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Research Article

Formulation and Evaluation of Orodispersible Tablets Containing Co-Crystals of Modafinil

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Abstract

Background: Modafinil is a CNS stimulant used to treat Narcolepsy, sleepiness and other disorders related to sleep. It is a BCS class II drug having poor aqueous solubility.

Objective: This study was aimed to formulate and evaluate orodispersible tablets of containing co-crystals of Modafinil for the improvisation of critical attributes of the product such as dissolution rates, solubility and oral bioavailability.

Methods: Co-crystals were prepared by dry grinding method using Sodium acetate, Nicotinic acid, Benzoic acid, Urea and Succinic acetate as co-formers. Tablets were compressed by using direct compression method using SSG, Crospovidone, and Croscarmellose sodium as super disintegrants in different concentration.

Results: Pre-formulation studies were performed and evaluation of prepared co-crystals revealed that Co-crystals formulated with sodium acetate showed best results. The manufactured orodispersible tablets were evaluated for different parameters including weight variation, hardness, thickness, friability, drug content, In-vitro disintegration and In-vitro dissolution studies. Formulation F2 shows significant change in dissolution rate and also helped to increase the solubility of poorly water soluble drugs and both of them i.e. solubility and percentage of drug release are the key factors to exhibit the efficiency of the drug. Formulation of co-crystal with sodium acetate in 1:1 ratio showed highest drug content (97.97%), while Benzoic acid in ratio 1:2 showed least drug content (56.48%).

Conclusion: According to the result obtained, an orodispersible tablet containing co-crystals of modafinil enhances the dissolution rate, solubility and hence increases the therapeutic efficacy and could be considered convenient oral delivery systems to enhance the drug bioavailability.

Keywords: Co-crystal, Oro-dispersible, Sodium acetate, Narcolepsy, Sleepiness

1. INTRODUCTION

To define the effectiveness of a drug, solubility, and percentage of drug release are the important aspects that play a crucial role in the development and preparation of effective drugs in the pharmaceutical industry.[1] Nevertheless, about sixty percent of medicines are synthesized and the remaining forty percent of drugs possess solubility challenges that trigger bioavailability disputes and compatibility issues. Various strategies were proposed to boost the solubility and % of drug release of sparingly soluble drugs. The addition of cyclodextrins, solid dispersion, salt formation, micro emulsification, and the inclusion of complex formations contribute to the improvement of solubility profile of the drugs. [1 2]

Co-crystallization is one of the promising techniques used in the pharmacy sector that can be effective in life cycle management due to its potential benefits of improved solubility, dissolution, bioavailability, permeability, and stabilisation of unstable compounds through intermolecular interactions.[3] The Biopharmaceutical Classification System divides poorly soluble medications into classes BCS II & IV. [4] Since pharmaceutical crystallization is also applicable to non-ionisable APIs, this adds an additional advantage in the era of salt formation technique.[2] Physically, solid form of drug can be obtained from active pharmaceutical ingredient prepared by co-crystals that helps in achieving an elevated dissolution amount in contrast to amorphous form crystals.[5] Pharmaceutical co-crystals contain a couple of molecules or supplementary molecules which are vowed by H-bonding and stoichiometric ratio. Pharmaceutical co-crystals unite pharmaceutically satisfactory conformational isomer and the drug into the similar crystal network which led to the origination of new composition of the API /APIs. In addition to this, it was identified that co-crystals are scrutinized as drug discrete instead a new APIs bearing a momentous impact on the drug.[6 7] The present study was focused to improve the solubility as well as bioavailability of Modafinil which is a CNS stimulant used in the treatment of day time sleepiness, in Narcolepsy and other sleep related disorders. [8 9]

2. MATERIALS AND METHOD:

2.1 Drug & excipients:

Modafinil was gift sample from the Sidmak Lab Pvt. Ltd (India). All other chemicals including Sodium acetate, Urea, Nicotinamide, Benzoic acid, Succinic acid, Sodium starch

glycolate, Crospovidone, Croscarmellose sodium, Microcrystalline cellulose, Mannitol, Aspartame, Magnesium stearate, Talc were taken from the college drug store.

2.2 Instruments: Digital balance, PH meter, UV spectrophotometry, Melting point apparatus, Hardness tester, Thickness tester, Disintegration apparatus, Probe sonicator, Fourier Transform Infrared Spectrophotometer, Friability test apparatus, Differential scanning calorimeter.

2.3 Pre-formulation studies: Determination of λ_{max}, Calibration curve, Solubility of pure drug, FT-IR study.

2.4 Formulation of Co-crystals [10]

The method used to prepare Modafinil co-crystals was dry grinding. To create co-crystals, drug and coformer were combined in a mortar and pestle for 45 minutes at varied molar ratios (1:1 and 1:2). This was dried at room temperature for an entire night before being sealed in containers. The following 10 coformers were screened: Benzoic acid, citric acid, urea, nicotine, succinic acid, glutaric acid, cinnamic acid, adipic acid, sodium acetate, and saccharine sodium.

