Research Article **ISSN: 2349 – 4492**

Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com

INFLUENCE OF FAST DISINTEGRATING AGENTS IN *IN-VITRO* DISSOLUTION DRUG RELEASE OF ANTI MIGRANE DRUG

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ABSTRACT

The present study is done on fast dissolving tablets of the almotriptan. Almotriptan is used to treat to severe migraine. The major problem in oral drug formulation is less bioavailability which mainly results from poor aqueous solubility. The idea of formulating fast disintegrating tablets by super disintegrates offers a suitable practical approach for faster dissolving and dissolution characteristics. Among the various methods of preparations fast dissolving tablets were prepared by using super disintegrates like croscarmellose sodium, crospovidone, sodium starch glycolate by direct compression. The prepared almotriptan tablets were evaluated for free compression parameters like angle of repose, bulk density, tapped density, carr's index and post compression parameters like hardness, friability and weight variation, drug content uniformity, disintegration time and *In-vitro* dissolution studies. Among various fast dissolving tablets of Almotriptan, F9 formulation shows maximum drug release of 30min (100.3%).

KEYWORDS

Almotriptan, Croscarmellose sodium, Crospovidone and sodium starch glycolate, *In vitro* release and Kinetic treatment.

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INTRODUCTON

Among the available routes of administration Oral route is found to be widely accepted routes of drug delivery because of its patient compliance, administration, flexible design of dosage forms and least sterility constraints and. For many decades treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Till date these conservative drug delivery systems are extensively prescribed. Rapid and complete systemic drug absorption of active principles were achieved by

oral route of administration. Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation[1]. Systemic drug absorption from a drug product consists of a succession of rate process for solid oral, immediate release drug products. Disintegrants added in tablets to ensure their breakup in to smaller fragments readily in oral cavity resulting in solution or suspension without the requirement of water administration is known as fast-disintegrating dosage form[2].

Almotriptan is an antimigrane drug used in treatment of migrane head ache was used as a model drug to develop a fast disintegration release formulation. Almotriptan has a short biological half-life of 2-3 hrs and the main aim of present work is to formulate fast disintegrating tablets by direct compression technique containing Almotriptan, and the application of direct compression results in increasing the bioavailability, solubility by using different super disintegrates like crospovidone, croscarmellose sodium, sodium starch glycolate, which give more rapid onset of action compared to oral conventional dosage form to improve patient compliance.

MATERIAL AND METHODS

Materials

Almotriptan was obtained as a gift sample from Arizest Pvt Ltd, Bangalore. Crospovidone, croscarmellose sodium and sodium starch glycolate were obtained from Himedia laboratories, Mumbai. All the ingredients used were of analytical grade.

Methods

Preparation of tablets by direct compression

The steps in direct compression are

Step-I

All the materials were sifted according to the following indications.

Step-II: Preparation of Blend

Loaded sifted Part-2 material into a Polyethylene bag and mixed for 5 min. and to this added part-1 sifted material and mixed for 10 min. loaded the part-3 and part-4 materials into another polyethylene bag and mixed for 5 min and th is mixed material was transferred into a former polyethylene bag and mixed for 10 min.

Step-III Compression

Almotriptan blend was compressed using 12 stationary rotary punching machines until desired hardness was obtained. All compressed tablets were stored in air tight container at room temperature for the study.

EVALUATION PARAMETERS

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy[3]

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using Agilent Technologies; carry 630 FT-IR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr; samples were scanned in the IR range from 1475to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Pre-compression studies of almotriptanfast disintegrating tablets

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through stand ardsieve#20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expresse ding/mlandis given by.

b

D_b=M/ Vb

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipientsblend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2second intervals. The tapping was done until no change in volume was noted.

D_t=M/ Vt

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was

determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

Tan θ = h/r

Therefore $\theta = \text{Tan}^{-1} h/r$

Where,

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%)=[(D_t-D_b)X100]/ D_t

Where,

D_t is the tapped density

D_b is the bulk density

Hauser's ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

Hausners ratio = D_t/D_b

Where, Dt is the tapped density,

Db is the bulk density.

