FORMULATION AND EVALUATION OF ARMODAFINIL SUSTAINED RELEASE TABLETS

[1]SHAKERA SULTANA, [3]H.PADMALATHA
Assistant professor, Principal
Pharmaceutics department
Gyana jyothi college of pharmacy, Uppal, Hyderabad.

ABSTRACT: ***Armodafinil is a wake promoting agent, used in the treatment of excessive daytime sleepiness arising from narcolepsy, obstructive sleep apnea and shift-work disorders. Therefore the present investigation concerned with the development of once-a-day armodafinil sustained release tablets to extend the duration of action up to 24hrs. About eight different formulations were developed by direct compression method using HPMC K4M CR and HPMC K100M CR, as polymers at different ratios and all the formulations were evaluated for their micromeritic properties and in-vitro dissolution studies. From the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e. 82% of drug release was observed in 16hrs & up to 98% in 24hrs. Kinetics to the in-vitro release of drug for the formulation, F-6 showed that it followed first order release (R^2=0.9686) and release mechanism followed was Hixson Crowell cube root law (R^2=0.9816). Further, in-vitro release pattern of drug from the optimized formulation, F-6 was found to be super imposable (i.e. the similarity factor f2 was found to be 81.90) with the marketed product NUVIGIL. The optimized formulation, F-6 was found to be stable during accelerated stability studies conducted at 40°C/75% RH for three months as per ICH guidelines.***

Keywords: Armodafinil; sustained release; once-a-day; HPMC K4M CR; HPMC K100M CR; dissolution.

1. INTRODUCTION

Conventional medication systems that require multi-dose therapy are not without problems. With a view of overcoming these problems, the current trend in pharmaceutical research is to design and develop new formulations, thereby enhancing the therapeutic efficacy of existing drugs. Moreover, the impetus for research into drug delivery can be attributed to the exorbitant cost and large development period involved in 'new drug development' with concomitant recognition of the therapeutic advantages of controlled / sustained drug delivery. Controlled release (CR)/Sustained release (SR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate.

The terms sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. In-vivo performance of these dosage forms depends greatly on their physical and structural properties, and consequently on their drug release mechanisms and its kinetics. However, a particular formulation may exhibit different drug release profiles under different physical states owing to the nature of excipients and the method of manufacturing. CR / SR formulations with drug release patterns independent of these variable factors, encountered most commonly when administered through per oral route are always desirable in order to ensure a reliable in-vivo performance.

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

2. MATERIALS AND METHODS

Table-1:.List of chemicals & their suppliers used in the study

S.no.	Ingredients	Suppliers	Specifications
1	Armodafinil	MSN Laboratories, Hyderabad	IH
2	Lactose anhydrous	SD Fine Chemicals Ltd, Mumbai	USP
3	Microcrystalline cellulose	SD Fine Chemicals Ltd, Mumbai	USP
4	MethocelK4M CR	Signet Chemicals, Mumbai	USP
5	MethocelK100M CR	Signet Chemicals, Mumbai	USP
6	Magnesium Stearate	SD Fine Chemicals Ltd, Mumbai	USP

Preformulation studies

Bulk density and Tapped density

An accurately weighed quantity of the powder was carefully poured into the graduated cylinder and the volume was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus for 500 taps and the final volume was measured.

Bulk density = Weight of the powder (W) / Initial volume (V_o)

Tapped density = Weight of the powder (W) / Final volume (V_F)

Flow Properties

The flow characteristics are measured by angle of repose. The angle of repose of powder was determined by the funnel method.

Compatibility Studies:

The compatibility studies were carried out by taking a mixture of drug and excipients at the ratio 1:1. Such samples are placed in previously labeled glass vials and properly closed using strips of aluminum foil. These samples are exposed to pre-determined storage conditions like 40°C/75% RH, 30°C/60 % RH, etc. In the present study, room conditions (25 °C/60 %RH) were selected.