2.5 Formulation of Orodispersible tablet [11 12]

All additional excipients and a precisely weighed quantity of Modafinil co-crystal equal to 100 mg of Modafinil were filtered through a 60-mesh sieve before being combined in a mortar and pestle for 30 minutes. A single punch tablet machine was used to immediately compress the mixture into tablets. With the exception of the super disintegrant and the binder, all excipient quantities remained constant as given in **table 1.**

Table 1: Composition of different batches of tablets

S.No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1.	Co-crystals	147	147	147	147	147	147
2.	SSG	9	15	-	-	-	-
3.	CP	-	-	9	15	-	-
4.	CCS	-	-	-	-	9	15
5.	MCC	118	112	118	112	118	112
6.	Mannitol	54	54	54	54	54	54
7.	Aspartame	2	2	2	2	2	2
8.	Magnesium Stearate	2	2	2	2	2	2
9.	Talc	2	2	2	2	2	2

2.6 Evaluation of Co-crystals

2.6.1 Determination of Melting Point

Automated melting point apparatus was used to measure the melting point of manufactured co-crystals.

2.6.2 Saturation Solubility [13]

By dissolving extra co-crystals in water-filled 10 ml vials, the solubility was ascertained. The vials were shaken on a rotary shaker and left for 24 hours to allow for equilibrations. After 24 hours, the co-crystals were filtered, diluted with water, and subjected to 222 nm UV Spectrophotometer analysis.

2.6.3 Drug content of the prepared Co-crystals [14]

Drug content was calculated by adding 25 mg of co-crystals in 50 ml of ethanol. The solution was kept for 24 hr then, filtered and diluted with ethanol to make a concentration 10µg/ml. This was analyzed by using UV Visible spectroscopy. Drug percentage was calculated by the formula given below:

% Drug content = Obtained Conc. / Theoretical Conc. * 100

2.6.4 IR Spectroscopy [15]

FTIR was used to assess whether the medication and co-former had any interactions. Separately placed on an IR plate, pure drug and mixture of drug and manufactured co-crystals produced spectra between 4000 and 400 cm-1.

2.7 Evaluation of Post Compression Parameter

2.7.1 Weight variation [16]

A random sample of 20 tablets from a batch was weighed separately, and the average weight was calculated using an electronic balance (Shimadzu).To determine the % average weight formula used as:

% weight variation = weight of individual tablet – Average weight of tablets/ Average weights of tablets x100

2.7.2 Thickness [16]

Vernier caliper was used to determine the tablets' thickness. From each batch, ten tablets were chosen at random, and the thickness was measured. The results are shown as the mean standard deviation (SD).

2.7.3 Hardness [17]

The crushing load, also referred to as hardness, is the amount of force required to crack a tablet in a radial direction. Ten tablets were randomly selected from each batch and tested for hardness using Monsanto's hardness tester. Each batch's mean values and standard deviation were computed.

2.7.4 Friability [18]

Using a Roche friabilator of the USP type, the friability of tablets was tested. Tablets equivalent to 6.5gm were weighed and putted into a friabilator chambered that was connected to a motor and rotated at 25 rpm for 4 minutes. The tablets were

then cleaned, weighed again, and the formula was used to determine the % weight reduction:

% Friability = {(Initial weight – Final weight**) /** Initial weight**)} × 100**

2.7.5 Wetting Time [19]

Six round tissue papers with a 10 cm diameter were placed in a petri dish, and 10 ml of water dyed with amaranth was added to it to test whether the tablet surface had been completely moistened. In a Petri dish with tissue paper on top, a tablet was carefully positioned at room temperature. Wetting time is the duration that it takes for water to thoroughly moistening the tablet's top surface. The research was carried out in duplicate, and stopwatches were used to record the time.

2.7.6 Drug Content [20]

The weight and powder of twenty tablets were done. Weighed amount was dissolved in some amount of ethanol, and diluted with 0.1N HCl a single dose of modafinil powder was analyzed for drug concentration at 222 nm using a UV-Visible spectrophotometer (Shimadzu).

2.7.7 In Vitro Disintegration Time [21]

Using distilled water at 37°±2⁰C and the digital tablet disintegration test device, the in vitro disintegration time (DT) was calculated. The mean SD value was calculated as the number of seconds required for the pill to completely dissolve with no residue remaining in the apparatus.

