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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF ORALLY DISINTEGRATING TABLET FOR ENHANCING PATIENT COMPLIANCE.

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Abstract:

An Orally disintegrating tablet disperses readily in saliva and the drug is available in solution or suspension form for the immediate absorption and resulting in rapid onset of action. In the present research work Modafinil Orally disintegrating tablet were prepared by wet granulation method using varying concentrations of Lycoat, Crosspovidone & Sodium alginate as superdisintegrants. The formulations prepared were evaluated for precompression & post compression parameters. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Modafinil) and optimized formulation (Modafinil+ excipients) which indicates there are no physical changes. Post compression parameters was found to be within the limits. Among the formulation prepared the tablet containing concentration of Crosspovidone shows 99.18% of the drug release within 10 min, 28 sec Disintegration time & follows first order kinetics. The overall result indicated that the formulation F8 containing Crosspovidone is better and fulfilling of the needs of the Orally disintegrating tablet.

Key words: Orally disintegrating tablet, Modafinil, Crosspovidone, Lycoat, superdisintegrant.

Introduction:

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually[1].

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more costeffective dosage forms. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes[2].

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected[3].

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms[4-5]

Although chewable tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth[6].

ODTs technology, which makes tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. ODTs are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited bio-fluid[8-9]. Orally disintegrating tablets are known by various names such as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, fast or rapid dissolving tablets, porous tablets, mouth dissolving tablets and rapimelts. The excipients used in ODT technology are usually hydrophilic in nature and can be selected on the basis of drug's physicochemical properties like hydrophilicity or hydrophobicity. If the active pharmaceutical ingredient is hydrophobic in nature, then dosage form is called disintegrating tablet whereas, if it is hydrophilic, then the dosage form is called fast dissolving tablet [10-11]. The ODT formulation defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medicinal substances which disintegrates

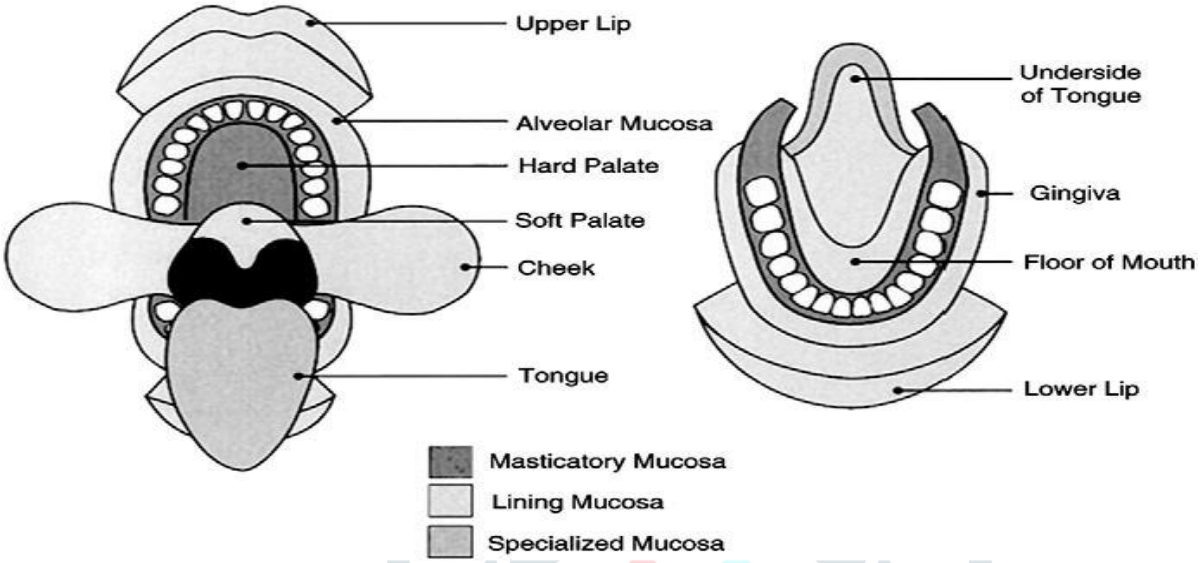
rapidly, usually within a matter of seconds when placed upon the tongue". U.S. Food and Drug Administration approved Zydis, ODT formulation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998. Further a number of drugs have been approved by regulatory authorities for ODT formulations. The aim of this article is to review the advantages, limitations, formulation challenges, manufacturing techniques, patented technologies, marketed formulations and evaluation tests of ODTs.[12-13]

Overview of Oral Mucosa

The anatomical and physiological properties of the oral mucosa have been extensivelyreviewed by several authors. The oral cavity comprisesJournal of Applied Pharmaceutical Science 01 (04); 2011: 35-45the lips, cheek, tongue, hard palate, soft palate and floor of themouth (Fig. 1).[14-16] The lining of the oral cavity is referred to as theoral mucosa, and includes the buccal, sublingual, gingival, palataland labial mucosa. The buccal, sublingual and the mucosal tissuesat the ventral surface of the tongue account for about 60% of theoral mucosal surface area. The top quarter to one-third of the oralmucosa is made up of closely compacted epithelial cells (Fig. 2).The primary function of the oral epithelium is to protectthe underlying tissue against potential harmful agents in the oralenvironment and from fluid loss.[17-19] Beneath theepithelium are the basement membranes, lamina propia andsubmucosa. The oral mucosa also contains many sensory receptorsincluding the taste receptors of the tongue. Three types of oralmucosa can be found in the oral cavity; the lining mucosa is foundin the outer oral vestibule (the buccal mucosa) and the sublingualregion (floor of the mouth) (Fig. 1). The specialized mucosa isfound on the dorsal surface of tongue, while the masticatorymucosa is found on the hard palate (the upper surface of themouth) and the gingival (gums) (Smart et al, 2004).The lining mucosa comprises approximately 60%, themasticatory mucosa approximately 25%, and the specializedmucosa approximately 15% of the total surface area of the oralmucosal lining in an adult human. The masticatory mucosa islocated in the regions particularly susceptible to the stress andstrains resulting from masticatory activity. The superficial cells ofthe masticatory mucosa are keratinized, and a thick lamina propiatightly binds the mucosa to the underlying periosteum. Liningmucosa on the other hand is not nearly as subject to masticatoryloads and consequently, has a non-keratinized epithelium, whichsits on a thin and elastic lamina propia and a sub mucosa. Themucosa of the dorsum of the tongue is a specialized gustatorymucosa, which has well papillated surfaces which are bothkeratinized

