RESEARCH ARTICLE

Enhancement Solubilization of Dutasteride using Microsponge Formulation

Hassanien S. Taghi[1]*, Mustafa R. Abdulbaqi[1], Esraa G. Jabar[2]

[1]*Department of Pharmaceutics, College of Pharmacy, Al-Bayan University, Iraq.*
[2]*Department of Pharmacy, Al-Rasheed University College, Iraq.*

Received: 22th Dec, 19; Revised: 16th Jan, 20, Accepted: 12th Feb, 20; Available Online: 25th Mar, 2020

ABSTRACT

Dutasteride (DU) (5α-reductase inhibitor) that is used for the treatment of benign prostate hyperplasia (BPH), DU has low water solubility and poor oral absorption that classified as Biopharmaceutics Classification System (BCS) class II.

This study aims to improve the physical properties of Dutasteride (DU) like solubility by the preparation of microsponge (MS). Microsponges are spherical in shape, sponge-like structure, polymeric delivery systems composed of porous microspheres with a large internal surface area. Nine formulations of DU MS had been prepared by the technique of quasi-emulsion solvent diffusion (QESD) and utilizing Eudragit S100 as major polymer and glycerol as a plasticizer that dissolved in dichloromethane where polyvinyl alcohol PVA serves as a stabilizer in the external phase.

The formulas were employed to optimize preparation variable factors include; different drug to polymer ratio, the addition of different concentrations of PVA, and stirring rate. Optimization was done using the response of production yield (PY), entrapment efficiency EE), particle size, and *in vitro* drug release; The results display that the best ratio of (drug: polymer) was 5:1, and the best rate of stirring was 1,000 rpm respecting the optimum characteristics of microsponge. The best-selected formula prepared (F2) was underwent to evaluation regarding saturated solubility, FTIR, DSC, and SEM and showed 1.28 folds enhancement in saturated solubility compared to plain DU, and was well fabricated with high entrapment efficiency (83.7% ± 1.37), production yield (85.61% ± 0.6), and particle size of 77µm. Moreover, the percent release of DU was 75.74 ± 1.5 after 4 hours, with good compatibility as confirmed by XRD, SEM, DSC, and fourier-transform infrared spectroscopy (FTIR) analysis.

It can be concluded that the selected formula prepared (F2) of DU microsponge is reassuring and promising drug delivery with improved pharmaceutical physical properties.

Keywords: Dutasteride (DU), Eudragit S100, Microsponge (MS).

International Journal of Drug Delivery Technology (2020); DOI: 10.25258/ijddt.10.1.10

How to cite this article: Taghi HS, Abdulbaqi MR, Jabar EG. Enhancement Solubilization of Dutasteride using Microsponge Formulation. International Journal of Drug Delivery Technology. 2020; 10(1): 60-67.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Carrier technology offers an intelligent gate for delivery of the drug via pairing the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc., which, then modulates the release and absorption of the drug.[1] Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier characteristics.[2]

Microsponges are porous polymer-based microspheres, tiny spongy in shape, spherical particles, where the drug can be molecularly dispersed within the SP structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased.[3] This technology has many agreeable features, which make it a versatile drug delivery system.[4,5]

It has recently been noted that good control of the formulation development over the therapeutic efficacy of a drug is through an important decisive factor, namely, drug solubility.[6] This can be achieved by a microsponge where it was found to enhance the solubilization of poorly water-soluble drugs by entrapping such drugs in microsponge pores.[7] Furthermore, the dissolution rates of the drugs are related to the particle size. So, any reduction in particle size by micronization of such drugs leads to an improvement in the dissolution rate.[8,9]

Dutasteride (DU) (a 5α-reductase inhibitor) that is used for the treatment of benign prostate hyperplasia (BPH).[10]

Dutasteride is poorly water-soluble is classified as (BCS) class II, it has low water solubility that is 0.038 ng/mL in water,[11] in addition to its low dissolution rate[12] and is commercially available in the market only as a soft gelatin

**Author for Correspondence: taghipharma@gmail.com*

capsule formulation due to its low aqueous solubility, the conversion of testosterone hormone to a more potent one, named dihydrotestosterone (DHI), is achieved by dutasteride.[13] Dutasteride is 45 times more potent than finasteride; consequently have a more considerable impact in reducing DHT counts.[14]

The present research aimed to design microsponge as an inventive carrier for DU to improving the solubility and dissolution characteristics of DU.

MATERIALS

Dutasteride (DU) obtained as an appreciated gift sample from Hyperchem Ltd. (China), polyvinyl alcohol (PVA), was kindly offered by Himedi (India). Eudragit S 100 and dichloromethane and were purchased from Hyperchem, Ltd. (China). All other chemicals were procured from local sources and are of high purity.

METHODS

Preparation of Dutasteride (DU) Microsponge (MS)

Microsponges were prepared by QESD method. At which, the inner organic phase was prepared by dissolving different concentrations of Eudragit S100 (polymer) in 5 mL of dichloromethane (solvent), and the drug was added gradually to the internal phase at a different drug: polymer ratio under ultrasonication at 35°C for 15 minutes. An outer phase containing an aqueous solution of different amounts of PVA, e.g., 0.05, 0.15, and 0.2 gm of PVA (200 mL), was prepared separately, and the inner phase was added dropwise into it under continuous stirring (500 rpm) for 3 hours. MS.s were filtered by filtration and dried in an oven at 40°C for 12 hours and stored in desiccators till use.[15]

In this study, different factors had been studied to reveal their effect on the SP preparation in order to select the best formula that achieves the goal of our study.

