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FORMULATION AND EVALUATION OF FUDOSTEINE FILM COATED IMMEDIATE RELEASE TABLETS

M. CHANDRAKANTH, P. PREM KUMAR, MANOHAR BABU S

Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur,-522001, Andhra Pradesh, India.

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Abstract: The selected method yielded uniform and reproducible film coated tablets of Fudosteine with the given excipients. The hardness, friability, weight variation, drug content, and *in vitro* release were uniform and reproducible. The release was inversely proportional to the binder concentration irrespective of the polymer used. The dissolution profile of the formulation F10 was found to have equivalent percentage drug release with that of the innovator product. Selected Fudosteine tablets were found to be stable with respect to drug content, drug release, friability, weight variation, hardness and thickness. FTIR studies revealed no chemical interaction and indicating stability of drug in tablets. Hence, Fudosteine tablets containing mannitol (diluent), Povidone K-30 (binder), croscaramellose sodium (disintegrant), Colloidal Silicon Dioxide (glidant), Magnesium Stearate (Lubricant) and Opadry – AMB (coating Material) showed promising results and there exist a scope for *in vivo* evaluation using suitable animal models.

Keywords: Povidone K-30 (binder), croscaramellose sodium (disintegrant), Colloidal Silicon Dioxide (glidant), Magnesium Stearate (Lubricant)

Corresponding Author: MR. M. CHANDRAKANTH

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INTRODUCTION

Dosage forms are also referred to as "Drug Delivery Systems" or "Finished Drug Products". A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration[1, 2]. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. The tablet is one of the most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms. Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable excipients and prepared by either compression or molding methods[3, 4].

The first step in the development of dosage form is preformulation, which can be defined as investigation of physiochemical properties of drug substances alone and when combined with excipients. The main objective of preformulation studies, is to develop stable and bioavailable dosage form and study of factors affecting such as stability, bioavailability and to optimize so as to formulate the best dosage form. Here, optimization of formulation means finding the best possible composition. Compressed tablets are formed by applying pressure, for which compression machines (tablet presses) are used and they are made from powdered crystalline or granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases with colorant[5-10].

MATERIALS AND EQUPIMENTS USED

Table.1- List of materials used

S No	Name of the product	Grade	Function	Name of the supplier
1.	Fudosteine	-	Active Pharmaceutical Ingredient	Aurobindo Pharma Ltd; Hyderabad.
2.	Micro crystalline cellulose USP-NF (Avicel Ph 101)	Avicel Ph 101	Diluent	FMC biopolymer
3	Povidone K-30	Kollidon 30	Binder	BASF, Germany
4	Sodium starch glycolate	Primogel	Disintegrant	FMC biopolymer

5	Colloidal silicon dioxide	Aerosil 200 Pharma	Glidant	Meruchem
6	Magnesium Stearate USP-NF	-	Lubricant	Ligamade
7	Opadry White	-	Film Coating Agent	Colorcon
8	Opadry AMB	-	Film Coating Agnet	Colorcon

Table.2- List of Equipments used

S. No.	Equipment	Manufacturer	Model no
1	Electronic Balance	Sartorius AG	GP3202
2	Sieves	Scientific Engineering corporation Ltd.	ASL00
3	Blender	RIMEK(KALWEKA)	HD-410AC
4	Rapid Dryer	Retsch	TG-100
5	Co-Mill(COMIL) Rpm: 1000-6500	Quadro(220 Volts)	U5-0280
6	Compression 16 Station	Cadmach	SS00001
7	Compression 20 Station	Cadmach	PR/SD/COMO1
8	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
9	Stability chambers	Thermo labs	Standard
10	Coating Machine	Gansons	GAC-250
11	Hardness tester	Tanco labs	T3
12	Friabilator	Electro Lab	EF2
13	Mixer	Philips	HL1628
14	Sieve Shaker	Retsch	AS200digit
15	Bulk Density Apparatus	Electro Lab	ETD-1020
16	Fluid Bed Processor	Pam-Glatt	FP-01
17	Stirrer	REMI-Motors	RQT-124A

Table.3-List of Components used in the Formulation

S.No	Components	Function
1	Mannitol – 35	Diluent
2.	Povidone K-30	Binder
3	Iso-propyl alcohol	Granulating Fluid
4	Cross Caramellose Sodium	Disintegrant
5	Aerosil	Glidant
6	Magnesium Stearate	Lubricant

7	Opadry White	Coating Material
8	Opadry AMB	Coating Material
9	Purified Water	Vehicle

RESULTS AND DISCUSSIONS

Table.4- List of Formulation Trials

Prototype Formulations										
Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Fudosteine	200	200	200	200	200	200	200	200	200	200
Mannitol 35	21	21	19.5	15.5	13	11	11	8.5	6.5	6.5
Granulation										
Povidone K-30	-	-	4	4	4	4	5	5	4.5	4.5
Iso-propyl alcohol	-	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Extra-Granular										
Ac-Di-Sol	4	4	4	4	4	4	4	6.5	9	9
Talc	-	-	1.5	-	-	-	-	-	-	
Aerosil	-	-	-	1.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	-	-	-	-	1.5	2.5	2.5	2.5	2.5	2.5
Core Tablet Wt.	225	225	225	225	225	224	225	225	225	225
Coating										
Opadry White	-	6.75	6.75	6.75	6.75	6.75	6.75	-	-	-
Opadry AMB	-	-	-	-	-	-	-	6.75	6.75	6.75
Coated Tablet Wt.		231.75	231.75	231.75	231.75	231.75	231.75	231.75	231.75	231.75