Post compression studies of almotriptan fast disintegrating tablets

Weight variation test

The weight variation testis implement edin order to conform uniform it yin the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of tablet hardness

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

Content uniformity

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 50 ml pH 1.2 buffer was added and then the solution was subjected to sonication for about 2 hrs. The solution was made up to the mark with pH 1.2buffers. The solution was filtered and suitable dilutions were prepared with pH 1.2 buffer. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 283 nm by using UV-Visible spectrophotometer.

***In vitro* dissolution**[4]

The release of Almotriptan from the fast disintegrating tablet was studied up to 30 min in 900 ml of 0.1 N HCL as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37^o ± 0.5^o C. An aliquot (1 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with the dissolution medium, and drug content was determined by UV-visible spectrophotometer at 283 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Data Analysis (Curve Fitting Analysis)[5]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the

Data obtained were plotted as:

1. Cumulative percentage drug released Vs time (Zero order plots)
2. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3. Log cumulative percentage drug remaining Vs time (First order plots)
4. Log percentage drug released Vs log time (Peppas plots)

RESULTS AND DISCUSSION

In order to achieve the development of anti-migraine dosage forms, Almotriptan was used as a model drug for the therapy of Migraine, which was formulated by direct compression method employing different concentrations of fast disintegrating agents for fast release of drug, talc as diluents and magnesium stearate as lubricant. Hence in the present work, an attempt has been made to formulate nine formulations (F1-F9) with variable concentrations of fast disintegrating agents (croscarmellose sodium, crospovidone, sodium starch glycolate) with different ratios such as (5mg, 7.5mg, and 10mg).On the basis of In-vitro release studies the best formulation (F9) was selected

To know the mechanism of drug release from these formulations, the data were handled with first-order release, Higuchi's, and Korsmeyer equation / Peppa's model et al's equations along with zero order (cumulative amount of drug released verses time).

Characterization of bulk drug and effect of various formulation excipients

FT-IR spectra of pure Almotriptan and its physical mixtures (1:1 ratio w/w) with disintegrating agents used in this study. The characteristic peak are present in entire spectrum indicates the stable structure of Almotriptanin solid admixture.

Physical properties of granules

The granules for the tablet preparation were prepared according to formula given in (Table No.1). The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, Hauser's factor and drug content (Table No.2). The results of angle of repose 28.005^0 to 29.942^0 indicating good flow properties of granules.

This was further supported by lower compressibility index values (Table No.2).Generally, compressibility index values from 14.10 to 14.92 result in fair flow properties. The Hauser's ratio of granules of all formulations was <1.2 indicating free flowing. Other parameter, such as bulk density, tapped density was found to be within acceptable limits (Table No.2). All these results indicate that the granules possessed satisfactory flow properties, compressibility and drug content. Finally variable concentrations of fast disintegrating agents did not affect the physical properties of the prepared granules.

Physical properties of tablets

The tablets of different formulations were subjected to various evaluations tests such as hardness, friability and uniformity of weight, drug content and in-vitro dissolution. Good uniformity in drug content was found among different batches of the tablet. All the tablets formulation showed acceptable pharmacopoeia limit specifications for weight variation drug content, hardness, and friability.

IN VITRO RELEASE STUDIES

The *in vitro* drug release characteristics were studied in 900ml of 0.1NHcl for 30min, using USP. XXIII Dissolution apparatus type II (paddle) method.

The results of dissolution studies indicate that F1, F2, F3 released 92%, 96%, and 97% of Almotriptan at the end of 30 min. Formulation F1, F2, F3 formulated with crospovidone by gradual increasing the ratio of crospovidone (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of wicking.

The results of dissolution studies indicate that F4, F5, F6 released 94%, 95%, and 97% of Almotriptan at the end of 30 min. Formulation F4, F5, F6 formulated with croscarmellose sodium by gradual increasing the ratio of croscarmellose sodium (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of minimum of gelling and wicking due to fibrous structure.

The results of dissolution studies indicate that F7, F8, F9 released 96%, 99%, and 100.3% of Almotriptan at the end of 30 min. Formulation F7, F8, F9 formulated with sodium starch glycolate by gradual increasing the ratio of sodium starch glycolate (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of rapid and extensive swelling with minimum gelling. It is noticed that all the 9 formulations shows maximum release at the end of 30 minutes by increasing the concentration of super disintegrating agents (crospovidone, croscarmellose sodium and sodium starch glycolate). By comparing all these 9 formulations by using *In-vitro* drug release. The *In-vitro* drug release reveals that

formulation F7, F8, F9 which is formulated with SSG shows better result in all the ratios by comparing with F1-F6.

