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## FORMULATION AND EVALUATION OF INDAPAMIDE SUSTAINED RELEASE MATRIX TABLETS

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### Keywords:

Sustained release matrix tablets, Indapamide, HPMC K 100, Pre-formulations and wet granulation.

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**ABSTRACT:** The study was undertaken with an aim to formulate anti-hypertensive agents as sustained release matrix tablets. The literature review showed that Indapamide is an anti hypertensive / diuretics in SR dosage form 50% of drug is released between 5-14hrs and 20-80ng/ml blood level is obtained for 24 hrs and SR form permits uniform and constant blood level after absorption of galenic form by oral route up to now it is available as IR with an dose of 2.5mg/day which results in considerable blood peaks, it is formulated as SR form to avoid and maintain constant blood level and to maintain better therapeutic index. In the present study, HPMC was found to play a great role in controlling release of drug Indapamide from the matrix system. Incorporation of HPMC K 100 M CR as release controlling polymer in extra granular fraction was found helpful in restoring the original and still closer release profile.

**INTRODUCTION:** Indapamide is the first of a new class of antihypertensive/diuretics, the indolines. It has been reported that the oral administration of 2.5 mg (two 1.25 mg tablets) of Indapamide to male subjects produced peak concentrations of approximately 115 ng/mL of the drug in blood within two hours. It has been reported that the oral administration of 5 mg (two 2.5 mg tablets) of Indapamide to healthy male subjects produced peak concentrations of approximately 260 ng/mL of the drug in the blood within two hours. A minimum of 70% of a single oral dose is eliminated by the kidneys and an additional 23% by the gastrointestinal tract, probably including the biliary route.

The half-life of Indapamide in whole blood is approximately 14 hours<sup>1, 2, 3</sup>. Indapamide is preferentially and reversibly taken up by the erythrocytes in the peripheral blood. The whole blood/plasma ratio is approximately 6:1 at the time of peak concentration and decreases to 3.5:1 at eight hours. From 71 to 79% of the indapamide in plasma is reversibly bound to plasma proteins.

Indapamide is an extensively metabolized drug with only about 7% of the total dose administered, recovered in the urine a pharmacokinetic unchanged drug during the first 48 hours after administration. The urinary pharmacokinetic elimination of <sup>14</sup>C-labeled Indapamide and metabolites is biphasic with a terminal half-life of excretion of total radioactivity of 26 hours.

In a parallel design double-blind, placebo controlled trial in hypertension, daily doses of indapamide between 1.25 mg and 10 mg produced dose-related antihypertensive effects. Doses of 5 and 10 mg were not distinguishable from each other although each was differentiated from

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placebo and 1.25 mg Indapamide. At daily doses of 1.25 mg, 5 mg and 10 mg, a mean decrease of serum potassium of 0.28, 0.61 and 0.76 mEq/L, respectively, were observed and uric acid increased by about 0.69 mg/100 ml<sup>6,7,8</sup>.

**MATERIALS AND METHODS:** Indapamide was obtained as a gift sample from Dr Reddy's Laboratories Ltd, Hyderabad, Telangana state. Micro crystalline cellulose pH 102, Micro crystalline cellulose pH 114, Mannitol, Iso propyl

alcohol, HPC-LF, Zinc stearate, HPMC K 100 M, Ly coat, Aerosil.

**Method of preparation of tablets:** Wet granulation is a process of dry mixing, wet mixing, and particle size enlargement, and is a process of particle attachment (agglomeration). It consists of six steps: Dry mixing, wet mixing, Milling of the wetted mass, Drying, Milling and sizing of the dried mass, final blending and coating.

