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Formulation and evaluation of Indapamide sustained release matrix tablets

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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 in Sustained Release 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 Sustained Release form to avoid and maintain constant blood level and to obtain 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 as release controlling polymer in extra granular fraction was found helpful in restoring the original and still closer drug release profile.

1. 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 mg/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 mg/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 1, 2, 3. 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 s unchanged drug during the first 48 hours after administration. The urinary pharmacokinetic elimination of 14C-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 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 m Eq/ L, respectively, were observed and uric acid increased by about 0.69 mg/100 ml.

2. Materials and method

Indapamide was obtained as a gift sample from Hetero Laboratories Ltd, Hyderabad, Telangana state. Micro crystalline cellulose pH 114, Mannitol, Iso propyl alcohol, HPC-LF, Zinc stearate, HPMC K 100 M, Aerosil were of analytical grade.

Preparation of Indapamide sustained release matrix tablets

The ingredients were weighed accurately and mixed thoroughly powder passed through 44 mesh sieve. 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 compression as tablets.

Evaluation of powder

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner's ratio.

Angle of repose

Angle of repose was determined using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap D was measured. The angle of repose Ɵ was calculated by formula:

$$\text{Tan } \Theta = h/r \quad \Theta = \tan^{-1}(h/r)$$

Where Ɵ is the angle of repose, h is the height in cm and r is the radius

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Bulk density (Db)

Apparent bulk density was determined by pouring pre-sieved drug-excipient blend into graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by:

$$Db = M / V0$$

Where M is the mass of powder and V0 is the bulk volume of the powder.

Tapped density (DT)

It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by:

$$DT = M / VT$$

Where M is the mass of powder and VT is the tapped volume of the powder

Carr's Index

It is expressed in percentage and is expressed by

$$\text{Carr's index} = [\text{d tap-d bulk} / \text{d tap}] \times 100$$

Where, d tap= Tapped density or True density, d bulk = Bulk density.

Hausner's ratio

Tapped density and bulk density were determined and the Hausner's ratio was calculated by the following formula,

Hausner's ratio= Tapped density/ Bulk density

Table No. 1: Specifications for powder flow properties

Flow character	Carr's index (%)	Hausner's ratio	Angle of repose [0]
Excellent	< 10	1.00 – 1.11	25-30
Good	11-15	1.1 – 1.18	31-35
Fair	16-20	1.19 – 1.25	36-40
Possible	21-25	1.26 -1.34	41-45
Very poor	26-31	1.35 -1.45	46-55
Very very poor	> 31	>1.60	> 55

Table No. 2: Composition of different formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Indapamide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	45	24	24	45	24	45	24	45
MCC 114	-	21	23	-	-	-	-	-
HPMC K 100 M	7.50	-	-	-	-	-	-	-
HPC-LF	0.75	0.75	0.75	1.75	0.75	0.75	1.5	0.75
Zinc stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Aerosil	-	-	-	-	-	-	0.25	-
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
HPMC K 4M/15M/100M	-	7.5	5.5	6.5	28.5	7.5	27	7.5
Total	55	55	55	55	55	55	55	55

Table No. 3: Evaluation of powder

Formulation code	Angle of repose(^{0})	Bulk density(gm/cc)	Tapped density(gm/cc)	Carr's Index (%)	Hausner's ratio
F-1	31.4	0.52	0.69	25.0	1.32
F-2	32.3	0.49	0.67	24.0	1.36
F-3	34.5	0.52	0.59	25.5	1.13
F-4	33.2	0.53	0.62	23.5	1.16
F-5	35.4	0.50	0.70	27.5	1.40
F-6	34.2	0.52	0.52	25.5	1.0
F-7	33.5	0.55	0.65	23.5	1.18
F-8	31.4	0.53	0.68	28.5	1.28

Evaluation of tablets

The formulated tablets were evaluated for the following physicochemical characteristics

Hardness

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 5% for the tablets and none by more than double that percentage.