Table.5-Flow Properties of A.P.I

S. No	Bulk Density (gm/ml)	Tap Density (gm/ml)	Compressibility Index	Hausner's Ratio
1	0.215	0.389	44.706	1.808
2	0.215	0.389	44.706	1.808
3	0.215	0.389	44.706	1.808
4	0.215	0.389	44.706	1.808

Table.6--Standard curve of Fudosteine in water at λmax 279nm

Concentration (µg/ml)	Absorbance (279nm)
0	0
1	0.109

2	0.204
3	0.317
4	0.412
5	0.537
6	0.627
7	0.747

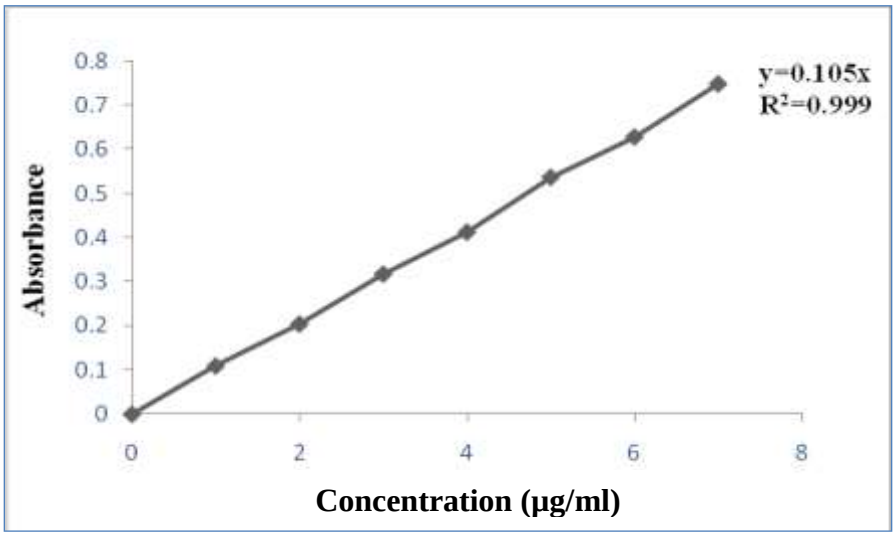

Fig: 1. Standard calibration curve of Fudosteine

Table.7- showing the solubility of Fudosteine (API) in various solvents.

Solvents	Solubility
Water	Freely Soluble
Formic Acid	Very Soluble
Acetic Acid	Slightly Soluble
Ethanol	Very Slightly soluble
Diethyl Ether	Insoluble

Table.8-Data of average Hardness for all the formulations of Fudosteine

Formulation	Average Hardness (Kp)
F1	12±0.09
F2	8± 0.05
F3	11.5 ± 0.32

F4	13± 0.12
F5	12± 0.08
F6	10.5± 0.33
F7	12 ± 0.25
F8	10.5 ± 0.12
F9	11 ± 0.13
F10	10± 0.15

Table.9- Data showing the thickness for all formulations of Fudosteine

Formulation	Thickness (mm)
F1	3.8-4.1
F2	4.1-4.2
F3	3.7-4.1
F4	4.0-4.1
F5	3.8-4.2
F6	3.9-4.1
F7	3.7-3.9
F8	4.0-4.2
F9	3.9-4.2
F10	3.9-4.2

Table.10- Data showing the results of Friability for all the formulations of Fudosteine

Formulation	Percentage of weight loss (%)
F1	1.02±1.27
F2	0.05±0.01
F3	0.04±0.11
F4	0.028±0.02
F5	0.019±0.05
F6	0.013±0.06
F7	0.03±0.05
F8	0.04±0.012
F9	0.02±0.02
F10	0.012±0.03

Table.11- Data of average weight of tablets for all the formulation of Fudosteine

Formulation	Average Weight (mg)
F1	210-237
F2	215-235
F3	215-234
F4	213-233
F5	216-229
F6	213-232
F7	214-234
F8	213-232
F9	215-236
F10	218-230

Table.12-Data of time for disintegration for all formulations of Fudosteine (n=6)

Formulation	Disintegration time (minutes)
F1	6.0-6.5
F2	6.0-6.5
F3	8.0-8.5
F4	7.5-8.0
F5	7.5-8.0
F6	7.5-8.0
F7	7.0-7.5
F8	7.0
F9	6.5-7.0
F10	6.5-7.0