and some non-keratinized. Table 1depicted the advantages and disadvantages associated withutilizing the oral mucosa as a drug delivery site.[19-21]

Figure No. 1: Schematic representation of the different linings of mucosa in mouth



DRUG PROFILE

Modafinil is a stimulant used to improve wakefulness in patients with sleep apnea, narcolepsy, or shift work disorder.

Brand Names

Provigil

Generic Name

Modafinil

Background

Modafinil is a stimulant drug marketed as a 'wakefulness promoting agent' and is one of the stimulants used in the treatment of narcolepsy. Narcolepsy is caused by dysfunction of a family of wakefulness-promoting and sleep-suppressing peptides, the orexins, whose neurons are activated by modafinil. The prexin neuron activation is associated with psychoactivation and euphoria. The exact mechanism of action is unclear, although in vitro studies have shown it to inhibit the reuptake of dopamine by binding to the dopamine reuptake pump, and lead to an increase in extracellular dopamine. Modafinil activates glutamatergic circuits while inhibiting GABA.

Structure

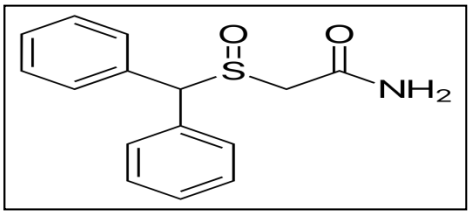


Figure no. 2 Chemical Structure of Modafinil

Weight

Average:273.35

Monoisotopic: 273.082349419

Chemical Formula

$C_{15}H_{15}NO_2S$

Synonyms

- Modafinil
- Modafinilo
- Modafinilum

Pharmacology

Indication

To improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with narcolepsy.

Associated Conditions

Attention Deficit Hyperactivity Disorder (ADHD)

Fatigue

Major Depressive Disorder (MDD)

Narcolepsy

Obstructive Sleep Apnea (OSA)

Shift-work related sleep disturbance

Pharmacodynamics

Modafinil is a stimulant drug marketed as a 'wakefulness promoting agent' and is one of the stimulants used in the treatment of narcolepsy. Narcolepsy is caused by dysfunction of a family of wakefulness-promoting and sleep-suppressing peptides, the orexins, whose neurons are activated by modafinil. The prexin neuron activation is associated with psycho activation and euphoria. Modafinil is not indicated for complaints of lack of energy or fatigue; but it appears to be very helpful for some patients. Also, it has been used in the

treatment of hypersomnia, a disorder in which patients lack the capacity for meaningful sleep and may require ten or more hours per day. Recent studies have have found that modafinil may help recovering cocaine addicts fight their addiction.

Mechanism of action

The exact mechanism of action is unclear, although *in vitro* studies have shown it to inhibit the reuptake of dopamine by binding to the dopamine reuptake pump, and lead to an increase in extracellular dopamine. Modafinil activates glutamatergic circuits while inhibiting GABA. Modafinil is thought to have less potential for abuse than other stimulants due to the absence of any significant euphoric or pleasurable effects. It is possible that modafinil acts by a synergistic combination of mechanisms including direct inhibition of dopamine reuptake, indirect inhibition of noradrenalin reuptake in the VLPO and orexin activation. Modafinil has partial alpha 1B-adrenergic agonist effects by directly stimulating the receptors.

Absorption

Rapid following oral administration.

Volume of distribution

- 0.9 L/kg

Protein binding

60%

Metabolism

Hepatic

How over products below to view reaction partners

- Modafinil
- modafinil acid

Route of elimination

The major route of elimination is metabolism (~90%), primarily by the liver, with subsequent renal elimination of the metabolites.

Half-life

23-215 hours

Materials Used

Table no. 1 Materials used for formulation

Sr. No	Materials
1.	Modafinil
2.	Lycoat
3.	Crosspovidone
4.	Sodium alginate
5.	Aspartame
6	MCC
7.	Talc
8.	Magnesium stearate

Formulation Table:

Table no. 2 : Formulation of Modafinil

Ingredient (mg)	F1	F2	F3	F4	F5	F6
Modafinil	25	25	25	25	25	25
MCC pH 101	19.75	19	18.25	17.5	19.75	19
Povidone K30	2.5	2.5	2.5	2.5	2.5	2.5
Sodium alginate	0.75	1.5	2.25	3	-	-
Lycoat	-	-	-	-	0.75	1.5
Crosspovidone	-	-	-	-	-	-
Aspartame	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75
Total	50	50	50	50	50	50

Ingredient (mg)	F7	F8	F9	F10	F11	F12
Modafinil	25	25	25	25	25	25
MCC pH 101	18.25	17.5	19.75	19	18.25	17.5
Povidone K30	2.5	2.5	2.5	2.5	2.5	2.5
Sodium alginate	-	-	-	-	-	-
Lycoat	2.25	3	-	-	-	-
Crosspovidone	-	-	0.75	1.5	2.25	3
Aspartame	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75
Total	50	50	50	50	50	50

