Formulation, Development and Evaluation of Mouth Dissolving Tablets (MDTs) of Indapamide

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Abstract: **Mouth Dissolving Tablets (MDTs) dissolves in saliva and swallowed without need for water also it overcomes the problem arises with swallowing by pediatric and geriatrics patients. It having fast onset of action, required therapeutic efficiency, Increase patient compliance and convenience. An effort was made to formulate, development and evaluations of MDTs of Indapamide which gives actions against hypertension. The MDTs of Indapamide was developed by direct compression method by adding superdisintegrants as well as subliming agents and many mores. To develop this formulation, six formulations were prepared and evaluated successfully. The optimized test formulations F4 showed superior drug release to reference product which having good stability.**

Keywords: **Mouth Dissolving Tablets; Direct compression; β-Cyclodextrin; Croscarmellose; Crospovidone; Mannitol; Citric acid; Indapamide.**

1. INTRODUCTION:

MDTs release drug in our mouth quickly by undergoing disintegration in the salivary fluids of the oral cavity within short interval of time. Orally they release the API i. e. Active Pharmaceutical Ingredient by rapid dissolving unique properties and advantages. So we need to develop dosage forms in pharmaceutical industry which gives rapid onset of action, minimizes drug loss, avoids 1st pass metabolism, gives high bioavailability, requires less time to absorption, having accurate dosing, this dosage form easy to handle and transfer, having long durability and improve patient compliances [1, 2].

Indapamide is mainly used to reduce blood pressure which arises in hypertension. It is non-thiazide sulfonamide diuretic class which acts onto kidney by reabsorbing salt and water to increase urine output i. e. Diuresis effect. It lowers salt from muscle so ultimately it causes relaxation of the vessels. That's gives reduction into the blood pressure [3]. Structure of Indapamide is given in figure 1.

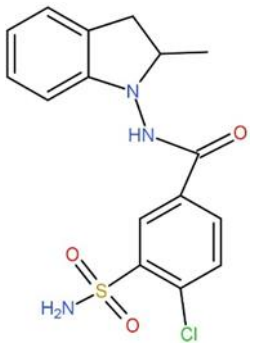

Figure 1: Structure of Indapamide

2. MATERIALS AND METHODS:

2.1. Materials:

The pure Indapamide drug was obtained as a gift sample from Supra Chemical Thane, Mumbai (Maharashtra), India. Other required excipients used from College Laboratories which are analytical grades.

2.2. Methods:

A. Preparation of β-Cyclodextrininclusion complex: [14]

In that preparation we have used kneading method to prepare binary mixtures of drug β-Cyclodextrinin the 1:1 ratio. Firstly, Cyclodextrin is added to motor, in that small quantity of 50% Ethanol is added and smoothly triturated it to get slurry like consistency. After preparation of slurry, in that drug is added and triturated it with air dried at 25 °C for 24 hours then this dried powder sieved through sieve no. 100, quantity of powder equivalent to required drug was taken for the preparation of MDTs.

B. Role of excipients in formulation:

In that we have used Indapamide as Active Pharmaceutical Ingredient which is responsible for required action and other many excipients was used on their properties and uses basis. It includes β-Cyclodextrin which used as solubility enhancer and as an binder, Polyethylene glycol 400 is used to augment the solubility and bioavailability, Croscarmellose sodium used as superdisintegrant, Crospovidone having superdisintegrant property which allow rapid absorption, Sodium Starch Glycolate is a pharmaceutical grade dissolution, Microcrystalline Cellulose works as binder, Mannitol is a sweeting agent, Magnesium Stearate working as lubricant, Citric acid having antioxidant properties mainly used as a preservative. And finally, distilled water was used to make final volume i. e. as a quantity sufficient (Q. S.) in whole preparation.