**TABLE 1: COMPOSITION OF DIFFERENT BATCHES OF INDAPAMIDE TABLETS:**

Ingredients (mg/tab)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Indapamide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	45.00	24.00	-	45.00	24.00	45.00	24.00	45.00
HPMC K 100 M	7.50	-	-	-	-	-	-	-
HPC – LF	0.75	0.75	0.75	0.75	0.75	0.75	1.1	0.75
Zinc stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
MCC 114	-	21.00	23.00	-	-	-	-	-
HPMC K 4M/15M/100M	-	7.50	4.00	8.00	38.5	33.0	33.0	11.0
Aerosil	-	-	-	-	-	-	0.25	-

#### Characterization of the tablets:

- **Average Weight:** Weigh accurately 20 Tablets and calculate the average weight.
- **Hardness:** Determine the hardness of 10 Tablets, using a suitable calibrated hardness tester.
- **Thickness:** Determine the thickness of 10 Tablets, using a Vernier calipers.
- **Friability:** Weigh accurately 20 tablets and place them in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus at 25+1rpm and observe the tablets while rotating. No tablets should stick to the walls of the apparatus. Take the tablets out and observe. No capping should be observed. Weigh the tablets, after dedusting excess powder from their surface.
- **Uniformity of weight:** Weigh accurately 20 tablets and calculate the average weight. Then weigh the 20 tablets individually. Find out the tablets having the highest weight and the tablets having the lowest weight, in the above 20 tablets.
- **Dissolution by HPLC:**

**Apparatus:** USP Apparatus II

**RPM:** 50

**Medium:** 900ml pH 6.8 Phosphate buffer

**Temp:** 37±0.5°C

**Sampling Interval:** 1, 4, 8, 12, 16, 20, 24 hours

**Preparation of 0.2M monobasic potassium phosphate solution:** Dissolve 27.22gms of monobasic potassium phosphate in water dilute with water to 1000 ml,

**Preparation of 0.2M sodium hydroxide solution:** Dissolve sodium hydroxide in water and dilute to 1000 ml Heat the medium.

**Preparation of 6.8 pH phosphate buffer:** Place 250ml of 0.2M monobasic potassium phosphate solution and 112 ml of 0.2 M sodium hydroxide in 1000ml volumetric flask and dilute to 1000 ml with water.

#### Chromatographic Conditions:

**Buffer :** Dissolve 0.05M 8.71gms of dipotassium hydrogen phosphate in 1000ml of Milli-Q – water and mix and add 1ml of Triethylamine adjust pH to 3.60 with ortho phosphoric acid filter above solution through 0.45µm filter.

**Mobile Phase :** Acetonitrile and buffer in ratio 40:60 ( degas and sonicate for 10 mins)

**Column :** Intersil ODS 3V 150 x 4.6 mm, 4 $\mu$

**Flow rate :** 1.0ml/minute

**Wave length :** 240nm

**Temperature :** 65

**Load :** 50  $\mu$ l

**Run time :** 10.minutes

**Standard Preparation:** Weigh and place 52mg of standard into 250ml volumetric flask. Dissolve and dilute with Methanol. Pipette 2ml of solution in to 250ml volumetric flask make up vol with medium.

**Sample preparation:** Transfer 6 tablets individually in six dissolution flasks containing 900ml of the medium that has been equilibrated to 37°C  $\pm$  0.5°C. Take care to exclude air bubbles from the surface of the tablets, start the apparatus immediately. Collect the sample after the specified time, withdraw sample from a zone midway between the surface of the medium and top of the rotating blade and not less than 1cm from the vessel wall and filter through 0.45 $\mu$  membrane filter by discarding the 5ml.

**Procedure:** Separately inject the standard preparation into the liquid chromatography and record the area due to major peaks.

## RESULTS and DISCUSSION:

TABLE 2: ???