Table.13- Blend Flow Properties of Fudosteine Film Coated Tablets

Formulation Code	Bulk Density (gm/cc)	Tap Density (gm/cc)	Compressibility Index	Hausner's Ratio
F1	0.436	0.577	24.44	1.32
F2	0.432	0.572	24.48	1.32
F3	0.436	0.577	24.44	1.32
F4	0.417	0.498	16.27	1.19
F5	0.399	0.6	33.50	1.50
F6	0.498	0.581	14.29	1.17
F7	0.379	0.498	23.90	1.31
F8	0.417	0.612	31.86	1.47

F9	0.498	0.64	22.19	1.29
F10*	0.379	0.489	22.49	1.29

Table.14- Physical Characteristics of Fudosteine Film Coated Tablets

Formulation code	Weight (mg/Tab)	Hardness (kg/cm^2)	Thickness (mm)	Labelled Drug Content (mg)	% drug content	% Friability
F1	210-237	12±0.09	3.8-4.1	200	99.6	1.02±1.27
F2	215-235	8± 0.05	4.1-4.2	200	99	0.05±0.01
F3	215-234	11.5 ± 0.32	3.7-4.1	200	99.8	0.04±0.11
F4	213-233	13± 0.12	4.0-4.1	200	100.6	0.028±0.02
F5	216-229	12± 0.08	3.8-4.2	200	99.8	0.019±0.05
F6	213-232	10.5± 0.33	3.9-4.1	200	101	0.013±0.06
F7	214-234	12 ± 0.25	3.7-3.9	200	100	0.03±0.05
F8	213-232	10.5 ± 0.12	4.0-4.2	200	99.6	0.04±0.012
F9	215-236	11 ± 0.13	3.9-4.2	200	99.2	0.02±0.02
F10*	**218-230**	**10± 0.15**	**3.9-4.2**	**200**	**99.89**	**0.012±0.03**

Table.15-Dissolution profiles of all Formulations

Time (h)	Cumulative % drug dissolved									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10***
5	54.2	55.5	48.8	53.4	49.2	51.6	43.5	51.2	42.2	**58.8**
10	86.4	82.1	83.2	82.1	80.6	81.5	70.6	81.6	70.5	**87**
15	99.2	97.4	98.7	96.8	94.6	95.5	87.3	95.1	86.8	**98.6**
20	100.7	100.2	100.6	99.8	97.9	98.6	97.1	100.2	96.2	**100.2**
30	100.9	99.9	100.7	100.3	100.01	100.5	100.8	100.4	101.5	**100.4**