2.7.8 In Vitro Drug Release Study [22]

Utilizing the USP dissolving test apparatus (Lab India) and the paddle method, drug release investigations were carried out. 900 ml of 0.1N hydrochloric acid was used as dissolution media, and test was performed at 37±0.5°C and 50 rpm with the paddle. At predefined intervals (5 min), samples (5 ml) were taken and replaced with an equivalent volume of new medium. The samples were filtrated through a 0.45-m membrane filter and then examined at 222 nm using a UV spectrophotometer after the study had been running for 45 minutes (Shimadzu).

Dissolution Apparatus	USP type II (Paddle)
Media volume	900ml
Temperature	37+ 0.5
RPM	50 RPM
Volume withdrawn	5ml
Media used	0.1 N Hcl
Stirrer	Paddle Type

3. RESULT AND DISCUSSION

3.1 Pre-Formulation studies:

3.1.1 Determination of λ_{max} of Modafinil

The λ_{max} was found to be 222 nm in ethanol.

3.1.2 Calibration curve of Modafinil in Ethanol, Methanol, 0.1 N HCl and water

Table 2: Absorbance in different solvent

S.No.	Concentration (µg/ml)	Absorbance at 222 nm			
		Ethanol	Methanol	0.1 N HCl	Water
1.	0	0	0	0	0
2.	2	0.215	0.185	0.138	0.118
3.	4	0.329	0.309	0.241	0.181
4.	6	0.495	0.428	0.339	0.265
5.	8	0.700	0.618	0.459	0.345
6.	10	0.820	0.755	0.597	0.428