For the optimization of the formulations of DU MS, many factors had been studied. These factors include the effect of drug: polymer ratio (2.5:1, 5:1, 7.5:1, 10:1), addition of PVA with different concentrations (0.05, 1, 0.15 g) and stirring rate. The composition of DU MS formulas is revealed in Table 1.

Evaluation of Dutasteride (DU) Microsponge (MS) Formulations

Saturation Solubility Study

The saturated solubility of DU was determined using different media such as 0.1 N HCL containing 2% sodium dodecyl sulfate (SDS) and water. Similarly, the saturated solubility is performed by adding an excess quantity of drug into the volumetric flask containing 25 mL from the specific medium. The volumetric flask placed in magnetic stirrer at 25 ± 0.5°C for 72 hours and then sonicated for 10 minutes. This procedure provides sufficient time and stress conditions to produce saturated solubility.[16]

The solutions were then filtered by a 0.45 µm filter paper, diluted suitably and measured using the HPLC with a mobile phase of acetonitrile: water (50:50 v/v) and the flow rate was 1.5 mL/min. The selected λ_{max} is 244 nm. The area under the peak (AUP) for each solution is recorded, and the concentration is estimated using the constructed calibration curve.[17,18] Three determinations ± SD were carried out for each sample to measure the saturation solubility of the drug.

Determination of Production Yield

The production yield (PY) of all MS was calculated using the following equation: (Equation 1).[19]

$$PY\ (\%) = \frac{\text{Practical weight of MS}}{\text{Theoretical weight (polymer + drug)}} \times 100 \quad (1)$$

Determination of Loading Efficiency (LE)

To determine the content of DU in the DU MS, a sample of DU MS equivalent to 0.5 mg was dissolved in 100 mL of DCM. The solution was diluted suitably with DCM, and spectrophotometric absorbance was measured at λ_{max} of DU. The drug content was measured from the calibration curve and expressed as a percent LE as explained in equation 2.[20] To minimize the error, LE was carried out in triplicate ± SD.

$$LE\ (\%) = \frac{\text{Actual weight of TEL in SP}}{\text{Theoretical weight of TEL}} \times 100 \quad (2)$$

Determination of Particle Size

The particle size determination of DU MS was done by using ABT-9000 nanolaser particle size analyzer, which

Table 1: Composition of DU MS formulas prepared by QESD method

	Internal phase				*External phase*			
Formulas	*Drug:polymer ratio*	*DU (gm)*	*Eudragit S100 (gm)*	*DCM (mL) **	*PVA (gm) **	*Glycerol (mL)*	*Water (mL)*	*Stirring rate (rpm)*
F1	2.5:1	0.5	0.2	5	0.05	1	200	1,000
F2	5:01	1	0.2	5	0.05	1	200	1,000
F3	7.5:1	1.5	0.2	5	0.05	1	200	1,000
F4	10:01	2	0.2	5	0.05	1	200	1,000
F5	5:01	1	0.2	5	0.1	1	200	3,000
F6	5:01	1	0.2	5	0.1	1	200	6,000
F7	5:01	1	0.2	5	0.1	1	200	1,000
F8	5:01	1	0.2	5	0.15	1	200	1,000
F9	5:01	1	0.2	5	0.2	1	200	1,000

is a dynamic light scattering, at scattering angle 90º and a constant temperature of 25ºC without dilution the samples.[21] The average particle size was measured for all the prepared microsponge.

In vitro Dissolution Studies of the Prepared Dutasteride (DU) Microsponge (MS)

The in-vitro dissolution study of the prepared DU MS is performed using rotary paddle dissolution apparatus (type II). The dissolution medium is 900 mL of 0.1 N HCl (pH 1.2), contains 2% w/v sodium dodecyl phosphate and the paddle rotates at 50 rpm.[22] The accurately weighted loaded microsponge that contains 0.5 mg dutasteride added into the dissolution vessel, 3 mL sample is withdrawn from the dissolution medium and immediately replaced with 3 mL of fresh dissolution medium, then, filtered using 0.11 µm filter syringe. The concentration of dutasteride in a different sample is measured using HPLC and the wave length used to detect dutasteride is 244 nm.[17]

Fourier Transform Infrared (FTIR) Analysis

The FTIR spectra of the plain DU, Eudragit S 100, and selected DU MS formula were obtained using potassium bromide (KBr) disc and performed by FTIR spectrometer (8300 Shimadzu, Japan) to ascertain compatibility.[23]

Scanning Electron Microscope (SEM)

The surface morphology of the formula F2 was observed under SEM (VEGA3 Tescan Czech republic). It was coated with gold-palladium at room temperature under an argon atmosphere.[24]

Differential Scanning Calorimetry (DSC)

The DSC used to assess the crystalline state of the drugs, especially when converted to microscale particles and elucidates a likely interaction between drug and other materials. Thermal characteristics of the pure drug DU, physical mixture (PM) of DU: Eudragit S100 at 1:1 ratio, and selected microsponge formula F2, were characterized by an automatic thermal analyzer system using DSC-60 plus (Shimadzu, Japan).[25]

Powder X-ray Diffraction (XRD) Studies

Powder XRD is used to study the atomic and molecular structure of the crystalline nature of DU, physical mixture of DU, and Eudragit S100, and DU MS. The study was confirmed by powder X-ray diffraction (XRD-6000, Shimadzu, Japan 220V/50Hz) at a continuous scan range of 2θ = 5 – 80º.[26]