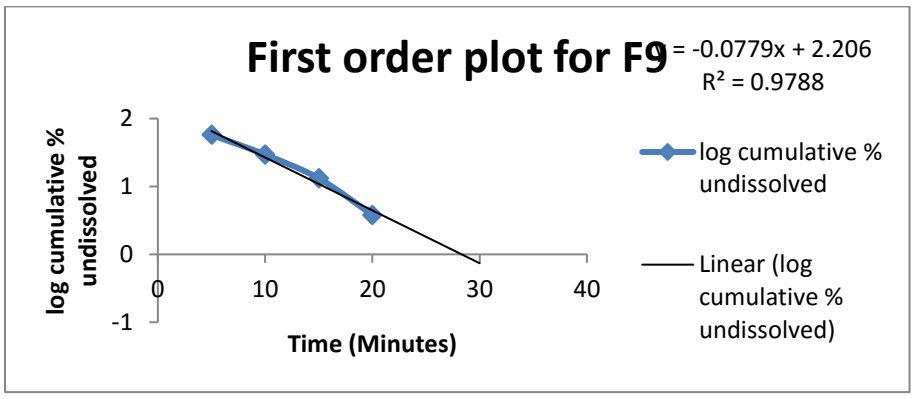

Fig-2: First Order plot for F9

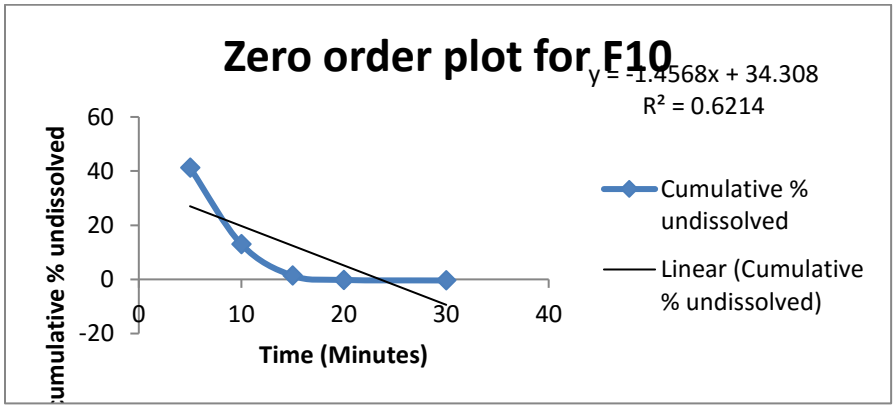

Fig-3: Zero Order plot for F10

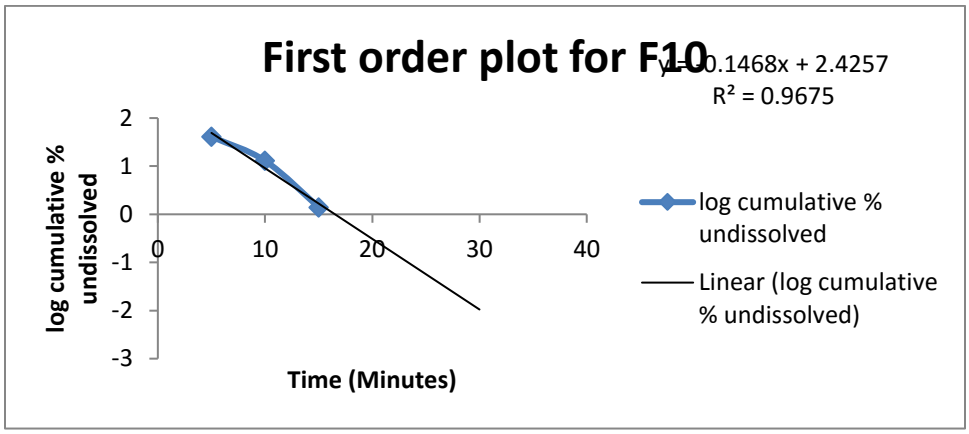

Fig-4: First Order plot for F10

Table.16- Dissolution profiles of all 10 formulations with innovator

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10*	innovator
0	0	0	0	0	0	0	0	0	0	0	0
5	54.2	55.5	48.8	53.4	49.2	51.6	43.5	51.2	42.2	58.8	58.8
10	86.4	82.1	83.2	82.1	80.6	81.5	70.6	81.6	70.5	87	87.8
15	99.2	97.4	98.7	96.8	94.6	95.5	87.3	95.1	86.8	98.6	99.2
20	100.7	100.2	100.6	99.8	97.9	98.6	97.1	100.2	96.2	100.2	100.9
30	100.9	99.9	100.7	100.3	100.01	100.5	100.8	100.4	101.5	100.4	101.4