C. Preparation of MDTs: [4, 7]

MDTs of Indapamide was prepared by enhancing solubility of the drug by inclusion with β-Cyclodextrin. The blend of tablet forming polymer and superdisintegrants was used with suitable properties to prepared MDTs of Indapamide and β-Cyclodextrin complex. Then blend was evaluated by different evaluations parameters as a pre-compression parameter. By using direct compression method, we have prepared MDTs with adding different excipients with required quantities and then evaluated for various parameters. The combination which shows lowest disintegration time, high drug release, optimum wetting time and hardness was selected for further study. The table 1 shows compositions which we have used in this preparation in different quantities. The excipients selected in this development were sieved through sieve no. 40 and nextly mixed properly in mentioned proportions which is shows in below table using mortar pestle and spatula. Then this formula was compressed and formulated into Mouth Dissolving Tablets using multiple punch tablet machine. The final weight of tablets was adjusted to 200 mg and then tablets were evaluated for a various parameter as a post-compression parameter.

Table 1: Formula of different trials for the selection of excipients (data in mg).

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Indapamide	2.5	2.5	2.5	2.5	2.5	2.5
2.	β-Cyclodextrin	2.5	5	2.5	5	2.5	2.5
3.	Polyethylene glycol 400	3	4	5	6	7	8
4.	Croscarmellose Sodium	3	5	7	9	11	13
5.	Crospovidone	4	5	6	7	8	9
6.	Sodium Starch Glycolate	9	8	7	6	5	4
7.	Microcrystalline Cellulose	55	50	55	50	55	50
8.	Mannitol	30	30	30	30	30	30
9.	Magnesium Stearate	2	2	2	2	2	2
10.	Citric Acid	3	4	5	6	7	8
11.	Distilled Water	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.

3. EVALUATION OF TABLETS:

3.1. Pre-Compression Parameters: [10, 11, 15]

Before compression, the blend was evaluated for various parameters like Bulk density, Tapped density, Angle of repose and finally Compressibility Index. Results of these Per-Compression parameters are given in table 2.

3.2. Post-Compression Parameters: [12,13,16]

Post-Compression parameter was conducted onto the final productions of the MDTs.

These are involved many parameters like, Appearance, Thickness test, Hardness test, Friability test, Weight Variation test, Drug content uniformity, Wetting time, Wetting absorption ratio.

1) Appearance:

Randomly selected tablets were analysed for Appearance test. It shows flat circular shape without cracking and having white colon.

2) Thickness Test:

It is measured by randomly selecting prepared tablets from each formulation**.** It is measured by using Dial Calliper gauge. The uniformity of thickness is shown in table 3.

3) Hardness Test:

Monsanto Hardness tester is used to find out hardness of tablets and it was maintained within 3.78to 4.11 kg/cm^3.

The hardness test results are shown in table 3.

4) Fribility Test:

Roche Friability tester is used to find out friability of tablets.

The friability test results are shown in table 3.

5) Weight Variation Test:

20 tablets of each formulation were selected and their average weight was calculated and from this weight variation was calculated.

The weight variation test results are shown in table 3.

6) Drug content uniformity:

Tablets containing 100 mg of drug was dissolved into 100 ml methanol solutions. It was filtered by Whatmann filter paper no. 41 after that Sonicate this solution for 10 min. From this 1st stock, 1 ml solution was withdrawn and made up the 10 ml volume

by methanol in another flask named as 2nd stock solution. Again 1 ml solution from this stock 2nd was placed in another flask and made 10 ml quantity by methanol. This 3rd stock solution is used to find out maximum absorbance of drug [21] and it is given in fig. 2. By finding out beer's range calibration graph is obtained. The concentration range and absorbances which was used are given in table 4 and calibration curve is shown in figure 3. From that graph correlation coefficient was find out. Which is found as per ICH guidelines. The drug content was found satisfactory in the range 98.78 to 101.06 %.

7) Wetting Time:

The tablets were placed in a petridish of 6.5 cm in diameter which contains 10 ml of water at room temperature and the time required to complete wetting was recorded, from that reproducibility was found out. Six times measurement was carried out and finally mean value was calculated.

The results of wetting time are shown in Table 5.