RESULTS AND DISCUSSION

Determination of solubility is an important issue in the formulation of poorly soluble drugs. The results of the saturation solubility study are shown in Table 2 and Figure 1. These results reveal that pure dutasteride has very low water solubility. This fact is expected since dutasteride is a BCS class II drug with very low water solubility.[13] Similarly, the MS was expected to increase the solubility of dutasteride in all media since the drug is molecularly dispersed within the MS structure that contains voids and channels, which greatly increase the drug surface area exposed to the dissolving media.[14,27]

Determination of Production Yield and Loading Efficiency

The production yield (PY) and loading efficiency (LE) are important measures for microparticulate systems. They give an idea about the production and scale-up capabilities, and the encapsulation power of that particular technique. Some of the microparticulate techniques, e.g., liposomes, suffer from low PY and LE, whereas other techniques, such as the microsponge method, have good or even excellent PY and LE.[28]

The PY and LE of all of the DU MS formulas were measured, as shown in Table 3 and Figure 2. The PY was between 58–86% for all the formulas, whereas the LE varied between 41–83% for all formulas. Statistically, it was a different, significantly among formulas ($p < 0.05$) regarding both the PY and the LE.

It was noted that all the DU MS, to be uniform in size, in the range of 60 to 97 (Table 2).

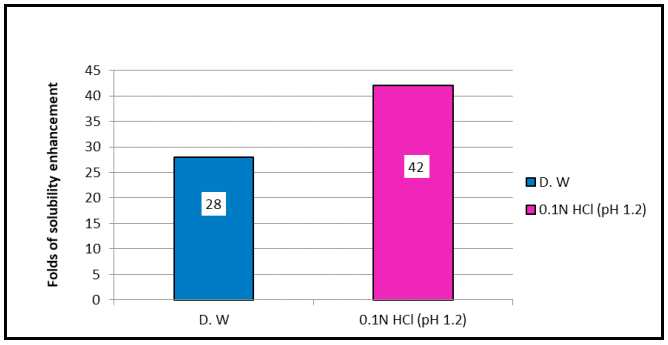

Figure 1: Influence of the MS formulation on the saturated solubility of DU

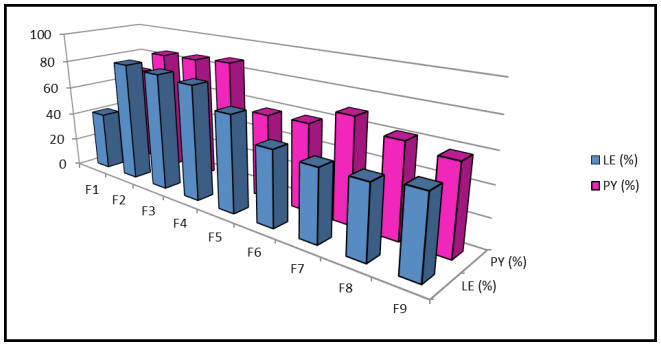

Figure 2: Effect of the microsponge formulation on the PY and LE of DU MS

Table 2: The saturation solubility of pure DU and DU MS in different media.

Solvent	*Solubility of pure DU (ng/mL) ± S.D.**	*Solubility of DU MS (ng/mL) ± S.D.**	*Solubility Enhancement (%)*
D. W	0.065 ± 0.06	0.083 ± 0.03	28
0.1N HCl (pH 1.2)	1.11 ± 0.070	1.55 ± 0.0047	42

*SD: Standard deviation, n = 3

Table 3: The PY, LE, and Mean particle size of all DU MS Formulas.

Formulas	*LE (%) **	*PY (%) **	*Mean particle size (µm)*
F1	41	68	88
F2	83	85	77
F3	81	86	76
F4	79	86	71
F5	66	58	66
F6	51	59	60
F7	48	70	89
F8	48	62	92
F9	52	58	97

*PY: Production yield, LE: Loading efficiency

It was noted that as there is an inverse relationship between the (drug to polymer) ratio and the particle size. This could probably be because as the ratio of (drug:polymer) increase, the amount of polymer in MS was relatively lesser.[27,30]

Effect of Stirring Rate on the Production Yield and Loading Efficiency LE of the DU MS

The formulas F2, F5, and F6 that designed employing stirring rate of 1,000, 3,000, and 6,000 rpm, respectively, were utilized to visualize the influence of stirring rate on the physical properties of the prepared DU MS.

It was found that at high stirring rates, more vigorous turbulence was generated within the external phase. The polymer may adhere to the stirrer and glassware, which led to a reduction of the PY.[31]

Herein, as we see in Table 2, it was noted that, as the stirring speed was a high pattern, the mean particle size of MS was small. This is supporting the fact that there is a true inverse relation between stirring speed and size, which may be attributed to the high mechanical shear that applied during the high stirring rates resulting in a quick splitting of the formed droplets, allowing less chance of coalescing into bigger droplets.[32]

However, the DU MS prepared with 1,000 rpm had higher and more acceptable PY and LE, and therefore, 1,000 rpm was selected to be the optimum rate.

