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FORMULATION AND EVALUATION OF FAST MOUTH DISSOLVING TABLETS OF FLUPIRITIN BY USING CASSAVA STARCH AS BINDING AGENT

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ABSTRACT

Flupiritin is an amino pyridine that functions as a centrally acting analgesic and anti-inflammatory. Flupiritin mainly using in Polycare therapy. It first became available in Europe in 1984. Flupiritin is sold by Intas Pharma under the brand name Pruf in India. Like Nefopam it is unique among analgesics in that it is a non-opioid, non-steroidal centrally acting analgesic. Flupiritin is formulated using direct compression technique. In 2010 the chemically related drug Retigabine was approved by the FDA as an anticonvulsant for the treatment of refractory partial-onset seizures in treatment-experienced patients. Flupiritin is used as an analgesic for acute and chronic pain, in moderate-to-severe cases. Its muscle relaxant properties make it popular for back pain and other orthopedic uses, but it is also used for migraines, in oncology, post-operative care, and gynecology. Flupiritin has been noted for its neuroprotective properties. It is used in the treatment of long chronic disorders.

KEYWORDS: Poly care therapy, analgesic, anti-inflammatory, neuroprotective, Retigabine and Nefopam.

INTRODUCTION

Tablets are solid unit dosage form of medicaments with or without suitable diluents and prepared either by molding or compression. They are solid, flat or biconvex disc in shape. ‘Fast dissolve’, ‘Quick dissolve’, ‘Rapid melt’, ‘Quick disintegrating’, ‘Mouth dissolving’, ‘Orally disintegrating’, ‘Oro-dispersible’, ‘Melt in mouth’ etc are the term that represent the same drug delivery system. Recently fast dissolving tablet technology has been approved by

the United State Pharmacopoeia (USP), Centre for Drug Evaluation and Research (CDER). USFDA define fast dissolving tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usual within a matter of second, when placed upon the tongue". Recently the European pharmacopoeia also adopted the term oro-dispersible tablet as tablet that is to be placed in mouth where it disperses rapidly before swallowing. This dosage forms dissolve or disintegrates in the patients mouth within 15 sec to 3 min without the need of water or chewing. Despite various terminologies used , Fast dissolving tablet are here to offer unique form of drug delivery with many advantages over the conventional oral solid dosage form.

Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

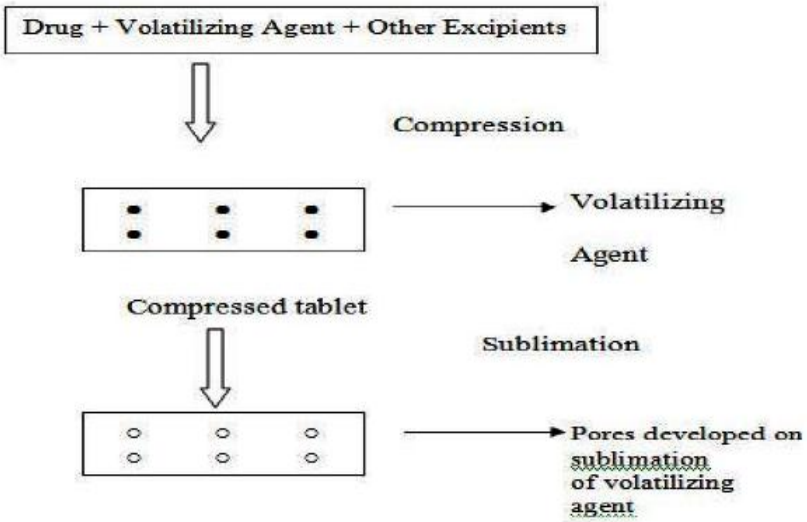
(b) Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Sublimation/Effervescence Technique

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Mouth dissolving tablets

with highly porous structure and good mechanical strength have been developed by this method.