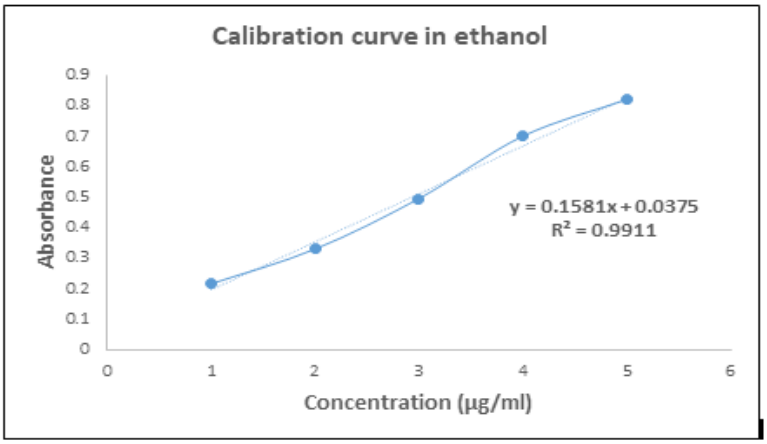

Figure 1: Calibration curve in ethanol

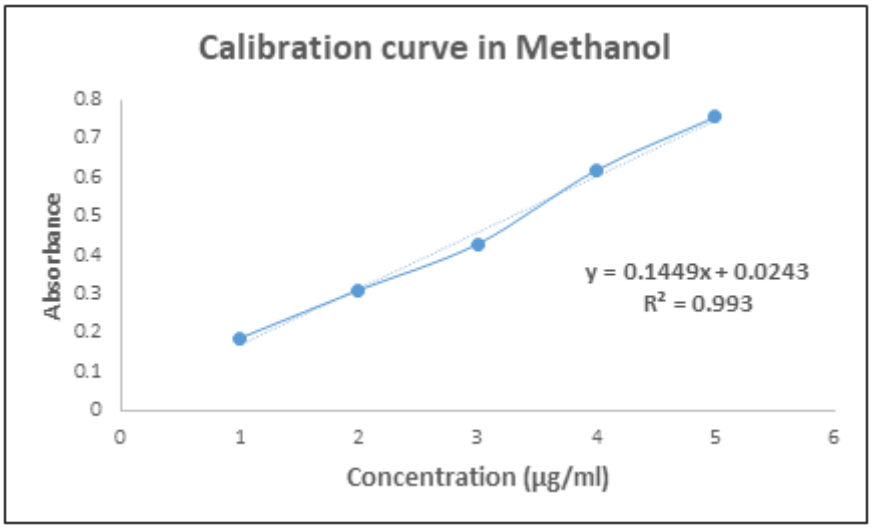

Figure 2: Calibration curve in methanol

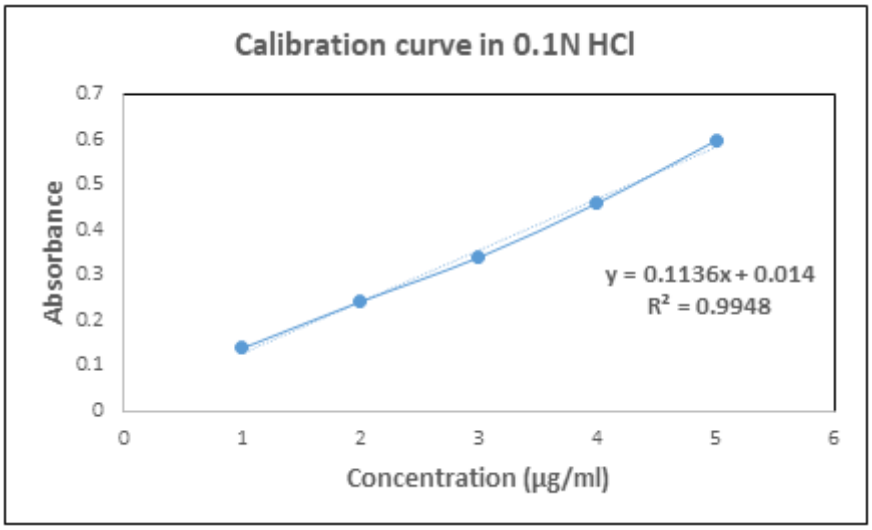

Figure 3: Calibration curve in 0.1N HCl

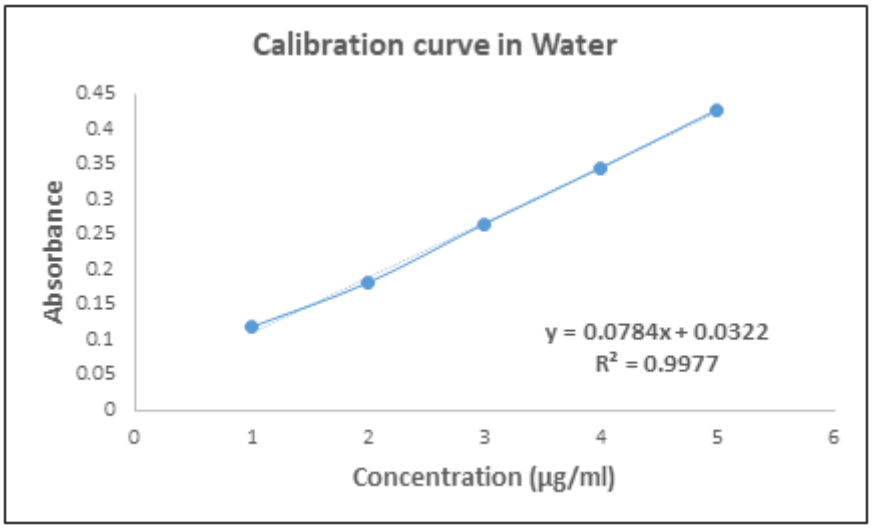

Figure 4: Calibration curve in water

3.1.3 Solubility study of pure drug

Solubility of pure drug was found to be 0.487 mg/ml.

3.1.4 FT-IR study for drug and carrier compatibility

FT-IR study was done for drug, co-former separately and then for the prepared co-crystals. The resulted spectrum revealed that there is no interaction between drug and co-former. The result showed that no functional group interfered that means drug and co-former are chemically compatible and also there is no change in drug's major peak as mention in **table 3**.

Table 3: Interpretation of IR-spectrum

Ingredients	C-H stretching	-NH- stretching	C-O stretching	C=C stretching	C=O stretching
Modafinil	3033	3336	1400	-	-
Sodium Acetate	-	-	-	1408	1736
Modafinil + Sodium acetate	3005	3338	1409	-	-

