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Enhancing the Oral Bioavailability of Poorly Water Soluble BCS Class IV Drug Docetaxel Using Mesoporous Silica Nanoparticles

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Abstract: ***This study involves the use of mesoporous silica to evaluate the in vivo performance of ordered mesoporous silica (OMS) as a carrier for poorly water soluble drugs. Mesoporous silica is selected as a carrier for poorly water-soluble drug. Docetaxel is selected as model compound. Solid dispersion technology was used to prepare the Docetaxel loaded mesoporous silica nanoparticles. Physicochemical characterization was carried out by SEM, IR, DSC, and PXRD. Percent drug release was calculated by in vitro dissolution. Because in vitro dissolution is directly correlated with bioavailability in pharmaceutical research, an emerging approach to enhance dissolution is encapsulation of hydrophobic amorphous drugs in ordered mesoporous silica materials. The outstanding features of ordered mesoporous silica materials, including their highly regular mesoporous structure, high surface area, large pore volume, tunable pore size, good biocompatibility, and thermal stability have led to these materials becoming important drug carriers. This work concluded that PARTECK SILICA SLC can therefore be considered as a promising carrier to achieve enhanced oral bioavailability for drugs with extremely low water solubility.***

Keywords: Docetaxel, Mesoporous silica, Parteck silica SLC, Solid dispersion

1. Introduction

BCS class IV drugs (e.g., Amphotericin B, Furosemide, Acetazolamide, Ritonavir, and Paclitaxel) have many characteristics that are problematic for effective oral & per oral delivery. Many of the problems associated with very low aqueous solubility, poor permeability and poor absorption, inter and intra subject variability and significant positive food effect which leads to low and variable bioavailability. Also, most of the class IV drugs are substrate for P-glycoprotein (low permeability) and substrate for CYP3A4 (extensive pre systemic metabolism) which further creates the problem of poor therapeutic potential of these drugs. For clinical effectiveness these drugs require the development of a proper delivery system for both oral and per oral delivery.[(1)]

Mesoporous silica nanoparticles are considered as one of the most promising nanovectors to perform controlled drug delivery for the design of drug nanocarriers, several factors taken into account. By using orgnosilicane functionalized chiral mesoporous silica we can improve drug loading capacity and drug dissolution of mesoporous silica. Also by using ordered mesoporous silica i.e. Parteck silica SLC we can give controlled release to the drug. Hence, mesoporous silica is very important drug carrier for poorly water soluble drugs.(2,3)

It has considered that porous silica and porous glasses are typically nonordered mesoporous materials. They have wide pore distribution and pore structure is nonordered. It is seen that M41S are highly ordered mesoporous materials but they are not crystalline material, instead of they are amorphous materials like glass.

Some important characteristics of mesoporous materials are:

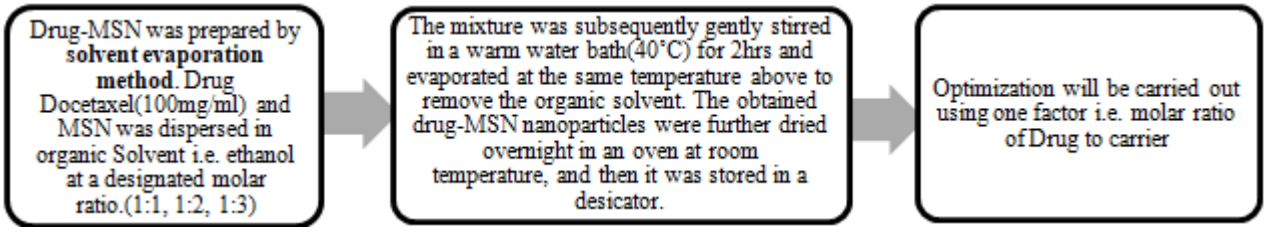
1) They have long range ordered porous structure.
2) Their pore size distribution is usually very narrow and the pore size can be varied from 2 nm to 30 nm by changing the composition of the synthesis mixture or surfactants;
3) They have large surface areas which enable them for sorption processes.
4) Different structure of these materials such as rods, sheets & 3D structures can be obtained by using different surfactants.
5) High thermal stability & hydrothermal stability can be obtained after modification. [(32)]

2. Material and Method

Docetaxel & Parteck silica SLC was obtained from Merck pharmaceuticals.Various chemicals like Ethanol,Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Conc.HCL, N-ocatnol was obtained from Modern science lab Nashik.