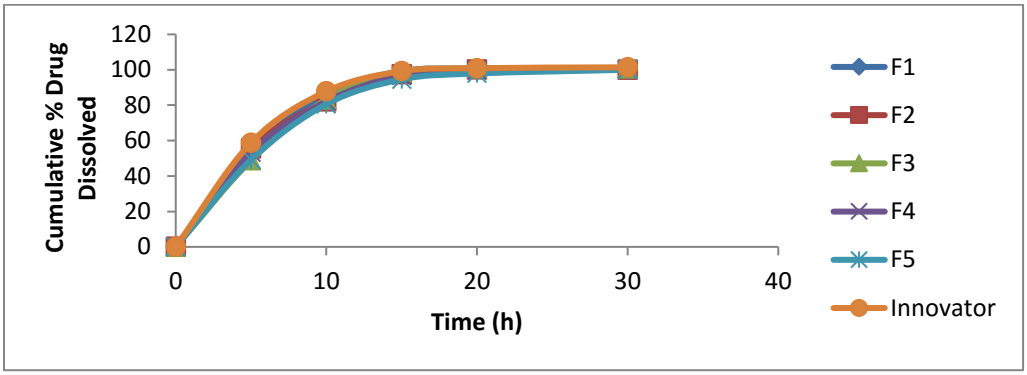

Fig: 5. Dissolution profiles of F1 – F5 formulations with innovator

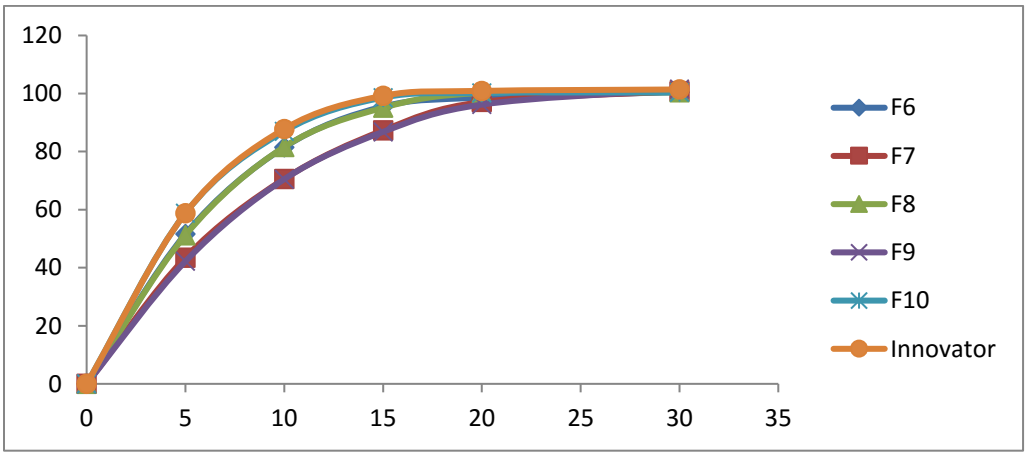

Fig: 6.Dissolution profiles of F6 – F10 formulations with innovator

Table.17-Innovator Product Dissolution Profile

Time (min)	Innovator dissolution
0	58.8
5	87.8
10	99.2
15	100.9
20	101.4
30	58.8

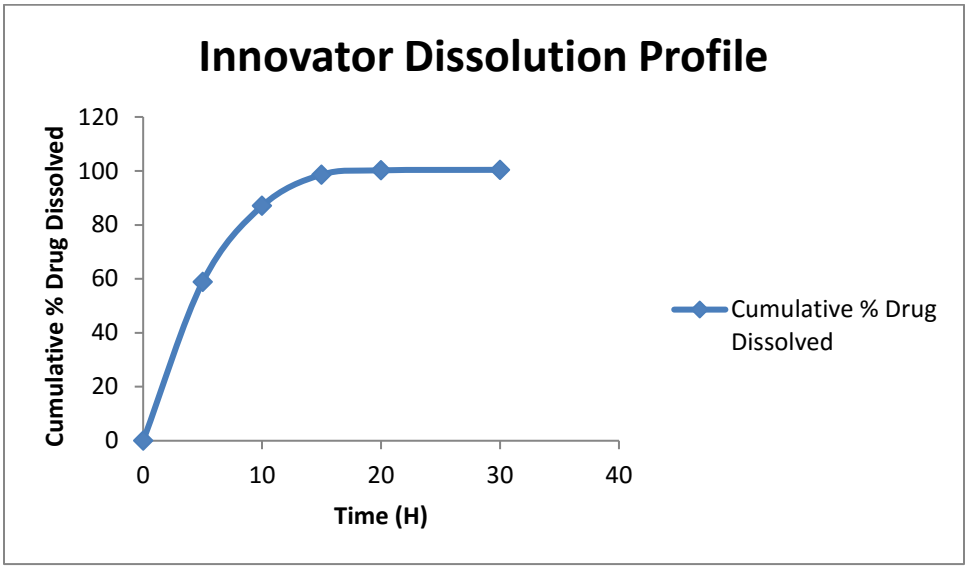

Fig: 7.Dissolution profile of innovator product

Table.18- Comparison of Innovator Product 'Vs' Best Formulation

Time (Mins)	Innovator	F10
0	0	0
5	58.8	58.8
10	87	87.8
15	98.6	99.2
20	100.2	100.9
30	100.4	101.4