We have studied the effect of concentration of polyvinyl alcohol (PVA) on size of microsponges, The selected concentration of PVA was 0.05%, but on taking 0.1% of PVA, particle size increases from 77 µm to 89 µm, further on taking 0.15% of PVA particle size increases to 92 µm, And the particle size measured 97µm, at a 0.2% of PVA. The dispersion of the solution of the DU and Eudragit s100 into small drops was influenced by the amount of PVA in the external phase. When the amount of PVA was increased, the size of microsponges was found to be increased because of the increased viscosity wherein larger emulsion droplets formed resulting in larger microsponges.[33]

Finally, according to the obtained results, the optimum DU MS formula selected for the subsequent evaluation was formula 2 (Table 1). This formula was selected depending upon the optimization of the formulation characteristics such as PY, LE, and the release profile, as will be seen later.

Fourier Transform Infrared (FTIR) Analysis

FTIR spectroscopic study (Figure 3) revealed that there was no disappearance of characteristic peaks of drug or appearance of any new peak, indicating there is chemical compatibility between the drug and polymer used.

FTIR study displayed that their spectrum of DU showed characteristic peaks of N-H stretch at 3,477 cm^{-1}, N-H bend at 1,583 cm^{-1}, C=O stretch at 1747.95 cm^{-1}, C=C, symmetric stretch at 1,510 cm^{-1} was assigned in plain DU; in addition to the presence of C=C-H, asymmetric stretch at 3,477.60 cm^{-1} in pure drug; 3379 and 3477 cm^{-1} in DU MS indicating the presence of aromatic ring. The existence of C-X is observed by the peak at 1136 cm^{-1} in the DU and DU MS.[22]

In conclusion, the FTIR spectrum of plain DU and DU MS were almost similar because of the presence of the same functional groups and proposed that DU was convenient and compatible with selected polymers, and it was stable in the microsponges.

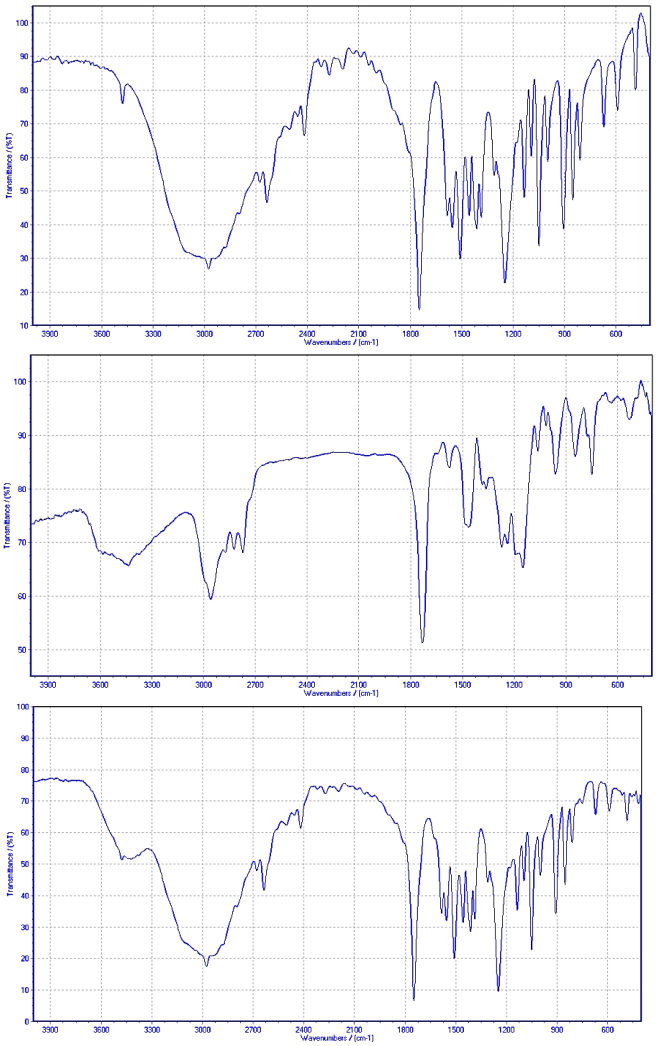

Figure 3: FTIR spectra of A) Plain DU, B) Eudragit S100, C) DU MS coded F2.

Differential Scanning Calorimetric (DSC) Analysis

The thermograms of dutasteride showed a sharp exothermic peak at 251°C, where the melting point of dutasteride is between 242 to 250˚C in accordance with the literature,[35] as reported in Figure 4.

In regard to the physical mixture's thermogram of drug and MS, the melting peak of 250.45°C for DU was obtained, although the peak was shifted due to eutectic effect, which refers that the DU is still in the crystalline state. Also, the thermogram showed a broad endothermic peak at about (77.4°C) over large temperature ranges, which could be attributed to the evaporation of residual water, which acts as the energy needed to vaporize water in the sample.[36,37]