Formula (Trials)	Bulk density	Tapped density	Carr's Index (%)	Diameter (mm)	Thickness (mm)	Friability (%)	Content uniformity (%)
F-1	0.52	0.69	25.0	7.0 $\pm$ 0.0	4.8 $\pm$ 0.0	0.12	95.0 $\pm$ 0.9
F-2	0.49	0.67	24.0	7.1 $\pm$ 0.0	4.6 $\pm$ 0.0	0.15	93.0 $\pm$ 0.9
F-3	0.52	0.59	25.5	6.9 $\pm$ 0.0	4.9 $\pm$ 0.0	0.13	98.0 $\pm$ 0.9
F-4	0.53	0.62	23.5	6.5 $\pm$ 0.0	4.3 $\pm$ 0.0	0.18	97.0 $\pm$ 0.9
F-5	0.50	0.70	27.5	7.3 $\pm$ 0.0	4.7 $\pm$ 0.0	0.16	96.0 $\pm$ 0.9
F-6	0.52	0.52	25.5	7.8 $\pm$ 0.0	4.6 $\pm$ 0.0	0.15	95.0 $\pm$ 0.9
F-7	0.55	0.65	23.5	6.9 $\pm$ 0.0	4.1 $\pm$ 0.0	0.12	94.0 $\pm$ 0.9
F-8	0.61	0.58	28.5	7.7 $\pm$ 0.0	4.5 $\pm$ 0.0	0.11	96.0 $\pm$ 0.9

Based on the preformulation data, HPMC K100M was taken as release controlling polymer, mannitol and MCC114 as diluents, HPC-LF as binder, aerosil as glidant, zinc stearate as lubricant.

In Trial 1, HPMC K100M was used as release controlling polymer and mannitol as diluent, this trial is taken to check various problems in processing of tablets, the tablets which are processed passed all the in process quality control tests (thickness, friability, hardness, weight variation,). But the flow of dried granules should be improved and compressibility of granules also to be improved.

In Trial 2, Mannitol and MCC114 are combinedly used as diluents to increase flow and compressibility of dried granules, and HPMC K (4M,15M,100M,) are used as release controlling polymer to check for their release profile, the tablets with HPMC

K100M are showing retarded release.

In Trial 3, 4 HPMC K100M taken as release controlling polymer in (7%, 14%, 20%) concentration to check for their release profile, tablets with higher concentration of polymer showing more retarded release.

In Trial 5, 6 HPMC K 100 M taken as release controlling polymer in (60%, 70%,) concentration to check for their release profile, tablets showing release profile similar to that of innovator product but during processing of tablets hard granules are formed which are very difficult to mill and sift. So the process to be optimized.

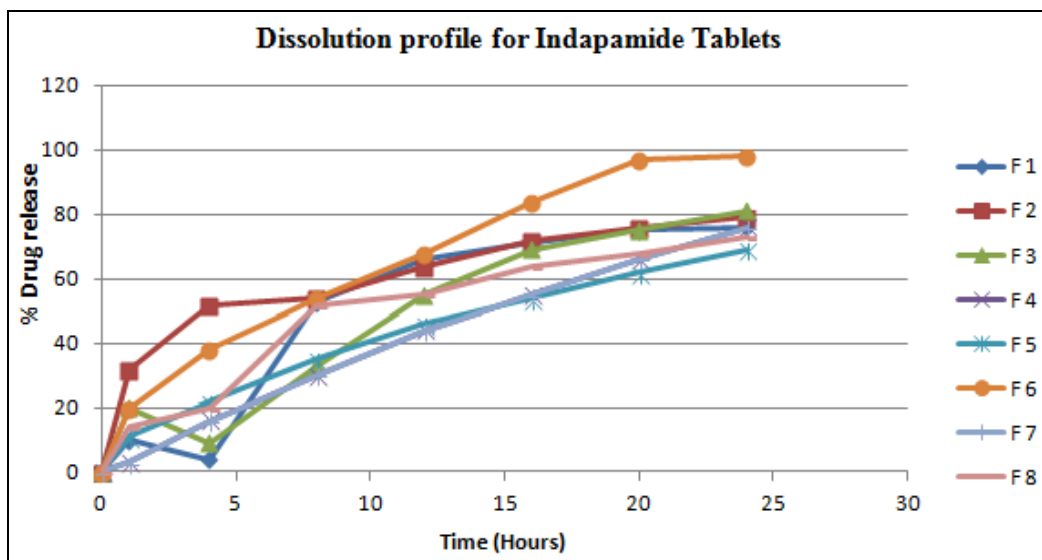
In Trial 7, binding solution water was replaced with alcohol and water in ratio of (9:1) respectively, no hard granules are observed but tablets dissolved totally in 0.1 N Hcl within 1 hour.