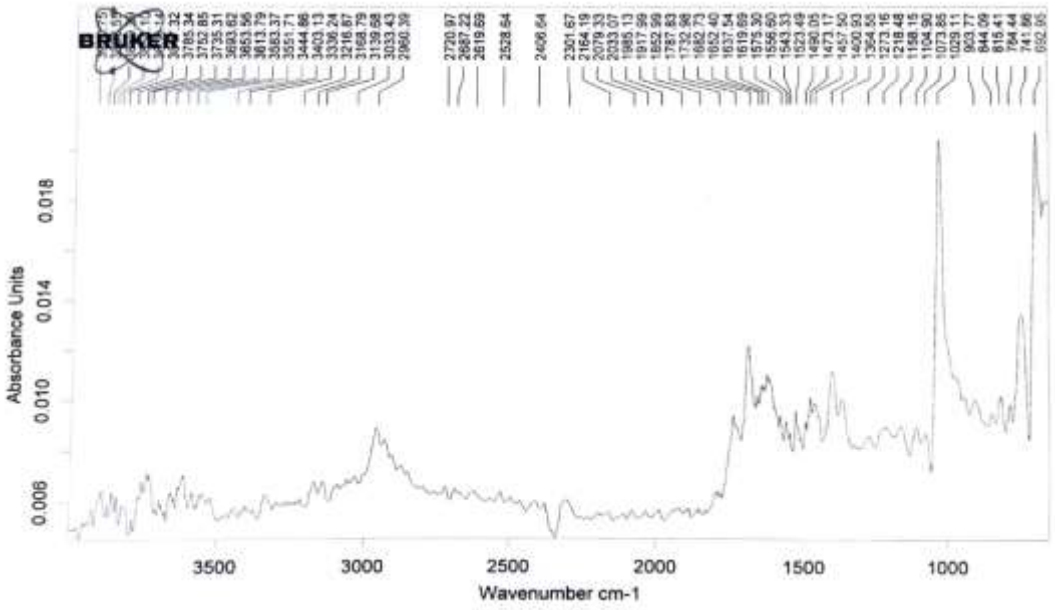

Figure 5: FT-IR spectrum of pure Modafinil

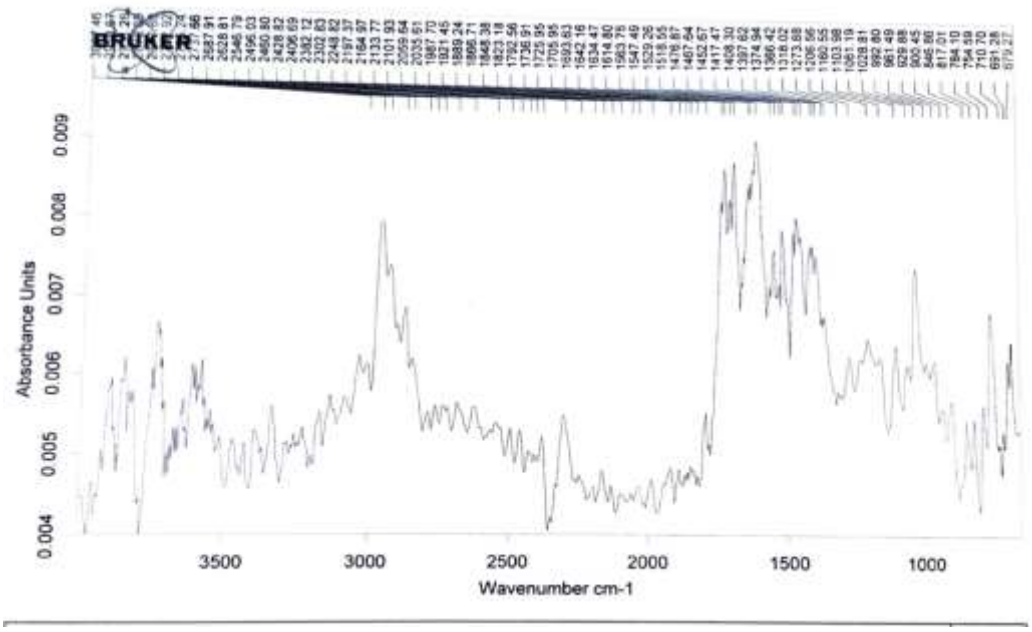

Figure 6: FT-IR spectrum of Sodium acetate

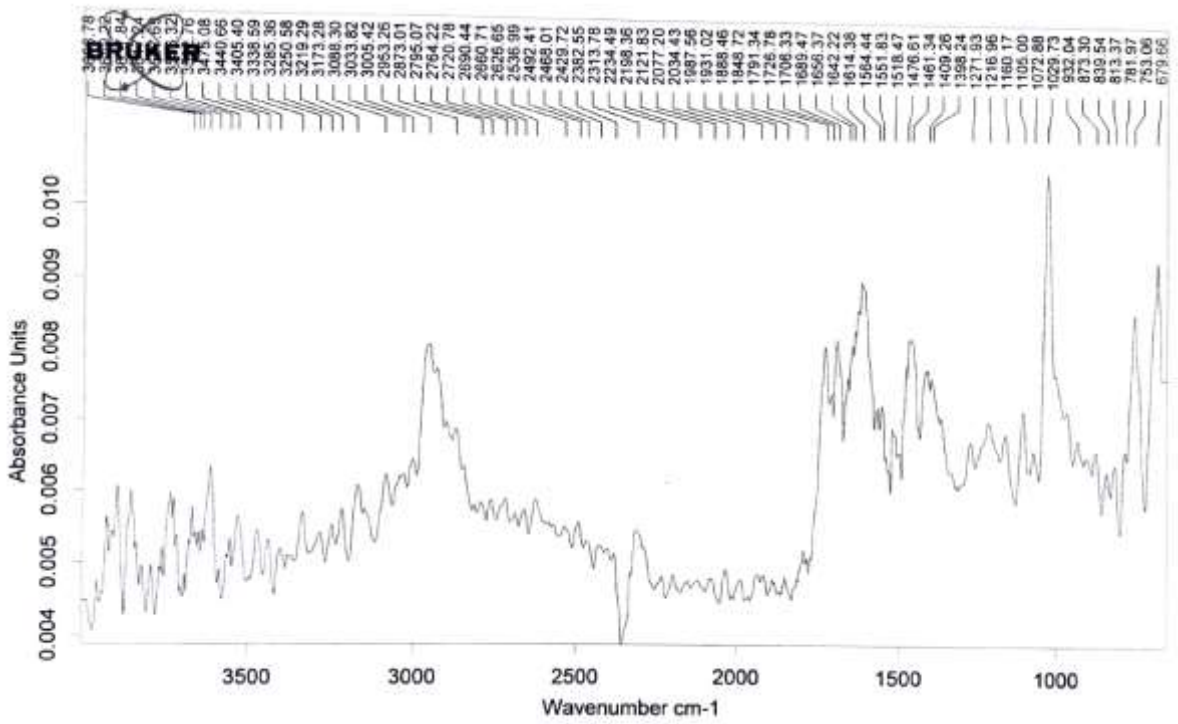

Figure 7: FT-IR spectrum of Modafinil and Sodium acetate

3.2 Evaluation of Co-crystals

Using a dry grinding process, a total of five coformers were evaluated for the possibility of co-crystal formation with Modafinil. Modafinil only successfully reacted with sodium acetate to produce a new co-crystal form. Modafinil co-crystal that was obtained underwent physicochemical analysis and orodispersible tablet formulation.

3.2.1 Melting point and saturation solubility

As a first step in the screening process for probable co-crystals, these two characteristics were estimated. Table 4 lists the determined melting points of pure drug, coformers, and co-crystals. Solubility was also determined and noted in a table 4. Co-crystal melting values were lower than those of Modafinil. Melting point depression revealed multi-component systems and indicated co-crystal formation. The interaction between Modafinil and coformers, a variation in the crystallinity of the molecules, or a new packing arrangement could all be responsible for the changing melting points of co-crystals. This contact causes a modification in the molecular arrangement, resulting in a new crystal structure with altered solubility and/or melting point. With each co-former, co-crystal solubility increased, but sodium acetate significantly (2.5 folds) improved it. This shows that Modafinil and coformers were able to interact effectively and produce co-crystals. Based on the findings, the co-crystal of modafinil sodium acetate, referred to as modafinil co-crystal in the parts that follow, was further studied and used in the creation of orodispersible tablets.

Table 4: Melting point and solubility of co-crystals

Drug/Coformer	Melting point (co-former)	Crystal Melting Point (1:1)	Solubility (mg/ml) (1:1)	Crystal Melting Point (1:2)	Solubility (mg/ml) (1:2)