Formulation of Armodafinil SR tablets

Table-2: Formulation development of various formulations of Armodafinil SR tablets

FORMULATION	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
MATERIAL	**mg**	**mg**	**mg**	**mg**	**mg**	**mg**	**mg**	**mg**
Armodafinil	17.96	17.96	17.96	17.96	17.96	**17.96**	17.96	17.96
Lactose anhydrous	40.04	40.04	40.04	40.04	40.04	**40.04**	40.04	40.04
Microcrystalline cellulose	40	40	40	40	40	**40**	40	40
Methocel K4M CR	100	50	60	70	80	**90**	95	0
Methocel K100M CR	0	50	40	30	20	**10**	5	100
Magnesium Stearate	2	2	2	2	2	**2**	2	2
Uncoated tablet wt(mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of Armodafinil Sustained release Tablets

Weight variation

20 tablets were selected randomly, weighed individually and average weight was determined.

Hardness

Ten tablets were selected randomly and the hardness was measured using a hardness tester.

Friability

Ten tablets were selected randomly and the friability was measured using roche friabilator.

Content Uniformity :

Twenty tablets were selected randomly from a batch, powdered and assayed.

***In vitro* drug release studies**

In-vitro drug dissolution studies were performed using USP-1(Basket) apparatus. The absorbance of the diluted samples was measured at 220nm.

3. RESULTS AND DISCUSSION

Preformulation study results

Table-3: Pre-formulation characteristics of Armodafinil

S.no.	Drug	Bulk density(g/ml)	Tapped density(g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
1.	Armodafinil	0.520	0.650	20.0	1.25	25

Table-4: Weight variation of various formulations of Armodafinil SR tablets

Formulation No.	Expected weight(mg)	Average weight(mg)
F-1	200 ± 15	195.577
F-2	200 ± 15	200.740
F-3	200 ± 15	201.500
F-4	200 ± 15	201.102
F-5	200 ± 15	200.906
F-6	200 ± 15	200.025
F-7	200 ± 15	200.150
F-8	200 ± 15	180.554

Discussion: The average weight of the formulation F-8 is found to be out of specifications.

Table-5: Thickness of various formulations of Armodafinil SR tablet

Formulation No.	Expected thickness range(mm)	Practical thickness(mm)
F-1	3.60 to 3.90	3.37
F-2	3.60 to 3.90	3.62
F-3	3.60 to 3.90	3.63
F-4	3.60 to 3.90	3.72
F-5	3.60 to 3.90	3.80
F-6	3.60 to 3.90	3.76
F-7	3.60 to 3.90	3.80
F-8	3.60 to 3.90	2.45

Discussion: The thickness of all the formulations is found to be within the limits (except for F-1).

Table-6: Hardness of various formulations of Armodafinil SR tablets

Formulation No.	Expected hardness(Kg/cm2)	Practical hardness(Kg/cm2)
F-1	NLT 5	7.53 ± 0.150
F-2	NLT 5	10.02
F-3	NLT 5	8.53
F-4	NLT 5	9.05
F-5	NLT 5	9.53
F-6	NLT 5	10.37
F-7	NLT 5	9.06
F-8	NLT 5	4.97

Discussion: The hardness of all the formulations is found to be within the limits.

Table -7: Friability of various formulations of Armodafinil SR tablets

Formulation No.	Expected friability (%)	Practical friability (%)
F-1	NMT 1.0% w/w	0.682
F-2	NMT 1.0% w/w	0.582
F-3	NMT 1.0% w/w	0.189
F-4	NMT 1.0% w/w	0.299
F-5	NMT 1.0% w/w	0.18
F-6	NMT 1.0% w/w	0.152
F-7	NMT 1.0% w/w	0.256
F-8	NMT 1.0% w/w	0.967

Discussion: The friability of all the formulations was < 1%, showing the acceptability.

