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Enhancement of solubility and bioavailability of modafinil using nanoparticles

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ABSTRACT

The aim of the present work is to develop polymeric nanoparticles using Modafinil to improve its solubility thereby increasing its bioavailability. Ionic-Gelation method has been employed for the preparation of nanoparticles using chitosan, a natural polymer and TPP, cross linking agent. In this method the drug is mixed with polymer and maintained at pH between 4.5 - 5.5 and the solution of TPP is added to the polymer-drug mixture under magnetic stirring. The size of nanoparticles prepared by this method usually ranges from 1-1000 nm. The reduction in size of particles directly enhances the solubility of drug that increases its bioavailability. Nine formulations (F_1-F_9) of nanoparticles were optimized by varying the concentrations of chitosan and TPP. Prepared nanoparticles were evaluated for size, zeta potential, PDI and drug content. Formulation F_9 with 0.25% of chitosan & 0.5% of TPP concentration has been choosed as best formulation and lyophilized to obtain solid nanoparticles. The obtained nanoparticles loaded with modafinil are used for the preparation of tablets and the *in-vitro* dissolution characteristics are compared with the marketed tablet of modafinil. *in-vitro*characteristics of tablets with modafinil loaded polymeric nanoparticles showed improved solubility than marketed tablet.

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INTRODUCTION

Modafinil is a CNS stimulant that promotes wakefulness. Modafinil is used in the treatment of narcolepsy, ADHD (Attention Deficient Hyperactivity Disorder), shift work sleep disorder, hypersomnia and excessive daytime sleepiness. The chemical name for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide that belongs to BCS Class-II with low solubility and high permeability. The absolute bioavailability of modafinil is not clear due to its aqueous insolubility (Robertson and Hellriegel, 2003). However, in-vitro modafinil binds to the dopamine transporter and inhibits dopamine reuptake, this activity has been associated with in-vivo with increased extracellular dopamine.

For BCS Class-II substances the bioavailability may be enhanced by increasing the solubility of drug and its dissolution rate in gastro intestinal fluid (Khadka *et al.*, 2014). Considering the drugs with low solubility, the relation between dissolution rate and absorption is very distinct. Improvement of drug solubility thereby increasing its bioavailability is the most challenging aspect of drug development. Many techniques have been made to modify the dissolution characteristics of drugs to attain more rapid absorption.

Particle size reduction is a physical modification technique in which the size of drug particle can be reduced by techniques like micronization and nanonization (nanotechnology). In nanotechnology the particle size of drug can be reduced to nanoscale level, by different methods of preparation of nanoparticles such as nanoencapsulation, nanosuspension, nanoprecipitation, etc., Nanoencapsulation of drug is the method of preparing loaded particles in the size range of 1 to 1000 nm (Malodia *et al.*, 2012). Nanoencapsulation includes both nanospheres and nanocapsules. Nanospheres are matrix type of system in which the drug may be absorbed to the surface or encapsulated within the particle (polymer) (Reis *et al.*, 2006).

The present study is an approach for improving the solubility characteristic of modafinil. For this, polymeric nanoparticles were prepared by ionic-gelation method in which chitosan is used as polymer and tripolyphosphate (TPP) is used as cross linking agent (Ahirrao *et al.*, 2014). The best formulation has been choosed and lyophilized to obtain solid nanoparticles of modafinil and tablets were prepared and compared with the *in-vitro* characteristics of marketed tablet of modafinil.

MATERIALS AND METHODS

Modafinil (Free sample); Acetic acid, Sodium tripolyphosphate [TPP], Povidone, Talc (Loba Chemie); Chitosan, Magnesium stearate (HI-media Laboratries); Crosspovidone (Yarrow Chem Products).

Melting pointing and solubility

Melting point of the drug was determined using digital melting point apparatus in which a capillary tube fused at one end was placed with drug and introduced in the melting point viewer and the degree at which the drug melted was noted down. Test for solubility was performed by dissolving minimum quantity of drug in various solvents (Jigar *et al.*, 2012).

Calibration Study – UV Spectroscopy Study

Modafinil standard stock solution was prepared by dissolving 100mg of modafinil in 10ml of ethanol and sonicated for 10 minutes and the solution was made upto 100ml using 0.1 N Hydrochloric acid (1000μg/ml). 10ml of prepared solution was diluted to 100ml using 0.1 N Hcl (100μg/ml). To form concentration of 1μg/ml, 1ml of 100μg/ml stock solution was diluted to 10ml with 0.1 N Hcl and scanned using UV visible spectrophotometer in the spectrum mode between the wavelength ranges of 200nm to 400nm, to determine the maximum absorbance (Mahapatra *et al.*, 2011).

