AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation Development and Evaluation of Immediate Release Tablet of Armodafinil by Drygranulation Method Using Superdisintegrants

Iswaryakarapareddy[1]*, Imrankhanpatan[2], Nagarjuna Reddy[3]. K, Subhojit samanta[1], C.M.Vaijayanthi[1], Mrs. Ramya[1]

1. Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore. India.

2. Department of Pharmaceutics, Sanjeevan College of Pharmacy, Dausa, Jaipur.

3. Department of Quality Assurance, Krupanidhi College of Pharmacy, Bangalore.

ABSTRACT

Armodafinil is very slightly soluble in water; hence the drug may be slowly or incompletely dissolved in the gastro intestinal tract. So the rate of dissolution and therefore its bioavailability is less. In the present study an attempt has been made to prepare immediate release tablets of Armodafinil by using different superdisintegrants (croscarmellose sodium, pregelatinized starch and Avicel pH 101 to increase the rate of drug release from dosage form or the dissolution rate and hence its bioavailability. The prepared granules and tablets were evaluated for their physiochemical properties and in-vitro dissolution study was conducted for the prepared tablets. The *in-vitro* dissolution studies shows the release in the following order of superdisintegrants is croscarmellose sodium> Pregelatinized starch> Avicel P^H 101. It was concluded that the immediate release tablets with proper hardness, disintegration time and with increase rate of dissolution can be made using croscarmellose sodium as superdisintegrants (F9). The formulation F9 was selected as an optimized formulation for stability study and the in-vitro dissolution study showed that was no difference in percent of drug released between 1st month and 3rd month sample.

Keywords: Armodafinil, Immediate release tablets, Superdisintegrants, Magnesiumsterate

*Corresponding Author Email: iswaryakarapareddy@gmail.com

Received 15 August 2012, Accepted 21 August 2012

Please cite this article in press as: Reddy IK *et al.*, Formulation Development and Evaluation of Immediate Release Tablet of Armodafinil by Drygranulation Method Using Superdisintegrants. American Journal of PharmTech Research 2012.

INTRODUCTION

Armodafinil is used to treat excessive sleepiness caused by certain sleep disorders and is associated with brain arousal on awakening. Armodafinil is effective in fatigue associated with sleep apnea, shift work sleep disorder, and narcolepsy. It may also be beneficially used in excessive sleepiness associated with jet lag, depression, schizophrenia, parkinson's disease, alzheimers disease, multiple sclerosis and anti depressant therapy.

Armodafinil is the active R-enantiomer of modafinil and the chemical name is 2-[(R)-(diphenylmethyl) sulfinyl] acetamide (Figure 1). Armodafinil is a white to off-white, crystalline powder that is very slightly soluble in water, sparingly soluble in acetone and soluble in methanol. The peak plasma concentrations of armodafinil are attained at approximately 2-4 hours. After oral administration of armodafinil exhibits an apparent monoexponential decline from the peak plasma concentration, apparent terminal t½ is approximately 15 hours.

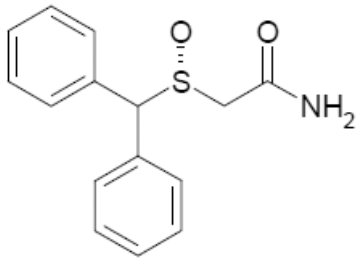


Figure 1 Structure of Armodafinil

Armodafinil is very slightly soluble in water; hence the drug may be slowly or incompletely dissolved in the gastro intestinal tract, so the rate of dissolution and therefore its bioavailability is less. Therefore the bioavailability of the drug could be improved by developing an immediate release drug delivery system for Armodafinil. Immediate release drug delivery system is also conventional type of drug delivery system and the immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic[1,2]. A superdisintegrants is an excipient which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. This is especially important for immediate release products, where the rapid release of drug substance is required. Dry granulation technique is used to granulate powders for compression into a tablet. In dry granulation technique, the most widely used method is slugging, where the powder is pre-compressed and the resulting tablet or slug are milled to yield the granules. The other method is to pre-compress the powder rolls using a machine such as

chilosonator[3,4].

In the present study an attempt has been made to prepare immediate release tablets of Armodafinil by using different superdisintegrants (croscarmellose sodium, pregelatinized starch and Avicel PH 101) to increase the rate of drug release from dosage form or the dissolution rate and hence its bioavailability.