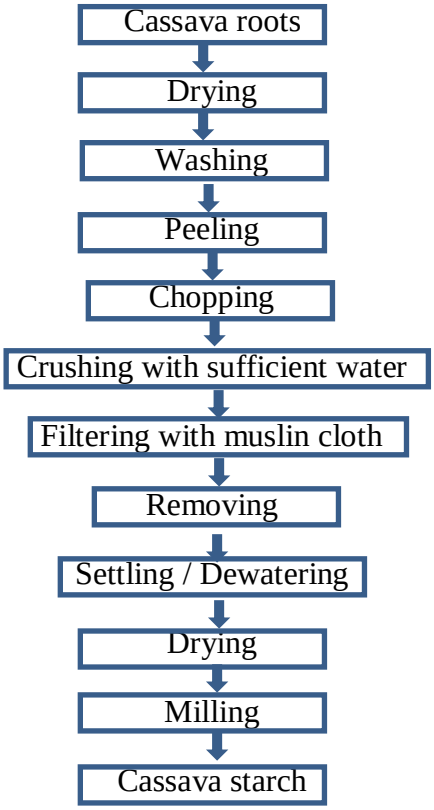
Schematic Diagram of Sublimation Technique for Preparation of FDT.

MATERIALS AND METHODS

1. Collection of Cassava Plant Material

- Fresh tubers of cassava are collected in our college scientific garden.
- We took authentication to our plant from Osmania University.

2. Isolation and Purification of Cassava Starch



MATERIALS

Flupiritin,

Crosscaramellosesodium,

SodiumStarchGlycolate,

Sodiumaurylsulphate,

SodiumSachaarin,

Magnesiumstearate,

Methanol,

Cassava starch.

Objective of the Work

To formulate fast mouth dissolving tablets by using direct compression method by using natural binding agent and synthetic polymers different ratios and different concentrations. To perform compatibility studies by FTIR and DSC studies and other characterization studies like disintegration time and drug content uniformity of the prepared formulations. To evaluate *in-vitro* dissolution and other parameters of the prepared tablets.

STANDARDIZATION OF DRUG

Identification of pure drug: Identification of Flupiritin was carried out by UV Spectrophotometry.

Determination of Melting Point: Melting point of flupiritin was determined by capillary method. Fine powder of flupiritin was filled in glass capillary tube (previously sealed on one end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt by using the thermometer which was already immersed into the liquid paraffin in the apparatus.

Solubility study: This study includes selection of suitable solvent to dissolve the pure drug as well as excipients used for the design of inclusion complex and fast dissolving tablets.

U.V-Visible Spectrophotometry

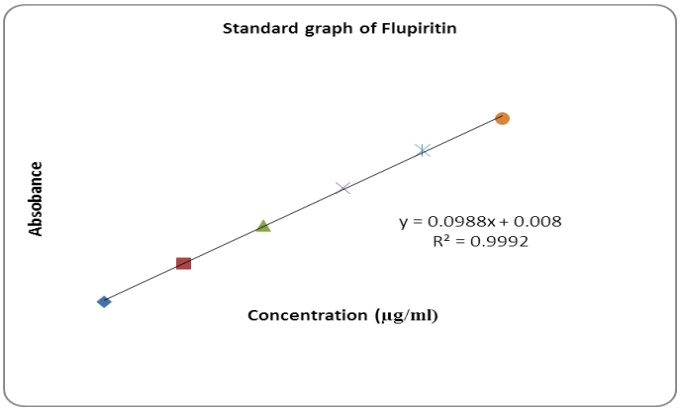
Analytical method development

Determination of analytical wavelength

The Standard Stock Solution was prepared as per the method described in Methodology and scanned by UV Spectrophotometer as per Methodology.The λ_{max} was found to be at 210.0 nm against distilled water used as blank.

Preparation of Standard graph of Flupiritin in pH 6.8 buffer Solution

S.no	Concentration (ug/ml)	Absorbance
1	0	0
2	2	0.205
3	4	0.408
4	6	0.608
5	8	0.811
6	10	0.980



EXPERIMENTAL WORKS

Preparation of Fast Dissolving Tablets

Direct compression: This is most popular technique because of its easy implementation and cost-effectiveness. The basic principle involves addition of disintegrates and/or water soluble excipients and/or effervescent agents. Superdisintegrants in optimum concentration are mostly used so as to achieve rapid disintegration along with the good mouth feel.