The prepared stock solution was serially diluted to get different concentrations 2, 4, 6, 8 and 10μg/ml to determine the linearity range. The standard samples were analyzed at 222nm using UV Spectrophotometer.

Formulation of modafinil nanoparticles

Modafinil polymeric nanoparticles were prepared by ionic-gelation method. Chitosan solution of concentrations 0.25, 0.50 & 0.75% was prepared by dissolving the required quantities of chitosanin 0.1% acetic acid and allowed to stir for 6 hours under magnetic stirring and the solution was allowed to set constant for upto 18 hours. TPP solution of concentrations 0.50, 1 & 1.5% was prepared by dissolving the weighed quantities of TPP in 100ml of distilled water and kept under magnetic stirring for 15 minutes.Chitosan solution was taken in a beaker and the pH of solution was adjusted to pH 4.5-5.5, to this solution 100mg of modafinil was added and dissolved and the pH of solution was maintained between 4.5-5.5.

The above prepared solution was constantly kept in magnetic stirrer to this, a mixture of TPP was added dropwise with constant stirring and allowed for 30 minutes (Grenha, 2012; Fàbregas *et al.*, 2013; Kunjachan and Jose, 2010; Agarwal *et al.*, 2018; Papadimitriou *et al.*, 2008).

Chitosan and TPP were added in the ratio of 6:1. Table 1 shows nine different formulations with three different ratios of chitosan and TPP for modafinil nanoparticles.

Evaluation of prepared modafinil nanoparticles

Particle size and polydispersity index (PDI)

Particle size and PDI value were determined using Zetasizer (Nano ZS90, Malvern Instruments) at 25° C. For the measurement of particle size and PDI value the samples were kept in polystyrene cuvette and the readings were found out at a fixed angle.

Zeta potential

The electrophoretic mobility (zeta potential) measurement of polymeric nano-particles was done by using Zetasizer (Nano ZS90, Malvern Instruments). The samples were placed in a polystyrene cuvette (at 25 °C) combined with Zeta dip cell was used to measure the potential.

Entrapment efficiency

2 ml of the formulation was taken and centrifuged at 12,000 rpm 60 minutes. The supernatant was recovered using micro pipette and was analyzed under UV spectrophotometer at 222nm

Table 1: Formulation table of modafinil nanoparticles

Formulation code	Drug	Polymer	TPP
F1	1	0.25	0.25
F2	1	0.25	0.50
F3	1	0.25	0.75
F4	1	0.50	0.25
F5	1	0.50	0.50
F6	1	0.50	0.75
F7	1	0.75	0.25
F8	1	0.75	0.50
F9	1	0.75	0.75

Encapsulation efficiency (%) =

$$\frac{Total\ amount\ of\ drug\ added - Free\ drug}{Total\ amount\ of\ drug\ added} \times 100$$

Lyophilization technique

Entrapment efficiency, particle size and zeta potential were taken as important factors and based on their values best formulation was selected. The selected formulations were kept in well closed containers and allowed to freeze under -80° C for 4 hours. Then the formulations were kept in Lyodel freeze drier at -40° C.

Characterization of freeze dried formulation of modafinil nanoparticle - SEM analysis

The surface morphology of lyophilized nanoparticle was observed using SEM (Scanning Electron Microscopy). The stub containing sample was placed in the chamber of scanning electron microscope to confirm the particles are in nano range (Heera and Shanmugam, 2015).

Preparation of modafinil nanoparticle tablets

Modafinil tablets were prepared by direct compression method. Cross-Povidone, Povidone, Talc and Magnesium Stearate were added respectively as disintegrant, binder, glidant and lubricant to this formulation in different concentrations and compressed into tablets (Bushra, 2018; Upadhyay and Gupta, 2018).Table 2 shows the formulationsprepared for tablets loaded with modafinil nanoparticles.

Evaluation of prepared modafinil nanoparticle loaded tablet

Thickness and diameter

Thickness and Diameter of the tablet is important for the uniformity of the tablet size. Tablets are selected and thickness of the tablet was measured by using Screw Gauge and Vernier Caliper apparatus.

Weight variation test

The prepared tablets were individually weighed using electronic balance and the test was performed and the deviation was calculated with respect to average weight. The percentage deviation of tablets between the weight 80 mg – 250 mg is $\pm$ 7.5% as per pharmacopoeial limits.

Hardness test

The prepared tablets were subjected to hardness test which was determined using Pfizer hardness tester and it was measured in kg/cm^2.