8) Wetting Absorption ratio:

Tissue paper was used to carried out this ratio in that a piece of paper folded twice and this was placed in a small petridish containing 6 ml of distilled water. Prepared tablets were placed on the paper and time required to complete wetting was measured.

Three tablets from six formulations were analysed and standard deviation (S.D) was also determined.

Weight absorption ratio i. e. R was determined by using following equations.

$$R = 10 * (Wa- W_b)/W_b.$$

Where, W_a was the weight of the tablet before water absorption.

And W_b was the weight of the tablets after water absorption.

The results of wetting absorption ratio are shown in table 5.

9) *In-Vitro* dissolution studies: [8]

This study was conducted by using 6 tablets of each formulation. For that study USP type 1 dissolution apparatus containing 30 ml of the simulated salivary fluid having pH 6.8 as a dissolution medium which was maintained at 37 ± 0.5 ºC at 100 rpm was used. Aliquots of 5 ml sample were withdrawn at selected time intervals i. e. at 01, 02, 03, 04, 05, 06, 07, 08, 09, and finally at 10 minutes. And same amount was replaced with a prepared fresh medium having same conditions. This sample were analysed by using UV-Spectrophotometry at 258 nm after proper dilutions and furthermore 3 trials were carried out for all the samples and the average values have finally taken. Comparative *In-Vitro* dissolution study has conducted for selected test formulations with reference products. In the results, the percentage (%) of the dug dissolved at different time intervals has calculated and it was plotted against time, given in figure 4.

10) Disintegration test: [15]

Disintegration test was performed to ensure the disintegration of the tablets in phosphate buffer of pH 6.8 by using Disintegration test apparatus. One prepared tablet from six formulation was introduced into one tube of disintegration apparatus I.P. respectively. In that assembly, A disc was added into the tube and the assembly was suspended in a beaker containing simulated saliva furthermore, the apparatus was operated until the tablet disintegrated with no palatable mass remaining in the apparatus was ensured. The time required to complete disintegration of the tablet was taken in seconds, which are given in table 5.

11) FT-IR Spectra of Drug: [9]

The FT-IR spectra were obtained using KBr solutions for Indapamide. The scanning range used for FT-IR Spectra was 400-4000 cm^{-1}. The FT-IR Spectra's revealed study has shown that the polymers and excipients used in this formulation were compatible with selected drug. There was no notable difference in those spectra.

12) Stability Studies: [20]

As per ICH guideline, we have performed stability study of the optimized formulation of F4 under different environmental conditions. The prepared MDTs placed in stability chamber for stability studies at 2 to 8 ºC (45 % RH.), 25 to 30 ºC (60 % RH.) and 45 to 50 ºC (75 % RH.) for a period of 90 days. The tablets were taken from stability chamber after 1st, 2nd and 3rd months and evaluated for different parameters during the stability period. The stability studies results are given into the table 6.

4. RESULT AND DISCUSSION:

4.1. Pre-Compression Parameters:

The prepared blend was evaluated for various parameters like Bulk density, Tapped density, Angle of repose and finally Compressibility Index. Results of these Pre-Compression Parameters are given in table 2.

Table 2: Evaluation parameters of the Pre-Compression powder blend.

Sr. No.	Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm3)	Angle of Repose (^{0})	Compressibility Index (%)
1.	F1	0.56	0.68	25.97	18.23
2.	F2	0.52	0.61	24.23	14.03
3.	F3	0.58	0.70	26.73	19.78
4.	F4	0.53	0.62	24.57	14.37
5.	F5	0.55	0.64	25.12	16.35
6.	F6	0.54	0.63	24.89	14.52

4.2. Post-Compression Parameters:

Post-Compression parameter was conducted onto the final productions of the MDTs. These are involved many parameters like, Appearance, Thickness test, Hardness test, Friability test, Weight Variation test, Drug content uniformity are given in table 3. And Wetting time, Wetting absorption ratio and disintegration time of tablets are given in table 5.

Table 3: Evaluation parameters of the Post-Compression of MDTs.

