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Formulation, Development and Evaluation of Fast Dissolving Film of an Antihypertensive Drug

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ABSTRACT

Hypertension is a major cause of concern not just in the elderly but also in the youngsters. An effort was made to formulate a fast dissolving film(FDF) containing Indipamide which is used in the treatment of hypertension with a view to improve the onset of action, therapeutic efficacy, patient compliance and convenience. The major challenge in formulation of oral films of Indipamide is that it shows very less solubility in the pH range of 3–9. Various film forming agents and polyhydric alcohols were evaluated for optimizing composition of fast dissolving films. Fast dissolving films were formulated using solvent casting method. Optimized formulations were evaluated for their weight, thickness, folding endurance, appearance, tensile strength, and disintegration time and dissolution profile.

Key-words: Fast dissolving film (FDF), Hydroxypropyl Methylcellulose, Polyethylene glycol-400, Solvent casting, Indipamide

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INTRODUCTION [1,4,6,8]

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastrointestinal tract. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms. These dosage forms possess certain specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance.

Indapamide, 4-chloro-N-(2-methyl-2, 3-dihydroindol-1- yl) - 3-sulfamoyl-benzamide, is a non-thiazide sulfonamide diuretic drug that is used primarily for the treatment of high blood pressure. It works by preventing the kidney from reabsorbing (retaining in the body) salt and water that is destined to be eliminated in the urine. This results in increased urine output (diuresis). Indapamide also is thought to reduce the salt in the smooth muscle of the walls of blood vessels. (The salt ultimately is eliminated in the urine.) The loss of salt from the muscle causes the muscle to relax, and the relaxation of the vessels results in reduced blood pressure.

Definition: The Center for Drug Evaluation and Research (CDER), US FDA defined fast dissolving film (FDF) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."FDTs disintegrate and/or dissolve instantaneously in the saliva without the use of water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast disintegrating tablets, as they may take up to a minute to completely disintegrate. When placed on tongue, this film disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach.

MATERIAL

The drug Indapamide was obtained as a gift sample from Supra Chemical Thane, Mumbai (MAH) India. The other excipients are used from college drug laboratory.

Preparation of drug: β-CD inclusion complex [3]

The binary mixture of drug: β-CD complex was prepared by kneading method in which drug with β-CD (1:1) was taken. Firstly cyclodextrin is added to mortar; small quantity of 50% ethanol is added and triturated to get slurry like consistency. Then drug is added to the slurry and triturated. Slurry is then air dried at 25^0C for 24 hours. Dried powder passed through sieve No.100.Quantity of powder equivalent to 2.5 mg of drug was taken for the preparation of films.

METHOD [4 , 5]

Fast dissolving film of Indapamide an Antihypertensive Drug is prepared by enhancing solubility of drug by inclusion with β-CD. The fast dissolving film of Indapamide and β-CD complex is prepared by using blend of film forming polymer and superdisintegrants with suitable proportion. Fast-dissolving films of Indipamide were prepared by a solvent casting technique in petridish.

Preparation of casting solutions: [1, 10]

The weighed quantities of polymers (HPMC) were kept for swelling overnight in distilled water and dissolved (heated, if necessary). The inclusion complex (equivalent to 2.5 mg of drug) and mannitol were dissolved in distilled water and added to the above mentioned polymer solution along with polyethylene glycol-400 as a plasticizer, mixed thoroughly to form a homogenous mixture. The volume was made up to 10 ml with distilled water. Entrapped air bubbles were removed by applying vacuum.

Preparation of fast-dissolving films:

The casting solution (10 ml) was poured into petridish and dried at 40°C in a vacuum oven for 24hrs for solvent evaporation. The patches were removed by peeling and cut into a square dimension of 1.30cm ×1.30cm. These

patches were kept in a desiccator for 2 days for further drying and wrapped in aluminium foil, and packed in self-sealing covers. Fast-dissolving films were prepared with different polymers and ratios by maintaining the concentration of the surfactant, citric acid and sweetener constant.