Result and discussion:

Spectroscopic studies:

UV SpectroscopyDetermination of λ_{max}: -

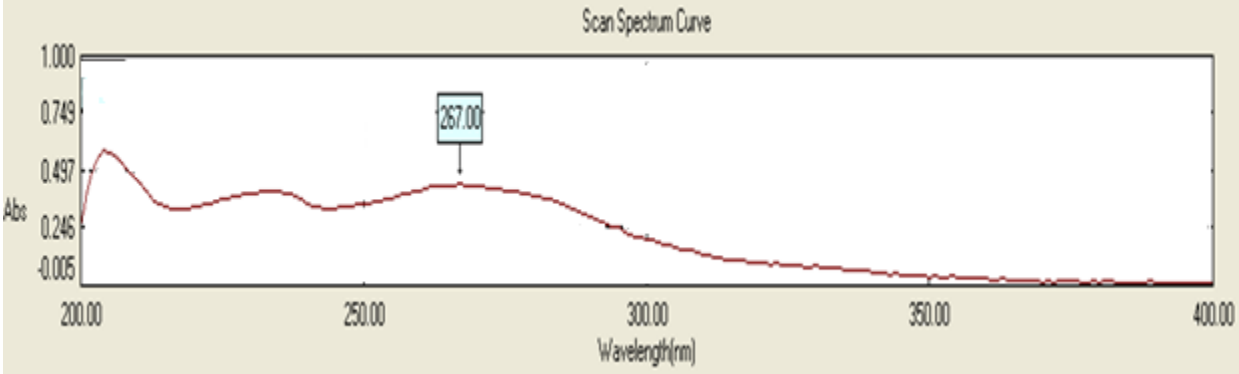


Figure no. : 3 UV Spectrum curve of Modafinil

Discussion:λ_{max}ofModafinilwas found to be 267 nm

FTIR Spectroscopy:

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

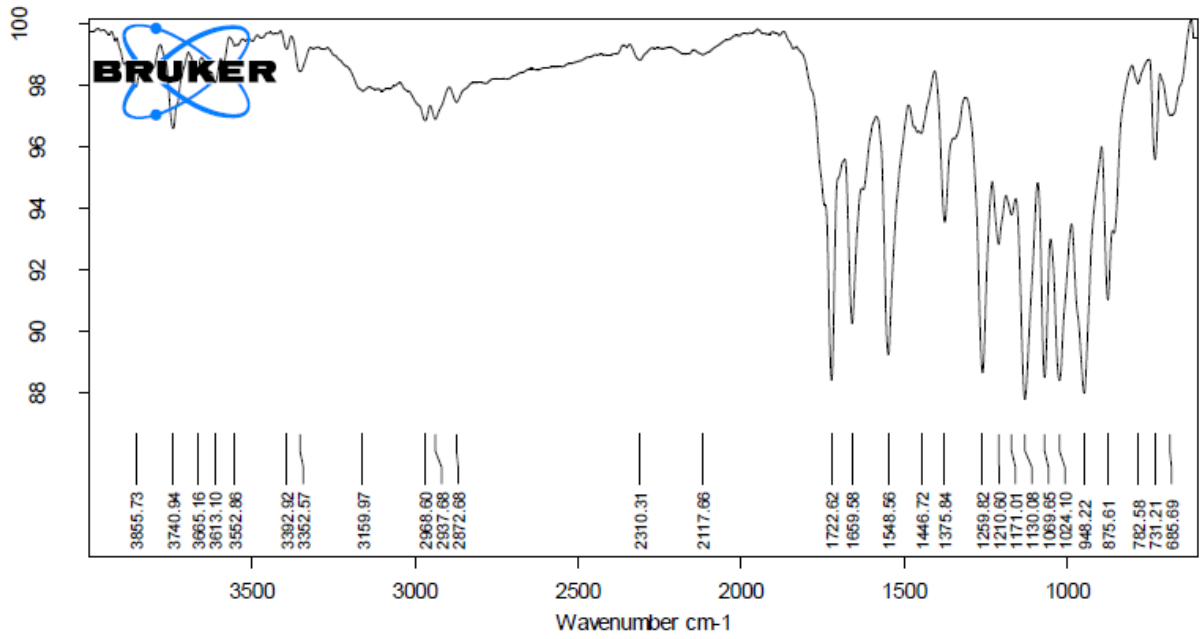


Figure no. 4: IR spectrum of Modafinil.