Disintegration test

Disintegration test for the prepared tablets was performed using Basket-rack assembly. One tablet was placed in each of the basket and the test was performed using 0.1N Hcl buffer as the immersion fluid maintained at 37$\pm$ 2° C. Time for completely disintegrated tablets was noted.

Dissolution test

Dissolution studies were carried out by using USP-II dissolution test apparatus. The paddle was rotated at 50 rpm and depth of 25 mm in a buffer volume of 900ml. Dissolution testing, was carried out using buffer of pH 1.2 representing the stomach pH. Samples were periodically and it was replaced with fresh buffer in order to maintain sink conditions. The samples were filtered through filter paper and diluted to suitable concentration. Then, the samples were analyzed using UV-spectrophotometer at 222nm.

Based on the above three factors, tablet formulation FT_3 was selected as best formulation and the *in-vitro* characteristics of FT_3 was compared with marketed modafinil tablet.

***In-vitro* release study of marketed modafinil tablet**

Same dissolution procedure followed to the prepared modafinil nanoparticle loaded tablet was fol-

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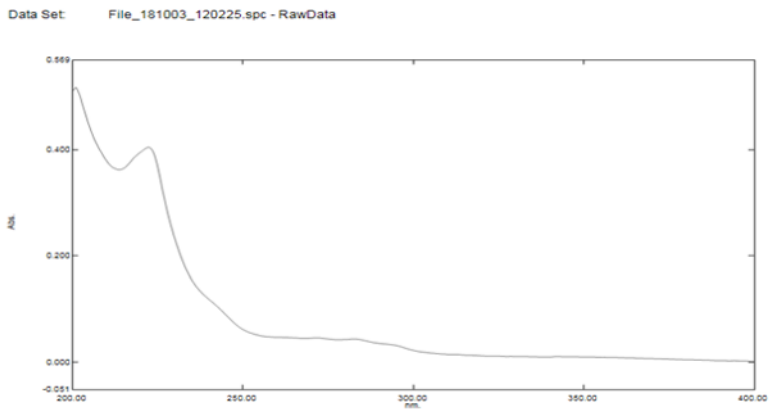