MATERIALS AND METHODS:

Armodafinil is obtained from Natco pharma, Hyderabad. Lactose anhydrous, Povidone K-30, Croscarmellose sodium, Pregelatinized starch, Avicel P^H 101(Microcrystalline cellulose), Magnesiumsteate and Ethinylbehenate from SD fine chemicals Ltd, Mumbai.india and solvents from chemical solvent center, Mumbai. India, all other chemical are used were of analytical grade.

Preparation of Tablets

The tablets were prepared by dry granulation techniques. The Armodafinil drug, superdisintegrants, diluents, some amount of lubricants is mixed and form the slugs and compressed the tablet. Then milled the compressed tablets and passed through sieve #40 and #60 for 3-4 times for getting optimized particle size. At last the retained powder and remaining quantity of pregelatinized starch, croscarmellose sodium, and glycerylbehenate or magnesium sterate is mix and sift the ingredients. Finally collect the blend for compressing the tablet with14.0×8.00mm oval shaped punches in a Rimek mini tablet press. The composition of each formulated tablets are shown in Table 1

Table 1: Composition of Formulation of Immediate Release Tablet of an Armodafinil

sr.no	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Armodafinil	250	250	250	250	250	250	250	250	250
2	Lactose anhydrase	188.4	185.5	180.5	176	171	176	180.5	185.5	188.4
3	Pregelatinized starch	68.79	71.7	76.7	81.2	45	-	-	-	-
4	CMC	-	-	-	-	41.2	81.2	76.7	71.7	68.79
5	Avicel P^H 101	32.3	32.3	32.3	32.3	32.3	32.3	32.3	32.3	32.3
6	Povidone(k-30)	68.5	68.5	68.5	68.5	68.5	68.5	68.5	68.5	68.5
7	Glyceryl behenate	17	17	17	17	17	-	-	-	-
8	Magnesium stearate	-	-	-	-	-	17	17	17	17
		625	625	625	625	625	625	625	625	625

EVALUATION PARAMETERS:

Determination of Flow Properties

Bulk Density

Weighed quantity of the powder was taken in a graduated measuring cylinder and volume was measured and bulk density as calculated using formula,

Bulk density (D_b) = Weight of powder/Volume of powder

Tapped density

Weighed of powder was taken in a graduated cylinder and the volume was measured . The graduated cylinder was fixed in the tapped densitometer and tapped for 500, 750 and, 1250 times until the difference in the volume after consecutive tapping was less than 2%.

Tapped density =Weight of powder /Tapped volume

Carr's Compressibility Index

The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below

Carr's Compressibility Index (%) = [Tapped density - bulk density X 100] / Tapped density

Hausner's Ratio

Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner's Ratio = Tapped density/Bulk Density

Angle of repose

The frictional force in a loose powder can be measured by angle of repose, θ. It is an indicative of the flow properties of the powder. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Tan θ = Height of the powder in cm / Radius of the powder in cm

The angle of repose of granules was determined by the fixed funnel and free standing cone method. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules.

FTIR Spectroscopy Study

Armodafinil, Excipient and their combination were analyzed by FTIR spectroscopy studies were conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1} by KBr pellet method by applying a pressure of 7 tons for 5 min The pellet was placed in the light path and the spectrum was obtained. The peaks of pure drug are checked with drug- excipient combination graphs.

Physicochemical Evaluation of Tablet

Thickness

Ten tablets were randomly selected and the thickness of each was measured by digital vernier caliper. Mean and standard deviation were measured. It is expressed in mm

Hardness

The hardness of ten tablets was measured using Monsanto hardness tester. Mean and standard deviation were computed. It is expressed in kg/cm^2.

Friability

A pre-weighed sample (20 tablets) were placed in the friabilator, and operated for 100 revolutions, then again weighed the tablets and % friability was calculated using the formula

F = 1 – Weight of tablet before test / Weight of tablet after test × 100

Weight Variation

Twenty tablets were selected at random and weighed individually. The average weight of 20 tablets was calculated. Individual weights of the tablets were compared with the average weight.