Table No.1-Composition of FDF

Sr. No.	Ingredients (mg)	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	2.5	2.5	2.5	2.5	2.5
3	HPMC	10	11	12	13	14	15
4	PEG-400	6	5	4	3	2	1
5	Mannitol	10	10	10	10	10	10
6	Tween-80	4	4	4	4	4	4
7	Citric Acid	5	5	5	5	5	5
8	SSG	4	5	6	7	8	9
9	Crosspovidone	6	5	4	3	2	1
10	Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

*Quantity of drug was calculated as per the area of petridish so that each film (1.30X1.30cm^2) contains 2.5mg of drug.

EVALUATION OF FAST-DISSOLVING FILM [6, 7, 8, 9]

Drug content uniformity:

A fast-dissolving film 1.30cm ×1.30cm was transferred into a graduated flask containing 100 ml of methanol. The flask was shaken for 4 h in a mechanical shaker. The solution was filtered and after suitable dilutions with methanol, the absorbance value was measured at 242 nm using the placebo patch (patch without drug) solution as a blank, and the drug content was calculated from UV graph (fig.4).

Folding endurance:

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 1.30cm × 1.30cm was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed, and the values were reported.

Surface pH:

The film to be tested was placed in a Petridish and was moistened with 0.5 ml of distilled water and kept for 30 seconds. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

Elongation and tensile strength:

This mechanical property was evaluated using the Instron universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. Film strips in a special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamps at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely, tensile strength and percentage elongation were computed for the evaluation of the film. Tensile strength is the maximum

stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture. It can be calculated by using following formula,

Tensile strength = Load at breakage/ Strip thickness X Strip width

Disintegration test:

Disintegration test was performed to ensure the disintegration of the film in phosphate buffer of PH 6.8. One film from each formulation was introduced into one tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing simulated saliva and the apparatus was operated until the film disintegrated.

In vitro dissolution studies:

The simulated salivary fluid was taken as the dissolution medium to determine the drug release. The dissolution profile of quick release films of Indipamide was carried out in a beaker containing 30 ml of the simulated salivary fluid (pH 6.8) as a dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and10 min time intervals and the same amount was replaced with the fresh medium. Samples were assayed spectrophotometerically at 242 nm. Three trials were carried out for all the samples and the average value was taken. The percentage of the drug dissolved at various time intervals was calculated and plotted against time as shown in fig.5.

Stability studies:

The stability study of the formulated fast-dissolving films was carried out under different environmental conditions. The film was packed in the aluminum foil and stored in a stability chamber for stability studies at 2-8°C (45% RH), 25-30°C (60% RH), and 45-50°C (75% RH) for a period of 90 days. The patches were characterized for the drug content and other parameters during the stability study period and data is shown in table no.5.

RESULT

Characterization of inclusion complex:

Drug content estimation:

UV spectroscopy was used to determine the drug content of the Indapamide:β-CD inclusion complex (1:1). The drug content in all the system was found to be 98.56% to 101.23%.

1) UV Spectrophotometric Analysis:

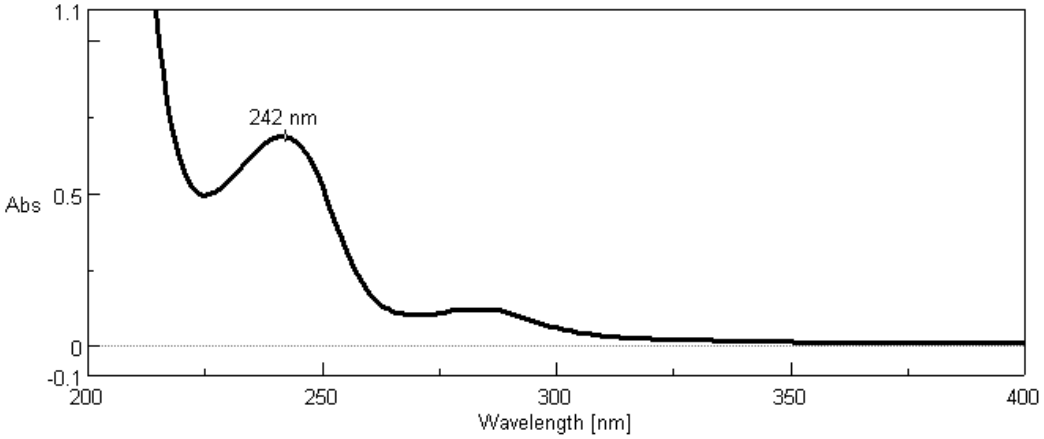

Fig.1- λ max of Indapamide obtained at 242nm

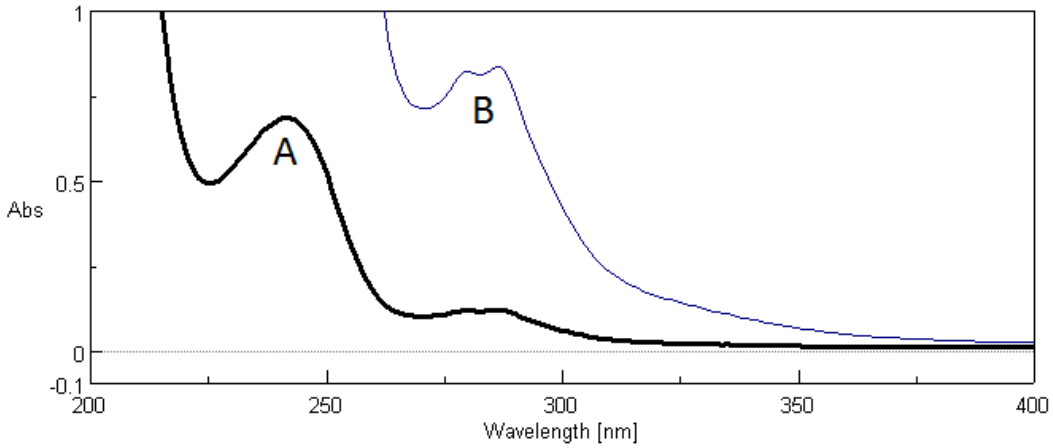

Fig.2-Absorption Spectra of (A) Pure Indapamide and (B) Indapamide:β-CD Complex

UV spectra of the inclusion complex: [11]

UV spectra of pure Indapamide and inclusion complex in methanol solution were obtained by UV –visible spectrometer, model JASCO1505 instrument. The scans were registered from 200 to 400 nm.. There were several changes on the UV/VIS spectra of Indapamide/β-CD complex compared with that of Indapamide. The intensity absorption peak at 284 nm increased greatly. The peak at 242 nm increased too by the formation of complex, inclusion complex had an increased intensity at all points of wavelength due to the formation inclusion phenomena between β-CD and Indapamide as shown in fig.2.

2) FTIR of Inclusion Complex:

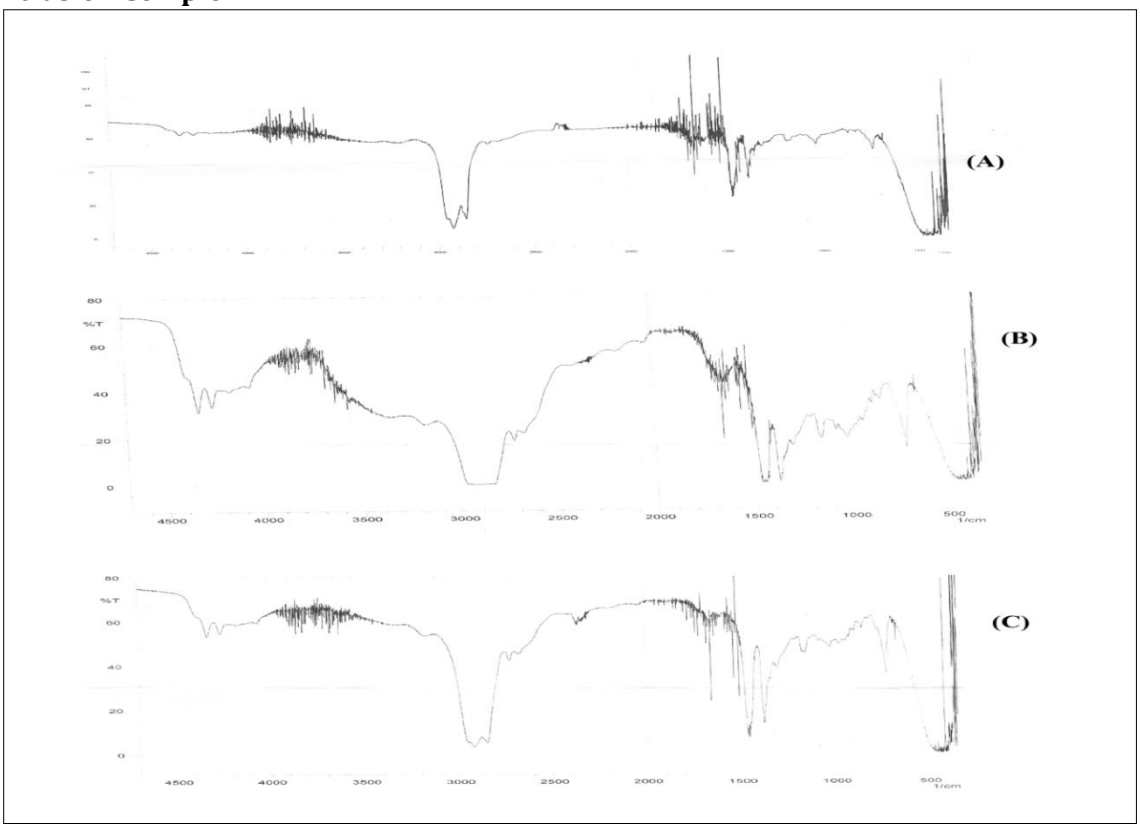

Fig.3-FTIR Spectra of (A) Pure Indapamide, (B) Pure β-CD, (C) Indapamide:β-CD Complex(1:1)

FTIR spectra studies:

FTIR was conducted using a FTIR-8400S Spectrometer (SHIMADZU). The diffuse reflectance technique was utilized in the mid-IR (400–4000 cm−1) spectral region. The procedure consisted of grinding the sample (2mg) together with KBr (about 200mg) into a fine powder, placing the powder into the sampling cup, smoothing the powder, and compressing the powder bed. The variation of the shape, shift, and intensity of the IR absorption peaks of the guest or host can provide enough information for the occurrence of the inclusion. Fig. 3 showed the IR spectra of Indapamide (A), β-CD (B) and their inclusion complex(C). The IR spectrum of Indapamide showed its characteristic bands in agreement with the previously report. The IR spectrums of the inclusion complex are similar to that of β-CD, due to the low quantity of Indapamide in the system. As clearly seen from the spectra, the characteristic peaks of Indapamide were modified significantly as a result of complex formation. As shown in fig.3C slightly shifting in absorbance of Indapamide indicates no strong interactions between drug and β-CD.

Content Uniformity:

From the graph of absorption spectra the drug content was found to be 2.43mg (97.20%)

Table No.2- Content uniformity study

Sr.No.	Concentration (ppm)	Absorbance
1	5	0.232
2	10	0.441
3	15	0.645
4	20	0.837
5	25	1.062
6	30	1.341
7	35	1.449
8	40	1.621
9	Unknown	1.013