Figure 1: Lambdamax of modafinil by UV-Spectrophotometer

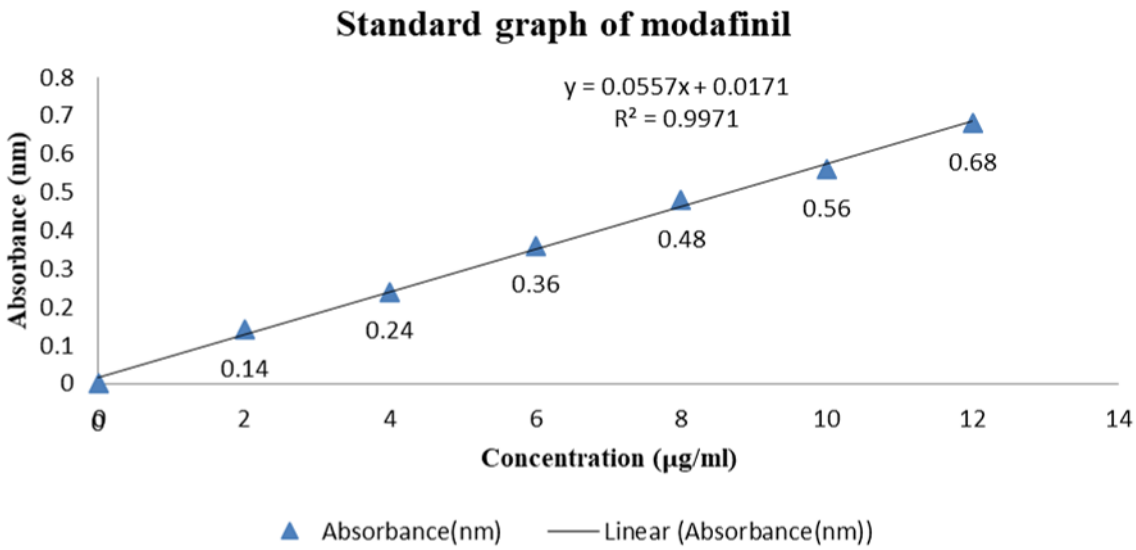

Figure 2: Standard graph of modafinil by UV-Spectroscopy

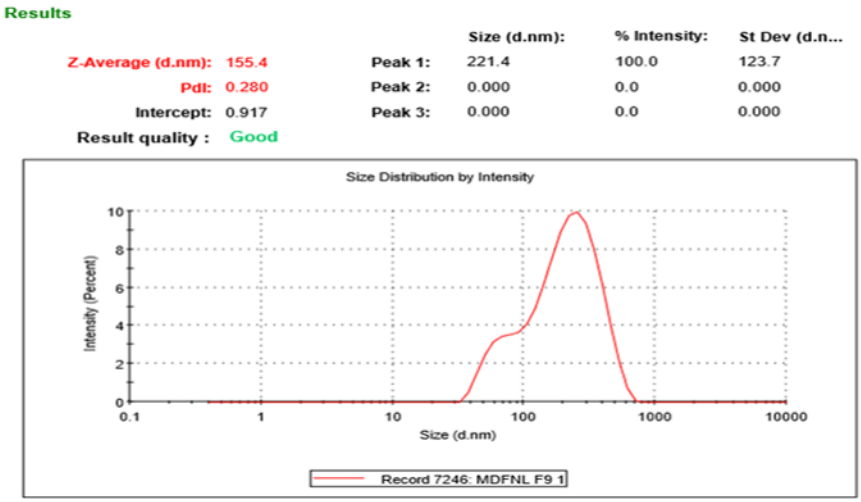

Figure 3: Particle size and PDI value for formulation F_7

Table 2: Formulation of modafinil tablets

Formulation code	Formulation F7(mg)	Tablet excipients			
		Povidone	Cross-povidone	Talc	Magnesium stearate
FT1	100	15	10	20	5
FT2	100	15	15	15	5
FT3	100	25	10	10	5
FT4	100	25	15	5	5

Table 3: Particle size, PDI, Zeta potential and entrapment efficiency values of modafinil nanoparticles

Formulation Code	Particle size (nm)	PDI	Zeta potential (mV)	Entrapment efficiency(%)
F1	280	0.516	24.5	60
F2	176	0.382	16.1	64
F3	403	0.502	25.4	67
F4	538	0.830	13.4	65
F5	549	0.137	16.3	70
F6	237	0.513	21.4	63
F7	155	0.280	30.3	80
F8	113	0.294	28.3	74
F9	271	0.499	21.1	76

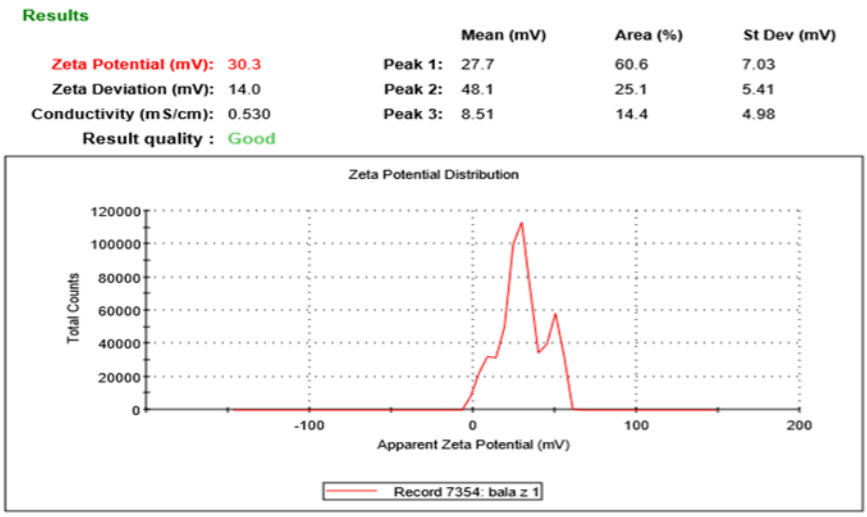

Figure 4: Zeta potential of formulation F_7

Table 4: Average thickness and diameter of prepared tablets

Formulation code	Average thickness (mm)	Average diameter (cm)
FT1	4.02	1.2
FT2	4.04	1.4
FT3	4.05	1.5
FT4	4.04	1.4