Ex. Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt**)**

Formulations of fast mouth Dissolving tablets of Flupiritin

Ingredient (mg)	formulation Composition(mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Flupiritin	100	100	100	100	100	100	100	100	100	100	100	100
Sodium starch glycolate	20	15	10	5	-	-	-	-	-	-	-	-
Cross caramellose sodium	-	-	-	-	5	10	15	20	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	5	10	15	20
Cassava starch	25	25	25	25	25	25	25	25	25	25	25	25
Lactose	100	105	110	115	115	110	105	100	115	110	105	100
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total	250	250	250	250	250	250	250	250	250	250	250	250

EVALUATION OF FAST MOUTH DISSOLVINGING TABLETS

DRUG CONTENT(%)

For the determination of drug content total 10 FDTs were weighed and powdered, powder equivalent to 100 mg of Flupiritin was weighed and dissolved in 6.8 buffer solution and filtered the solution through the whattman filter paper. The filtrate was collected and diluted with sufficient amount with buffer solution till the concentration of the drug lies within the standard plot range. The diluted solution was analysed for the flupiritin content by UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 210.4 nm using distilled as a blank.

In-vitro Dissolution Studies

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) [Electrolab (TDT-06T) Tablet Dissolution Tester] at 100 rpm. Distilled water 900 ml was used as dissolution medium, and the temperature of which maintained at 37 ± 0.5ºC. Aliquots

of dissolution medium (10ml) was withdrawn at specific time intervals (2 minutes) and was filtered and the first 5 ml of the filtrate was rejected. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 210nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

RESULTS AND DISSCUSSION

PRE-COMPRESSION PARAMETERS

S.no	Batch	Angle of repose	Hausner`s ratio	Compressability (%)
1	F1	26.15 ± 0.12	1.13 ± 0.04	12.22 ± 0.11
2	F2	27.10 ± 0.16	1.14 ± 0.08	12.82 ± 0.20
3	F3	21.70 ± 0.15	1.17 ± 0.06	14.69 ± 0.25
4	F4	27.25 ± 0.14	1.15 ± 0.08	13.38 ± 0.14
5	F5	24.39 ± 0.16	1.19 ± 0.06	16.60 ± 0.16
6	F6	22.17 ± 0.21	1.16 ± 0.09	14.52 ± 0.18
7	F7	20.25 ± 0.24	1.17 ± 0.10	15.41 ± 0.14
8	F8	26.49 ± 0.14	1.15 ± 0.11	13.61 ± 0.16
9	F9	27.75 ± 0.16	1.17 ± 0.08	14.97 ± 0.15
10	F10	18.45 ± 0.18	1.17 ± 0.04	14.75 ± 0.19
11	F11	23.05 ± 0.11	1.14 ± 0.10	12.76 ± 0.15
12	F12	19.17 ± 0.14	1.13 ± 0.10	12o ± 0.11

***Angle of repose, n=3**

Post- Compressional parameters of Fast Dissolving tablets of Flupiritin:

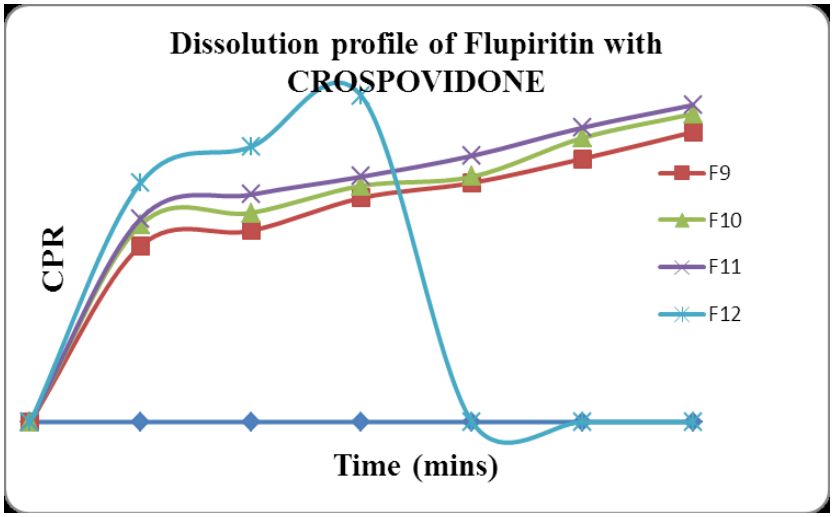
Formulation	Hardness Kg/cm^2	Friability (%)	Drug content	Invitro Disintegration time(sec)	Wetting time(sec)	Weight variation (mg)
F1	3.2 ± 0.13	0.66 ± 0.8	99.86 ± 0.4	21.18 ± 1.2	32.14 ± 1.6	201.58 ± 1.7
F2	3.2 ± 0.12	0.64 ± 0.4	99.49 ± 0.9	42.39 ± 0.5	74.04 ± 1.1	200.45 ± 0.8
F3	3.3 ± 0.13	0.57 ± 0.5	99.51 ± 0.7	53.20 ± 2.2	88.11 ± 1.8	199.68 ± 0.4
F4	3.3 ± 0.14	0.61 ± 0.2	99.22 ± 10	14.22 ± 0.8	51.16 ± 1.4	200.48 ± 1.5
F5	3.5 ± 0.11	0.65 ± 1.4	99.92 ± 0.8	13.21 ± 0.6	48.21 ± 1.2	201.64 ± 1.9
F6	3.2 ± 0.14	0.62 ± 0.9	99.52 ± 0.4	12.80 ± 0.9	41.23 ± 1.6	200.55 ± 2.1
F7	3.2 ± 0.14	0.59 ± 0.6	99.34 ± 1.1	12.50 ± 0.8	38.31 ± 1.2	201.48 ± 1.1
F8	3.1 ± 0.15	0.63 ± 0.4	99.64 ± 0.9	14.18 ± 0.9	22.11 ± 1.1	200.64 ± 1.1
F9	3.4 ± 0.14	0.61 ± 1.6	99.41 ± 0.6	10.30 ± 0.7	18.10 ± 1.8	202.51 ± 1.8
F10	3.2 ± 0.11	0.59 ± 0.6	99.28 ± 0.4	11.30 ± 0.7	14.10 ± 1.3	200.66 ± 1.2
F11	3.2 ± 0.14	0.59 ± 0.3	99.64 ± 0.9	9.32 ± 0.5	16.14 ± 1.6	201.45 ± 1.8
F12	3.1 ± 0.11	0.55 ± 1.1	99.44 ± 1.1	9.13 ± 0.6	12.18 ± 1.4	200.68 ± 0.9

IN VITRO RELEASE SUDIES

Optimized Formulation:

In-vitro drug release studies of fast dissolving tablets : CROSPOVIDONE.

S.no	Time (mins)	% cumulative drug release			
		F9	F10	F11	F12
1	0	0	0	0	0
2	2	54.1	60.6	62.4	73.4
3	4	58.7	64.2	69.79	84.48
4	6	68.8	72.5	75.3	99.98
5	8	73.4	75.3	81.7	-
6	10	80.8	87.2	90.34	-
7	12	89.8	94.59	97.3	-



