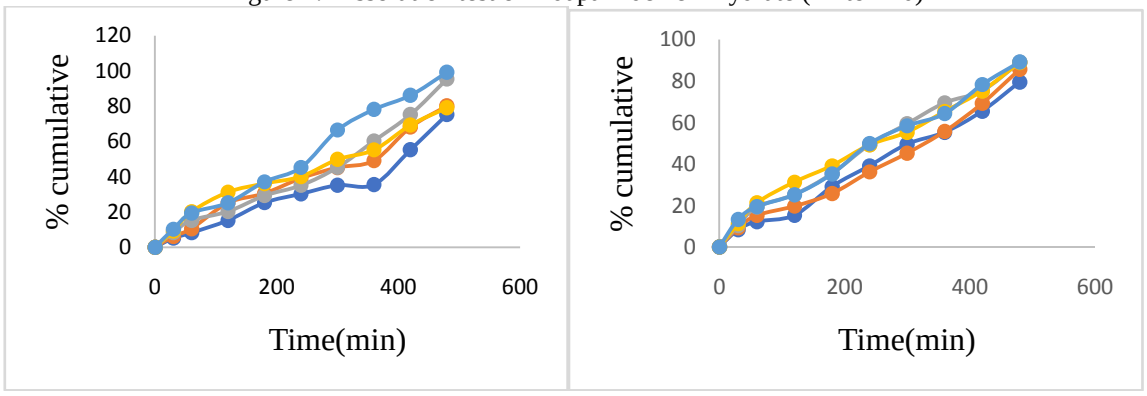

Figure 5. Dissolution test of indapamide hemihydrate (F11 to F20)

3.5 DRUG RELEASE STUDY

Different kinetic model is been used for the release of drug from all the formulation.

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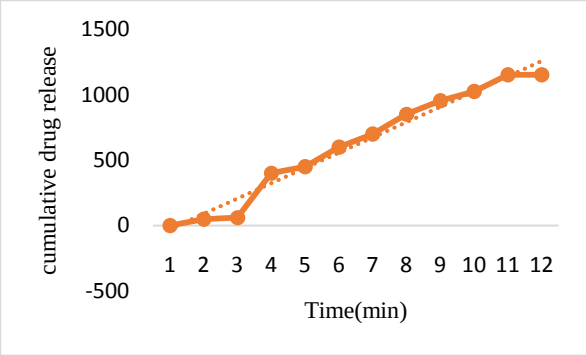


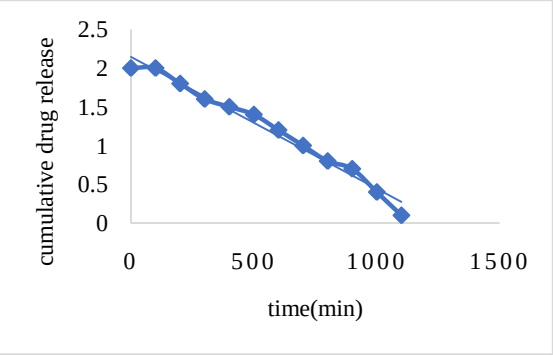
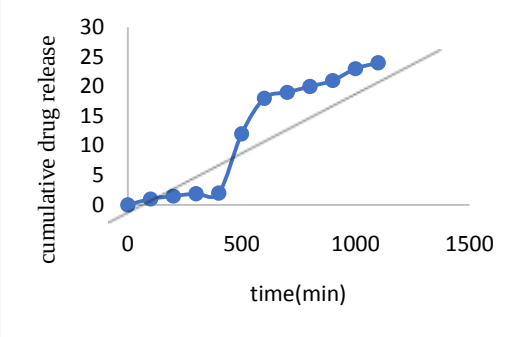


Figure 6. zero order kinetics Figure 7. first order kinetic



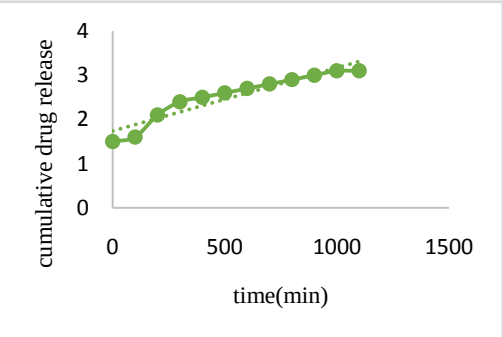


Figure 8.Higuchi release kinetic Figure 9.Peppas release kinetic

3.6 DSC of Sustained Release Tablet of indapamide hemihydrate

There is no change of peak is observed in sustained release tablet of indapamide hemihydrate and also there is no interaction between the drug and excipient which is used in the formulation.

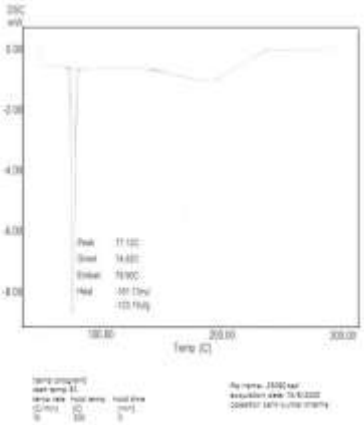


Figure 10. Sustained release of indapamide hemihydrate

3.7STABILITY STUDIES

Six to seven tables were used for this test. The result shows that tablets were stable at 40°C/ 76%RH for 6 months. These result shows no difference in between hardness, drug content, floating characteristics and percentage of drug release at 23 hours.

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Time (Month)	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Drug Content Uniformity (%)
0	88±3.72	7.35±0.15	5.45±0.18	0.45	100.2 ± 0.9
1	95±2.65	7.45±0.17	5.86±0.19	0.44	100.2 ±0.7
2	96±3.51	7.59±0.26	5.48±0.25	0.49	99.3 ± 0.6
3	99±2.84	7.96±0.27	5.47±0.34	0.44	99.1± 0.3
4	97±1.95	7.96±0.85	5.74±0.94	0.56	100±0.8
5	96±2.63	7.94±0.94	5.79±0.85	0.58	99±0.5
6	95±2.78	7.20±0.64	5.61±0.74	0.66	99±0.3

Table 5. stability study from 0 to 6 week

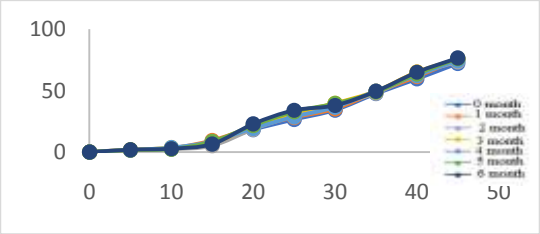

Figure 11.Indapamide hemihydrate release from bi-layer tablet after stability study

IV. SUMMARY AND CONCLUSION

Study shows that for the control release of drug (indapamide hemihydrate) in the matrix system HPMC (excipients) show the greater role. Result of precompression study shows that F2 granules of indapamide hemihydrate tablet show good compressibility. The flow property of power is found in good and excellent range. The hardness and thickness is found to 3-5 kg/cm^2 and 2.5 to 3mm. According to ICH guidelines the stability study was carry out and found that the batch were stable for 6 months. The statistical analysis show that optimized formulation shows the improved bioavailability as compared to marketed formulation.in-vitro evaluation of all the batches floating time is more than 23 hours with 4 to 8 min of floating lag time. These tablets were sustained up to 23 hours.

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