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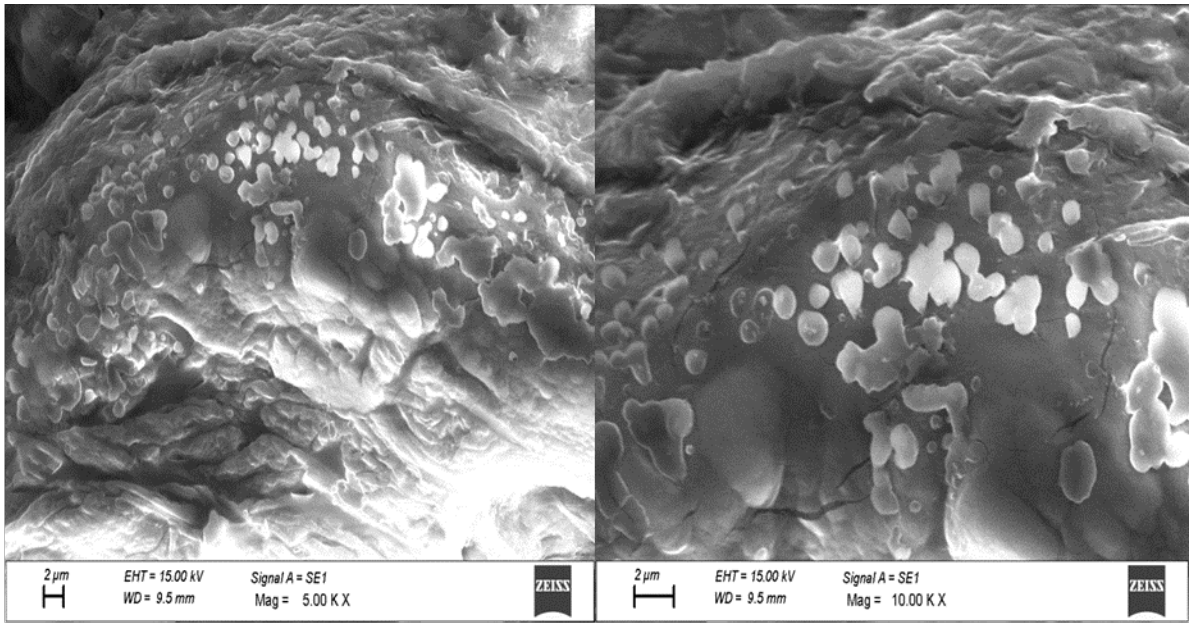

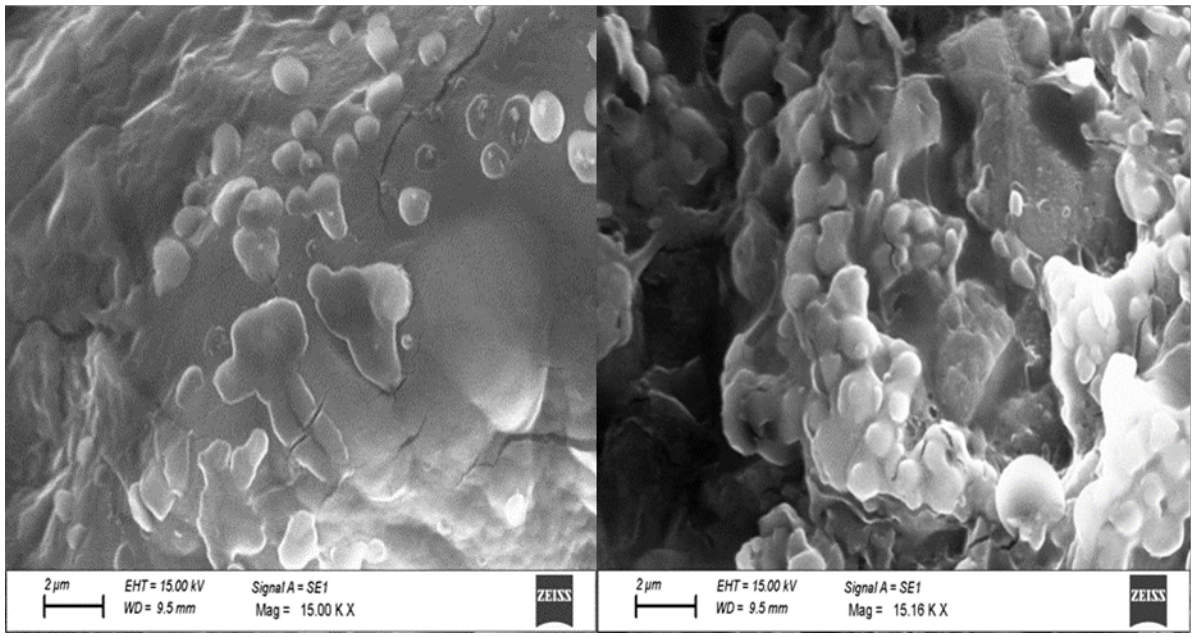

Figure 5: Scanning electron microscope image showing themorphology of freeze-dried modafinil nanoparticle (F_7)

Table 5: % Deviation of prepared tablets

Formulation code	Average weight of tablets (mg)	% Deviation
FT1	178.73	-0.005
FT2	178.93	0.072
FT3	178.70	0
FT4	178.93	0.072