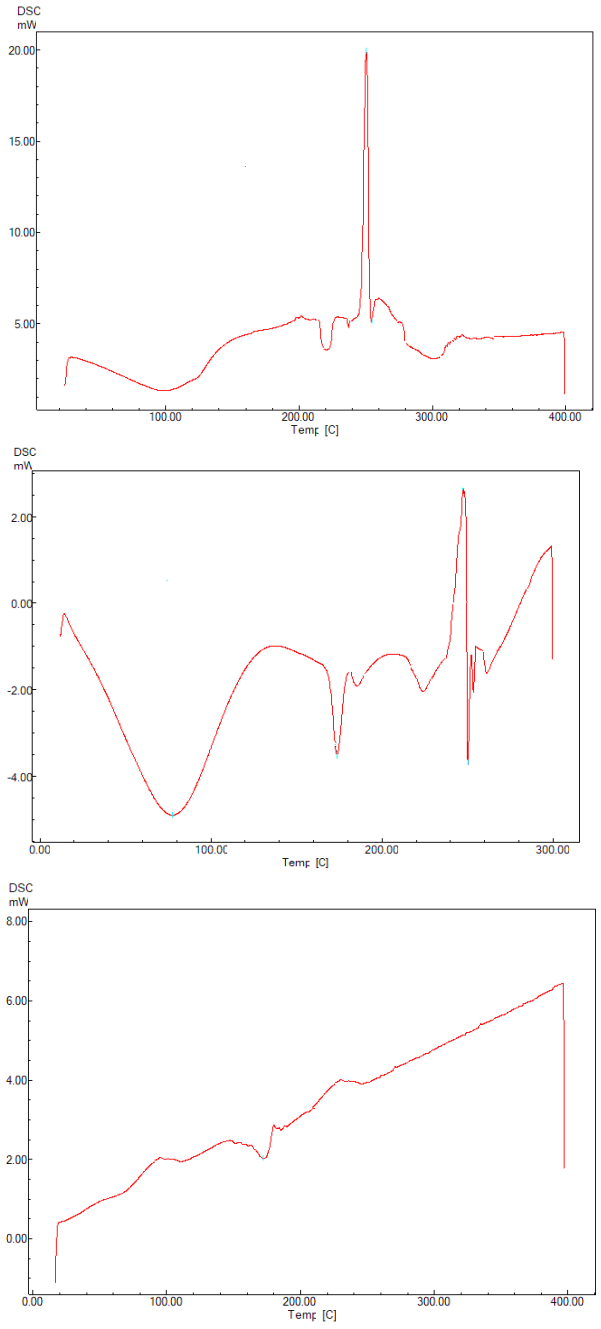

Figure 4: DSC of A) Plain DU, B) PM, C) Selected DU MS (F2).

The endothermic peak corresponding to dutasteride fusion was absent following its inclusion into microsponges, as displayed in Figure 4 of selected DU MU formula (F2). So, this disappearance evidenced that dutasteride is unable to crystallize and that it is mainly molecularly dispersed in the microsponge structure without the capacity of crystallization, and changed the nature of the drug in microsponges.[38]

This behavior confirms the interaction of DU with the microsponge structure. Conversely, the DU peak is detectable in the physical drug mixture and agreed with, and Andreea Alexandra, who declared that the amorphous solid pattern would certainly be indicated and beyond the doubt, only in the case of indications of suppression in the thermal indicators of the drug.[39]

Scanning Electron Microscope (SEM) Study

The SEM analysis of the prepared MS, coded F2, is revealed in Figure 5 at 1400, 2500, and 6600X magnification, respectively.

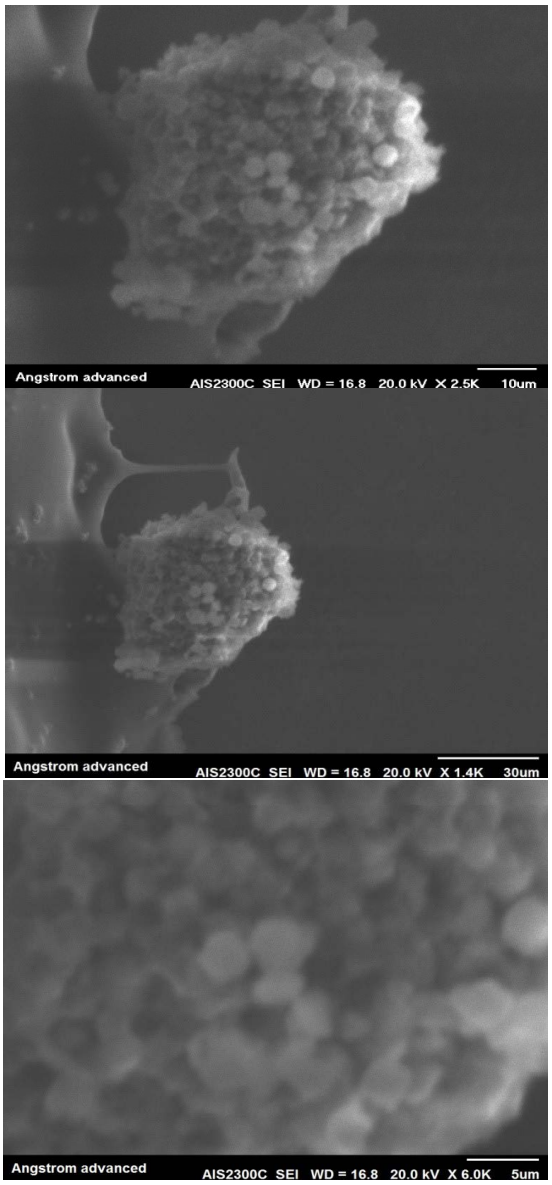

Figure 5: SEM of selected DU microsponges formula (F2)

It seemed that the MS was highly porous, finely distributed, and smooth uniform spheres. The SEM study reveals the presence of tiny pores in the analyzed formula. The highly porous nature indicates the validity of the method that was used for the formulation of DU MS, i.e., QESD method, in which an organic solvent diffuses out of the SP, leaving pores and channels behind it. The so-called "sponge-like" particles are truly evident in their photomicrographs. These findings are similar to the results reported in literature.[40]

Powder X-Ray Diffraction Analysis

To further study the physical nature of dutasteride, powder X-ray diffraction was performed, at which it yielded very useful data on the degree of sample crystallinity, and considered a proven tool for studying the arrangements of the crystal lattice of solid substances.