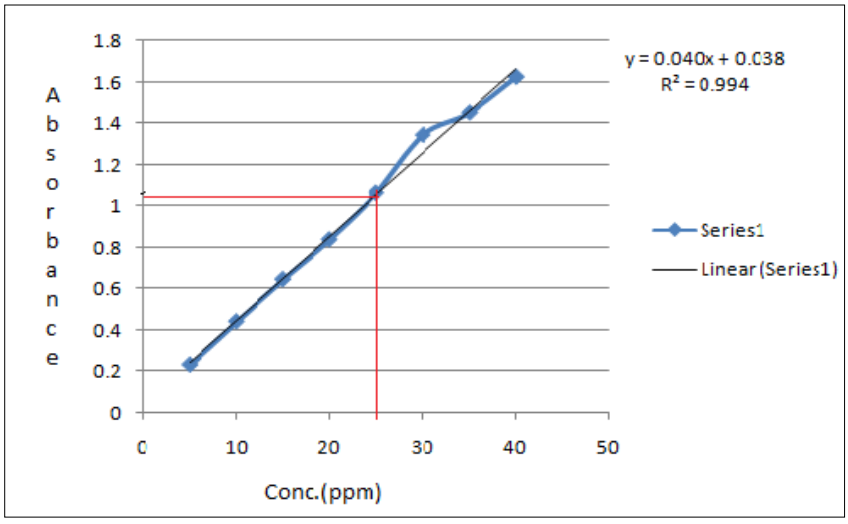

Fig.4-Calibration curve of Indapamide

Table No.3- Evaluation parameters for FDF

Formulation	F1	F2	F3	F4	F5	F6
Thickness(mm)	1.40± 0.03	1.43±0.02	1.50±0.03	1.48±0.01	1.52±0.01	1.54±0.02
Weight (mg)	49.24±0.03	49.73±0.05	50.80±0.05	51.75±0.02	48.85±0.03	48.75±0.02
Folding Endurance	62±2	80±3	125±2	136±4	155±3	162±2
% Drug Content	92.52±0.30	94.46±0.20	96.56±0.50	91.27±0.46	92.12±0.27	94.02±0.22
Surface PH	6.78±0.43	6.42±0.22	6.52±0.15	6.66±0.32	6.92±0.12	6.68±0.10
Disintegration Time (Sec)	35±4	40±2	45±4	55±3	60±3	62±2
Tensile strength (N/cm^2)	3.04±0.12	2.36±0.32	7.64±0.28	2.08±0.24	6.01±0.42	4.14±0.31

Table No.4-In Vitro Release Data

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	44.20	47.28	50.24	43.77	55.59	47.13
2	60.89	55.12	59.86	48.27	57.84	54.33
3	61.34	58.24	64.73	53.52	63.01	58.97
4	63.25	62.22	69.77	60.31	66.72	64.14
5	65.31	65.11	74.98	71.24	67.00	69.90
6	67.65	67.93	77.33	75.84	71.92	75.98
7	69.82	70.91	82.90	77.82	76.03	81.24
8	72.12	73.18	86.17	83.61	79.80	85.37
9	78.98	79.79	89.93	88.78	86.27	88.26
10	84.21	87.92	94.54	92.50	89.18	90.56

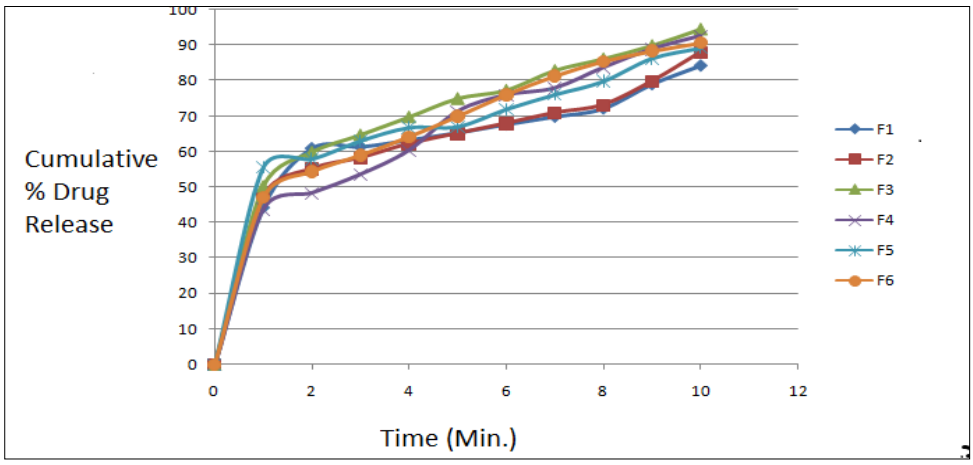

Fig.5- In-vitro %CDR profile of fast dissolving film

Table No.5-Stability Study Data for F3

Formulation	Month	Disintegration Time	Surface PH	Drug Content
F3	1	45	6.45	97.45
	2	43	6.78	97.22
	3	44	6.61	97.16

DISCUSSION

Films were found to be satisfactory when evaluated for-

1. Thickness, In vitro drug release, folding endurance, disintegration time, content uniformity.
2. The in vitro drug release in optimized formulation F3 was found to be 94.54 % in 10 min. and satisfactory stability.

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