Table 6: Disintegration and hardness values of prepared tablets

Formulation code	Hardness value(kg/cm^2)	Disintegration time (min)
FT1	5.5	10
FT2	4.2	8
FT3	6.5	17
FT4	6.2	15

Table 7: Drug release data of prepared tablets

Time (min)	% Drug release of prepared tablets				% Drug release of marketed tablet
	FT1	FT2	FT3	FT4	
0	0	0	0	0	0
5	25.58	54.41	40.07	28.96	59.24
10	31.38	63.11	44.75	30.57	61.5
15	38.14	66.49	47.81	39.43	64.72
20	42.17	72.61	49.09	44.42	69.715
25	49.58	79.86	51.67	48.13	72.61
30	56.5	85.17	54.09	51.03	74.86
45	61.98	90.16	56.5	53.44	77.44
60	68.1	97.41	58.44	61.98	80.0226

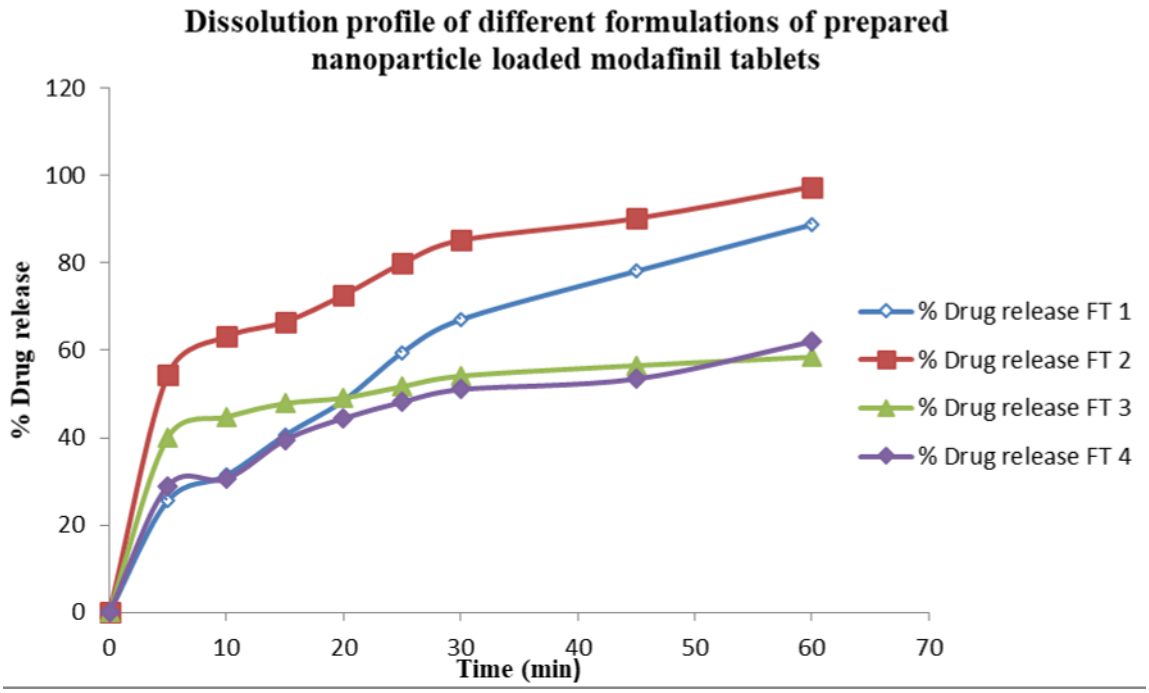

Figure 6: Dissolution profile data of prepared Tablets

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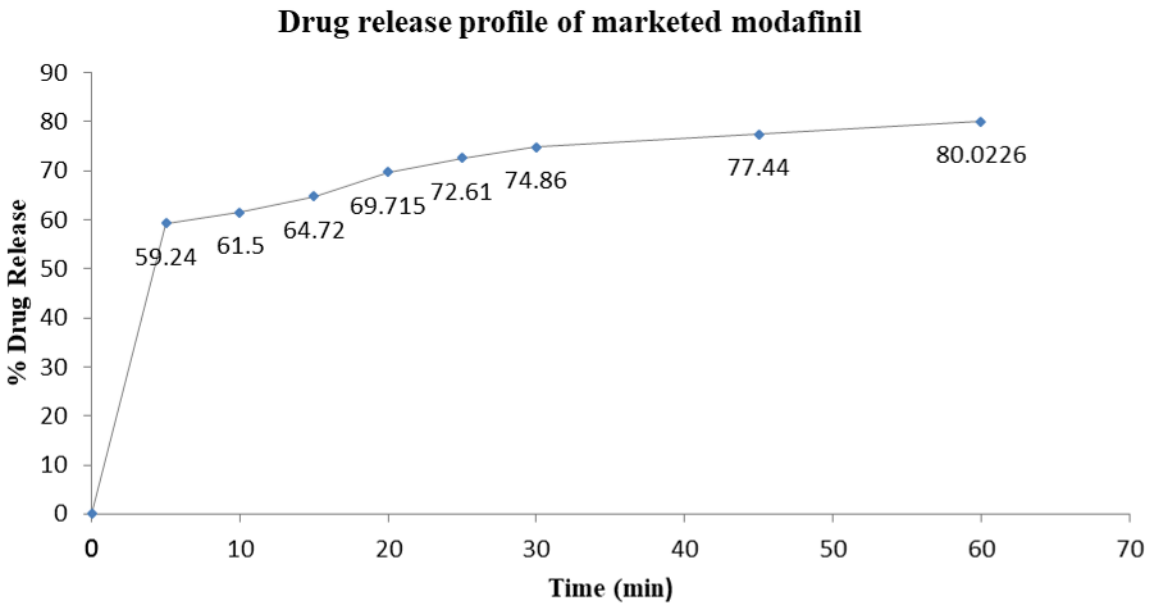

Figure 7: Dissolution profile data of marketed modafinil tablet

lowed to the marketed tablet of modafinil, using USP-II apparatus, rotated at 50 rpm in buffer volume of 900 ml using buffer of pH 1.2. Samples were periodically taken and replaced with fresh buffer at required time intervals. The samples were filtered, diluted to equivalent concentration and analyzed at 222 nm using UV spectrophotometer.

RESULTS AND DISCUSSION

Melting point is found to be 165° C which confirms Modafinil drug. Solubility of modafinil in different solvent was carried out and found that modafinil is soluble in acetic acid (150mg/ml) and slightly soluble in ethanol (10mg/ml).

The prepared stock solution of modafinil was scanned in UV-Visible spectrophotometer from 200 – 400 nm and the maximum wavelength occurs at 222nm that is shown in Figure 1 and it is selected as the maximum absorbance.

A series of concentrations of solution 2, 4, 6, 8 and 10μg/ml were prepared and the absorbances were noted at 222nm using UV spectrophotometer.The standard graph of modafinil is plotted in Figure 2. The regression value was found to be 0.997 from the graph.