% Weight variation = Individual weight – Average weight/ Average weight ×100

Disintegration test

The disintegration test was carried out using USP Disintegration test apparatus type –II. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. 0.1N HCl was used as the medium maintained at 37°C±0.5°C and the time taken for each tablet to disintegrate completely was recorded.

Drugs content

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar and pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml Methanol, filtered and diluted up to 50µg/ml, and analyze spectrophotometrically at 220nm. The concentration of drug was determined using standard calibration curve.

In-vitro dissolution study

The in vitro dissolution test was carried out using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for 1 hr in 900 ml of dissolution media, maintained at 37±0.5°C and agitated at 100 rpm. Periodically 5 ml samples were withdrawn and filtered through Whattman filter paper and samples were replaced by its equivalent volume of dissolution media. Collected samples were measured by UV- spectrophotometrically at 220 nm. Percentage drug release was calculated using an equation obtained from a standard curve. Analysis of data was done by using 'Disso V-3' software; India. The graphs of times vs. percentage release were plotted.

In-vitro drug release kinetic studies

To analyze the *In-vitro* release data various kinetic models were used to describe the release

kinetics. The zero order rate Equation no: 1 describes the systems where the drug release rate is independent of its concentration. The first order Equation no: (2) describe the release from the system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion Equation no: (3). The Hixson-Crowell root law Equation no: (4) describes the release from the systems where there is a change in surface area and diameter of particles. The Koresmeyer-peppas Equation no: (5) describes the mode of release of drug from swellable matrices.

$C = K_0t$ ---------- (1)

Where, K_0 is zero order rate constant expressed in units of concentration/time and t is the time.

$Log\ C = Log\ C_0 - Kt/2.303$ ---------- (2)

Where, C_0 is the initial concentration of drug and K is first order rate constant.= $Kt^{1/2}$-Q---------- (3)

Where, K is the constant reflecting the design variables of the system.

$Q_0^{1/3} - Q_t^{1/3} = K_{HCl}$ ---------- (4)

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug and K_{HC} is the rate constant for Hixson-Crowell rate equation.

$M_t/M = Kt^n$ ---------- (5)

Where, M_t/M is fraction of drug release at time t, K is constant incorporating the structural and geometrical characteristics of the drug/ polymer system, n is diffusion exponent related to the mechanism of the release

Stability studies:

Stability studies were carried out for optimized formulation. In order to determine the change in evaluation parameters and in vitro release profile on storage, stability study of optimized batch was carried out at accelerated storage condition at temperature 40° ± 2° C and 75% ± 5% RH in a humidity chamber for 90 days. Sample were withdrawn after 90 days interval and evaluated for change in in-vitro drug release pattern, physical appearance and drug content.

RESULT AND DISSCUSION

Immediate release drug delivery system is also conventional type of drug delivery system with several advantages such as release the drug immediately, more flexibility for adjusting the dose, no dose dumping problem, used in initial stage of disease, the drug is released at particular site from the system and shows its action. In present study, attempt was made to prepare such a tablet for reducing the sleep-wake disorders and the drug was selected for the study from the category

of wake promoting agent and CNS stimulant on the basis of immediate action.

Flow Properties of Blend

Nine formulations was prepared by using dry granulation method, with different excipients like Lactose anhydrous, Povidone k-30, Croscarmellose sodium, Pregelatinized starch, Avicel P^H 101(Microcrystalline cellulose), Magnesium steate and Ethinyl behenate. Blend of drug and excipients were evaluated for various parameters as follows.

Angle of repose

The angle of repose of six batches was found to be below 30, which indicated the blend having Excellent flow property. Angle of repose was found in the range of 25.56-28.14 (Ɵ) the results was given in Table 2.