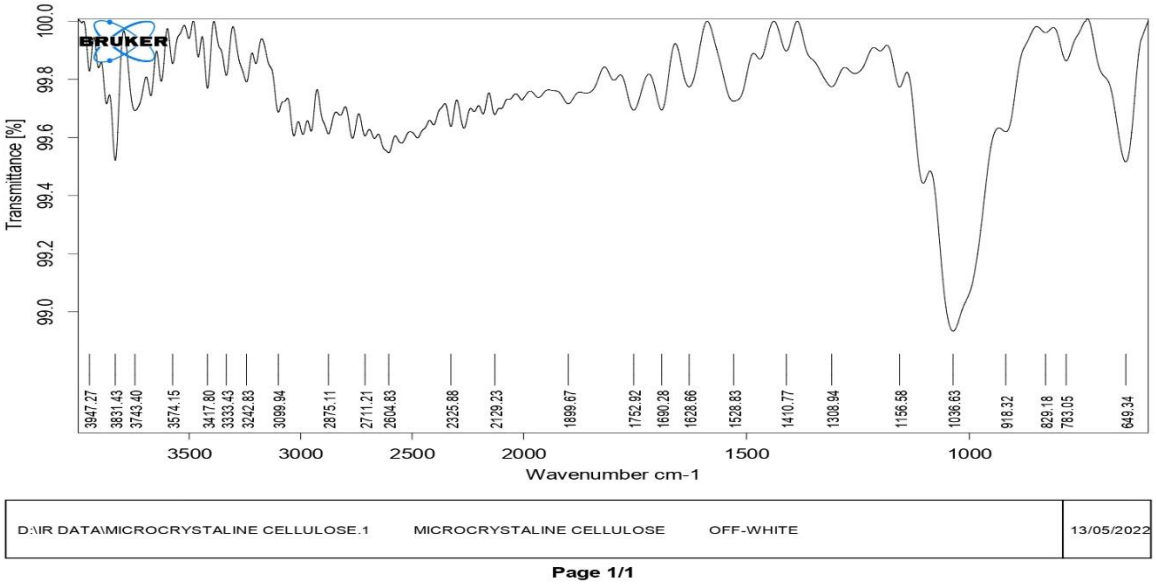


Figure 5 : IR Spectrum of Microcrystalline Cellulose

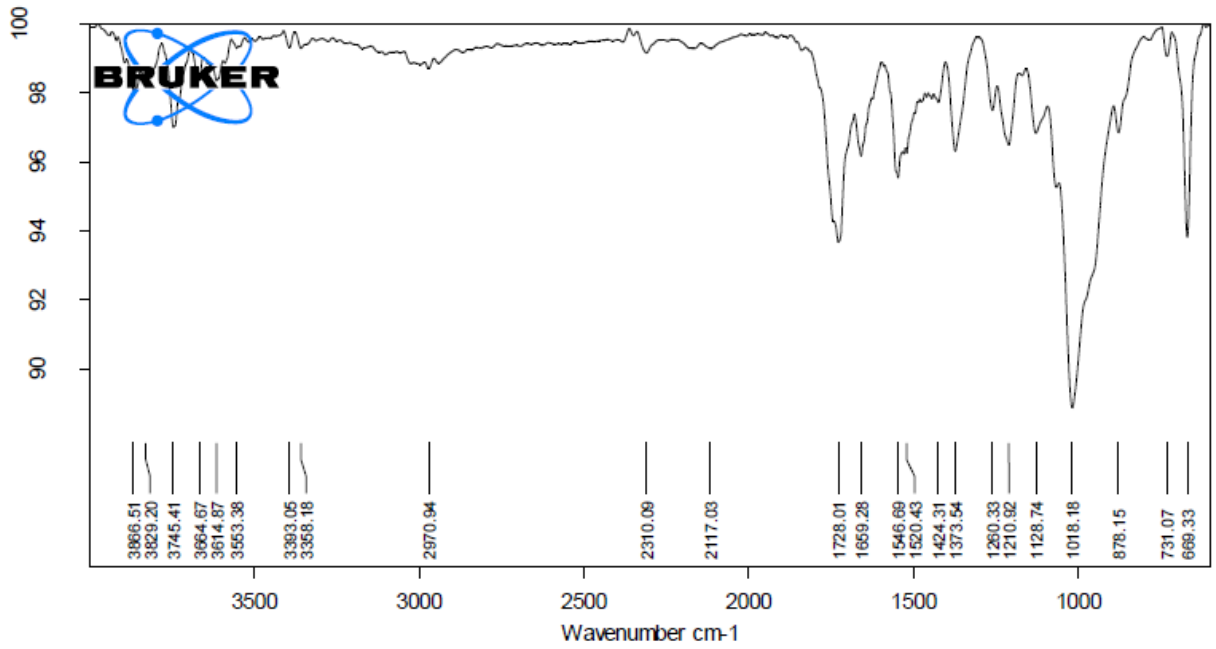


Figure no. 6: IR spectrum of Modafinil & excipients.

Discussion: Form the drug excipient compatibility studies we observe that there are no Drastic changes between the pure drug (Modafinil) and optimized formulation (Modafinil + excipients) which indicates there are no physical changes.

Calibration curve of Modafinil in 6.8 pH buffer

Table No. 3 Calibration Curve of Modafinil

Concentration(µg/ml)	Absorbance
0	0
2	0.139
4	0.284
6	0.435
8	0.543
10	0.695
12	0.827