Sr. No.	Formulation Code	Uniformity of Thickness (mm)	Hardness (kg/cm3)	Fribility (%)	Weight Variation (mg)	Drug Content Uniformity (mg)
1.	F1	3.06	3.78	0.98	200.02	2.4
2.	F2	2.89	3.96	0.92	199.97	2.5
3.	F3	2.99	4.11	0.89	200.01	2.4
4.	F4	3.02	3.94	0.94	200.00	2.5
5.	F5	3. 12	4.08	0.98	199.96	2.4
6.	F6	3.01	4.03	0.96	199.98	2.6

4.3. Content Uniformity:

The graph of maximum absorption spectra of the drug found at 258 nm are given in figure 2 and Standard Calibration Curve of Indapamide are given in table 4. The Calibration Curve of drug are given in figure 3 and in this drug absorption content was found to be 0.9931.

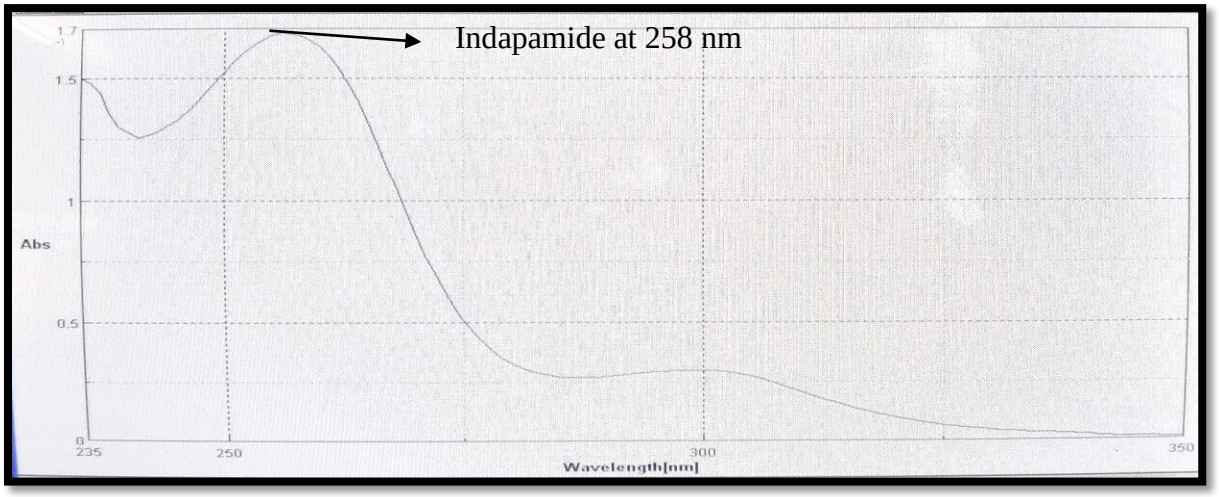

Figure 2: Spectra of Indapamide at 10 µg/ml.

Table 4: Standard Calibration Curve of Indapamide at 258 nm in methanol.

Sr. No.	Concentrations (µg/ml)	Absorbances
1.	0.5	0.5463
2.	1.0	0.6543
3.	1.5	0.7123
4.	2.0	0.7946
5.	2.5	0.8756

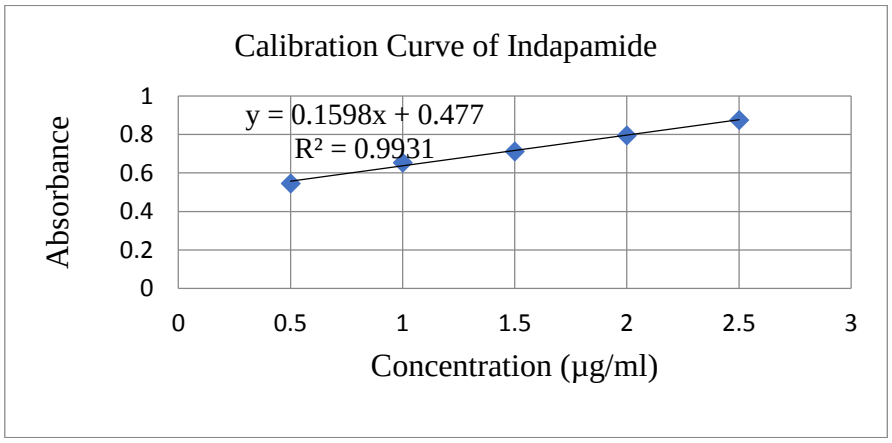

Figure 3: Calibration Curve of Indapamide.