In formulation F1-F3 formulated with crospovidone shows less *invitro* drug release (all 3 ratios of fast disintegrating agents). Because crospovidone is insoluble in water and also the average particle size greater than sodium starch glycolate.

In formulation F4-F6 formulated with CCS shows better *invitro* drug release (all 3 ratios of fast disintegrating agents when compared with F1-F3 (formulated with crospovidone). Because they have less particle size than crospovidone. Even though it is insoluble in water they rapidly swell 4-8 times to its original volume and contact with water.

In formulation F7-F9 formulated with sodium starch glycolate shows best invitro drug release (all 3 ratios of fast disintegrating agents). This is due to rapid and extensive swelling with minimum gelling of sodium starch glycolate. Average particle size of sodium starch glycolate (38nm-42nm) which is less than croscarmellose sodium and crospovidone. In contact with water SSG swells up to 300 times to its original volume which is less than croscarmellose sodium/crospovidone and gives translucent suspension in water.

Hence F9 formulation shows an best formulation with maximum drug release of 100.3% at the end of 30 minutes.

To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and korsmeyer equation / peppa's model et al's equation along with zero order release pattern. The release rate kinetic data for all the other equations can be seen (Table 29). The formulations F1-F9 showed higher Regression values for first order plots indicating that drug release followed first order kinetics. The in vitro release profiles of drug from all the formulations could be best expressed by Higuch's equation, as the plots showed high linearity Regression 0.7945 to 0.9259. To confirm the diffusion mechanism, the data were fit into korsmeyer, et al's equation, with slope (n) values ranging from 0.2132 to 0.3413. This indicates that the release of drug follows Fickian transport. It means in release of drug from the tablet dissolution and diffusion both mechanisms are used.

Part-1

Sift the active ingredient mixture through the following mesh.

Material	Mesh size
Almotriptan	Mesh #40
Optimized Almotriptan and Mannitol	Mesh #40

Part-2

Sift the direct compressible vehicles through the following mesh.

Material	Mesh size
MCC	Mesh #30

Part-3

Sift the disintegrates through the following mesh.

Material	Mesh size
Croscarmellose	Mesh #30
Crospovidone	Mesh #30
Sodium starch glycolate	Mesh #40

Part-4

Sift the lubricants and glidants through the following mesh.

Material	Mesh size
Mg. stearate	Mesh #60
Talc	Mesh #60

Table No.1: Composition of 150mg Almotriptan tablets

S.No	Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Almotriptan	5	5	5	5	5	5	5	5	5
2.	CP	5	7.5	10	---	---	---	---	---	---
3.	CCS	---	---		5	7.5	10	---	---	---
4.	SSG	---	---	---	---	---	---	5	7.5	10
5.	Magnesium Stearate	1	1	1	1	1	1	1	1	1
6.	Talc	70	70	70	70	70	70	70	70	70
7.	Mannitol	69	66.5	64	69	66.5	64	69	66.5	64

Table No.2: Results of flow properties of Almotriptanfast disintegrating tablets (F1 to F9)

S.No	Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hausner's ratio
1	F1	28.00	0.4150	0.4832	14.107	1.164
2	F2	29.095	0.4099	0.4808	14.753	1.173
3	F3	29.031	0.4049	0.4695	13.763	1.160
4	F4	28.030	0.4033	0.4740	14..922	1.176
5	F5	29.654	0.4001	0.4695	14.794	1.174
6	F6	29.374	0.3969	0.4652	14..682	1.172
7	F7	28.639	0.4210	0.4635	14.742	1.172
8	F8	29.942	0.4110±	0.4601	14.671	1.168
9	F9	29.322	0.4001	0.4580	14.528	1.170

Table No.3: Hardness, Friability, and Weight variation of Almotriptan fast disintegrating tablets (F1 to F9)