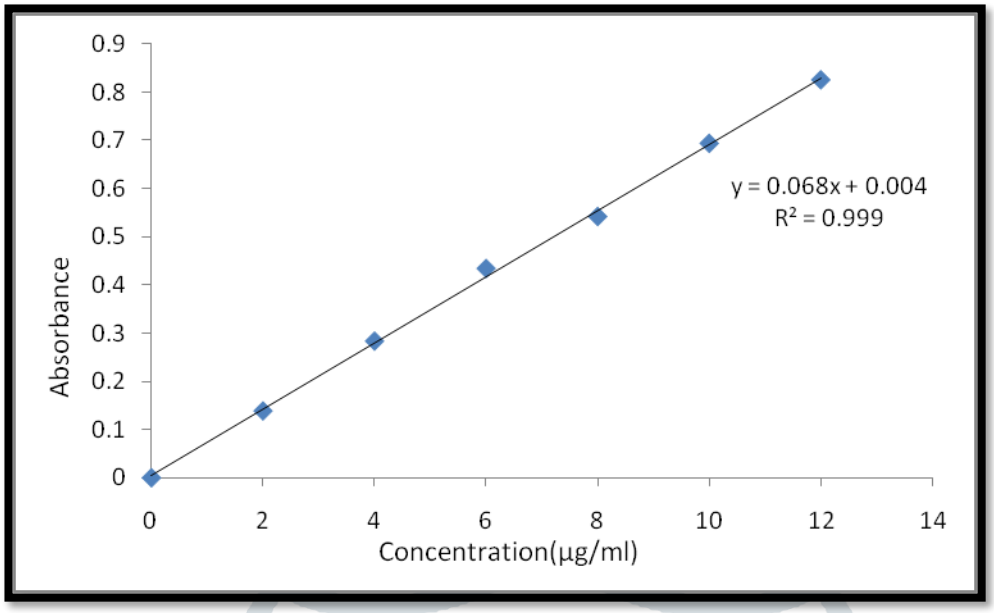


Figure no. 7 : Standard graph of Modafinil

Evalution of Oral Disintegrating Tablet of Modafinil Drug

Precompression Parameters

Table no. 4 : Pre Compression parameters

Formulation Code	Derivedproperties		Flowproperties		
	Bulkdensity (mean±SD)	Tapped density (mean±SD)	Angleof repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.62±0.01	0.71±0.015	27.36±0.30	12.67±1.02	1.14±0.06
F2	0.64±0.01	0.74±0.02	26.15±0.39	13.51±1.26	1.15±0.03
F3	0.61±0.04	0.72±0.01	28.04±0.68	15.27±2.08	1.18±0.05
F4	0.66±0.02	0.74±0.015	29.42±0.96	10.81±1.28	1.12±0.02
F5	0.62±0.6	0.72±0.03	28.49±0.73	13.88±1.86	1.16±0.04
F6	0.64±0.2	0.76±0.006	27.75±0.36	15.78±1.96	1.18±0.05
F7	0.65±0.02	0.75±0.025	26.18±0.29	13.33±1.46	1.15±0.04
F8	0.62±0.6	0.70±0.017	25.63±0.40	11.42±1.42	1.12±0.05

F9	0.68±0.4	0.77±0.025	27.85±0.34	11.68±2.02	1.13±0.06
F10	0.62±0.28	0.71±0.01	28.75±0.20	12.57±1.02	1.13±0.06
F11	0.64±0.59	0.74±0.42	29.14±0.29	13.51±1.12	1.15±0.08
F12	0.61±0.36	0.72±0.36	25.05±0.28	15.27±0.57	1.18±0.26

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table no. 5 : Characterization Modafinil oral disintegrating tablets

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)
F1	50.2±0.02	3.4±0.02	3.6±0.01	0.68±0.02	39 ±0.02
F2	51.3±0.06	3.5±0.04	4.2±0.03	0.62±0.06	35 ±0.05
F3	50.4±0.07	3.7±0.06	3.5±0.02	0.79±0.08	38 ±0.06
F4	51.6±0.04	3.4±0.01	3.9±0.01	0.65±0.02	39 ±0.08
F5	51.2±0.03	3.2±0.01	3.7±0.01	0.59±0.08	34 ±0.02
F6	50.8±0.02	3.5±0.02	4.1±0.06	0.48±0.06	32 ±0.07
F7	50.3±0.01	3.8±0.06	4.2±0.05	0.64±0.04	35 ±0.09
F8	**50.6±0.06**	**3.5±0.08**	**3.9±0.07**	**0.69±0.08**	**28 ±0.02**
F9	51.2±0.06	3.6±0.02	3.2±0.08	0.85±0.02	34 ±0.06
F10	50.2±0.52	3.5±0.12	4.2±0.22	0.62±0.46	35 ±0.02
F11	50.5±0.23	3.2±0.11	3.7±0.28	0.59±0.32	34 ±0.12
F12	51.2±0.12	3.5±0.04	4.1±0.46	0.48±0.58	36 ±0.04

Discussion:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.2–3.8 kg/cm^2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1–F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Disintegration time as per IP, for all the formulations was found to be within 28 seconds, which was well within IP limit.

Formulations with Crosspovidone as super disintegrants shows quiker disintegration among all the formulations. Lycoat with 3 mg concentration as a super disintegrant shows very less disintegration time.

Drug content uniformity of formulations:

The prepared formulations were analysed for drug content and the data is reported in below Table. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Table no. 6 : Drug content uniformity of formulations F1-F12:

Tablet formulation	%of drug content
F1	90.96
F2	92.65
F3	94.62
F4	96.02
F5	91.71
F6	94.16
F7	97.24
F8	**99.18**

F9	90.06
F10	92.68
F11	94.29
F12	96.64

Discussion: % drug content values of formulation F1 –F12 was found to be in the range of

90.96 -99.18%

Dissolution studies:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. As the concentration of superdisintegrant increased, the drug release time Increased.

Table no. 7 : % Cumulative drug release of formulations F1-F12

Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	**0**
1	32.45	39.85	43.18	50.48	36.41	39.05	55.61	**59.64**
2	39.78	42.75	54.17	62.45	48.61	46.38	69.42	**73.42**
4	45.63	49.61	61.31	78.05	56.3	50.85	75.63	**86.71**
6	59.61	58.34	79.46	86.49	63.64	65.23	82.45	**98.43**
8	65.43	72.46	89.82	96.42	79.84	79.53	96.45	**98.44**
10	79.42	86.49	97.53	98.98	81.59	86.74	97.85	**99.14**

Time(Min)	F9	F10	F11	F12
0	0	0	0	0
1	18.38	34.86	39.21	41.9
2	27.85	43.24	47.81	56.13
4	38.23	57.72	62.98	68.47
6	45.53	61.32	76.85	74.21
8	56.74	67.48	74.25	87.43
10	69.85	79.42	83.46	98.46