4.4. Wetting time, Water absorption ratio and Disintegration time of prepared MDTs:

The formulation F4 displayed a good water absorption ratio indicating better and faster Swelling ability of the disintegrate in the presence of a small amount of water as compare to F3 formulations. So here our optimized formulation batch was F4.

These results are shown in table 5.

Table 5: Wetting time, Water absorption ratio and Disintegration time of formulated MDTs:

Sr. No.	Formulation code	Wetting time	Water Absorption ratio	Disintegration time (Sec.)
1.	F1	18.32	22.64	35 ±0.23
2.	F2	22.43	24.39	38 ± 1.00
3.	F3	17.78	29.92	32± 2.87
4.	F4	17.58	33.56	31 ± 2.03
5.	F5	25. 22	32.59	33 ± 2.76
6.	F6	21.87	29.40	36 ± 1.25

4.5. *In-Vitro* drug release:

The *In-Vitro* drug release studies were performed for all batches of tablets, however initial formulations i.e. F1, F2, F5 and F6 did not met the targeted release profile. Prepared formulation F3 and F4 were found to be satisfactory but the formulation F4 displayed a good water absorption ratio indicating better and faster Swelling ability of the disintegrates in the presence of a small amount of water as compare to F3 formulations. So here our optimized formulation batch was F4 and drug release data was shown in figure 4.

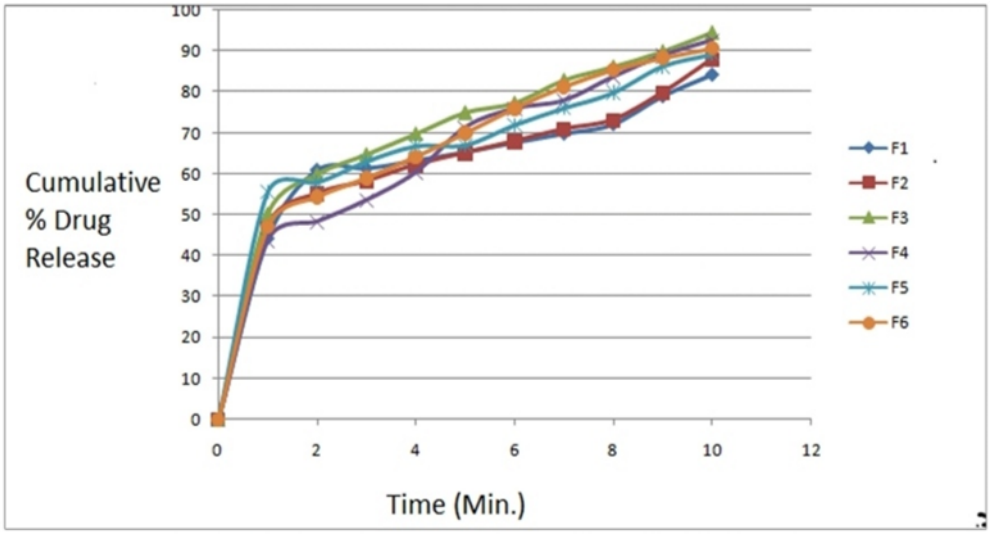

Figure 4: *In-Vitro* % Cumulative drug release profile of MDTs.