2.1 Preparation and optimization of Drug MSN Nanoparticles

Drug-MSN was prepared by using a solvent evaporation method. Drug and MSN was dispersed in anhydrous alcohol at a designated molar ratio. The mixture was subsequently gently stirred in a warm water bath (40˚C) for 2hrs and evaporated at the same temperature above to remove the anhydrous alcohol. Optimization was carried out. In the study, one factor the drug concentration in solvent was selected as independent variables. The mixture was subsequently gently stirred in a warm water bath (40˚C) for 2hrs and evaporated at the same temperature above to remove the organic solvent. The obtained drug-MSN nanoparticles were further dried overnight in an oven at room temperature, and then it was stored in a desicator.



Preparation of Drug: MSN

Design factor and levels for the optimization of Drug-MSN

Factors	Levels		
	1	2	3
Molar ratio of DTX to MSN	01:01	01:02	01:03

2.2 Determination of drug content

Docetaxel content in all drug loaded mesoporous silica nanoparticles were determined by taking weighed quantity of DTX-MSN i.e. 200mg in 10 ml ethanol. Then sonicated (CITIZEN LAB CD 4820.) for 10 min. Concentration of Docetaxel was determined by analyzing the supernatant by UV-visible spectrophotometer at 229nm after suitable dilutions in ethanol. The percentage drug loading was calculated by using the following formula:

$$\text{Drug content (\%)} = \frac{\text{Conc. of drug loaded mesoporous silica}}{\text{Conc. of pure drug}} * 100$$

2.3 Determination of drug loading

Drug loading capacity of all drug loaded mesoporous silica were determined by suspending drug loaded mesoporous silica equivalent to 100mg of Docetaxel plain drug in 10ml ethanol (n=3).this suspension was then subjected to vortex (REMI ELECTROTECHNIK Ltd.DSC) for 15 min and then sonicated (CITIZEN LAB CD4820) for 10 min. The undissolved mesoporous silica was separated by centrifuging the suspension at 15000rpm for 10 min. Concentration of Docetaxel was determined by analyzing the supernatant by UV-visible spectrophotometer Concentration of Docetaxel was determined by analyzing the supernatant by UV-visible spectrophotometer at 229nm after suitable dilutions in ethanol. The percentage drug loading capacity was calculated by using the following formula.

$$\%\ drug\ loading = \frac{\text{Amt. of drug added-Amt. of drug in supernatant}}{\text{Amt. of nanoparticles}} * 100$$

3. Sample Characterization

3.1 ATR Spectroscopy

All ATR spectra were obtained by using the Spectrum RX1 (Perkin-Elmer, UK) spectrometer. Accurately weighed (5 mg) samples were mixed thoroughly with 100 mg of potassium bromide IR powder and compressed under vacuum at a pressure of 12 psi for 3 min. The pellet obtained was affixed in a suitable holder and spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1} in a scan time of 12 min.

3.2 DSC Study

Thermal analysis of Docetaxel plain drug and drug loaded mesoporous carriers were carried out by using Mettler Toledo DSC system operating with STAR^e software. Indium was used for calibration. The sample cell was purged with dry nitrogen at a flow rate of 60 ml/min. Accurately weighed samples of 5 – 10 mg were placed in aluminum crimped pans with a pin hole and scanned at a heating rate of 10 ^{0}C/min over a temperature range of 30 – 300 ^{0}C.

3.3 Scanning Electonic Microscope

SEM image of DTX plain drug , mesoporous plain carrier and drug loaded mesoporous carrier were taken from the SEM (JEOL JSM -5600) instrument to study the morphology. The power samples were mounted over a double sided adhesive carbon tape which were mounted over aluminum pin stubs and sputter coated with gold using ion sputter. The powder samples which were not adhered on to carbon tape were blown out gently and finally the samples were visualized under SEM instrument.

3.4 In-Vitro Drug Release Study

A in-vitro dissolution study were carried out using USP-type II apparatus (LABINDIA DS8000) was performed on formulation DTX, DTX:MSN batch (1:1, 1:2, 1:3) using 900ml of PB (PH 7.4). Test were conducted at 37˚c with rotation speed of 100 rpm. Sample were collected at 1hr interval. These were filter through 0.45µm and analyzed using UV Spectrophotometer.

3.5 Powder X-Ray Diffraction Analysis (PXRD)

PXRD pattern of plain drug and drug loaded carriers were recorded by using an MAXima X XRD-7000 (Shimadzu, Japan) X-ray difractometer operated at a voltage of 40 kV and current of 30 mA using Cu Kα radiation source (1.54 Å) passing through nickel filter with divergence slit (1^0), scatter slit (1^0) and receiving slit (0.3 mm) over the angular range (2θ) of 10– 40^0 at a rate of 4° min^{-1} in steps of 0.02^0 with step time of 0.3 second.

4. Result and Discussion

4.1 Determination of Drug Content

The percent drug content was calculated by according to the absorbance determined by using the formula of regression coefficient: y=mx+c and was determined to be 28.99%.