Friability

Weigh accurately 20 tablets and place them in the friability test apparatus. Adjust the timer to four minutes. Operate the apparatus at 25rpm 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. The percentage friability was calculated by using the following formula,

Percentage friability = Initial weight-final weight /initial weight × 100.

Thickness

Determine the thickness of 10Tablets, using Vernier calipers.

Dissolution studies

900ml 0f pH 6.8 Phosphate buffer was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37± 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 24 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 241 nm. The optimized formulation was compared with marketed product. The evaluation parameters tested and compared with in-vitro dissolution profile.

Drug content

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Indapamide was transferred in to a 100 ml volumetric flask and the volume adjusted to 100ml with pH 6.8 Phosphate buffer. Further 1ml of the above solution was diluted to 100 ml with pH 6.8 Phosphate buffer and check the absorbance of the resulting solution was observed at 241nm by UV spectroscopy.

Stability studies

The optimized formulation was tested for a period of 30 days at 30^0C with 75% RH, for their drug content and other parameters.

Table No. 4: Evaluation parameters of tablets

Formulation Code	Weight Variation (%)	Hardness (kg/cm)	Friability (%)	Drug Content (%)	Thickness (mm)	Diameter (mm)
F1	3.57	5.4	0.12	90.06	4.8	7.0
F2	2.57	5.3	0.11	95.26	4.6	7.1
F3	1.87	5.3	0.18	91.05	4.9	6.9
F4	2.34	5.5	0.15	95.76	4.3	6.5
F5	4.32	5.4	0.14	94.51	4.7	7.3
F6	3.26	5.2	0.13	96.54	4.6	7.2
F7	4.12	5.3	0.15	95.34	4.1	6.9
F8	2.56	5.1	0.11	94.32	4.5	7.1

3. Results and discussion

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, and zinc stearate as lubricant. In Trial 1, HPMC K100M was used as release controlling polymer and mannitol as diluent, this trail 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 combined 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 HPMCK100M are showing retarded release. In Trial 3, 4

HPMC K100M taken as release controlling polymer in (7%, 14%, and 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 has 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 with in 1hour.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 No. 5: Dissolution profile of Indapamide tablets

Time (Hrs)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	Innovator
1	10.12	32.11	20.36	3.21	11.34	20.24	3.24	14.35	19.32
4	49.25	52.24	29.52	16.41	22.58	38.34	16.27	20.65	37.58
8	53.41	54.63	33.36	30.25	35.34	54.28	30.34	52.34	53.41
12	66.21	64.36	55.39	44.24	46.41	68.37	44.73	55.84	67.27
16	71.15	72.21	69.24	55.39	54.72	84.97	55.97	64.54	82.46
20	75.28	76.11	75.69	66.54	62.71	97.12	66.24	68.38	91.42
24	76.32	79.25	81.98	76.24	69.34	98.11	76.23	73.71	97.19