Table-8: Content Uniformity of various formulations of Armodafinil SR tablets

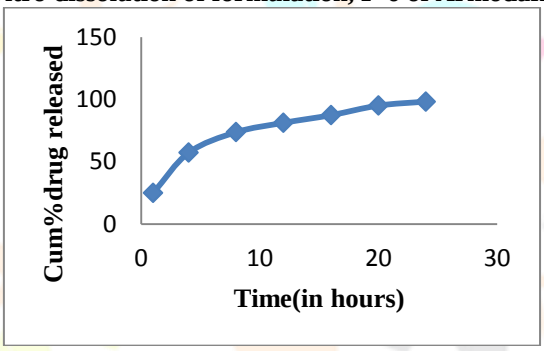
Formulation code	% Drug present
F-1	99.39±0.046
F-2	98.82±0.068
F-3	98.55±0.05
F-4	99.30±1.037
F-5	102.31±0.066
F-6	98.79±0.789
F-7	100.98±0.11
F-8	103.45±1.09

Discussion: All the formulations were as per the specification limits.

Table-9: In-vitro dissolution of optimised formulation, F-6 of Armodafinil SR tablets

Cum % drug dissolved*	Time(hours)						
	1	4	8	12	16	20	24
0.01M HCL	24.833±1.233	57.212±0.966	73.666±1.329	81.166±2.663	87.333±0.993	95.012±0.122	98.221±0.866

Figure-1: In-vitro dissolution of formulation, F-6 of Armodafinil SR tablets



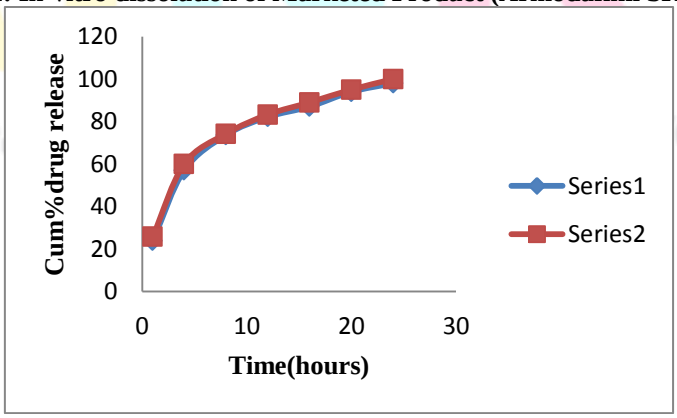
Discussion: The formulation F-6 was found to be the best formulation based on in-vitro drug release studies.

Comparison of dissolution profile of optimized formulation with the marketed product

Table-10: In vitro dissolution of marketed product

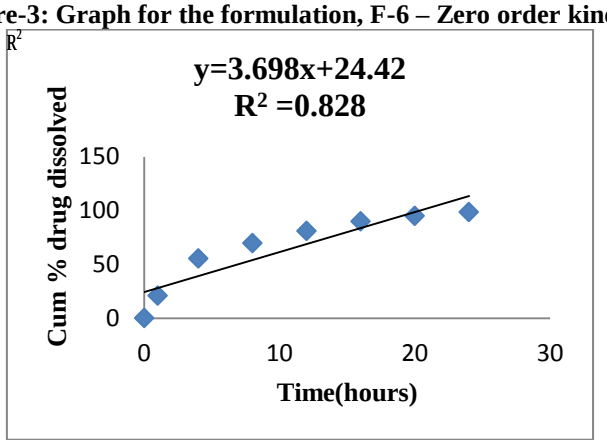
Cum % drug dissolved*	Time (hours)						
	1	4	8	12	16	20	24
0.01M HCL	25.83	60	74.23	83.26	89.26	95.02	100± 2.678

Figure-2: In-vitro dissolution of Marketed Product (Armodafinil SR tablets)