Bulk density

The bulk density of various granules blends were measured by graduated cylinder. The bulk density was found in the range 0.51-0.650g/ml the results in Table 2

Tapped density

The tapped density of various granules blends was determined by using measuring cylinder. The tapped density was found in the range of 0.72-0.781 g/ml the results are given in Table 2

Table 2: Flow properties of formulations (F1-F9)

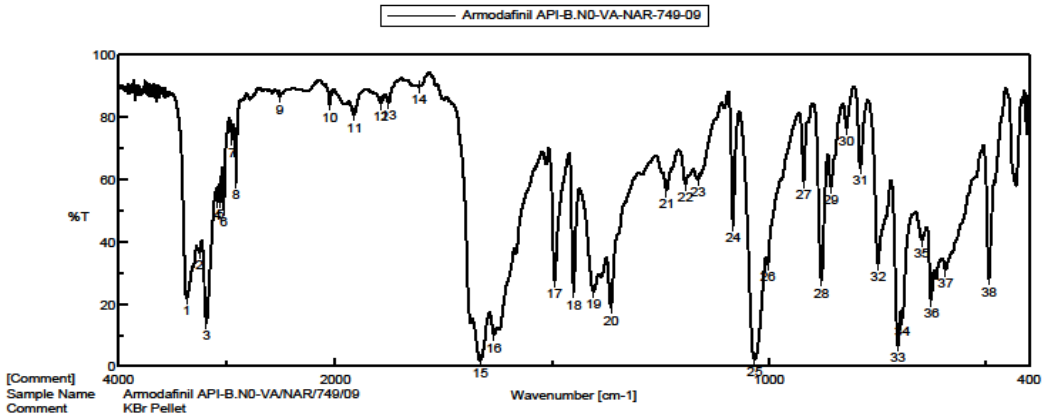
Formulation	Angle of repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio	Result
API	41	0.393	0.631	37.71	1.605	Very poor
F1	31.9	0.51	0.72	29.167	1.41	Poor
F2	30.8	0.588	0.75	21.6	1.28	Fair
F3	30	0.6	0.756	18.91	1.23	Fair
F4	28.14	0.61	0.75	18.67	1.23	Fair
F5	28.9	0.62	0.76	18.4	1.225	Fair
F6	26.51	0.63	0.776	18.14	1.22	Fair
F7	25.89	0.624	0.774	19.37	1.24	Fair
F8	25.64	0. 645	0.78	17.1	1.21	Good
F9	25.5	0.65	0.781	16.8	1.20	Good

Compressibility and Hausner's ratio

The Compressibility and Hausner's ratio of various granules blends was calculated by using bulk density and tapped density data. The compressibility index was found in the range 16.8 - 29.17%. The Hausner's ratio was found in the range 1.2-1.41. The results are given in Table 2. The Compressibility and Hausner's ratio of all batches were calculated. On the basis of batches F1-F9 will have to passable.

FTIR Compatibility Studies

IR spectra of Armodafinil and F9 formulation were determined using IR and are presented in Figure (1 and 2). Armodafinil spectra showed sharp characteristic peaks at 3252 cm^{-1}, 3029, 2915, 2954cm^{-1}, 1634 cm^{-1} (weak and overtone band), 1666cm^{-1},770.62 cm^{-1} and 564.70 cm^{-1}. IR spectra of Armodafinil and F9 formulation are exactly same and there are no shifts of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.



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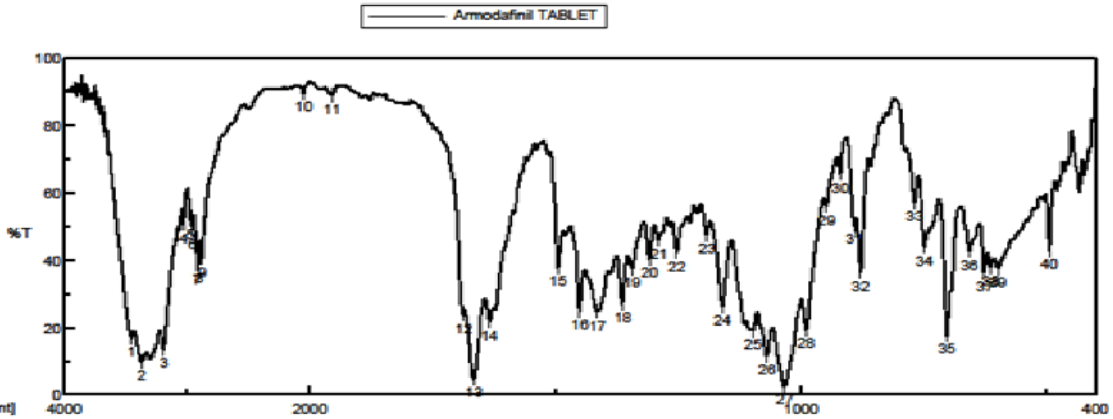
Data points 7677