In Trial 8, HPMC K100M (CR) is taken as release controlling polymer and used in extra granulation part, the granules which are formed are soft and no

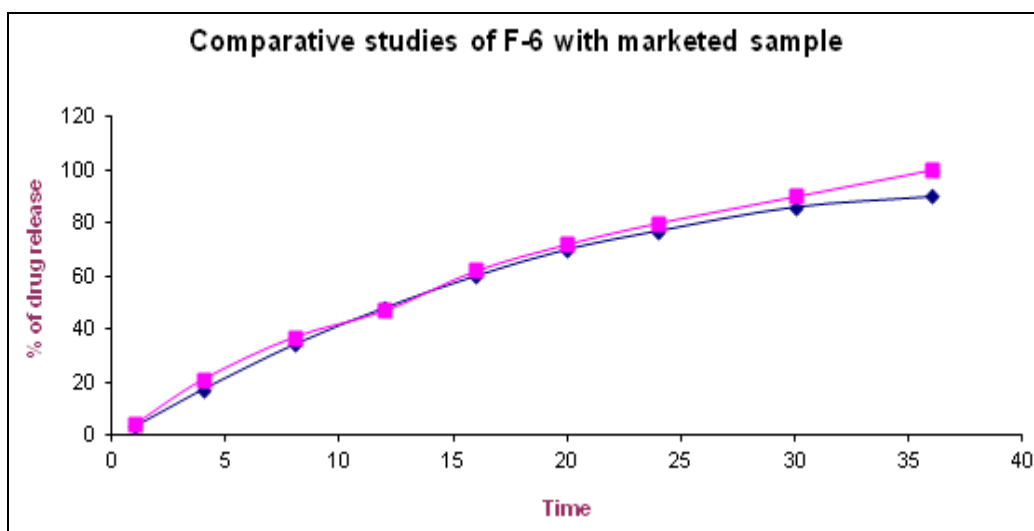
difficulties observed in sifting, the tablets showing release profile is 98%.

**TABLE 3: DISSOLUTION PROFILE FOR INDAPAMIDE TABLETS**

Time in Hours	% Drug Release							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	10	32	20	3	11	20	3	14
4	49	52	9	16	22	38	16	20
8	53	54	33	30	35	54	30	52
12	66	64	55	44	46	68	44	55
16	71	72	69	55	54	84	55	64
20	75	76	75	66	62	97	66	68
24	76	79	81	76	69	98	76	73



**FIG. 1: DISSOLUTION PROFILE FOR INDAPAMIDE TABLETS**



**FIG. 2: COMPARATIVE STUDIES OF F-6 WITH MARKETED SAMPLE**

**SUMMARY AND CONCLUSION:** In the present study, HPMC was found to play a great role in controlling release of drug indapamide from the matrix system. Incorporation of HPMC K 100 M CR as release controlling polymer in extra granular

fraction was found helpful in restoring the original and still closer release profile. Preformulation study and drug excipients compatibility study was done initially and results directed the further course of formulation. With the data from literature review,

Preformulation and Excipients compatibility study Prototype formulation trials were started. Wet granulation process was used for both the layers formulation by using the RMG Granules were evaluated for tests such as LOD, Bulk density, Tapped density, Compressibility Index and Hausner ratio & sieve analysis before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability, *In-vitro* dissolution tests were performed and f2 values were calculated. Dissolution profile matched with innovators product and f2 value was satisfactory. Accordingly, it can be concluded that the final formulation is a robust one and the performance is less likely to be affected by the various factors studied. An excellent *in vitro* –*in vivo* correlation is expected as evident from degree of similarity found in gradient dissolution in different media and release kinetics with respect to the reference listed drug products and as comparing with the commercial drugs also shows good dissolution studies.

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