Modafinil	164-166 ^{0}C		0.487		
Modafinil-Sodium acetate	324 ^{0}C	148 - 150 ^{0}C	1.22	153 – 155 ^{0}C	0.990
Modafinil-Urea	133-135 ^{0}C	137 – 140 ^{0}C	0.781	130 – 132 ^{0}C	0.891
Modafinil-Nicotinamide	125-130 ^{0}C	135 – 137 ^{0}C	0.914	140 – 142 ^{0}C	1.101
Modafinil-Benzoic acid	120 – 122 ^{0}C	147 – 149 ^{0}C	0.902	148 – 149 ^{0}C	0.962
Modafinil-Succinic acid	184 – 186 ^{0}C	142 – 144 ^{0}C	0.973	138- 140 ^{0}C	0.720

3.2.2 Drug Content

Formulation of co-crystal with sodium acetate in 1:1 ratio showed highest drug content (97.97 %), while Benzoic acid in ratio 1:2 showed least drug content (56.48%). Data obtained showed that drug content was decreased on increasing co-former amount, as seen in 1:2 ratios of drug and co-former.

Table 5: Drug content of prepared co-crystals

Co-crystals with coformers	% Drug Content (1:1)	% Drug Content (1:2)
Sodium acetate	97.97	84
Nicotinic acid	91	78.6
Succinic acid	70.08	63.84
Urea	64.32	59.64
Benzoic acid	60	56.48

3.3 Pre-Compression parameters

Table 6: Pre-compression parameters result

Parameter	F1	F2	F3	F4	F5	F6
Bulk density (gm/cm^3)	0.349	0.346	0.331	0.344	0.397	0.369
Tapped density (gm/cm^3)	0.399	0.422	0.390	0.420	0.472	0.425
Hausner's ratio	1.14	1.22	1.12	1.22	1.19	1.15
Compressibility index (%)	12.31	18.00	10.79	18.01	15.89	13.18
Angle of repose	29.74	27.14	29.05	30.47	30.47	31.22

3.4 Post-Compression Parameters:

The resulted data of post compression parameters revealed that all the prepared tablets had uniform weight. Weight variation and thickness were found to be in acceptable range. Tablet hardness was retained in range of 3.18-3.25 kg/cm^2 for all the tablets. Friability was also in acceptable range between 0.74 to 85%. The hardness and friability data indicated that the tablets had good mechanical resistance. Formulation F1 was promising as it exhibited least disintegration time (34 ± 3.71 sec), and wetting time (24 ± 0.45 sec).