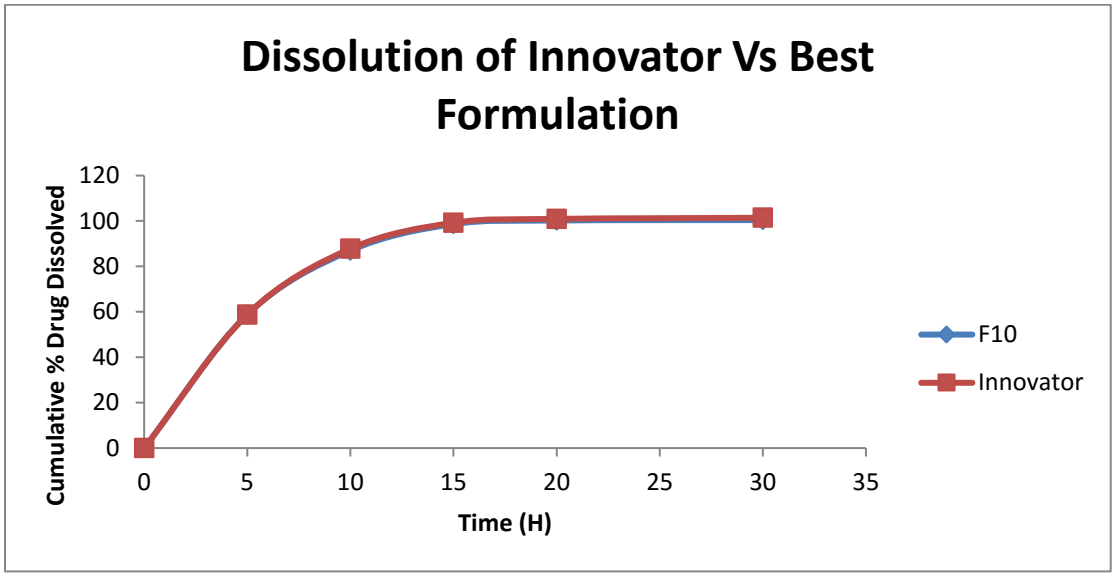

Fig: 8.Dissolution profile of best formulation with innovator

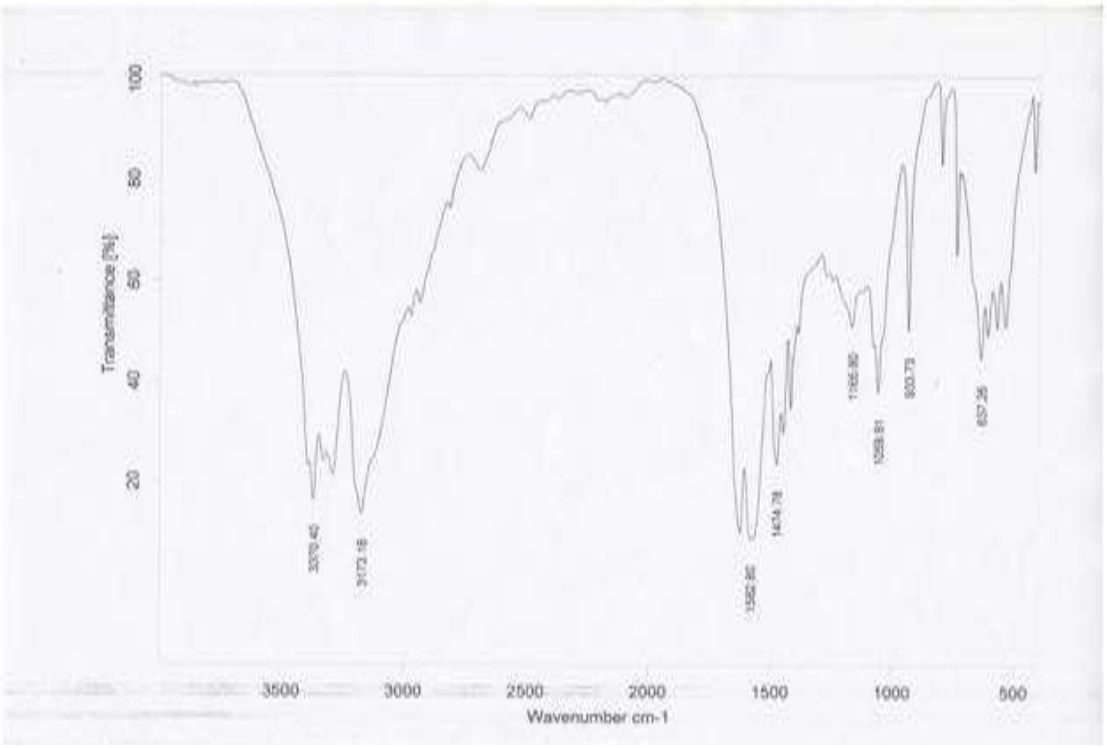

Fig- 9: FTIR of Pure drug Fudosteine

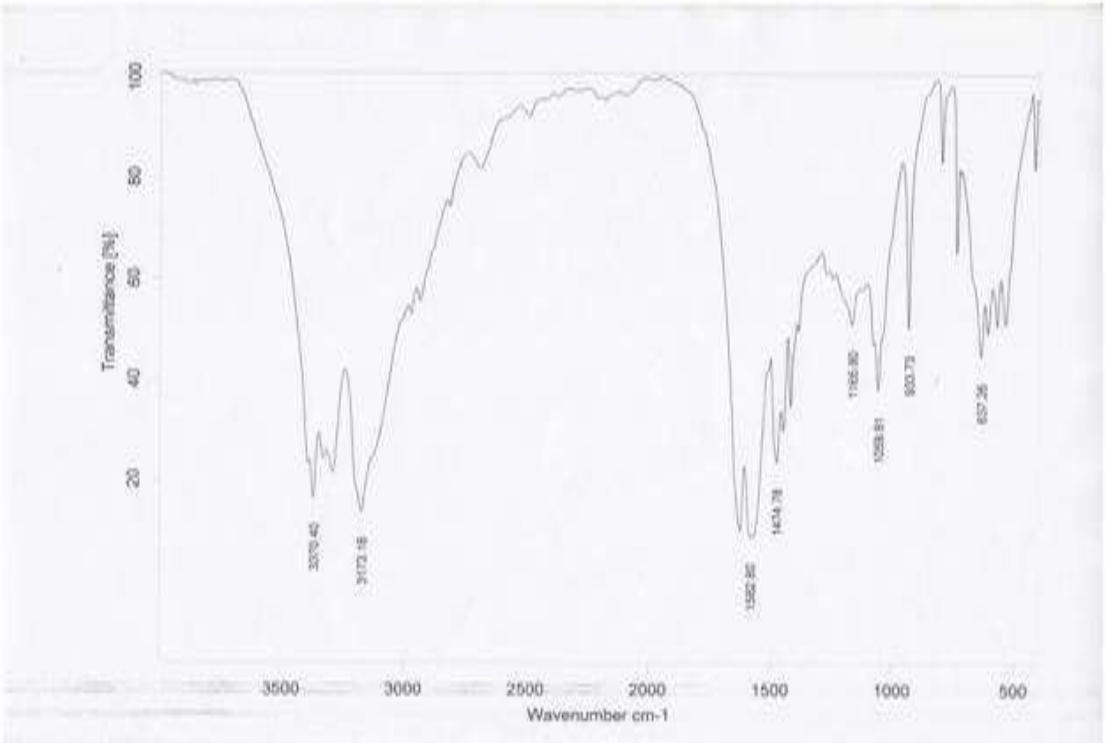

Fig- 10: FTIR of Fudosteine + Povidone k-30

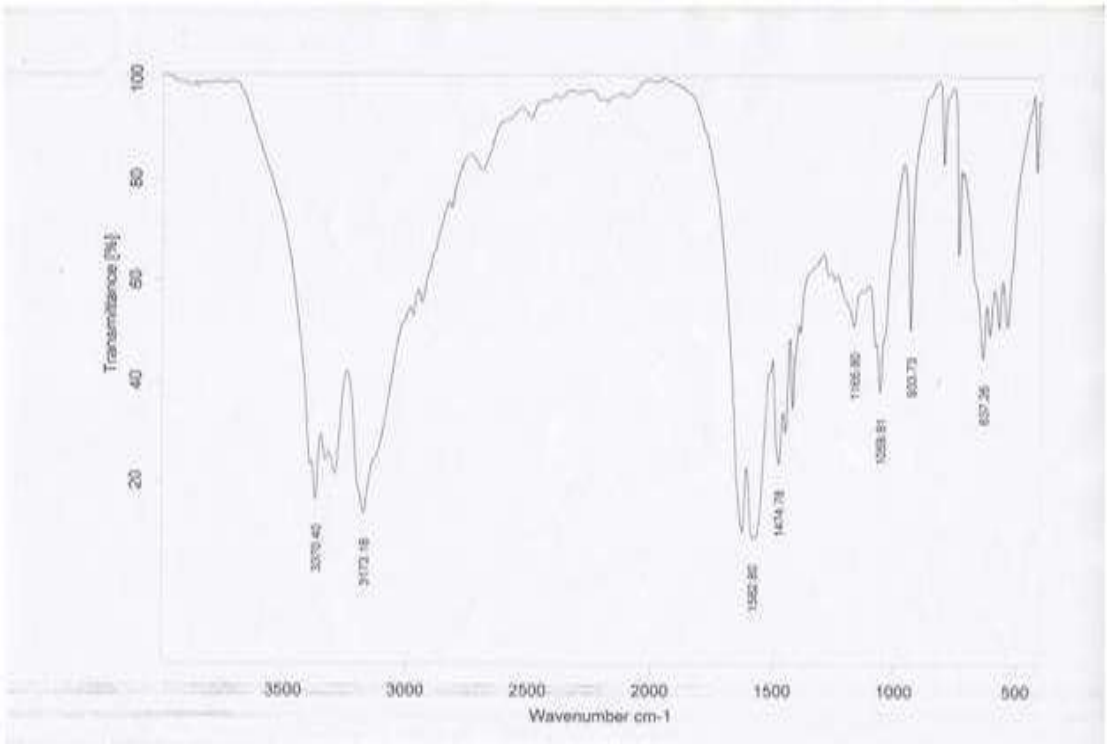

Fig- 11: FTIR of Fudosteine + Cross Carmellose Sodium

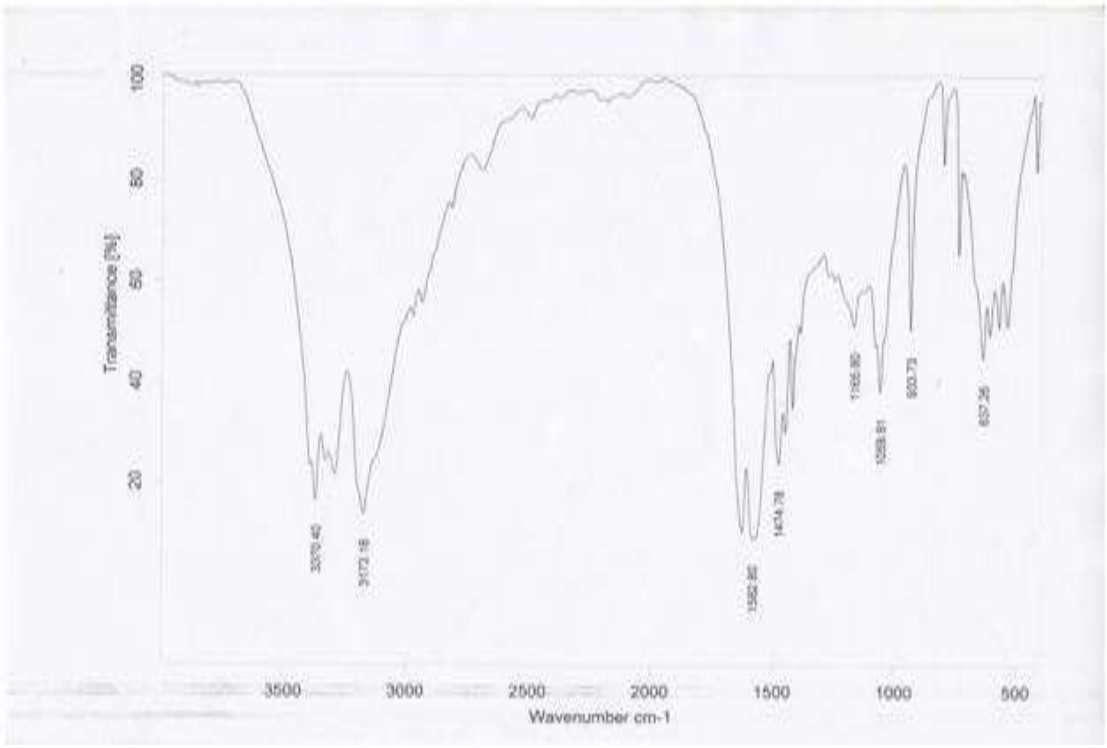

Fig- 12: FTIR of Optimised Formulation (F10)

Table.19-Data showing various physico-chemical parameters after stability study

Conditions	Parameter	Initial data	Data after one month
Long term storage conditions	Hardness (kp)	10± 0.15	10± 0.15
Long term storage conditions	Friability (%)	0.012±0.03	0.012±0.03
Long term storage conditions	Assay (%)	101.2	99.82
Intermediate	Hardness (kp)	10± 0.15	10± 0.15
Intermediate	Friability (%)	0.012±0.03	0.012±0.03
Intermediate	Assay (%)	101.2	99.37
Accelerated	Hardness (kg/cm2)	10± 0.15	10± 0.15
Accelerated	Friability (%)	0.012±0.03	0.012±0.03

Accelerated	Assay (%)	101.2	99.16

Table.20-Accelerated Stability Data for 1 Month

Condition	Initial	40°C / 75% RH - 1 Month			
		HDPE	**HDPE - 1g Silica**	**PVC in TLP**	**PVDC in TLP**
Description					
Assay (%)	98.30	98.85	99.53	98.93	99.15
Water content (%)	0.74	0.84	0.78	0.63	0.79