Figure no.8: %DR of F1-F4

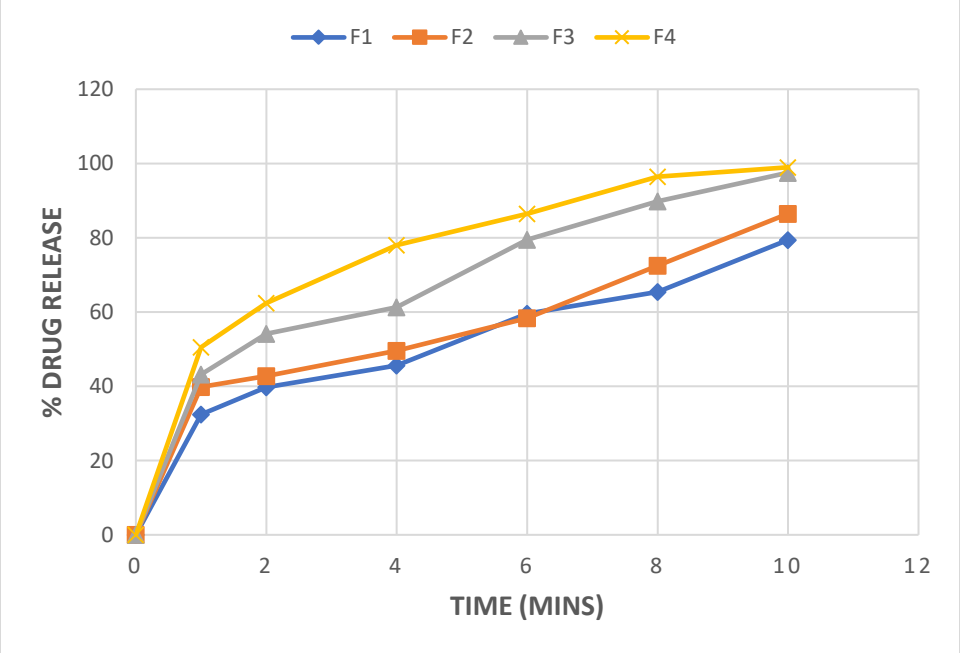


Figure no. 9: %DR of F5-F8

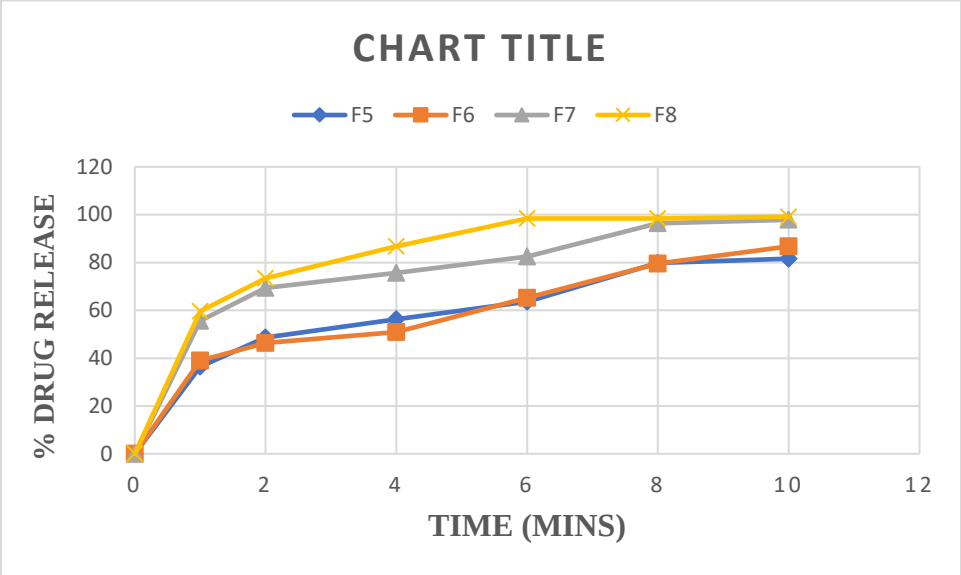
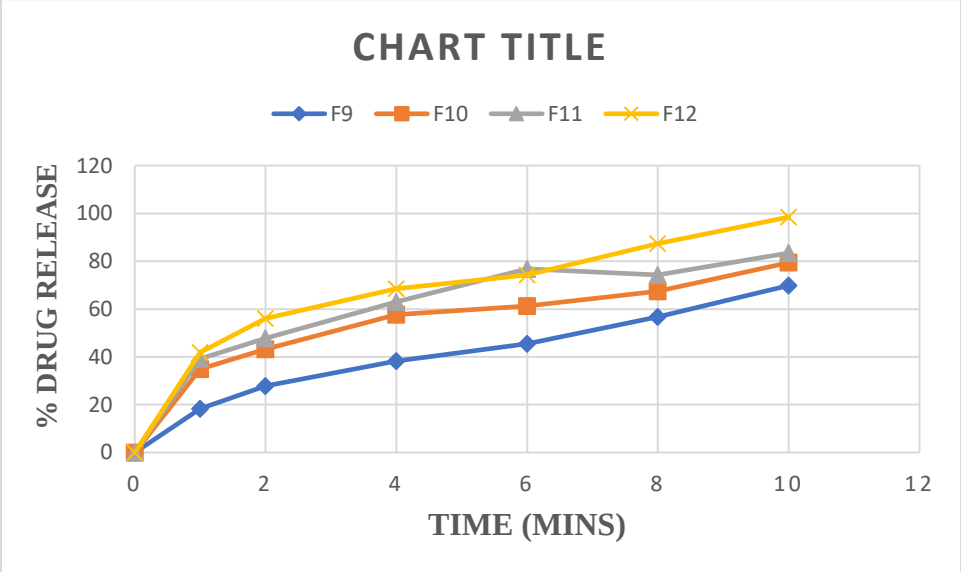


Figure no. 9 : % DR of F9 toF12



Discussion:

From the in vitro drug release studies it was observed that the formulations containing sodium alginate (F1-F4) as superdisintegrant in the concentrations of (0.75,1.5, 2.25, 3 mg). F1, F2, F3,F4 shows 79.42% , 86.49% , 97.53% drug release at the end of 10 minutes. Where as F4 shows 98.98% drug release at the end of 10 minutes.