Table 7: Post compression parameters result

S.No.	Weight Variation (mg) ± SD	Hardness (Kg/cm^2)	Thickness (mm)	Disintegration time (Sec)	Friability (%)	Wetting Time
F1	398.55 ± 5.80	3.21 ± 0.28	6.27 ± 0.41	34 ± 3.71	0.74	24 ± 0.45
F2	396.05 ± 7.11	3.25 ± 0.26	6.28 ± 0.32	35 ± 5.49	0.81	26 ± 0.68
F3	397.65 ± 7.13	3.18 ± 0.30	6.18 ± 0.23	35 ± 6.09	0.84	26 ± 0.34
F4	400.45 ± 5.63	3.24 ± 0.26	6.13 ± 0.21	36 ± 3.22	0.78	28 ± 0.59
F5	400.1 ± 4.86	3.23 ± 0.30	6.15 ± 0.29	41 ± 2.16	0.80	30 ± 0.25
F6	401 ± 4.94	3.15 ± 0.25	6.1 ± 0.23	42 ± 3.14	0.85	33 ± 0.86

3.4.1 In-vitro drug release:

In-vitro studies showed that formulation with SSG, obtained higher drug release. Formulation F2 showed highest drug release (96%) while formulation F3 had lowest drug release (83%). The results obtained are given below in Table 8.

Table 8: % drug release of prepared batches

% Drug Release						
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
5	32	39	24	28	31	32
10	49	53	46	42	46	49
15	58	61	52	63	53	52
20	68	70	69	71	69	70
30	81	88	78	79	81	86
45	86	96	83	89	85	89

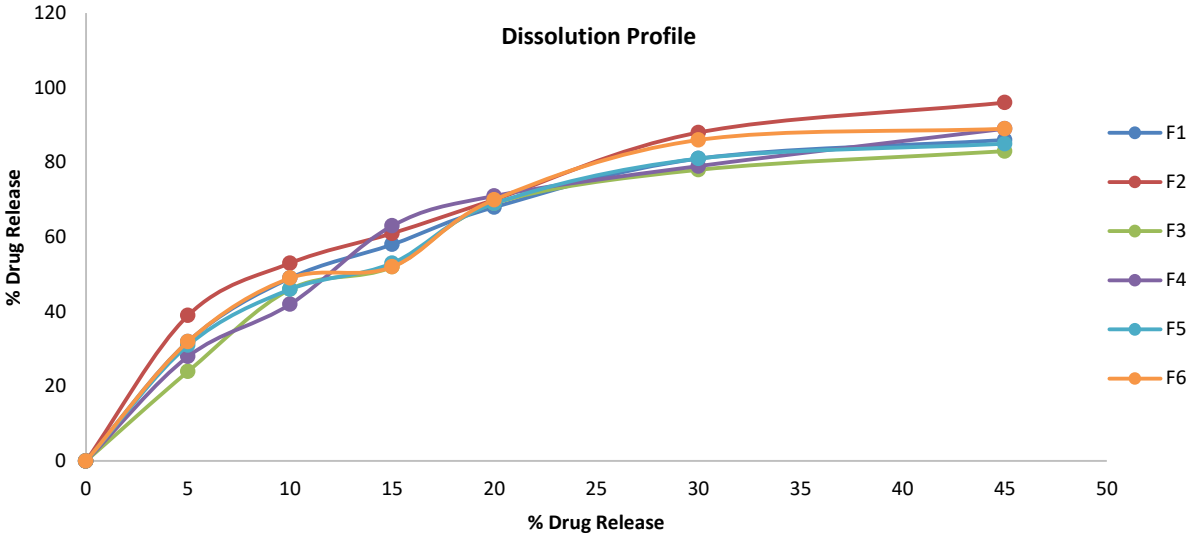

Figure 9: Comparative drug release profile of prepared batches

4. CONCLUSION:

The current study was conducted to formulate and evaluate orodispersible tablets containing co-crystals of poorly soluble Modafinil, to improve its dissolution rate, solubility and hence bioavailability. All the prepared batches of tablet were found to have physicochemical parameters in acceptable limit. Among all the formulated batches, F2 showed highest drug release containing SSG as super disintegrant that makes it a promising approach for increasing solubility of poorly water soluble drugs. Orodispersible tablets of Modafinil could be considered convenient oral delivery systems to enhance the drug bioavailability.