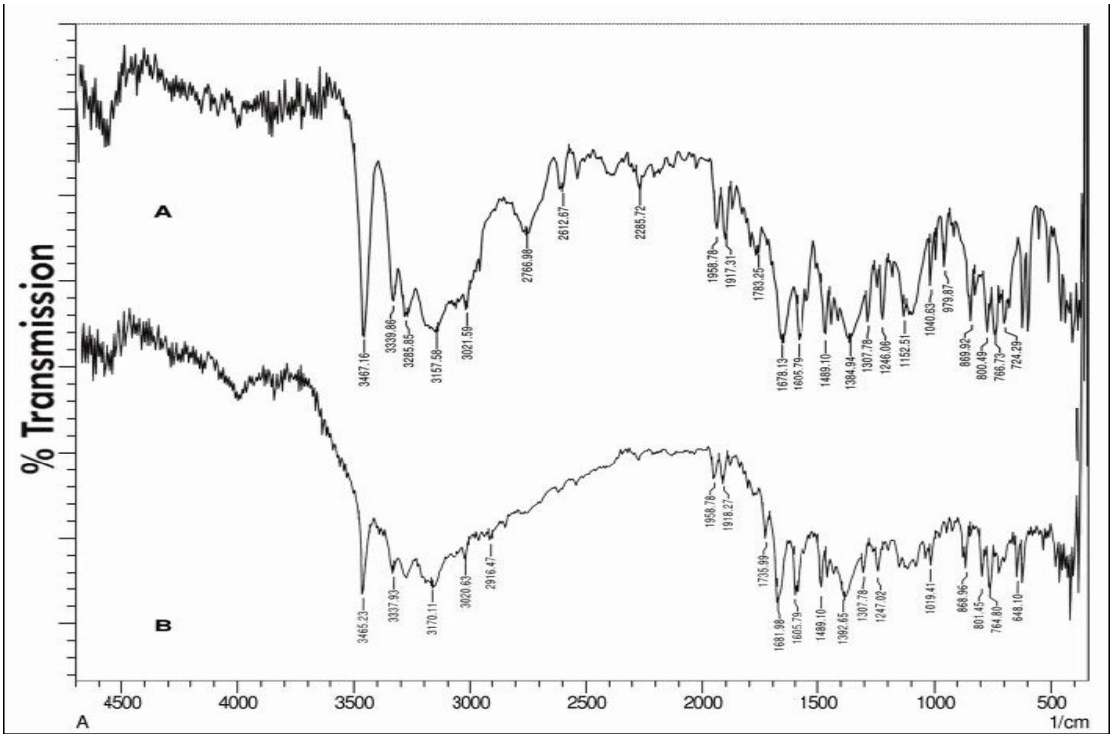
Dissolution Profile of flupiritin with (CROSPOVIDONE)

Stability studies

	Parameters	1st month	2nd month	3rd month
Optimized Formula	Thickness	22.55±0.02	22.60±0.04	23.89±0.19
	Hardness	3.1 ± 0.11	3.0± 0.11	2.9± 0.12
	Weight variation	200.68 ± 0.9	201.46 ± 0.8	206.24 ± 0.1
	Friability	0.55 ± 1.1	0.59 ± 2.1	0.60± 2.1
	Disintegration Time	9.13 ± 0.6	8.9 ± 0.2	8.7 ± 0.6

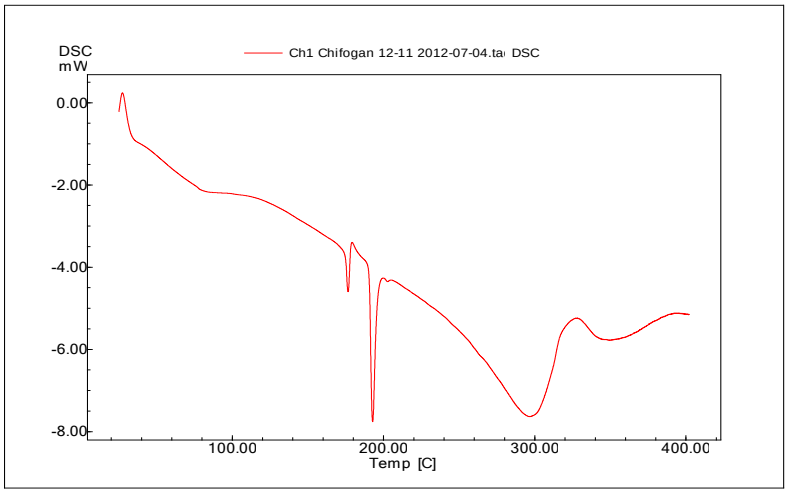
Table.38.In-Vitro Dissolution Stability Studies