Particle size and PDI were determined by photon correlation spectroscopy using Zetasizer (Nano ZS 90, Malvern instruments) at 25° C. Reduction in particle size enhances the rate of dissolution and PDI is the degree of particle size distribution, narrow the particle size distribution prevents the particle growth and maintains the stability. The zeta potential value determines the physical stability of the formulation. A minimum zeta potential value of $\pm$30mV is required, whereas a minimum zeta potential of $\pm$20mV is desirable. Entrapment efficiency is the amount of drug entrapped within in the formulation that was found out by centrifuging the 2 ml of formulation at 12,000 rpm for 60 minutes and analyzing the supernatant under UV spectroscopy at 222 nm. The amount of drug entrapped can be calculated by measuring the unbound free drug in the supernatant. Particle size, PDI, Zeta potential and Entrapment Efficiency of formulations are listed in Table 3.

Formulation – F_7 was choosed as the best formulation showing higher entrapment efficiency (%) of 80% and 155 nm of particle size with PDI value of 0.280 as shown in Figure 3 and zeta potential value with +30.3 mV as shown in Figure 4.

Morphological studies of modafinil nanoparticles were performed and shown Figure 5 using Scanning Electron Microscope. The image of SEM depends on signal produced by elastic and inelastic interactions between high energy electron beam and specimen surface.

Evaluation of prepared modafinil nanoparticle loaded tablets

Thickness and Diameter of the tablets was measured by using Screw Guage and Vernier Caliper apparatus and the average readings were tabulated in the following Table 4. The percentage weight variation for all formulations was performed. The percentage deviation of tablets between the weight 80 mg – 250 mg is $\pm$ 7.5% as per pharmacopoeial lim-

its. All the formulations passed the weight variation test as per the limits as shown in the Table 5. The hardness of prepared tablets were determined using Pfizer hardness tester. Hardness of the tablet is the indication of its strength against resistance of tablet. The hardness values of tablets of reported in Table 7. The average range of tablets prepared tablets are between 2 – 8 kg/cm^2. The prepared individual tablets of each formulation were tested for disintegration which in turn is the time required for the tablet to get finely dissolved in gastric tract, the disintegration time of each batch of tablet is listed in Table 6. Immediate release tablets disintegrate within a time a 15 minute.