5. Conflict of interest:

There is no conflict of interest.

REFERENCES

1. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst Growth Des*. 2009;9(6):2950-2967. doi:10.1021/cg900129f
2. Kuang W, Ji S, Wang X, Zhang J, Lan P. Relationship between crystal structures and physicochemical properties of lamotrigine cocrystal. *Powder Technol*. 2021;380:18-25. doi:10.1016/j.powtec.2020.11.039
3. Bolla G, Nangia A. Pharmaceutical cocrystals: Walking the talk. *Chem Commun*. 2016;52(54):8342-8360. doi:10.1039/c6cc02943d
4. Shan N, Perry ML, Weyna DR, Zaworotko MJ. Impact of pharmaceutical cocrystals: The effects on drug pharmacokinetics. *Expert Opin Drug Metab Toxicol*. 2014;10(9):1255-1271. doi:10.1517/17425255.2014.942281
5. Hickey MB, Peterson ML, Scoppettuolo LA, et al. Performance comparison of a co-crystal of carbamazepine with marketed product. *Eur J Pharm Biopharm*. 2007;67(1):112-119. doi:10.1016/j.ejpb.2006.12.016
6. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. *Int J Pharm*. 2011;419(1-2):1-11. doi:10.1016/j.ijpharm.2011.07.037
7. Tomaszewska I, Karki S, Shur J, Price R, Fotaki N. Pharmaceutical characterisation and evaluation of cocrystals: Importance of in vitro dissolution conditions and type of coformer. *Int J Pharm*. 2013;453(2):380-388. doi:10.1016/j.ijpharm.2013.05.048
8. Gerrard P, Malcolm R. Mechanisms of modafinil: a review of current research. Neuropsychiatr Dis Treat. 2007;3(3):349–364.
9. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. Ann Pharmacother. 2006;40(10):1829–1833.
10. Panzade P, Shendarkar G, Shaikh S, Rathi PB. Pharmaceutical Cocrystal of Piroxicam : Design , Formulation and Evaluation Pharmaceutical Cocrystal of Piroxicam : Design , Formulation and Evaluation. *Tabriz Univ Med Sci*. 2017;7(3):399-408. doi:10.15171/apb.2017.048
11. Mohan G, Kuriachan MA. Formulation and Evaluation of Orodispersible Tablet of Esomeprazole. 2018;(3).
12. Kiran NR, Palanichamy S, Rajesh M, et al. Formulation and Evaluation of Orodispersible Piroxicam Tablets. 2010;2(10):615-621.
13. Cocrystal F. Superior Solubility and Dissolution of Zaltoprofen via Pharmaceutical Cocrystals. 2019;16(3):310-316. doi:10.4274/tjps.galenos.2018.15013
14. Latif S, Abbas N, Hussain A, et al. Development of paracetamol-caffeine co-crystals to improve compressional, formulation and in vivo performance. *Drug Dev Ind Pharm*. 2018;44(7):1099-1108. doi:10.1080/03639045.2018.1435687
15. Shewale S, Shete AS, Doijad RC, Kadam SS, Patil VA, Yadav A V. Formulation and solid state characterization of nicotinamide-based co-crystals of fenofibrate. *Indian J Pharm Sci*. 2015;77(3):328-334. doi:10.4103/0250-474X.159669
16. Poonuru R, Cheruku R, Juluri P, et al. Original Article formulation and evaluation of orodispersible tablets of lamotrigineusing discrete super disintegrants and coprocessed excipients. 2020;12(6).
17. Abed KK, Hussein AA, Ghareeb MM, Abdulrasool AA. Formulation and Optimization of Orodispersible Tablets of Diazepam. 2010;11(1):356-361. doi:10.1208/s12249-010-9387-y
18. Rampure M, Shirsand SB, Deshpande R. Formulation and Evaluation of Orodispersible tablets of Alfuzosin. 2010;(January).
19. Basu B, Bagadiya A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. 2011;2(4). doi:10.4103/2231-4040.90885
20. P. Hyma ds, k. Jyothi. Formulation and evaluation of orodispersible tablets of naproxen sodium by direct compression method . 2021;11(09).
21. Panhale DP, Bachhav RS, Gondkar SB. Formulation and Evaluation of Orodispersible Tablets of Apremilast by Inclusion Complexation using β -Cyclodextrin. 2021;55(1). doi:10.5530/ijper.55.1s.42
22. Sirmour D. The formulation and evaluation of mouth dissolving tablet Levocetirizine by using synthetic Superdisintegrants. 2020;5(1):1-11. doi:10.22270/hjhs.v5i1.47