The PXRD patterns of dutasteride as a plain DU represented several sharp diffraction peaks at 2θ of 14.6°, 19.5°, 20.6°, and 28.4° as in Figure 6 suggested that the drug existed as crystalline nature.

For the blended powder of Eudragit S100, its XRD pattern showed a diffused pattern of low-intensity peaks, which demonstrated the disordered crystalline phase or amorphous solid state.

The XRD pattern of the DU MS, showed the main peaks of pure dutasteride at an angle (2θ) of 13.6°, 19.7°, and 28.5° and suggesting that there is no chemical interaction between the components.

The decrease in intensity of the strongest peaks of pure dutasteride in XRD pattern of DU MS (Figure 6) indicates a reduction in crystallinity and amorphous solid state. Furthermore, it indicates that the dutasteride was well dispersed in the amorphous phase in microsponge, loosing most of its crystallinity.[41]

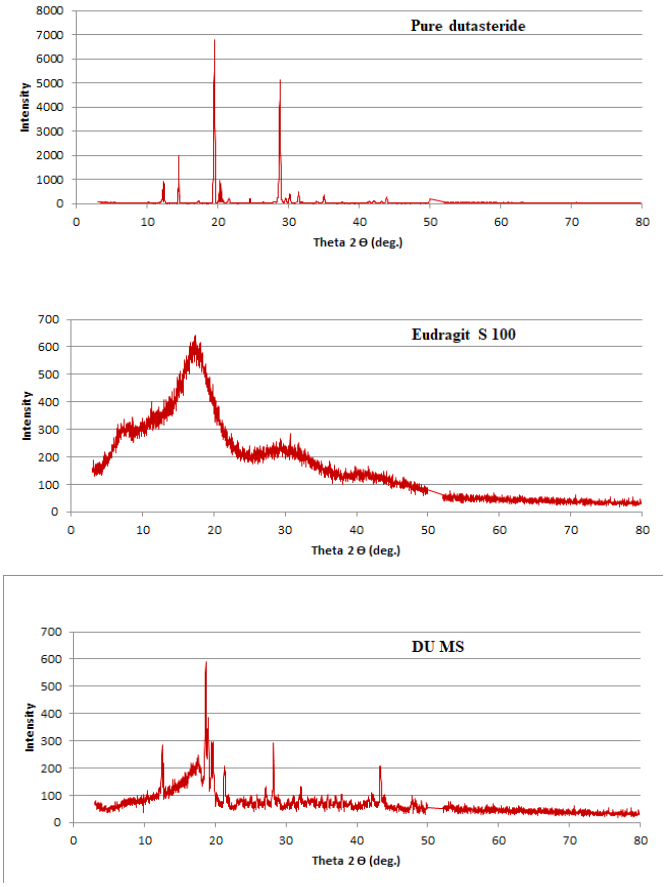

Figure 6: The XRD pattern of pure DU, eudragit s100 and DU MS

***In vitro* Dissolution Studies of dutasteride Loaded Microsponges.**

In vitro dissolution study was performed for all DU MS formulas in addition to pure DU, using USP dissolution test apparatus-II. The time for 75% release (T 75%) for all DU MS formulas in 0.1 N HCl (pH 1.2) used for the comparison of the dissolution results and listed in Table 4.

According to the results obtained Figure 7, it was concluded that the formula named F2 released drug at faster and higher rate when compared with other prepared microsponges and higher than pure dutasteride in term of T 75% (mins), that is why it was selected as the best formula.

In fact, the higher release of dutasteride from microsponges, possibly due to optimism and sufficiency nanopores of the intricate network created during MS synthesis, which allowed higher solubility. Furthermore, probably related to the physical nature of DU MS in term of disordered crystalline.[42]

As well as, it might be due to the dispersion of drug molecules in a molecular manner within nanochannels of MS, which have a primary effect on the release of the drug molecules without passing the dissolution step.[43] Finally, not to forget the fact, that the incorporation of the drug into the

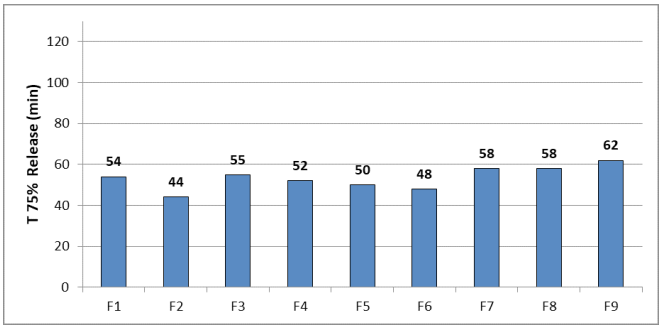

Figure 7: Time of 75% release of DU from DU MS, and raw material in 0.1 N HCl at 37 ± 0.5°C.