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3373	21.8481	2	3252	36.6253	3	3189	13.9815	4	3087	52.6084
5	3060	52.8752	6	3029	50.4471	7	2954	72.7212	8	2915	59.1415
9	2513	86.5727	10	2053	84.0565	11	1956	80.7382	12	1896	84.342
13	1877	84.5819	14	1807	89.6819	15	1666	1.81062	16	1634	9.989
17	1495	27.4825	18	1450	23.8546	19	1405	24.1209	20	1364	18.8316
21	1236	56.4173	22	1193	58.3303	23	1164	59.941	24	1083	45.2721
25	1033	2.37772	26	1003	32.736 27	920	59.2398	28	879	27.5889	
29	857	57.4861	30	822	76.3894	31	790	63.8181	32	748	32.8915
33	703	6.79155	34	692	15.3106	35	648	40.4589	36	626	21.161
37	593	30.7957	38	493	28.0695						

Figure 1. IR spectra of an Armodafinil



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Data pitch 0.964233 cm-1
Data points 7677

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3454	17.0101	2	3374	9.75747	3	3191	13.6156	4	3029	50.6807
5	2977	51.8142	6	2955	48.982 7	2915		38.3886	8	2902	38.8029
9	2877	40.6601	10	2053	89.5336	11	1955	88.988	12	1687	23.917
13	1666	4.70271	14	1634	21.7888	15	1495	37.696	16	1450	24.7302
17	1415	24.7008	18	1383	26.9044	19	1344	37.4717	20	1308	40.369
21	1290	46.0412	22	1253	42.228 23	1192		47.5158	24	1160	26.2472
25	1097	19.1082	26	1069	11.6756	27	1033	2.57959	28	989	19.4084
29	948	56.0503	30	920	65.6255	31	891	50.3059	32	878	36.4257
33	768	57.0379	34	748	43.9555	35	703	17.6355	36	657	42.6718
37	626	38.331 38	613	37.9122	39	599	37.5225	40	494	42.7419	

Figure 2. IR spectrum of optimized formulation of Armodafinil tablets

Evaluation of Armodafinil Immediate Release Tablets

The prepared tablets were subjected or evaluated to various parameters is as follows.

Weight variation

All the formulation were varied from 624.00 -627.00 mg with minimum standard deviation values indicate that the uniform distribution of excipients and drug in the tablets. The results are given in Table 3

Thickness

The tablets from 5.25-5.52mm in thickness with minimum standard deviation values, it assumed that the tablets show uniformity in thickness. The results are given in Table 3

Hardness

The hardness of the tablets was found to be 13.5-15.5 kp. The hardness of tablet varied although compression force was constant. This may be due to the increased concentration of the excipient in formulations. The results are given in Table 3

Friability

The friability of the tablets was found to be 0.1-1.12%. The results are given in Table 3

Drug Content

Drug content in the tablets was the limit of 96.4-100.5%. The results are given in Table 3

Table 3: Evaluation of Immediate release tablets (F1-F9)

Formulation code	Evaluation parameter					
	Thickness (mm) (n=10)	Hardness (kp) (n=10)	Friability (%)	Average weight variation (n=20)	Drug content	Disintegration Time (mins)
F1	5.33±0.15	12.5±1.0	1.12	624.14±0.4	96.40	8.5
F2	5.36±0.06	12.5±1.1	0.1	625.21±0.5	97.87	7-8
F3	5.28±0.01	13.5±1.0	0.14	626.35±0.6	98.71	5-6
F4	5.38±0.10	15.5±0.5	0.1	626.40±0.2	100.5	5-6
F5	5.32±0.14	15.2±0.8	0.12	625.23±0.7	99.45	6-7
F6	5.30±0.10	15.0±1.0	0.25	627.21±0.9	98.98	7.5
F7	5.36±0.20	14.5±1.5	0.11	626.67±0.8	99.76	6.5
F8	5.25±0.16	14.8±1.0	0.1	624.24±0.1	100.33	6.8
F9	5.28±0.10	14.2±1.2	0.12	626.81±0.4	100.1	6.3

In-Vitro Drug Release

The in-vitro drug release profile of batch F1 to F9 is displayed in Table 4 and figure 3&4. Results indicate that batch F9 shows best results in terms of drug release. Croscarmellose proves to be better super disintegrant in comparison with pregelatinized starch and avicel PH 101(Microcrystalline cellulose).