Table 4.1.1: Drug content (%) (n=3)

Docetaxel : MSN Batch	% Drug content
DTX:MSN (1:1)	59.87% ± 0.26%
DTX:MSN (1:2)	78.59% ±0.78%
DTX:MSN(1:3)	73.24% ±0.51%

4.2 Determination of drug loading

Table 4.2.1: Drug Load estimation (%wt), (n=3)

Silica carriers	% Drug loading capacity ±SD
DTX:MSN (1:1)	21.95% ± 1.03%
DTX:MSN (1:2)	14.28% ±0.92%
DTX:MSN(1:3)	16.73% ±0.64%

4.3 ATR Study

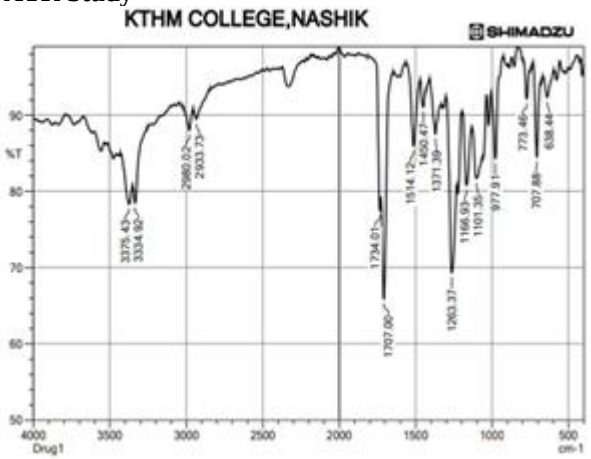


Figure 4.3.1: ATR spectra of Docetaxel

Table 4.3.1 Interpretation of ATR of Docetaxel

Frequency (cm^{-1})	Range (cm^{-1})	Group
3375	3200-3600	O-H
2980	2850-3000	C-H
1734	1734-1750	C=O
1101	1000-1300	C-O
1450	1450-1375	CH3
1263	1000-1350	C-N