Time in hours	Cumulative % drug release			
	Initial	1st month	2nd month	3rd month
0	0	0	0	0
1	73.4	72.1	72.8	71.12
2	84.48	83.81	82.81	81.31
4	99.98	98.18	97.98	96.19

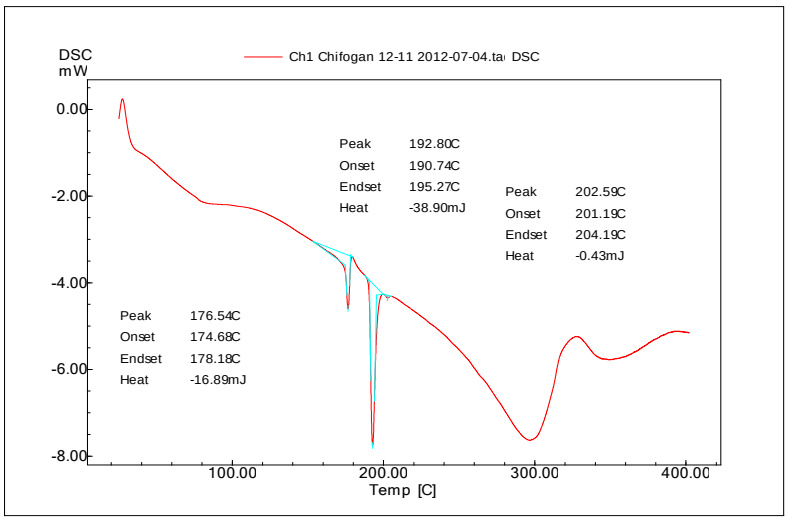


FTIR Studies of Optimised Formulation

FTIR spectra of Flupiritin and formulation F12 are shown in figure . Pure drug showed characteristic absorption bands at 3467 (NH Stretching of NH2), 3080 (Aromatic CH stretching), 1678 (C=O stretching of CO NH2), 1605, 1489 (C = C ring stretching) and the F12 showed characteristic absorption band at 3465 (NH Stretching of NH2), 3080 (Aromatic CH stretching), 1681 (C=O stretching of CO NH2), 1605, 1489 (C = C ring stretching). The FTIR spectra of pure flupiritin and F12 revealed that there was no appreciable change in the position of absorption band. This revealed that there was no chemical interaction between flupiritin and the excipients.



DSC Thermogram of Pure drug FLUPIRITIN



DSC Thermogram of drug +Crosspovidone

Nature of thermogram is totally changed and the sharp peaks are shifted to lower range around 17.61^0C and the peaks of pure drug have change to broad peaks with reduction of the height of each peak. These changes indicate that the dehydration of pure drug and change in the partical size giving more amorphous type of the product this may help in increasing the fast release of tablets.

CONCLUSION

From the present study it can be concluded that super disintegrant like *Crospovidone* showed batter disintegration property and better in vitro dissolution profile than the most widely used synthetic super disintegrant like Croscarmellose sodium and Sodium starch glycolate in the formulations of FDTs and it is cost effective because of use of cassava starch as natural binding agent.

Among all formulation F12 prepared with mucilage of *Crospovidone* showed 99.47% drug release in 6 min. FTIR spectra of flupiritin and formulation F12 are shown in figure . Pure drug showed characteristic absorption bands at 3467 (NH Stretching of NH2), 3080 (Aromatic CH stretching), 1678 (C=O stretching of CO NH2), 1605, 1489 (C = C ring stretching) and the F12 showed characteristic absorption band at 3465 (NH Stretching of NH2), 3080 (Aromatic CH stretching), 1681 (C=O stretching of CO NH2), 1605, 1489 (C = C ring stretching). The FTIR spectra of pure flupiritin and F12 revealed that there was no appreciable change in the position of absorption band. This revealed that there was no chemical interaction between flupiritin and the excipients.

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