Whereas the the formulations containing Lycoat (F5-F8) as superdisintegrant in the concentrations of (0.75,1.5, 2.25, 3 mg).F5 & F6 shows 81.59% & 86.74% drug release at the end of 10 minutes. Whereas F7 shows 97.85% drug release at the end of 10 minutes & F8 formualtion shows 99.14% drug release at the end of 10 minutes.

While the formulations containing natural super disintegrants such as Crospovidone(F9-F12)as

superdisintegrant in the concentrations of (0.75,1.5, 2.25, 3 mg) shows 69.85%,79.42%,83.46% & 99.18 % drug release at the end of 10 minutes.

By comparing the dissolutions profiles of formulations F1-F12 containg super disintegrants in the concentrations of 0.75,1.5, 2.25, 3 mg the drug release was not found to be satisfactory lycoat shows satisfactory drug release at the end of 10 mins. Among all the formulations F8 containing 3 mg Crosspovidone shows 99.18 % drug release at the end of 10 min. So F8 formulation was considered as the optimized formulation. Further kinetics were measured for F8 formulation.

DRUG RELEASE KINETICS STUDIES:

ZERO ORDER RELEASE KINETICS

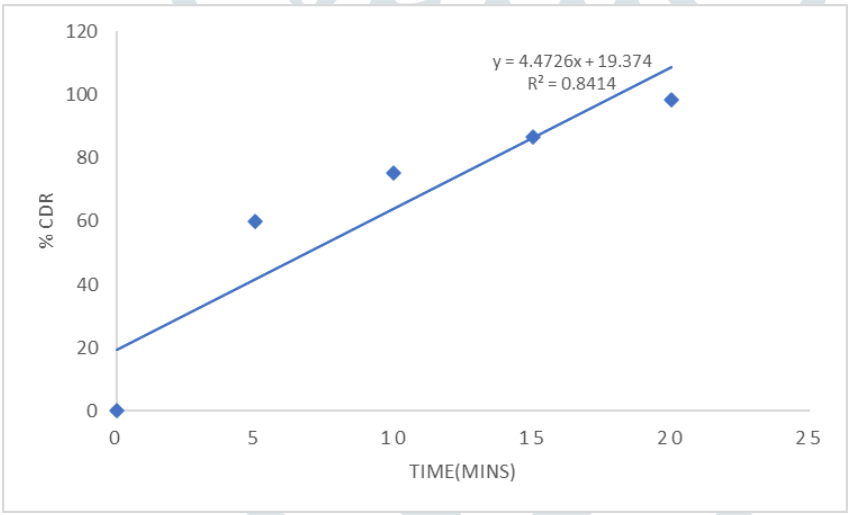


Figure no.10 : Zero order plot of Modafinil F8 Formulation

FIRST ORDER RELEASE KINETICS

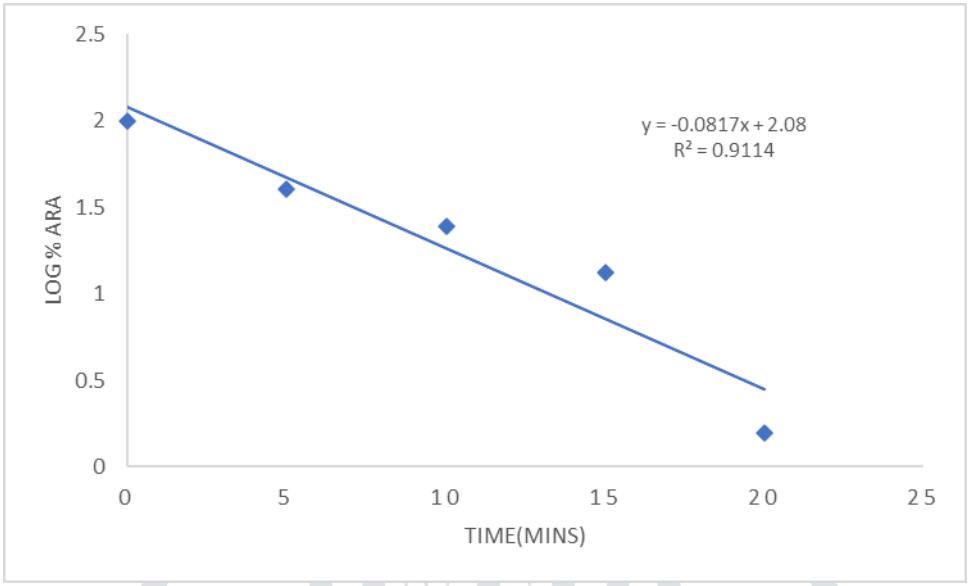


Figure no. 11: First order plot of ModafinilF8 Formulation(Time Vs Log% ARA

Table no. 8 : order of kinetic values of FormulationF8

Order of kinetics	Zero order	First order
Regression values	0.841	0.911

Discussion:

The drug release from the oral disintegrating tablets was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F8 follows First order drug release.