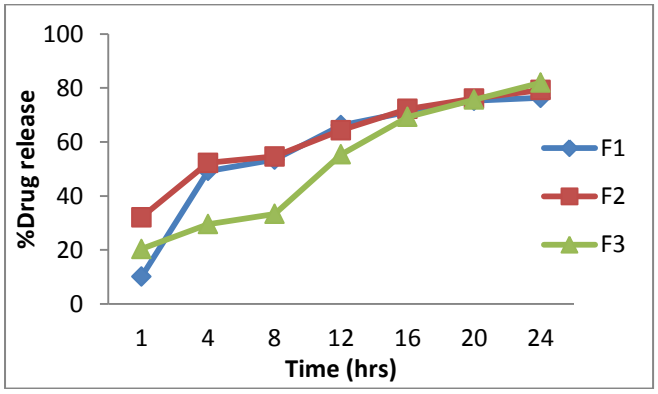

Figure No. 1: Dissolution profiles of F1, F2 and F3

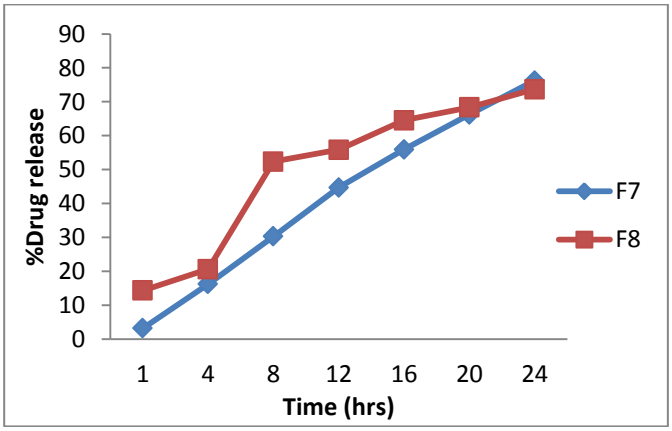

Figure No. 3: Dissolution profiles of F7and F8

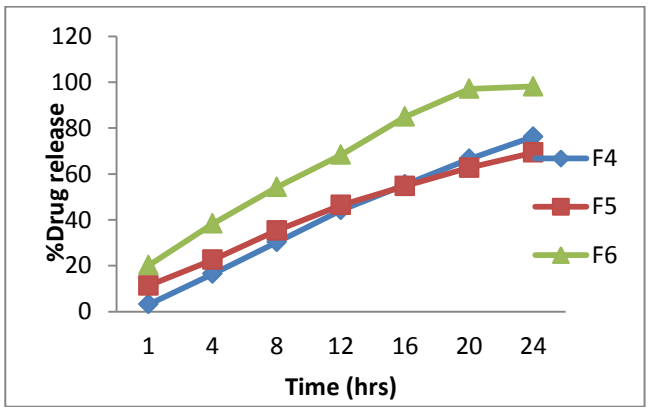

Figure No. 2: Dissolution profiles of F4, F5 AND F6

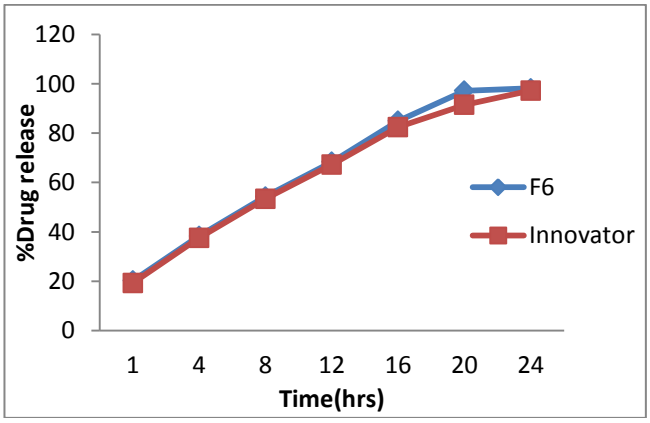

Figure No. 4: Dissolution profiles of F6 and innovator

Table No. 6: Stability Studies of the Optimized Batch (F6) at 30^0C/75%RH

S. No.	Parameters	Initial	15 days	30 days
1 .	Hardness (kg/cm)	5.2	5.1	5.1
2 .	Friability (%)	0.13	0.14	0.16
3 .	%Drug release	98.11	97.86	97.42

4. 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. Wet granulation process was used for both the layers formulation by using the RMG Granules were evaluated for tests such as Bulk density, Tapped density, Compressibility Index and Hausners ratio before being punched as tablets. Tablets were tested for weight variation, thickness, hardness, friability; *In-vitro* dissolution tests were performed. Dissolution profile matched with innovators product. 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* dissolution studies is expected as evident from degree of similarity found in gradient dissolution in media as comparing with the commercial drugs.

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