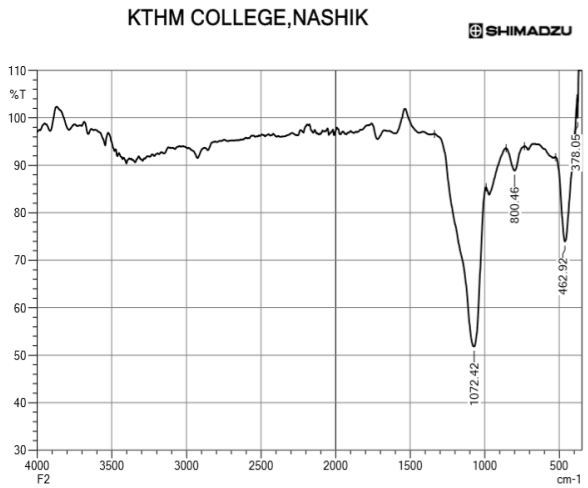


Figure 4.3.2: ATR spectra of Parteck silica SLC

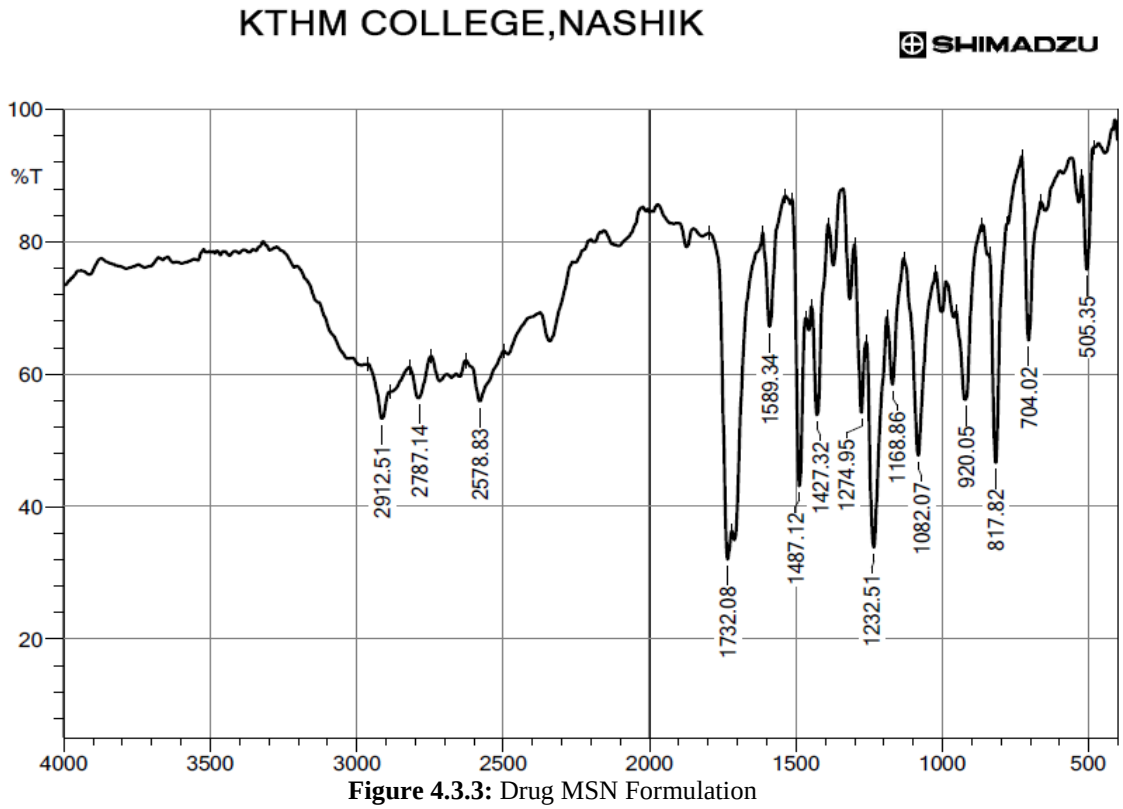


Figure 4.3.3: Drug MSN Formulation

Comparison of ATR spectra of Docetaxel pure drug (fig 12.3.1), Parteck silica SLC (fig 12.3.2) and Docetaxel-Parteck silica matrix (fig 12.3.3) reveals that some peaks have been masked while some are shifted due to loading of drug in carrier. Spectra of pure Docetaxel shows two distinct peaks in the region 3400-3300 cm^{-1}. These peaks have been completely masked in the spectra of formulation.

Some peaks from spectra of pure drug shows shifting towards lower frequency range. This shifting and masking of peaks confirms loading of Docetaxel in Parteck silica.

4.4 DSC study

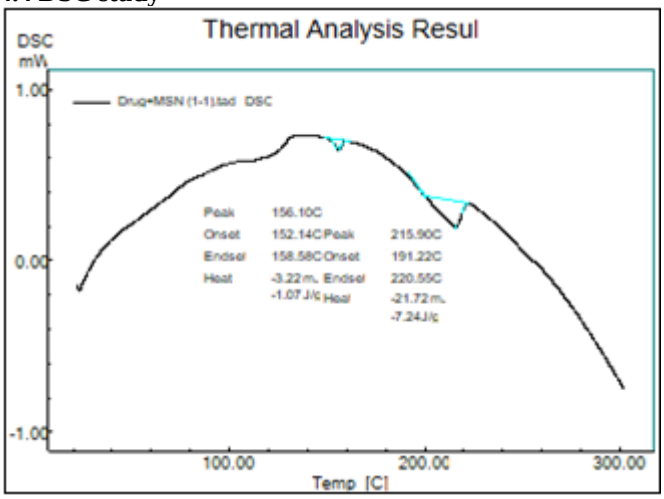


Figure 4.4.1: DSC thermogram of Docetaxel

Thermal behaviour of Docetaxel was studied by using DSC.

Characteristics endothermic peak of pure drug was observed at 190°C (Fig 4.4.4) corresponding to its melting point which indicates purity of its sample and crystallinity.

DSC thermographs of unformulated DTX, Parteck silica, Physical mixture of DTX-MSN and formulated DTX-MSN are illustrated in fig 4.4.1, 4.4.2, 4.4.3 and 4.4.4 respectively.

1) DSC of Parteck silica

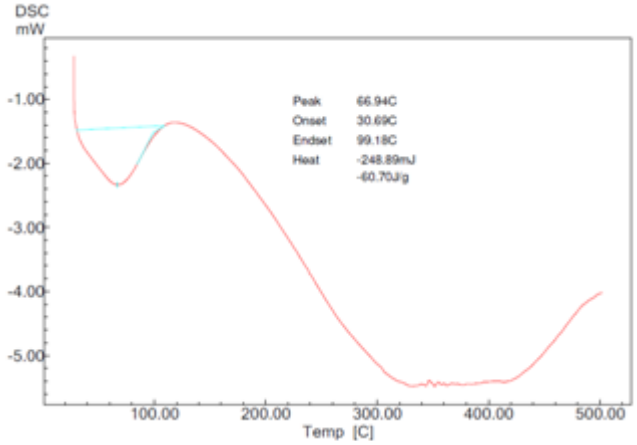


Figure 4.4.2: DSC of Parteck silica

2) DSC of Drug: MSN (50:50 physical mixture)