4.6. FT-IR Spectra:

The given FT-IR Spectrum of Indapamide showed its required characteristic bands. The characteristic peaks of Indapamide were modified slightly as a result of complex formation. Slightly shifting in absorbance of Indapamide indicates no strong interactions between drug and β-Cyclodextrin. The FT-IR Spectra's revealed study has shown that the polymers and excipients used in this formulation were compatible with selected drug.

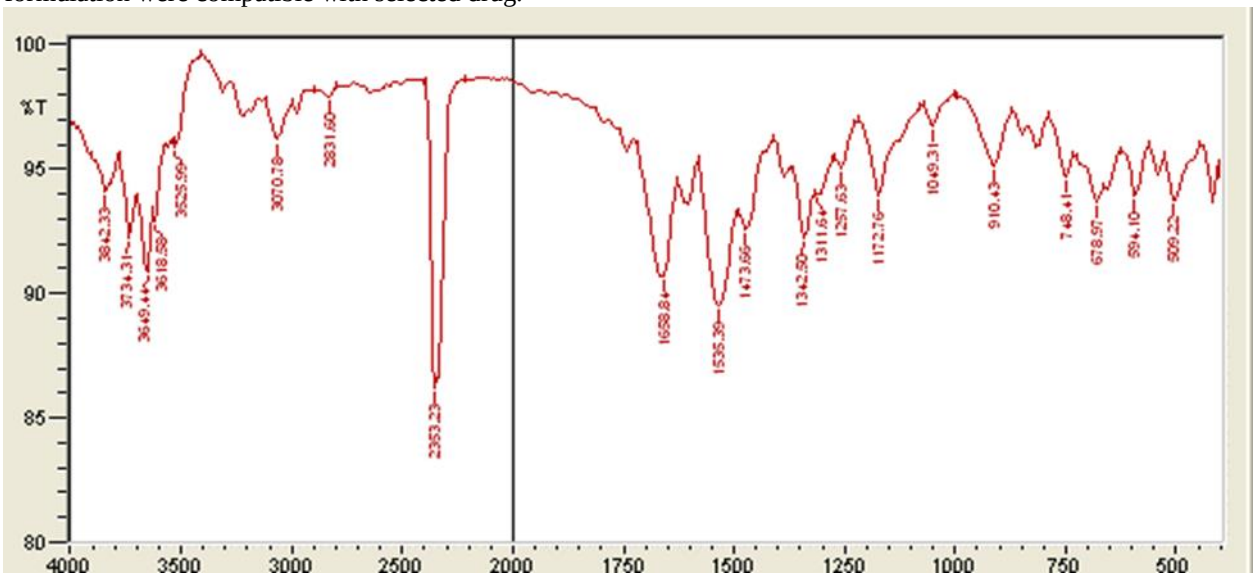

Figure 5: FT-IR Spectrum of the Indapamide.

4.7. Stability Studies:

The accelerated stability study was conducted for optimized formulation F4 for a period of 3 months and the results revealed that there were no noticeable major changes observed in Disintegration time, Friability, Surface pH and Drug content. These results are given in table 6.

Table 6: Stability Study Data for optimized formulation F4.

Sr. No.	Parameters	1st month	2nd month	3rd month
1.	Disintegration time (Sec.)	31 ± 2.03	33 ± 1.56	32 ± 1.11
2.	Fribility (%)	0.94	0.92	0.93
3.	Surface pH	6.88	6.56	6.76
4.	Drug content (%)	99.05	98.89	98.21

5. CONCLUSION:

We have successfully formulated, developed and evaluated the prepared Mouth Dissolving Tablets of Indapamide. The optimized test formulation showed superior drug release to reference product and also demonstrated good stability over a period of 3 months. The Bulk density, Tapped density, Angle of repose and Compressibility Index in optimized formulation F4 was found to be satisfactory. The *In-Vitro* drug release in optimized formulation F4 has found to be 93.89 % in 10 minutes and Wetting time, Hardness and Content uniformity studies shows good acceptable results and Water absorption ratio indicates good absorptivity in selected formulations.

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7. CONFLICT OF INTEREST:

The authors show that there is no conflict of interests.

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