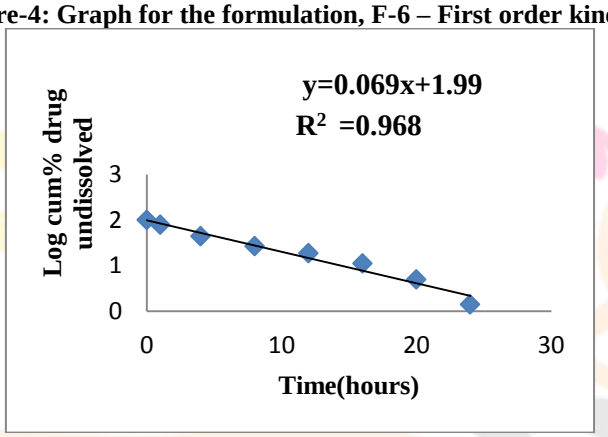
Dissolution-Application of kinetics:
Dissoluton – Zero order kinetics

Figure-3: Graph for the formulation, F-6 – Zero order kinetics



Dissolution- First order kinetics

Figure-4: Graph for the formulation, F-6 – First order kinetics



Similarity Factor and Dissimilarity Factor calculation

Table-11: *f1, f2* values for various formulations

Formulation No.	Dissimilarity factor(f1)	Similarity factor(f2)
F1	24.66	33.18
F2	45.86	22.43
F3	30.26	31.26
F4	14.23	46.82
F5	11.14	52.06
F6	1.97	81.9
F7	15	40.44
F8	77.97	11.26

Discussion: The values of F1& F2 were found to be 4.46 and 78.62 respectively for the comparison of dissolution profiles of formulation F6 and innovator product (Nuvigil). As such formulation-F6 developed is considered similar and equal to the innovator product.

Stability Study

Table-12: Stability data for Armodafinil SR tablets (F-6)

S.no.	Test	Specifications	Initial	Period in Months		
				1	2	3
1.	Description	White colored, capsule shaped uncoated tablets	Complies	Complies	Complies	Complies
2.	Hardness(kg/cm^2)	NLT 5	10.31 ± 0.408	9.53 ± 1.212	8.5 ± 0.969	9.89 ± 1.959
3.	Thickness(mm)	3.60 to 3.90	3.76 ± 0.102	3.67 ± 2.312	3.79 ± 0.225	3.82 ± 0.119
4.	Dissolution					
	1st	10-25%	22	23	19	19
	4thhr	30-50%	50	48	34	42

	16thhr	61%-75%	70	76	73	69
	24thhr	NLT 90%	99	98.9	98.8	98.5
5.	Assay	NLT 90.0% and NMT 110%	103.50%	103.30%	100.80%	99.99%

Discussion: Out of all the eight formulations, F-6 has shown the results as represented in table 12. From the results the formulation F-6 was found to be stable throughout the storage period.

4. CONCLUSION

Pre-formulation studies on the active powder blend were evaluated for physical characteristics like bulk density, tapped density, compressibility index, and Hausner's ratio Hausner's ratio of all the formulations was less than **1.25** indicating excellent flow properties. Eight formulations of Armodafinil granules were prepared by direct compression method and evaluated. The formulation F-6 containing 45% of HPMC K4M CR & 5% of HPMC K100M CR was found to be best formulation based on *in-vitro* drug dissolution studies. From the dissolution studies, it was found that 82% of the drug was released in 16 hrs & up to 98% in 24 hrs. The dissolution profile of the optimized formulation F-6 was compared with the marketed product **NUVIGIL**. The similarity factor, *f2* is 81.90 indicating that the dissolution profile of optimized formulation was super-imposable with the dissolution profile of the marketed product. Application of kinetics to the *in-vitro* dissolution profile of the optimized formulation showed that the release of drug followed first order kinetics (R^2=0.9686) and Hixson-Crowell cube root law (R^2=0.9816). Accelerated stability studies on all the formulations were conducted as per ICH guidelines (40±2°C and 75±5% RH) for 3 months and the optimized formulation was found to be stable. Further studies are needed to investigate the developed tablets for their performance *in-vivo* and it's equivalence with the marketed products. Scale up as well as validation batches can be planned.