Accelerated stability study:

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of the particular formulation. The stability studies conducted as per ICH guidelines revealed that there is no change in physical appearance, hardness, disintegration time, drug content, in-vitro drug release studies. The results were shown in table.

Table No. 9 : Stability studies of F8 batch ODT of Modafinil at 40± 2°C 75±5%.

Formulation	Before stability study F8 batch	After 30 days	After 60 days	After 90 days
Physical Apperance	No Change	No Change	No Change	No Change
Disintegration time	28±1.02 sec	29±1.05	29±0.60	30±1.00
Hardness	3.9 kg/cm^2	3.9 kg/cm^2	3.9 kg/cm^2	3.9 kg/cm^2
Thickness	3.5±0.08mm	3.5±0.08mm	3.5±0.08mm	3.5±0.08mm
% Friability	0.69±0.08	0.69	0.69	0.69
Weight variation	50.6	50.6	50.6	50.6

Table no. 10 Stability Dissolution Profile of ODT of Modafinil

Time(min)	Before stability study	After 30 days	After 60 days	After 90 days
0	**0**	0	0	0
1	**59.64**	59.98	60.20	60.50
2	**73.42**	73.89	74.10	74.40
4	**86.71**	87.10	87.50	87.90
6	**98.43**	98.78	98.95	99.12
8	**98.44**	98.90	98.95	98.99
10	**99.14**	99.25	99.45	99.65

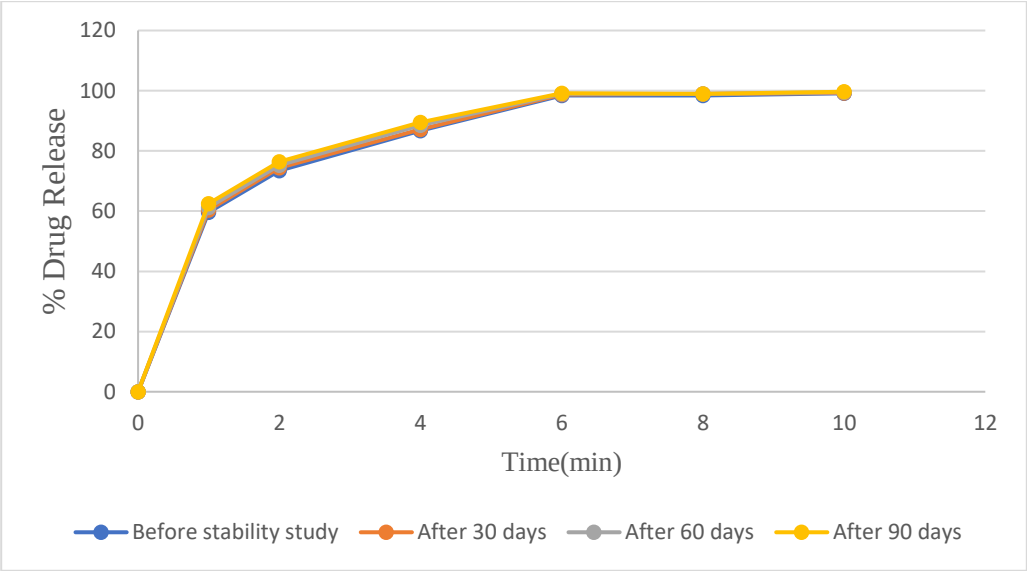


Figure no. 12 In vitro drug release profile of the formulation before stability and after stability study.

The stability study was carried out on optimized formulation F8. The tablets were wrapped in a aluminium foil and stored at 40+2°C/75+ 5% RH for 90days. After, each 30 days sample were withdrawn and tested for physical parameters, disintegration time, % drug release studies. Also, the batchF8 shows the good mouth feel after the stability studies. There, was no any significant changes takes place between dissolution profile of formulation F8 before and after stability study. Table no. 16 showed that there was no considerable change in thickness, hardness, percent friability, disintegration time, and wetting time of formulation F8 before and after accelerated stability study. Hence, orally disintegrating tablet prepared were found to be stable.

Summary and conclusion :

The present study was an attempt to select the best possible diluent - disintegrant combination to formulate Oral disintegrating tablets of Modafinil, which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action.

Lycoat, Cross povidone and Sodium alginate, were used as disintegrants. In all the formulations, Magnesium stearate and talc were used as lubricant and glidant respectively.

The results of the drug – excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients.

Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due

to reduced number of manufacturing steps.

The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the formulations showed acceptable flow properties.

The post compression parameters like the hardness, thickness, friability and weight variation, disintegration time, disintegration time in oral cavity and Invitro release were carried out and the values were found to be within IP limits.

The percentage drug content of all the tablets was found to be between 90.96to 99.18 %of Modafinil, which was within the acceptable limits.

After the stability studies the batch F8 showed the good mouth feel. There, was no any significant changes takes place between dissolution profile of formulation F8 before and after stability study. There was no considerable change in thickness, hardness, percent friability, disintegration time, and wetting time of formulation F8 before and after accelerated stability study. Hence, orally disintegrating tablet prepared were found to be stable.

Conclusion:-

Among all the formulations F8 shows 99.18% drug release at the end of 10 min. and disintegrating time is 28 sec. F8 contains Crosspovidone(3mg), it shows better % drug release and better disintegrating time when compared to other formulations.So F8 was considered as the optimized formulation.

The drug release kinetics shows that the optimized formulation F8 follows First order drug release. Hence, this formulation was found to be robust, stable and of an acceptable for future development in pharmaceutical field.

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