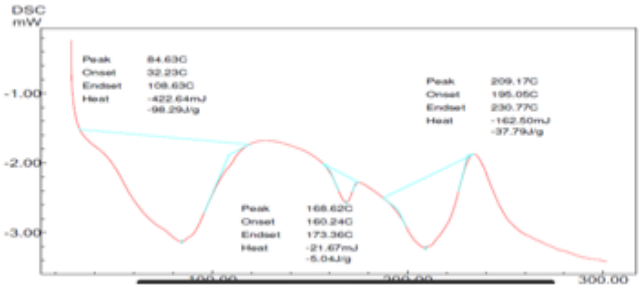


Figure 4.4.3: DSC of Drug: MSN (50:50 physical mixture)

3) DSC OF formulated DTX: MSN batch 1:2

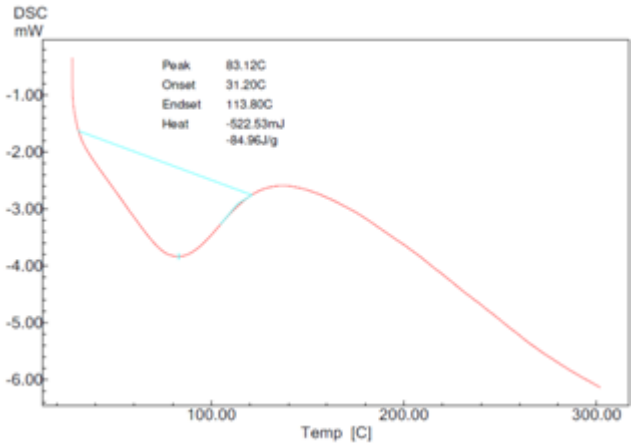


Figure 4.4.4: DSC of Docetaxel loaded MSN Formulation

As shown in figure, DTX exhibited a typical endotherm at approximately 190°C indicative of its anhydrous and crystalline nature. The typical peak of DTX can be seen clearly in the DSC curve of the physical mixture of unformulated DTX and MSN, but the melting point was decreased to 160°C and peak intensity was reduced. This phenomenon was caused by the partly complexing of the mixture during the melting process on DSC. Since the melting point of Mesoporous silica are too high to be shown in DSC study, flat curves without endothermic peaks confirmed the stability of the silica carrier. And in the DTX-MSN formulation, endothermic peak showed at approximately 83°C.

4.5 Scanning electron microscopy study

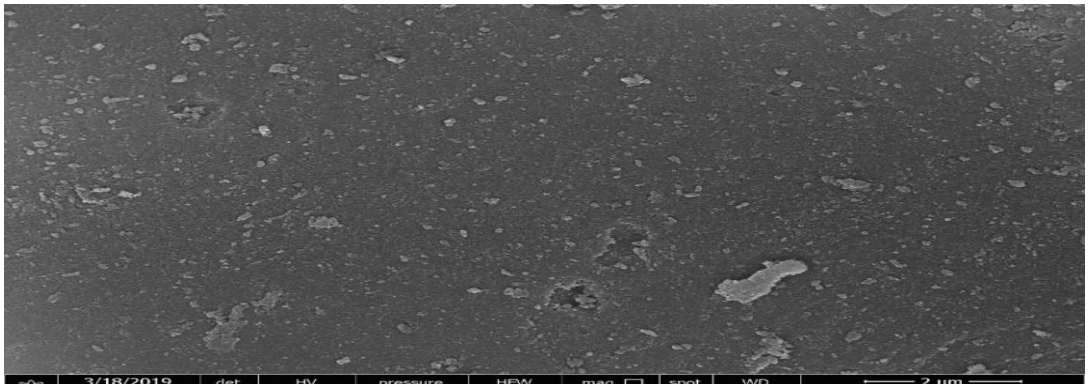


Figure 4.5.1: SEM image of Parteck silica SLC

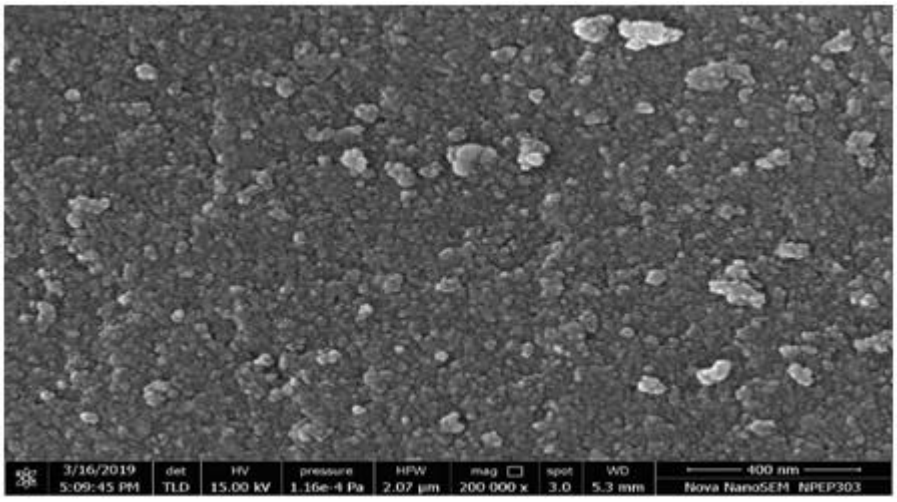


Figure 4.5.2: SEM image of drug loaded with MSN (1:2 batch)

From SEM, white fluorescence was clearly visualized to be uniformly concentrated inside the mesoporous silica nanoparticles which meant the active drug has been efficiently adsorbed into the silica.