5. BIBLIOGRAPHY

[1] Rubinstein, M.H. Tablets in Pharmaceutics: "The Science of dosage form design". Aulton M. E. Ed.; Churchill Livingstone*:* New York, **2000**, pp. 305.

[2] Grass, G. M.; Robinson, J. R. "Sustained and Controlled release drug delivery systems in modern Pharmaceutics". Vol. 40; 2nd ed., Banker, G. S.; Rhodes, C. T.; Eds.; *Marcel Dekker Inc*: New York. **1990**.

[3] Lordi, N. G. Sustained release dosage forms. "In The Theory and Practice of Industrial Pharmacy." 3rd ed., *Lachman, L.; Lieberman, H. A.; Kanig J. L. Eds.; Lea and Febiger: Philadelphia***, 1991**, pp. 430-435.

[4] Shargel, L.; Wu- Pong, S.; Yu, A. B. "Applied Biopharmaceutics and Pharmacokinetics". 5th ed., *Mc. Graw Hill*, **2005**, pp. 515-520.

[5] Hoffman A. Pharmacodynamic aspects of sustained release preparations. Advance Drug Delivery Rev.1998; 33:185-199.

[6] Banker GS, Rhodes CT, editor.Modern pharmaceutics. 4th ed. Marcel Dekker, Inc.; New York: Replica Press. vol 121; p. 501-23**.**

[7] Sack RL, Auckley D, Auger RR, et al. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. Sleep. 2007; 30(11):1460–1483.

[8] National Sleep Foundation. 2008 Sleep in America Poll. Washington DC: National Sleep Foundation; 2008.

[9] Parish JM. Sleep-related problems in common medical conditions. Chest. 2009; 135(2):563–572.

[10] Dodel R, Peter H, Noelker C, et al. Health-related quality of life in patients with narcolepsy. Sleep Med. 2007; 8(7–8):733–741.

[11] Harsh JR, Haydak R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin. 2006; 22(4):761–774.

[12] Nuvigil A. ® (Armodafinil) Tablets [C-IV] [Package Insert]. Frazer, PA: Cephalon, Inc; (2010).

[13] Drug Bank.

[14] www.drugs .com.

[15] "British Pharmacopoeia", **2003**, Electronic Version, p. 289.

[16] "United State Pharmacopoeia 28 National formulary 23, US Pharmacopoeial convention" *Inc: Rockville*, MD.**2005**; Asian ed. pp. 2859.

[17] Rowe, R. C.; Sheskey, P. J.; Weller, P. J. Eds." Hand Book of Pharmaceutical Excipients". Science and practice, *royal pharmaceutical society Of Great Britain London*, pp. 237, 294, 309, 373, 386,454-479, 636, 659, 665.

[18] Kelly, K. A. Motility of the stomach and gastro duodenal junction. In Johnson, L. R. ed. Physiology of the gastrointestinal tract, Vol. 1, *Raven*, New York, **1981**.pp.393-410.

[19] Devereux. J. E. Ph. D. Thesis, London University, Gastrointestinal transit of multiple unit dosage forms. 1987.

[20] Wells, James I. "Pharmaceutics Preformulation". *Ellis horwood ltd*. **1998**, pp. 208-209.

[21] ICH guidelines on stability study 2003.

[22] http://www.pharmpedia.com/Tablet:Manufacturing_methods/Granulation.

[23] Costa, P. An alternative method to the evaluation of similarity factor in Dissolution testing. *Int. J. Pharm*. **2000**, 220, 77-83.

[24] Wise DL, editor. "Hand book of pharmaceutical controlled release technology". *Marcel Dekker, Inc.;* New York: Replica Press; **2005**. p. 155-78, 465-500.

[25] Carteensen, J. T. Drug stability principles and practices. *Marcel Dekker*: New York. **1990**, pp. 349- 399.