In-vitro release study of marketed and prepared modafinil tablet

Dissolution studies were performed by USP-II type apparatus at speed of 50 rpm in 0.1 N Hcl buffer and drug release was calculated, which shows the drug release of four formulation of nanoparticle loaded tablet that is represented in Table 7 and Figure 6. From the parameters of hardness, disintegration and dissolution test formulation (FT_2) was selected as best formulation. *In-vitro* dissolution studies were performed for the marketed tablet of modafinil under the same conditions prescribed to dissolution test of prepared nanoparticle loaded modafinil tablet. The release profile data of marketed tablet and FT_2 formulated tablet where compared and the formulated tablet showed a better release. Drug release profile of marketed tablet is figured and tabulated in Table 7 and Figure 7.

CONCLUSION

From the above studies, it was concluded that Modafinil tablets loaded with polymeric nanoparticles of modafinil prepared by ionic-gelation has better solubility. Comparing the dissolution profile of prepared nanoparticle loaded modafinil tablet with the marketed tablet, the prepared tablet shows 97% drug release in an hour and proves 0.21 fold better drug release than marketed tablet. This confirms the enhanced solubility of modafinil, which may be useful confirmation for suggesting future study on increase in bioavailability of modafinil in animal study.

REFERENCES

Agarwal, M., Agarwal, M. K., Shrivastav, N., Pandey, S., Das, R., Gaur, P. 2018. Preparation of Chitosan Nanoparticles and their In-vitro Characterization. *International Journal of Life-Sciences Scientific Research*, 4(2):1713–1720.

Ahirrao, S. P., Gide, P. S., Shrivastav, B., Sharma, P. 2014. Ionotropic Gelation: A Promising Cross-Linking Technique for Hydrogels. *Journal of Pharmaceutics and Nanotechnology*, 2(1):1–5.

Bushra, R. 2018. Formulation & Characterization Study of Immediate Release Progestrin Tablet and its Comparative Study with Innovator Drug. *Pakistan Journal of Pharmaceutical Sciences*, 31(6):2725–2731.

Fàbregas, A., Miñarro, M., García-Montoya, E., Pérez-Lozano, P., Carrillo, C., Sarrate, R., Suñé-Negre, J. M. 2013. Impact of physical parameters on particle size and reaction yield when using the ionic gelation method to obtain cationic polymeric chitosan-tripolyphosphate nanoparticles. *International Journal of Pharmaceutics*, 446(1-2):199–204.

Grenha, A. 2012. Chitosan nanoparticles: a survey of preparation methods. *Journal of Drug Targeting*, 20(4):291–300.

Heera, P., Shanmugam, S. 2015. Nanoparticle Characterization and Application : An Overview. *International Journal of Current Microbiology and Applied Sciences*, 4(8):379–386.

Jigar, V., Jayvadan, P., Jain, D. A. 2012. Preparation and characterization of solid dispersion of Modafinil for improvement of dissolution profile. *International Journal of Pharmacy and Pharmaceutical Sciences*, 4(5):348–352.

Khadka, P., Ro, J., Kim, H., Kim, I., Kim, J. T., Kim, H., Lee, J. 2014. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. *Asian Journal of Pharmaceutical Sciences*, 9(6):304–316.

Kunjachan, S., Jose, S. 2010. Understanding the mechanism of ionic gelation for the synthesis of chitosan nanoparticles using qualitative techniques. *Asian Journal of Pharmaceutics*, 4(2).

Mahapatra, A. K., Murthy, P. N., Biswal, S., Mahapatra, A. P. K., Pradhan, S. P. 2011.

Malodia, Singh, S. K., Mishra, D. N., Shrivastava, B. 2012. Nanoparticles: An Advance Technique for Drug Delivery. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 3(3):1186–1208.

Papadimitriou, S., Bikiaris, D., Avgoustakis, K., Karavas, E., Georgarakis, M. 2008. Chitosan nanoparticles loaded with dorzolamide and pramipexole. *Carbohydrate Polymers*, 73(1):44–54.

Reis, C., Neufeld, R. J., Ribeiro, A. J., Veiga, F. 2006. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, 2(1):8–21.

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Robertson, P., Hellriegel, E. T. 2003. Clinical Pharmacokinetic Profile of Modafinil. *Clinical Pharmacokinetics*, 42(2):123–137.

Upadhyay, T. P., Gupta 2018. Formulation & Characterization Study of Immediate Release Progestrin Tablet and its Comparative Study with Innovator Drug. *SGVU Journal of Pharmaceutical Research & Education*, 3(1):279–306.