4.6 Drug Release Study

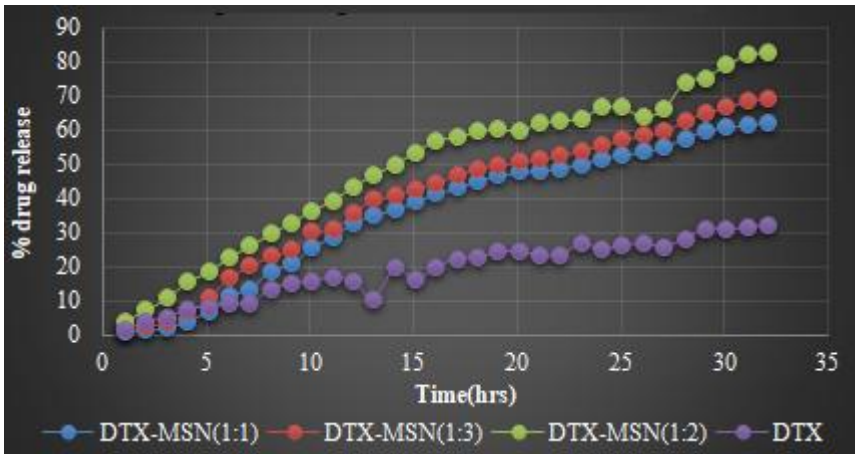


Figure 4.6.1: %Drug release vs. Time in hrs of all 3 batches

As results, DTX exhibited a dissolution percentage of 32.54% within 32 hrs, while DTX:MSN batch (1:1) had 62.09% drug release, DTX:MSN batch (1:3) had 70.02% drug release and DTX:MSN batch (1:2) significantly increased the percentage by 83.42%.

4.7 X- Ray Diffractometry (XRD)

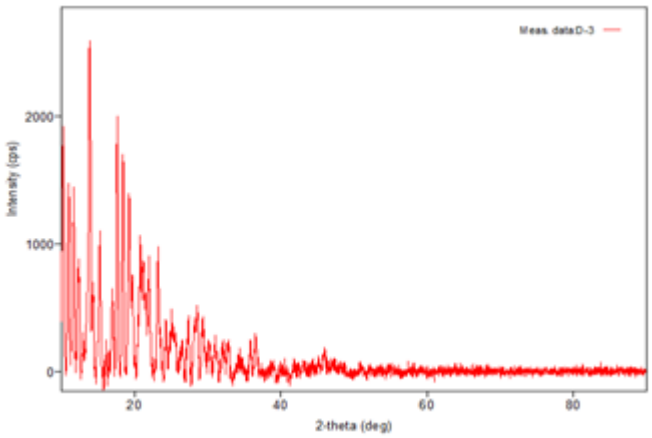


Figure 4.7.1: XRD of plain powder of Docetaxel

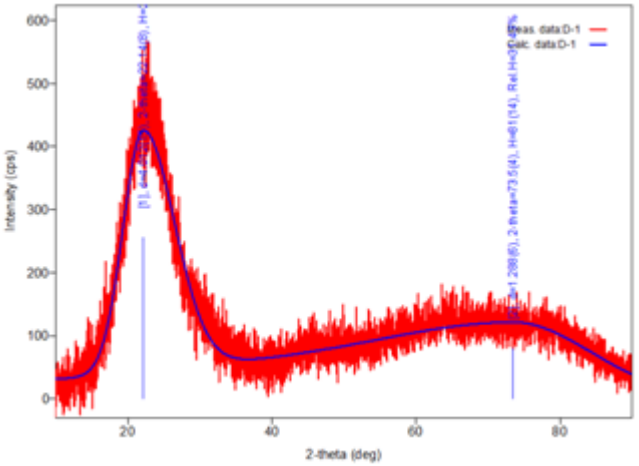


Figure 4.7.2: XRD of Docetaxel loaded MSN

Interpretation of XRD analysis

- XPRD analysis could clearly describe the crystalline degree of drug Docetaxel.As seen in fig 10.12 A, the XRD pattern of Docetaxel displayed multiple peaks between 2Ɵ to 25Ɵ and at theta value of 10,there are 3 peaks i.e. at 832°C, 1125 °C & 2172 °C respectively.
- While in the case of drug loaded MSN formulation, there are no intense peaks, & at theta value of 10, there is only one peak at 197.5 °C .
- The mesoporous silica and drug loaded formulation showed no typical crystal peak, which indicate that the drug is loaded inside the silica at amorphous state.