Table 4: Time for 75% release for all DU MS formulas in 0.1 N HCl (pH 1.2)

Formulas	*T 75% (min)* *
F1	64
F2	44
F3	55
F4	52
F5	50
F6	48
F7	58
F8	58
F9	62

* T75%: The time of 75% release

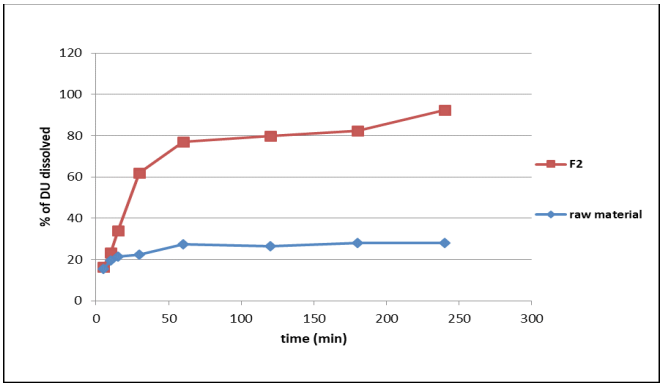

Figure 8: Release profile of DU from DU MS (F2), and raw material in 0.1 N HCl at 37 ± 0.5°C

nano-sized pore of microsponge resulted in the higher effective surface area, consequently enhanced the contact between MS and dissolution medium.[44]

CONCLUSION

Through the present study, it has been able to formulate successful dutasteride loaded microsponge with a noticed compatibility with other components, giving rise for an increase in the solubility of this drug to a great extent and without interfering with other components. The prepared dutasteride loaded microsponge show faster dissolution characteristics as compared to pure dutasteride.

DECLARATION OF INTEREST

The author declares no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

ACKNOWLEDGEMENT

Author is grateful to University of Baghdad-College of Education for Pure Sciences Ibn Al-Haitham/Central Serving Laboratory for performing the analytical methods in this study. Special thanks for Al-Bayan University for their support and encouragement.

AUTHOR CONTRIBUTION

The study was funded, written, revised, and performed (the experimental and analytical work) by the authors.

REFERENCES

1. Chowdary KP, Rao YS. Mucoadhesive microspheres for controlled drug delivery. Biological and pharmaceutical Bulletin. 2004;27(11):1717-24.
2. Sagavkar SR, Mohite DS. Innovative and Novel Strategy: Microsponges Drug Delivery System. International Journal of Universal Pharmacy and Bio Sciences. 2014;3(4):79-92.
3. Solanki D, Patidar S, Kag N, Motiwale M, Kushwah L, Mewade A. An Overview of Microsponge as a Novel Tool in Drug Delivery. Ijppr.Human. 2017;9(2);64-77.
4. Pradhan SK. Microsponges as the versatile tool for drug delivery system. International Journal of Research in Pharmacy and Chemistry. 2011;1(2):243-258.
5. Osmani AM, H Aloorkar N, S Kulkarni A, K Kulkarni P, Hani U, Thirumaleshwar S, R Bhosale R. Novel cream containing microsponges of anti-acne agent: Formulation development and evaluation. Current drug delivery. 2015 Oct 1;12(5):504-516.
6. Ghareeb MM. Improvement of Rebamipide Solubility via optimized Microsponge formulation. Journal of Pharmaceutical Sciences and Research. 2018 Jun 1;10(6):1525-1529.
7. Patil RS, Kemkar VU, Patil SS. Microsponge drug delivery system: a novel dosage form. Am J PharmTech Res. 2012 Jul;2(July):227-251.
8. Mosharraf M, Nyström C. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. International journal of pharmaceutics. 1995 Aug 1;122(1-2):35-47.
9. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian journal of pharmaceutical sciences. 2014 Dec 1;9(6):304-316.
10. Dolder CR. Dutasteride: a dual 5-α reductase inhibitor for the treatment of symptomatic benign prostatic hyperplasia. Annals of Pharmacotherapy. 2006 Apr;40(4):658-665.
11. Lee DH, Yeom DW, Song YS, Cho HR, Choi YS, Kang MJ, Choi YW. Improved oral absorption of dutasteride via Soluplus®-based supersaturable self-emulsifying drug delivery system (S-SEDDS). International journal of pharmaceutics. 2015 Jan 15;478(1):341-347.
12. US Food and Drug Administration, US Department of Health and Human Services, viewed November 2015, http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm.
13. Kim MS. Influence of hydrophilic additives on the supersaturation and bioavailability of dutasteride-loaded hydroxypropyl-β-cyclodextrin nanostructures. International journal of nanomedicine. 2013;8:2029.
14. Keam SJ, Scott LJ. Dutasteride. Drugs. 2008;68(4):463-85.
15. Desavathu M, Pathuri R, Chunduru M. Design, development and characterization of valsartan microsponges by quasi emulsion technique and the impact of stirring rate on microsponge formation. Journal of Applied Pharmaceutical Science. 2017 Jan;7(1):193-198.
16. Baka E. Development and examination of solubility measurement methods for drug solubility determination (Doctoral dissertation, Semmelweis University). 2010.
17. Choudhari VP, Nikalje AP. Stability-indicating TLC method for the determination of dutasteride in pharmaceutical dosage forms. Chromatographia. 2009 Jul 1;70(1-2):309-313.
18. Tong W-Q. Practical aspects of solubility determination in pharmaceutical preformulation In: Augustijns P. Brewster ME, editor. New York: Springer. 2007.
19. Kılıçarslan M, Baykara T. The effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres. International journal of pharmaceutics. 2003 Feb 18;252(1-2):99-109.
20. Gupta R, Prajapati SK, Pattnaik S, GANGULI A, MISHRA S. Performance and evaluation of floating microspheres of famotidine and comparison of their physical properties. Int J Pharm Pharm Sci. 2012;4(5):376-382.
21. Akbari B, Tavandashti MP, Zandrahimi M. Particle size characterization of nanoparticles–a practicalapproach. Iranian Journal of Materials Science and Engineering. 2011 Jun 10;8(2):48-56.
22. Poonguzhali Subramanian RS. Self-nanoemulsifying drug delivery systems of poorly soluble drug dutasteride: Formulation