Table 4: *In-vitro* Dissolution profile for F1-F5

Sl. no	Time (min)	Cumulative % Drug Release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	5	25.31	32.48	45.92	38.51	33.43	46.72	40.70	38.94	44.64
2.	10	46.40	47.24	55.34	42.94	59.64	54.82	53.82	55.62	57.87
3.	20	67.34	65.83	69.56	58.72	69.54	69.64	65.84	78.24	79.91
4.	30	78.54	79.26	82.64	78.89	85.48	78.42	89.46	90.40	92.61
5.	45	86.63	83.38	91.31	89.84	90.56	92.63	94.24	92.26	96.69
6.	60	91.82	93.68	94.23	94.44	94.82	95.45	96.50	97.65	99.59

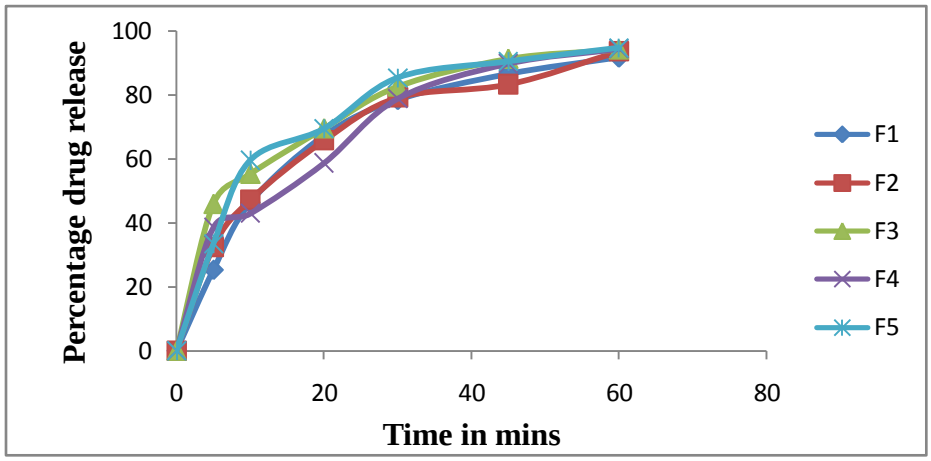

Figure 3. Comparative study on *In-vitro* Dissolution profile of batch F1-F5

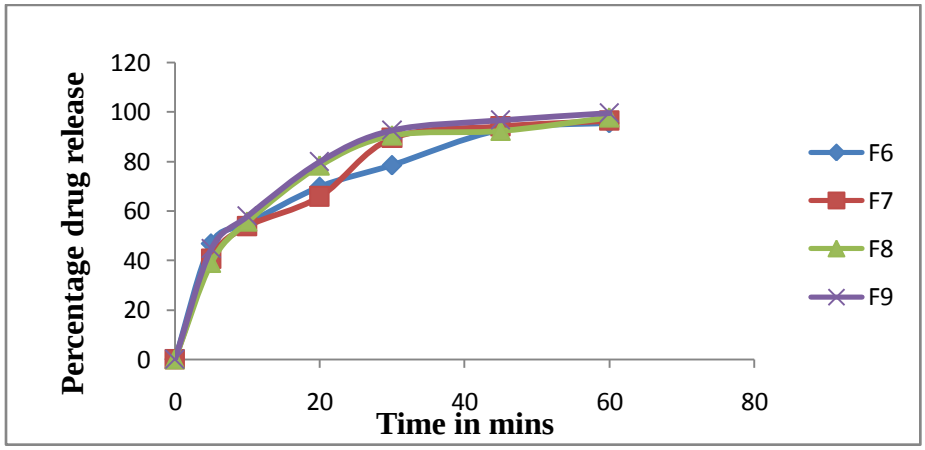

Figure 4. Comparative study on *In-vitro* Dissolution profile of batch F6-F9

KINETIC STUDIES DATA

Determination of order of release: F9

The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release Table 5and figure No. 5, 6, 7, 8. Based on the data analysis the drug release was found to follow First order release kinetics. This model indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process.