Related substance (%)					
Fudosteine sulfoxide	0.03	0.04	0.04	0.04	0.03
Cystine	0.04	0.04	0.04	0.04	0.04
Cysteine	0.00	0.00	0.00	0.00	0.00
N-Propanol Fudosteine	0.00	0.00	0.00	0.00	0.00
Bis Fudosteine	0.02	0.02	0.02	0.01	0.02
Fudosteine Disulfide	0.02	0.02	0.02	0.02	0.02
Fudosteine Ether	0.01	0.03	0.02	0.02	0.02
O-Acetyl Fudosteine	0.01	0.01	0.00	0.00	0.00
Unknown Impurity	0.02	0.02	0.01	0.00	0.00
Total Impurity	0.13	0.16	0.14	0.13	0.13

Table.21-Accelerated Stability data for 3 Months

Condition	**Initial**	**40°C / 75% RH - 3 Month**			
		HDPE	**HDPE - 1g Silica**	**PVC in TLP**	**PVDC in TLP**
Description					
Assay (%)	98.30	98.63	98.55	99.33	98.73
Water content (%)	0.74	1.42	1.39	1.34	1.45
Related substance (%)					
Fudosteine sulfoxide	0.03	0.02	0.02	0.03	0.04
Cystine	0.04	0.03	0.03	0.03	0.03
Cysteine	0.00	0.00	0.00	0.00	0.00
N-Propanol Fudosteine	0.00	0.03	0.02	0.02	0.03
Bis Fudosteine	0.02	0.00	0.00	0.00	0.00
Fudosteine Disulfide	0.02	0.02	0.01	0.02	0.02
Fudosteine Ether	0.01	0.03	0.03	0.03	0.02
O-Acetyl Fudosteine	0.01	0.00	0.00	0.00	0.00
Unknown Impurity	0.02	0.00	0.00	0.00	0.00

Total Impurity	0.13	0.13	0.12	0.14	0.15

CONCLUSION

The selected method yielded uniform and reproducible film coated tablets of Fudosteine with the given excipients. The hardness, friability, weight variation, drug content, and *in vitro* release were uniform and reproducible. The release was inversely proportional to the binder concentration irrespective of the polymer used. The release profile of fudosteine tablets containing 4.5mg binder, binder quantity 25% and kneading time is 2.5 min was better among all the trials. The mechanism of drug release was found to be Erosion of tablet. The dissolution profile of the formulation F10 was found to have equivalent percentage drug release with that of the innovator product. Selected Fudosteine tablets were found to be stable with respect to drug content, drug release, friability, weight variation, hardness and thickness. FTIR studies revealed no chemical interaction and indicating stability of drug in tablets. Hence, Fudosteine tablets containing mannitol (diluent), Povidone K-30 (binder), croscaramellose sodium (disintegrant), Colloidal Silicon Dioxide (glidant), Magnesium Stearate (Lubricant) and Opadry – AMB (coating Material) showed promising results and there exist a scope for *in vivo* evaluation using suitable animal models. The formulation F10 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good tablets.

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