5. Conclusion

From this work, it can be concluded that enhancement in the solubility of Docetaxel-loaded Parteck silica SLC matrix was observed as compared with Docetaxel pure drug, as the dissolution profile of optimized batch [DTX: MSN (1:2)] showed that there is increased in percent drug release within 32hrs as compared to pure drug.

Also from XRD study, it can be seen that the mesoporous silica and drug loaded formulation showed no typical crystal peak, which suggest that the drug is converted into amorphous form after it is being incorporated in Parteck silica SLC.

The surface morphology, size and size distribution of the DTX-loaded Parteck silica SLC was studied by XRD and result showed that the formed nanoparticles are of desired particle size and from scanning electron microscopy, white fluorescence was clearly visualized to be uniformly concentrated inside the mesoporous silica nanoparticles which meant the active drug has been efficiently adsorbed into the silica.

Conclusively, the current study attained the successful design, preparation and evaluation of drug-loaded Parteck silica nanoparticles.

6. Acknowledgement

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References

[1] G. Rohan, D. Neha. BCS class IV drugs: Highly notorious candidates for formulation development. JCR, 2018:1-41. [Accepted Manuscript]
[2] W. Xin, L. Chang, F. Na, L. Jing, Z. Haotian, S. Lei, et al. Amino functionalized chiral mesoporous silica nanoparticles for improved loading and release of poorly water soluble drug. AJPS, 2018; 1-8 [Article in Press]
[3] P. Santosh, R. Neeraj. Increasing the oral bioavailability of poorly water soluble Valsartan using non ordered mesoporous silica nanoparticles. AJP, 2016; 10(2): 86-95.
[4] X. Lawrence, E. Lipka, J. Crison, G. Amidon. Transport approaches to the biopharmaceutical design of oral drug delivery systems: Prediction of intestinal absorption. Adv. Drug Deliv. Rev, 1996; 12: 359-376.
[5] D. Sun, L. Yu, M. Hussain, D. Wall, R. Smith, G. Amidon. In vitro testing of drug absorption for drug 'developability' assessment: forming an interface between in vitro preclinical data and clinical outcome. Curr. Opin. Drug Discov. Devel, 2004; 7(1):75-85.
[6] G. Amidon, H. Lennernas, V. Shah, J. Crison, A theoretical basis for biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res, 1995; 12: 413-420.
[7] C. Lipinski, F. Lombardo, B. Dominy, P. Feeney. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev, 2012; 64: 4-17.
[8] G. Giliyar, D. Fikstad, S. Tyavanagimatt. Challenges and opportunities in oral delivery of poorly water soluble drugs. Drug Deliv. Technol, 2006; 6: 57-63.
[9] P. Stenberg, C. Bergstrom, K. Luthman, P. Artursson. Theoretical predictions of drug absorption in drug discovery and development. Clin. Pharmacokinet, 2002; 41: 877-899.
[10] Toutain P.L and Bousquet-Melou, Bioavailability and its assessment Journal of Veterinary pharmacology and therapeutics J.Vet.Pharmacol.Ther, 2004; 27(6): 1-12.