and in-vitro characterization. Journal of Applied Pharmaceutical Science. 2017 Apr;7(04):011-22.
23. Jain V, Singh R. Development and characterization of eudragit RS 100 loaded microsponges and its colonic delivery using natural polysaccharides. Acta poloniae pharmaceutica-drug research. 2010 Jul 1;67(4):407-415.
24. Patel R, Patel H, Baria A. Design Optimization and Evaluation of pH Responsive Prednisolone Sustained Release Tablet for Ileo-colonic Delivery. 2010; 9: 1-5.
25. Mohan KV, Veena NM, Manjula BP. Formulation and evaluation of microsponges for topical drug delivery of mupirocin. International Journal of Pharm Tech Research. 2013;5(3):1434-1440.
26. Łaszcz M, Trzcińska K, Witkowska A, Lipiec-Abramska E, Szczepek WJ. Phase transition studies of dutasteride crystalline forms. CrystEngComm. 2015;17(11):2346-2352.
27. Pande VV, Kadnor NA, Kadam RN, Upadhye SA. Fabrication and characterization of sertaconazole nitrate microsponge as a topical drug delivery system. Indian journal of pharmaceutical sciences. 2015 Nov;77(6):675–680.
28. Aloorkar NH, Kulkarni AS, Ingaleand DJ, Patil RA. Microsponges an innovative drug delivery systems; International Journal of Pharmaceutical Sciences and Nanotechnology. 2012;5(1):1597-1606.
29. Pagar PS, Savkare AD. Formulation and evaluation of omeprazole microspheres by different techniques. Indo American Journal of Pharmaceutical Research. 2017;7(8):426-440.
30. Patel N, Padia N, Vadgama N, Raval M, Sheth N. Formulation and evaluation of microsponge gel for topical delivery of fluconazole for fungal therapy. Journal of Pharmaceutical Investigation. 2016 Jun 1;46(3):221-238.
31. Desavathu M, Pathuri R, Chunduru M. Design, development and characterization of valsartan microsponges by quasi emulsion technique and the impact of stirring rate on microsponge formation. Journal of Applied Pharmaceutical Science. 2017 Jan;7(1):193-198.
32. Singh RP, Prajapati SK. Formulation and Evaluation of Prednisolone loaded Microsponges for Colon Drug Delivery: in-vitro and Pharmacokinetic study. International Journal of Pharmaceutical Sciences and Research. 2014 May 1;5(5): 1994.
33. Ghareeb MM. Improvement of Rebamipide Solubility via optimized Microsponge formulation. Journal of Pharmaceutical Sciences and Research. 2018 Jun 1;10(6):1525-1529.
34. Choi JS, Lee SE, Jang WS, Byeon JC, Park JS. Solid dispersion of dutasteride using the solvent evaporation method: Approaches to improve dissolution rate and oral bioavailability in rats. Materials Science and Engineering: C. 2018 Sep 1;90:387-396. DOI: 10.1016/j.msec.2018.04.074
35. Marcato PD, Durán N. New aspects of nanopharmaceutical delivery systems. Journal of nanoscience and nanotechnology. 2008 May 1;8(5):2216-2229.
36. Rossi B, Caponi S, Castiglione F, Corezzi S, Fontana A, Giarola M, Mariotto G, Mele A, Petrillo C, Trotta F, Viliani G. Networking properties of cyclodextrin-based cross-linked polymers probed by inelastic light-scattering experiments. The Journal of Physical Chemistry B. 2012 May 3;116(17):5323-5327.
37. Bharate SS, Bharate SB, Bajaj AN. Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. J. Excipients and Food Chem. 2010;1(3):1-26.
38. Olteanu AA. Effecteffect of b-cyclodextrins based nanosponges on the solubility of lipophilic pharmacological active substances (repaglinide). J. Incl. Phenom. Macrocycl. Chem. 2014;(80):17–24.
39. Orlu M, Cevher E, Araman A. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. Int J Pharm. 2007;318:103–117.
40. Rossi B, Fontana A, Giarola M, Mariotto G, Mele A, Punta C, Melone L, Toraldo F, Trotta F. Glass-like dynamics of new cross-linked polymeric systems: Behavior of the Boson peak. Journal of non-crystalline solids. 2014 Oct 1;401:73-77.
41. Swaminathan S, Cavalli R. *In vitro* release modulation and conformational stabilization of a model protein using swellable polyamidoamine nanosponges of b-cyclodextrin; J Incl Phenom Macrocycl Chem. 2010;68:183–191.
42. Rao M, Bajaj A, Khole I, *et al*. In vitro and in vivo evaluation of beta-cyclodextrin-based nanosponges of telmisartan. J Incl Phenom Macrocycl Chem. 2013;77(1-4):135-45.
43. Taghi HS, Abdul Rasool AA, Khalil YI. Enhancement of tenoxicam solubility by hp-beta-cyclodextrin based nanosponge; world journal of pharmacy and pharmaceutical sciences. 2016; 5(4):525-534.