Table 5: Data analysis for F9 optimized formulation

Time (mins)	% Drug release	Square root of time 't'	Log 't'	Cumulative % drug release	Log cumulative % drug release	% Drug remaining	Log % drug remaining
5	44.14	2.236	0.69	44.14	1.64	55.45	1.743
10	54.87	3.162	1	99.01	1.995	44.72	1.65
20	79.91	4.472	1.301	178.92	2.25	19.68	1.294
30	92.61	5.477	1.477	271.53	2.43	6.99	0.844
45	96.69	6.708	1.653	368.22	2.57	2.9	0.462
60	99.59	7.745	1.778	467.81	2.67	0	0

Table 6: Data analysis results for F9 optimized formulation

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0 (mg/L/hr)	R^2	K_1 (h^{-1})	R^2	K_{Hg} (h^{-1})	R^2	N
F9	0.987	0.806	0.999	-0.0322	0.845	0.1607	0.908	1.448

Also, the drug release mechanism was best explained by first order, as the plots showed the highest linearity (r^2 = 0.999) shows in Table 6, as the drug release was best fitted in first order kinetics, it indicated that the rate of drug release takes place by diffusion and erosion mechanism and follow Anomalous diffusion (non-fickian, super case-II transfer)

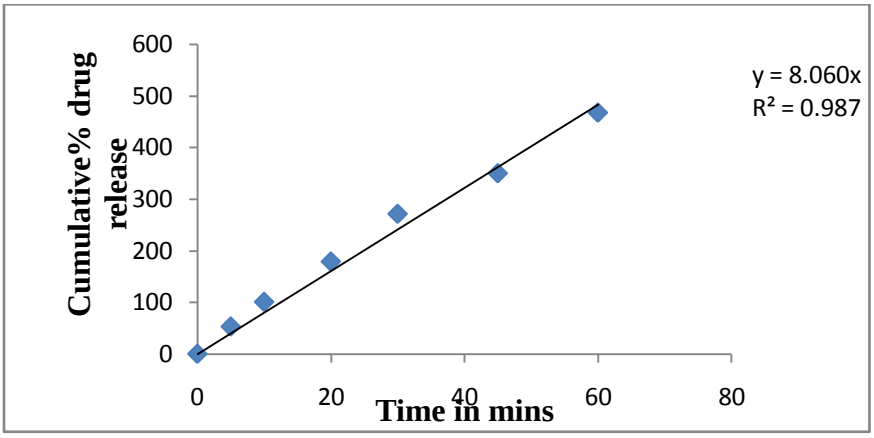

Figure 5. Zero order plot for F9 optimized formulation

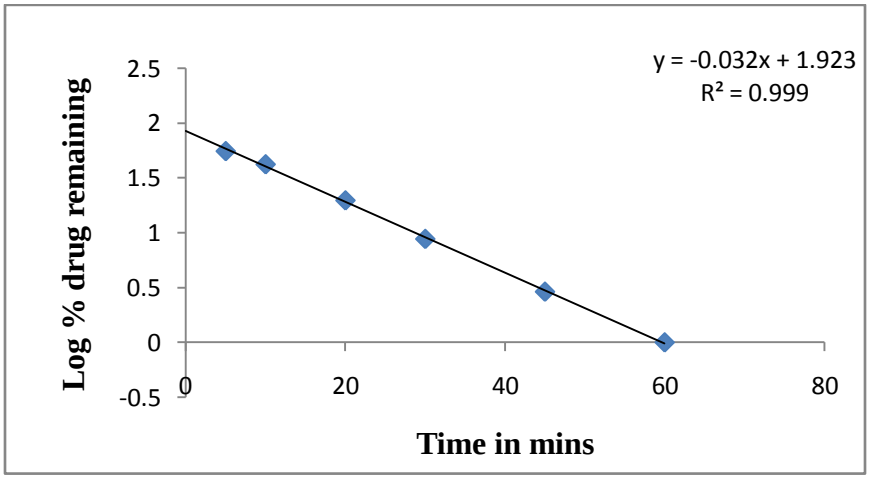

Figure 6. First order plot F9 optimized formulation

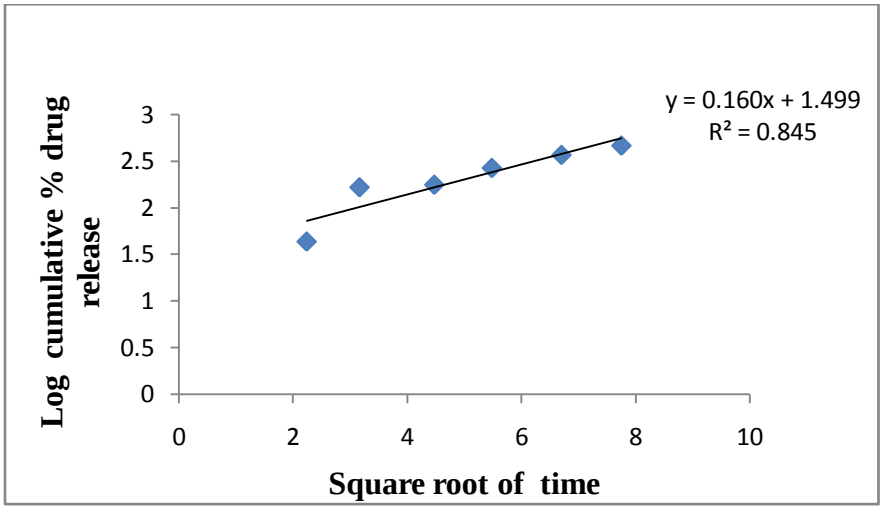

Figure 7. Higuchi release kinetics F9 optimized formulation