[11] Vural I, Sarisozen, S, Olmez, Chitosan coated Furosemide liposomes for improved Bioavailability, Journal of biomedical technology, 2011; 7: 426-430.
[12] Anton N, Vandamme T.F, Nano-emulsions and micro-emulsions clarifications of the Critical differences, Pharmaceutical research, 2011; 978-985.
[13] Woo J.S, Lee C.H., Shim C.J, Hwang S.J, Enhanced oral bioavailability of Paclitaxel by co administration of the P-glycoprotein inhibitor KR30031, Pharmaceutical research, 2003; 20: 24-30.
[14] Yin Y.M, Cui F.D, Mu C.F, Choi M.K, Kim J.S, Chung, Shim C.K, KimC.D, Docetaxel microemulsion for enhanced oral bioavailability preparation and in vitro and in vivo evaluation, Journal of Controlled Release, 2009 ;2 : 86-94.
[15] Butani D, Yewale C, Misra A, Amphotericin B topical microemulsion formulation, Characterization and evaluation of Colloids and Surfaces B Biointerfaces, 2014; 116: 351-358.
[16] Reiss H, Entropy-induced dispersion of bulk liquids, Journal of Colloid and Interface Science, 1975; 53: 61-70.
[17] Gursoy R.N, Benita S, Self-emulsifying drug delivery systems (SEDDS) for improved Oral delivery of lipophilic drugs, Biomedicine & Pharmacotherapy, 2004; 58: 173-182.
[18] Jaafar-Maale C, Diab R, rieu V, A. Elaissari, Fessi H, Ethanol injection method For hydrophilic and lipophilic drug-loaded liposome preparation, Journal of liposome Research, 2010; 20: 228-243.
[19] Nii T, Ishii F, Encapsulation efficiency of water-soluble and insoluble drugs in Liposomes prepared by the microencapsulation vesicle method, International journal of Pharmaceutics, 2005; 298: 198-205.
[20] Rathore A, Jain A, Gulbake A, Shilpi S, Khare P, Jain A, Jain S.K, Mannosylated liposomes bearing Amphotericin B for effective management of visceral Leishmaniasis, Journal of liposome research, 2011; 21: 333-340.
[21] Paul H,Cristina R, Harper T, Cientifica, Nonporous materials, London, UK, 2003.[Accepted Manuscript]
[22] Trewyn B.G, Slowing I.I, Giri S, Chen H.T, Lin S.Y, Chem. Res. 40 (2007)846–853.[Accepted Manuscript]
[23] N. Rahmat, A.Z. Abdullah, A. R. Mohamed, Am. J. Applied Sci. 7(2010) 1579−1586.
[24] D. Zhao, J. Feng, Q. Huo, N. Melosh, G.H. Frederickson, B.F. Chmelka, G.D. Stucky, Science 279 (1998)548–552.
[25] S.A. Bagshaw, E. Prouzet, T.J. Pinnavaia, Sci. 269 (1995) 1242–1244.
[26] S. Inagaki, Y. Fukushima, K. Kuroda, J. Chem. Soc., Chem. Commun. 8(1993) 680–682.
[27] C.T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli, J.S. Beck, Nature 359 (1992) 710–712.
[28] H.J. Kim, H.C. Yang, D.Y. Chung, I.H. Yang, Y.J. Choi, J.k. Moon, J. Chem. 2015 (2015) 305−353.
[29] E.M.R. Muñoz, R.H. Acuña, Int. J. Mol. Sci. 11(2010)3069–3086.
[30] T. Yu, H. Zhang, X. Yan, Z. Chen, X. Zou, P. Oleynikov, D. Zhao, J. Phy. Chem. B 110(2006)21467–21472.
[31] S. Ruthstein, J. Schmidt, E. Kesselman, R.P. Biro, L. Omer, V. Frydman, Y. Talmon, D. Goldfarb, Chem. Mater. 20; (2008):2779–2792.
[32] C. Yuan, W.H. Juan, X.Z. ning , C.A.O. Yuan, W.E.I. Hong-juan, X.I.A. Zhi-ning, Trans. Nonferrous Met. Soc.China 19 ;(2009): 656−664.
[33] F. Hoffmann, M. Cornelius, J. Morell, M. Froba, Angew. Chemie.Int.Ed. 45; (2006) 3216−3251.
[34] Suzuki N, Zakaria MB, Chiang YD, Wu KCW, Yamauchi Y (2012) Thermally stable polymer composites with improved transparency by using colloidal mesoporous silica nanoparticles as inorganic fillers. Physical Chemistry Chemical Physics, 14: 7427-7432.
[35] Liu J, Stace-Naughton A, Jiang X, Brinker CJ (2009) Porous nanoparticles supported lipid bilayers (protocells) as delivery vehicles. Journal of the American Chemical Society, 131: 1354-1355.
[36] Arif U and M. Pritesh Review on properties and applications of mesoporous silica nanoparticles, World journal of pharmaceutical research, Department of Pharmaceutics, M.V.P. Samaj's College of Pharmacy, Nashik – 422002, Maharashtra, India.1-12.
[37] T. Limnell, A. Heltdar, S.Santos, M.A.Ermei A. Kila et.al. Drug delivery system containing Formulations of Ordered and Nonordered Mesoporous Silica Comparison of Three Drug Loading Methods. Wiley Online Library, 2011; 13(2): 1-13.
[38] Mogal S.A2*, Gurjar P. N, Yamgar D. Kamod A.C. Solid dispersion technique for improving solubility of some poorly soluble drugs, Scholars Research Library, 2012, 4 (5):1574-1586.
[39] Indian pharmacopeia Vol.First.Government of India, Ministery of Health and family welfare, New Delhi; 2007:1.
[40] Nikaghalb L, Singh G, Singh G and kahkeshan K, Solid dispersion: methods and polymers to increase the solubility of poorly water soluble drugs, Journal of applied pharmaceutical science, 2012; 2 (10): 170-175.

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