S.No	Formulation code	Weight Variation (mg)	Hardness (kg/cm^3)	Friability %	Drug content uniformity%
1	F1	150.94	5.8	0.120	96.58
2	F2	150.21	5.5	0.066	97.50
3	F3	150.45	5.4	0.133	98.24
4	F4	150.81	5.5	0.132	97.86
5	F5	150.04	5.2	0.166	99.17
6	F6	150.58	5.6	0.232	97.15
7	F7	150.60	5.8	0.110	98.70
8	F8	150.35	5.7	0.125	99.30
9	F9	150.58	5.1	0.130	98.40

Table No.4: *Invitro* release study of Almotriptan fast disintegrating tablets (F1 to F9)

S.No	Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	5	51	61	58	60	62	64	58.82	64	69
3	10	64	72.2	70.4	73	77	83	63.7	77	82
4	15	87	89	87.5	88	93	94	86.4	92	94
5	30	92	96	97	94	95	97	96	99	100.3

Table No.5: Kinetic values obtained from different plots of Formulation (F1– F9)

Formulation code	Zero order plot		First order plot		Higuchi plot	Korsemeyer peppa,s plot		Possible mechanism of drug release
	R^2	Zero order rate constant	R^2	First order rate constant		R^2	N	
F1	0.771	1.5714	0.8665	-0.0318	0.8512	0.8993	0.3413	Fickian transport
F2	0.8219	1.34	0.96	-0.0402	0.9011	0.9422	0.2652	Fickian transport
F3	0.8599	1.4943	0.9869	-0.0468	0.9259	0.9604	0.2972	Fickian transport
F4	0.8051	1.2714	0.9323	-0.0329	0.888	0.9418	0.2542	Fickian transport
F5	0.7051	1.2	0.8039	-0.0347	0.807	0.8828	0.2392	Fickian transport
F6	0.6833	1.1429	0.8844	-0.0412	0.7942	0.874	0.2297	Fickian transport
F7	0.8514	1.5237	0.9625	-0.0426	0.8902	0.8846	0.2977	Fickian transport
F8	0.8237	1.3143	0.9918	-0.0639	0.9024	0.9546	0.2502	Fickian transport
F9	0.8158	1.1557	0.8731	-0.0381	0.8999	0.9576	0.2132	Fickian transport