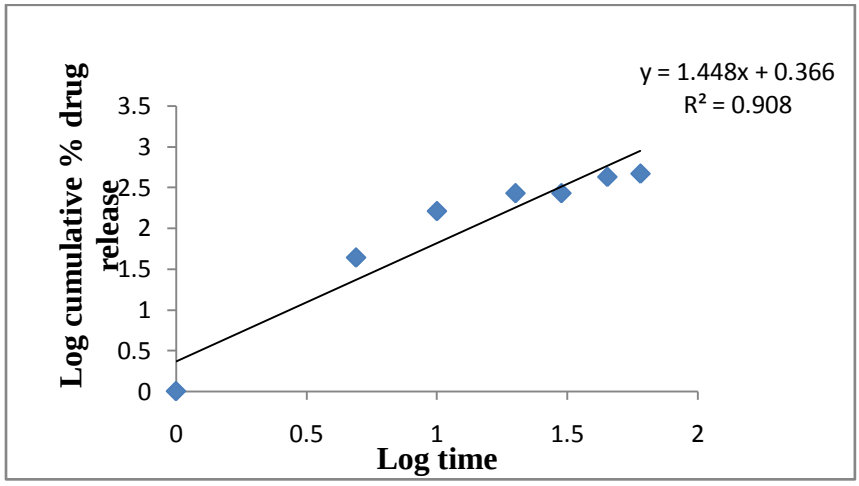

Figure 8.Korsemeyer and peppas release kinetics F9optimized formulation

Stability Studies

The optimized formulation F9 was charged on accelerated stability and monitored for physicochemical and drug release study at 30, 60 and 90 days. The stability study reveals no significant variation in physicochemical parameter and *in-vitro* release study up to 90 days. Stability studies for F9 formulation at 40 ± 2 ^{0}C & 75 ± 5% RH test Condition were shown in the Table 7

Table 7: Stability studies for the optimized formulation F9

Sr. No	Parameters	0 days	30 days	60 days	90days
1	IR studies	compiles	compiles	compiles	compiles
2	Weight Variation	626.81±0.4	626.51±0.35	625.92±0.41	625.83±0.42
3	Hardness (kp)	15.0	15.2	15.1	15.0
4	Friability (%)	0.12	0.13	0.11	0.1
5	Drug content (%)	100.1	99.98	99.82	99.8
6	*In-Vitro* drug release (%)	99.59	99.35	99.12	98.9

CONCLUSION:

It can be concluded that superdisintegrants concentration, granulation technique and lubricants play a key role in the development and optimization of the immediate release tablet of Armodafinil. The satisfactory drug release profile of Armodafinil immediate release F9 dosage form provides an increased therapeutic efficacy and follows first order release kinetics.

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