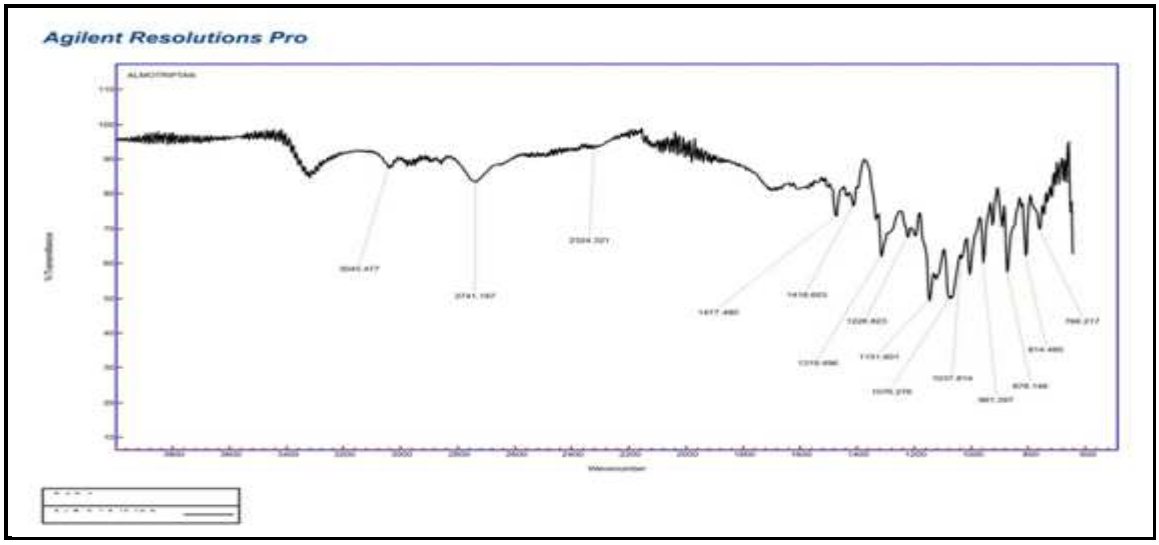

Figure No.1: FT-IR spectrum of pure Almotriptan

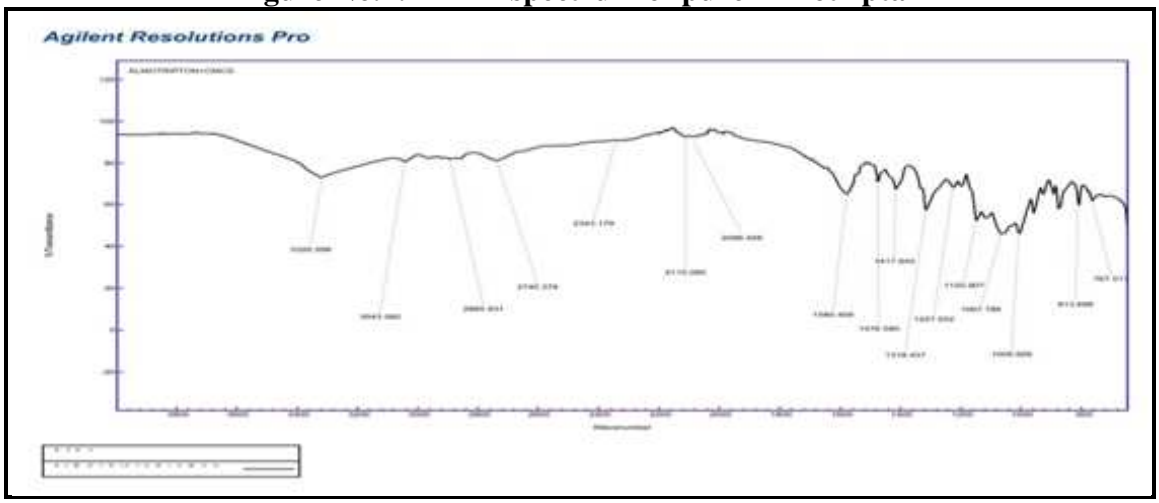

Figure No.2: FT-IR spectrum of pure Almotriptan and Croscarmellose sodium

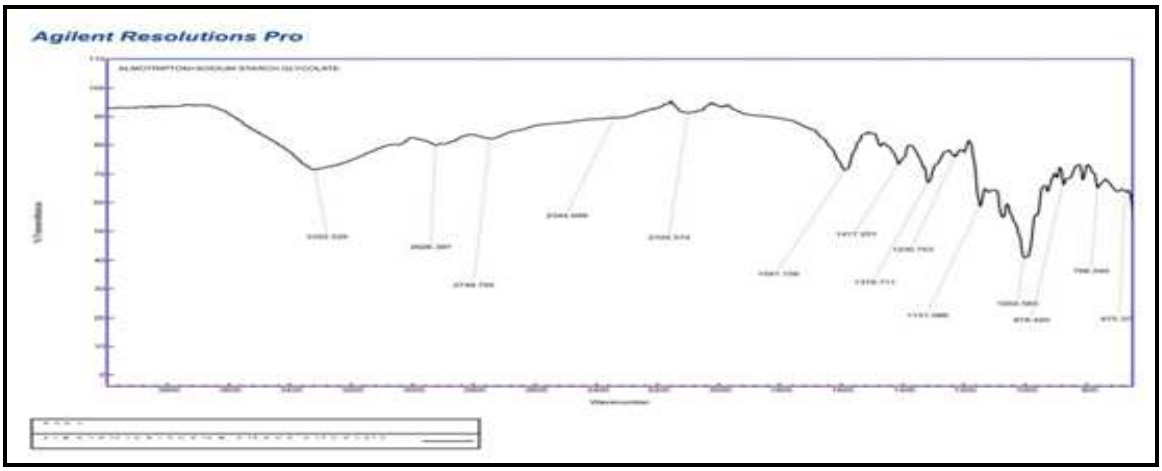

Figure No.3: FT-IR spectrum of pure Almotriptan and Sodium starch glycolate

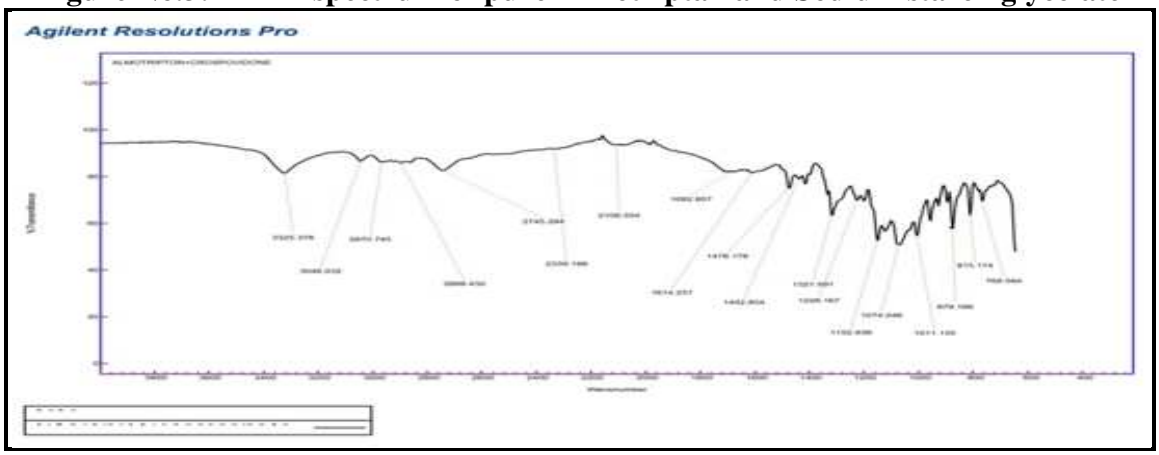

Figure No.4: FT-IR spectrum of pure Almotriptan and Crospovidone

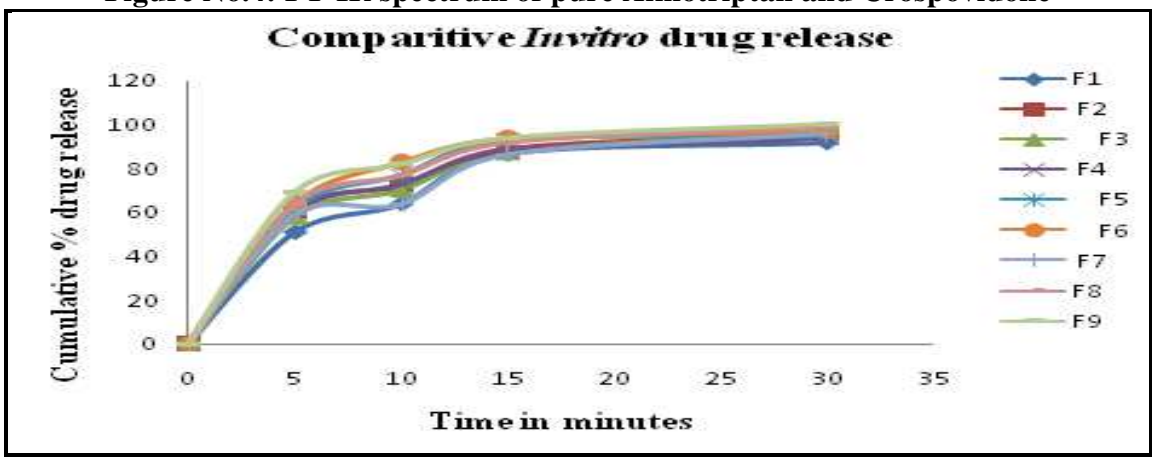

Figure No.5: *In-Vitro* Drug Release Profile of F1-F9

CONCLUSION

It is evident from the result of formulation F9 which is formulated with sodium starch glycolate (10mg) shows maximum and better release at the end of 30min, when comparatively with F1-F8. This may be due to their rapid swelling mechanism, less particle size, and also the cost of sodium starch glycolate is less when compared to crospovidone, croscarmellose sodium. Thus the work proves that sodium starch glycolate is better super disintegrating agent in the In-vitro drug release and it is cost effective. The formulation F1-F9 exhibited fickian drug release mechanism.

ACKWOLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, Andhra Pradesh, India for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Prathap M *et al*. Influence of fast disintegrating agents in *in-vitro* dissolution drug release of anti migrane drug, *Asian Journal of Research in Biological and Pharmaceutical Sciences,* 6(1), 2018, 1-9.